

**From Conventional to
Microphotochemistry: A study of
Phthalimide and Phthalonitrile
derivatives**

PhD Thesis

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Table of Contents

Acknowledgements	ix
List of abbreviations	x
Abstract	xii
1 Literature review	2
1.1 Photochemistry	2
1.1.1 Photoinduced Electron Transfer (PET)	4
1.2 Introduction to phthalimides	5
1.2.1 Pharmaceutical and industrial importance of phthalimides	5
1.2.2 Phthalimides in organic synthesis	7
1.2.3 Photophysical and electrochemical properties of phthalimides	8
1.3 Photoaddition reactions involving phthalimides	9
1.3.1 Photoadditions of arenes	9
1.3.2 Photoadditions of alkenes	9
1.3.2.1 Photoreductions	11
1.3.3 Photoadditions of oxygen containing compounds	12
1.3.3.1 Photoadditions of ethers	12
1.3.3.2 Photoadditions of α -trialkylsilylmethyl-substituted ethers	13
1.3.4 Photoadditions of nitrogen containing compounds	13
1.3.4.1 Photoadditions of amines	13
1.3.4.2 Photoadditions of α -trialkylsilylmethyl-substituted amines	14
1.3.5 Photoadditions of sulfur containing compounds	15
1.3.5.1 Photoadditions of thioethers	15
1.3.5.2 Photoadditions of α -trialkylsilylmethyl-substituted thioethers	15
1.3.6 Photoadditions of carboxylates	16
1.3.6.1 Photoadditions of alkyl carboxylates	16
1.3.6.2 Photoadditions of heteroatom substituted carboxylates	17
1.3.6.3 <i>Intramolecular</i> decarboxylative cyclisation reactions	19
1.4 Aristolactams	19
1.4.1 Naturally occurring aristolactams and their biological activity	19
1.4.1.1 Examples of related derivatives	21
1.4.1.2 Isolation of natural aristolactams	22
1.4.2 Synthesis of aristolactams	23

1.5	Phthalonitriles and phthalocyanines	25
1.5.1	General structure and properties	25
1.5.2	Photodynamic therapy and phthalocyanines.....	26
1.5.3	Synthesis of phthalocyanines	27
1.5.4	Solubility of phthalocyanines.....	29
1.5.5	Sulfonated phthalocyanines	30
1.6	Microphotochemistry.....	35
1.6.1	Examples of microstructured reactors.....	35
1.6.2	Selected examples of micro-photochemical reactions	38
	Thesis proposal	41
2	Photoaddition reactions of NMP and phthalimide	44
2.1	Introduction	44
2.2	Synthesis of starting material.....	45
2.2.1	Synthesis of <i>N</i> -methylphthalimide.....	45
2.3	Photoaddition reactions in solution	45
2.3.1	Experimental set-up	45
2.3.2	Reactions of alkyl carboxylates and phenylacetates with NMP	46
2.3.3	Reactions of phthalimide with phenylacetates.....	54
2.3.4	Reactions of NMP with α -keto carboxylates	57
2.4	Dehydration of photoaddition products.....	60
2.5	Summary.....	64
3	Photoaddition reactions of NMP with heteratom-containing addition partners	66
3.1	Introduction	66
3.2	Synthesis of starting materials	67
3.2.1	Synthesis of <i>N</i> -acetylated amino acids.....	67
3.2.2	Reactions of phthalimides with sulfur-containing addition partners	69
3.2.3	Reaction of NMP with oxygen-containing addition partner	73
3.2.4	Photodecarboxylative addition of <i>N</i> -protected amino acids to NMP.....	75
3.3	Summary.....	83
4	Synthesis of aristolactams using phthalimide derivatives as precursors	85
4.1	Introduction	85

4.2	Synthesis of starting materials	86
4.2.1	Synthesis of dimethoxy- <i>N</i> -methylphthalimide and its precursors	86
4.2.2	Iodination of di- and trimethoxyphenylacetic acids.....	87
4.3	Formation of aristolactams	87
4.3.1	Formation of aristolactam skeleton.....	87
4.3.2	Formation of substituted aristolactams with iodo-precursors	90
4.3.3	Formation of substituted aristolactams with non-iodo-precursors.....	99
4.3.3.1	Attempted electrocyclic ring closure	102
4.3.4	Further reactions for the synthesis of iodo precursors	103
4.3.4.1	Solvent study	104
4.3.5	Reactions of phthalimide and dimethoxyphthalimide with iodo-substituted phenylacetic acids.....	105
4.3.6	Attempted iodination of precursors.....	107
4.4	Summary	109
5	Synthesis of phthalocyanines from photochemically derived fluorinated phthalonitriles	111
5.1	Introduction	111
5.2	Synthesis of starting materials	112
5.2.1	Photochemical reactions.....	112
5.3	Sulfonation of phthalonitrile derivatives	115
5.3.1	Synthesis of sulfonated products.....	115
5.4	Synthesis of phthalocyanines	121
5.4.1	Synthesis of phthalocyanines from phthalonitrile precursors	121
5.4.2	Synthesis of sulfonated phthalocyanines	124
5.5	Summary	127
6	Microphotochemistry performed with selected reactions	129
6.1	Introduction	129
6.2	Synthesis of starting materials	130
6.2.1	Synthesis of <i>N</i> -phthalimido carboxylic acid derivatives.....	130
6.3	Microphotochemical reaction set-up	132
6.3.1	Experimental set-up	132
6.4	Comparison reactions	135
6.4.1	Reactions of NMP with phenylacetic acid and 2-iodophenylacetic acid	135

6.4.2	Reactions of NMP with selected phenylacetates	138
6.4.3	Reactions of phthalimide with selected phenylacetates	139
6.4.4	Photodecarboxylative addition of <i>N</i> -protected amino acids to NMP.....	140
6.4.5	Reaction of TFPN and trimethoxybenzene	143
6.4.6	<i>Intra</i> -molecular cyclisation reactions	144
6.5	Summary	149
	Thesis conclusions	150
7	Experimental	154
7.1	Chapter 2: Photoaddition reactions of NMP and phthalimide.....	156
7.1.1	General Procedure (A):	157
7.1.2	General Procedure (A1):	171
7.1.3	General Procedure (B):	176
7.1.4	General Procedure (C):	180
7.2	Chapter 3: Photoaddition reactions of phthalimides with heteroatom- containing addition partners.....	186
7.2.1	General Procedure (D):	186
7.3	Chapter 4: Synthesis of aristolactams using phthalimide derivatives as precursors	210
7.3.1	General Procedure (E).....	214
7.4	Chapter 5: Synthesis of phthalocyanines from photochemically derived fluorinated phthalonitriles.....	244
7.4.1	General Procedure (F):.....	244
7.4.2	General procedure (G):	247
7.4.3	General procedure (H):	251
7.5	Chapter 6: Microphotochemistry performed with selected reactions	256
7.5.1	General Procedure (I):.....	258
7.5.2	General Procedure (J):.....	262
7.5.3	General Procedure (J1):.....	277
7.5.4	General Procedure (K):	280
7.5.5	General Procedure (J2):.....	281
8	References	289
	Appendix	298

For Mum and Dad

xxx

Education is a wonderful thing, provided you always remember that nothing worth knowing can ever be taught.

-Oscar Wilde

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List of abbreviations

^{13}C -NMR	carbon nuclear magnetic resonance
^1H -NMR	proton nuclear magnetic resonance
AIBN	azobisisobutyronitrile
BET	back electron transfer
$\text{C}_2\text{D}_6\text{CO}$	deuterated acetone
CDCl_3	deuterated chloroform
CO_2	carbon dioxide
conc.	concentrated
DBN	1,8-diazabicyclonon-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of a doublet
ddd	doublet of a doublet of a doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAE	dimethylaminoethanol
DMF	dimethylformamide
DMSO-d_6	deuterated dimethyl sulphoxide
equiv.	equivalents
<i>et al.</i>	and others
g	gram
g/mol	gram per mole
H_2O	distilled water
H_2SO_4	sulfuric acid
$\text{H}_{\text{arom.}}$	aromatic proton
$\text{H}_{\text{olef.}}$	olefinic proton
hr	hour(s)
h ν	light
<i>i</i> -butyl	iso butyl group
IC	internal conversion
ISC	intersystem crossing
IUPAC	Internal Union of Pure and Applied Chemistry

<i>J</i>	coupling constant
K ₂ CO ₃	potassium carbonate
KHMDS	potassium bis(trimethylsilyl)amide
m	multiplet
MgSO ₄	magnesium sulphate
min	minute(s)
ml	millilitre(s)
mmol	millimole(s)
mol	mole(s)
MPc	metallo phthalocyanine
NaCl	sodium chloride
nm	nanometres
NMR	nuclear magnetic resonance
°C	degrees Celsius
Pc	phthalocyanine
PDT	photodynamic therapy
PET	photoinduced electron transfer
Ph	phenyl
ppm	parts per million
s	singlet
<i>s</i> -butyl	secondary butyl group
STY	space-time yield
t	triplet
<i>t</i> -butyl	tertiary butyl group
TFA	trifluoroacetic acid
TFPN	tetrafluorophthalonitrile
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
Δ	heat
μg/ml	microgram per millilitre
π	pi
σ	sigma

Abstract

This research explores the application of synthetic organic photochemistry for the preparation of new phthalimide and phthalonitrile derivatives. Photodecarboxylative (PDC) additions of carboxylates to phthalimides were explored, this work included addition reactions using phenyl acetates, α -keto carboxylates and protected amino acids. Once these photo-additions were optimised using a Rayonet reactor, interest was turned to the conversion of this chemistry to a micro-flow platform with a view to improving the results obtained using the large-scale Rayonet reactor. It was successfully demonstrated that the microreactor delivered comparable if not superior results.

The possibility of using the PDC addition products as precursors for the synthesis of aristolactams was investigated. Optimisation of a method for the preparation of several compounds related to the aristolactam family was attempted, with the successful preparation of two compounds achieved.

Also described is the photochemical synthesis of new phosphorescent phthalonitrile derivatives and their respective phthalocyanines. Two of the phthalonitrile derivatives were successfully converted to water soluble derivatives by selective sulfonation and one such derivative was screened as a potential cell-imaging agent.

Chapter 1

1 Literature review

1.1 Photochemistry

A photochemical process may be defined as a chemical reaction that proceeds under the influence of light. Photochemistry involves the interaction of matter with electromagnetic radiation. Normally, any type of reaction occurs when a molecule gains the necessary activation energy to undergo change. In the case of photochemical reactions light provides this activation energy.

The first law of photochemistry, known as the Grotthuss-Draper law, states that light must be absorbed by a chemical substance in order for a photochemical reaction to take place.¹ The second law of photochemistry, the Stark-Einstein law, states that for each photon of light absorbed by a chemical system, only one molecule is activated for a photochemical reaction. This is also known as the photoequivalence law and was derived by Albert Einstein at the time when the quantum (photon) theory of light was being developed.²

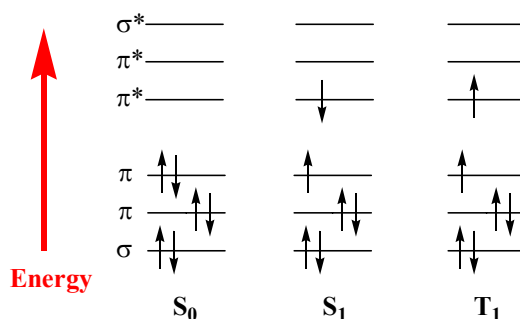


Figure 1.1 An orbital energy level diagram.

An example of an orbital energy diagram is shown in **Figure 1.1**. In the lowest-energy ground state molecule (S_0), the lower (bonding) orbitals are fully occupied by pairs of electrons and the upper (anti-bonding) orbitals remain unoccupied. Upon excitation, an electron is promoted from the highest-energy bonding orbital to the lowest energy anti-bonding orbital resulting in a (π , π^*) singlet state (S_1), where the two unpaired electrons have opposite spin. In the (π , π^*) triplet state (T_1) the electron spins are parallel. In molecules with heteroatoms but without extensive conjugation

the highest filled orbital in the ground state is often non-bonding (n), and so S_1 and T_1 may be (n, π^*) or (n, σ^*) in nature.³

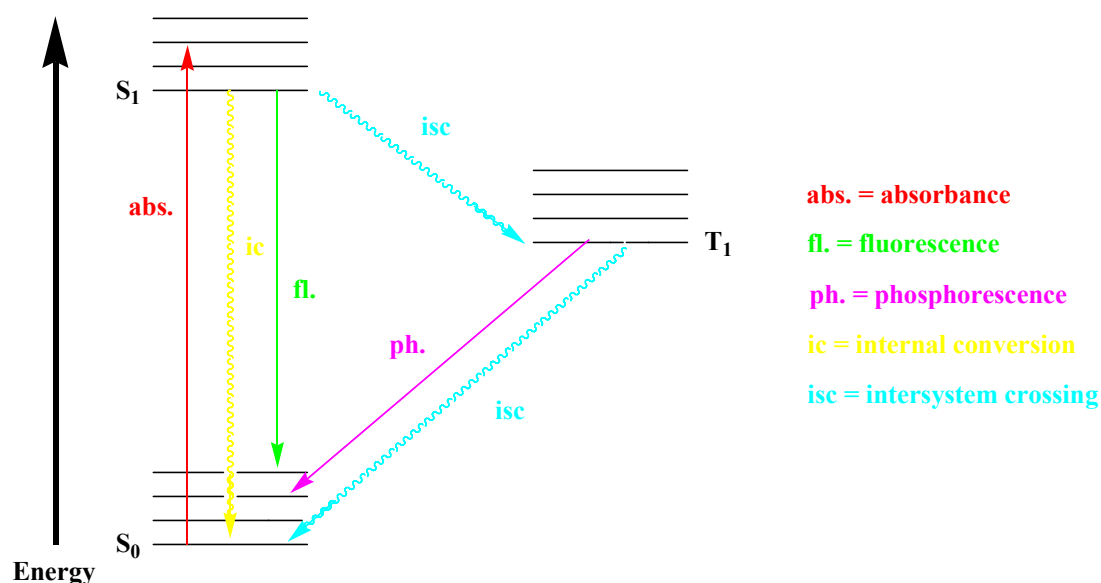


Figure 1.2 An example of a Jablonski diagram.

When an electron is promoted to the excited state, there are a number of ways the energy can be released, as shown in an example of a Jablonski diagram in **Figure 1.2**. Photochemical reactions generally occur through S_1 or T_1 states since most excited states of higher energy than these decay very rapidly to give the S_1 or T_1 state. Such processes are examples of radiationless decay as no light is emitted, and are known as internal conversion if they occur without a change in spin ($S_2 \rightarrow S_1$ or $T_2 \rightarrow T_1$), or intersystem crossing if there is a change in spin ($S_1 \rightarrow T_1$). Decay of the lowest excited states is much slower, because the energy gap between S_1 or T_1 and the ground state (S_0) is quite large. However, a chemical reaction still has to compete with radiationless decay to the ground state, and also with luminescent decay, which can occur in the form of either fluorescence [if there is no change of spin ($S_1 \rightarrow S_0 + h\nu$)] or phosphorescence [if there is a spin change ($T_1 \rightarrow S_0 + h\nu$)].³

1.1.1 Photoinduced Electron Transfer (PET)

According to “IUPAC Glossary of terms used in Photochemistry (3rd edition)” Photoinduced Electron Transfer (PET) is electron transfer resulting from an electronic state produced by the resonant interaction of electromagnetic radiation with matter. This facilitates reactions that would not usually take place in the ground state. When molecules absorb light, and are therefore in their excited states, they may become stronger oxidants and reductants than they would be in their natural ground states. Upon irradiation, an electron is promoted to a vacant orbital in the excited state where electron donation or acceptance occurs more readily in the molecule. There are two species involved in electron transfer (ET), namely the donor (D) and the acceptor (A). Upon electronic excitation the redox properties of either the electron donor (D) or the acceptor (A) are enhanced (**Figure 1.3**).

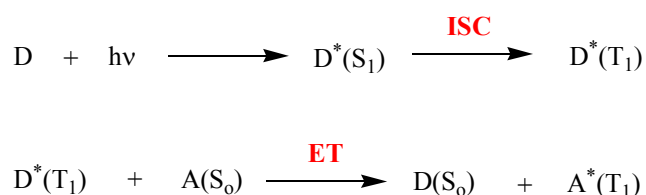


Figure 1.3 Schematic representation of electron transfer.

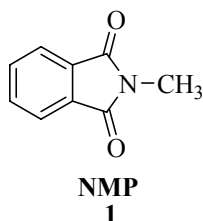
The Rehm-Weller equation (**Equation 1**)^[4,5] can be used to estimate the feasibility of electron transfer using a simple free reaction energy consideration, where $E_{1/2}^{\text{Ox}}(D)$ and $E_{1/2}^{\text{Red}}(A)$ represent the oxidation and reduction potential of the donor or the acceptor, respectively. ΔE_{excit} stands for the electronic excitation energy, whereas ΔE_{coul} indicates the coulombic interaction energy of the products formed (most commonly radical ions). This simplified approach allows a first approximation on the feasibility of a PET process. Only for exergonic processes ($\Delta G < 0$) a PET process becomes thermodynamically favourable.

$$\Delta G = F(E_{1/2}^{\text{Ox}}(D) - E_{1/2}^{\text{Red}}(A)) - \Delta E_{\text{excit}} + \Delta E_{\text{coul}}$$

Equation 1 The Rehm-Weller equation.

1.2 Introduction to phthalimides

Phthalimides are a group of compounds that can be described as the imides of phthalic acids. They are aromatic compounds which contain two carbonyl groups bound to a primary amine and their IUPAC name describes them as “isoindolin-1,3-diones”.



Solid, MW: 161.16 g/mol, mp: ~137°C

Figure 1.4 Structure of *N*-methylphthalimide.

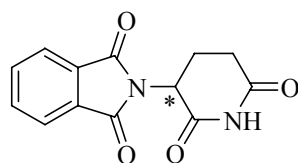
N-Methylphthalimide was the starting material for the majority of reactions that have been carried out in this study.

1.2.1 Pharmaceutical and industrial importance of phthalimides

Thalidomide (**Figure 1.5**) is probably the most “famous” or “infamous” phthalimide known today. It is a drug that was sold during the late 1950’s and early 1960’s as a sleeping aid and also to pregnant women as an antiemetic to combat morning sickness. It was synthesised in West Germany by the pharmaceutical company Grünenthal in 1953 and was available in around fifty countries, (although not in the United States), under at least forty names. It was later (1960–61) found to be teratogenic in fetal development. Around 15,000 fetuses were damaged by thalidomide, of whom about 12,000 in 46 countries were born with birth defects, with only 8,000 of them surviving past the first year of life. Most of these survivors are still alive, nearly all with disabilities caused by the drug.

Thalidomide is sold as a racemate: it was proposed that one enantiomer is effective against morning sickness, and the other is teratogenic. However, it was later found that the enantiomers are interconverted *in vivo*. Thalidomide was banned for its

initial intended use as sedative, however, it has been found to be effective for other applications in the treatment of leprosy and multiple myeloma.⁶



Thalidomide

Figure 1.5 Structure of Thalidomide.

Certain phthalimides are used in the agrochemical industry (**Figure 1.6**). As they display a wide range of properties they can be used as herbicides, insecticides and fungicides. An example of each is shown below, *e.g.* Diamate, Imidan, and Folpet.

Folpet and its derivative Captan are both non-systemic phthalimide fungicides. They are used in water as a spray for the control of fungal diseases on turf, on fruit such as apples, grapes and strawberries, on ornamental plants such as roses and on vegetables when they are seeds.⁷ They are mainly used to improve the finish of fruit by giving it a healthy, bright and coloured appearance. Imidan is also a non-systemic organophosphate insecticide. It is an excellent material for the control of major pests. The main advantage of this pesticide is its lower order of toxicity to humans and animals.⁸

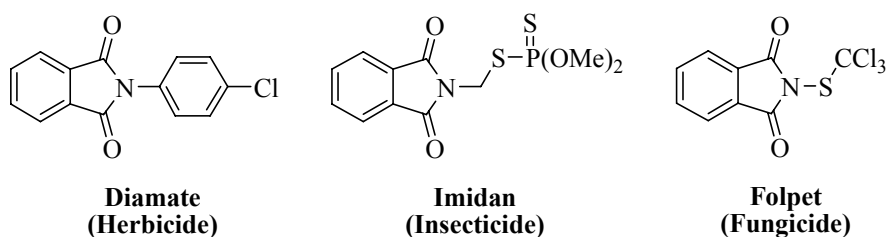
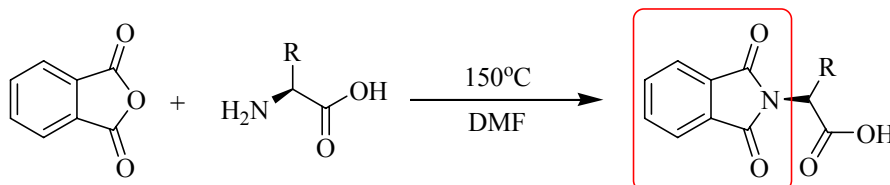


Figure 1.6 Examples of phthalimides used in the agrochemical industry.

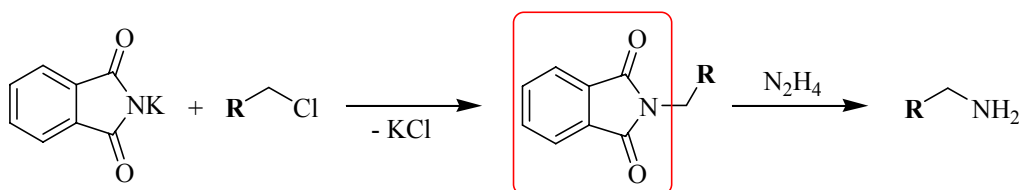
1.2.2 Phthalimides in organic synthesis

Phthalimides have a number of uses for example; they are used as nitrogen protecting groups for amino acids as seen in **Scheme 1.1**.



Scheme 1.1 Phthalimide as a protecting group for an amino acid.

They are also used in the Gabriel synthesis (**Scheme 1.2**) for the preparation of primary amines using potassium phthalimide.⁹



Scheme 1.2 Gabriel synthesis.

Due to the acidity of “free” phthalimides ($pK_a = 9$) potassium hydroxide can be used to easily convert them to the corresponding potassium phthalimide salt. The acidic hydrogen is removed from the phthalimide upon addition of base. This results in the formation of a phthalimide anion which is a good nucleophile that can react with alkyl halides to produce an intermediate *N*-alkylphthalimide. The *N*-alkylphthalimide can then be hydrolysed to the corresponding primary amine but this can be a slow and difficult procedure. Alternatively, *N*-alkylphthalimides can be treated with hydrazine (N₂H₄) to give the corresponding primary amine.¹⁰ Only primary amines can be synthesised by this method and as a result the use of the Gabriel Synthesis is limited to methyl and primary alkyl halides.¹¹

1.2.3 Photophysical and electrochemical properties of phthalimides

Phthalimides are versatile chromophores in photochemistry *e.g.* *N*-Methylphthalimide (NMP). Although the photochemistry of phthalimide derivatives is similar to that of carbonyl compounds, they boast additional reactivity features due to the remarkably high oxidizing power of the excited singlet and triplet states.

The photophysical¹²⁻¹⁴ and electrochemical¹⁵⁻¹⁷ properties of phthalimides have been well documented. In acetonitrile, *N*-alkylphthalimides show relatively simple UV-Vis absorption spectra with absorption maxima at $\lambda_{\text{max}} = 235 \text{ nm}$ (π, π^*) and $\lambda_{\text{max}} = 290 \text{ nm}$ (n, π^*), respectively.¹² The absorption spectra of NMP is shown in **Figure 1.7**.

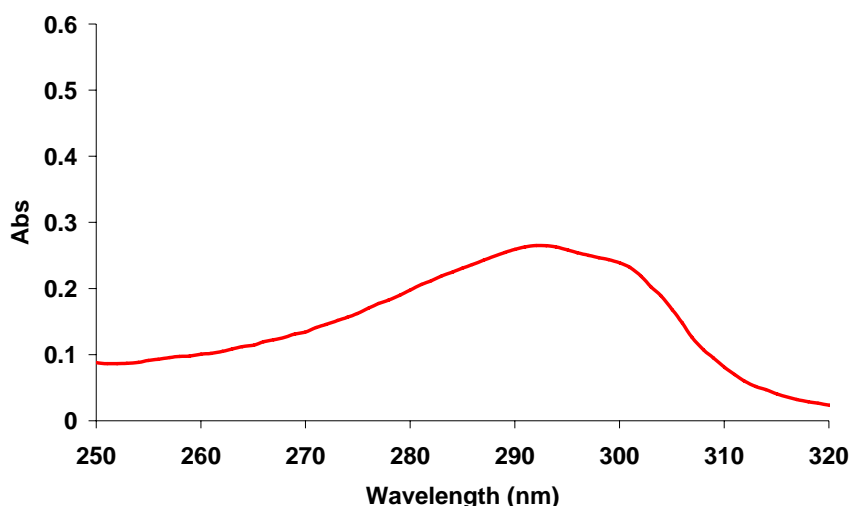


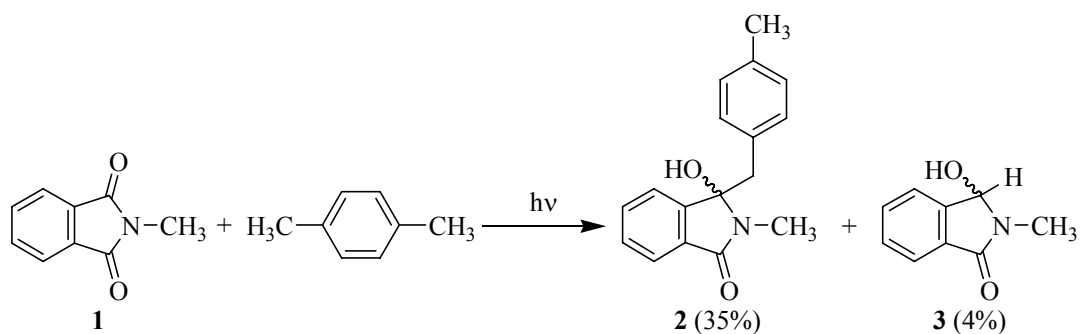
Figure 1.7 Absorption spectrum of NMP (obtained in acetonitrile).

At room temperature, they furthermore exhibit weak fluorescence in ethanol or acetonitrile.¹³ In the absence of oxygen in alcohol *N*-alkylphthalimides show broad phosphorescence centred around $\lambda_{\text{max}} = 450 \text{ nm}$. NMP is reversibly reduced to the corresponding radical anion at ca. -1.35 V in DMF, and at ca. -1.5 V in acetonitrile (vs. SCE).¹⁶ Based on the available photophysical and electrochemical data, it is possible to estimate the feasibility of a photoinduced electron transfer (PET) for various phthalimides/donor pairs (see **Equation 1**).

1.3 Photoaddition reactions involving phthalimides

1.3.1 Photoadditions of arenes

Kanaoka *et al.* have reported that a series of toluene derivatives add to electronically excited *N*-methylphthalimide **1** to give the corresponding addition products **2** in poor to moderate yields (5-35%).¹⁸ The best result, which was a yield of 35%, was obtained for *p*-xylene (**Scheme 1.3**) and the abstraction of a primary hydrogen from the benzylic position was suggested as the crucial key-step. In all cases, the phthalimide was irradiated in the aromatic solvent and larger amounts of the starting material **1**, which had not reacted, were recovered. Furthermore, due to a competing photoreduction reaction, the hydroxyphthalimide **3** was also isolated in low yields (1-4%).¹⁹



Scheme 1.3 Reaction scheme of **1** and *p*-xylene.

1.3.2 Photoadditions of alkenes

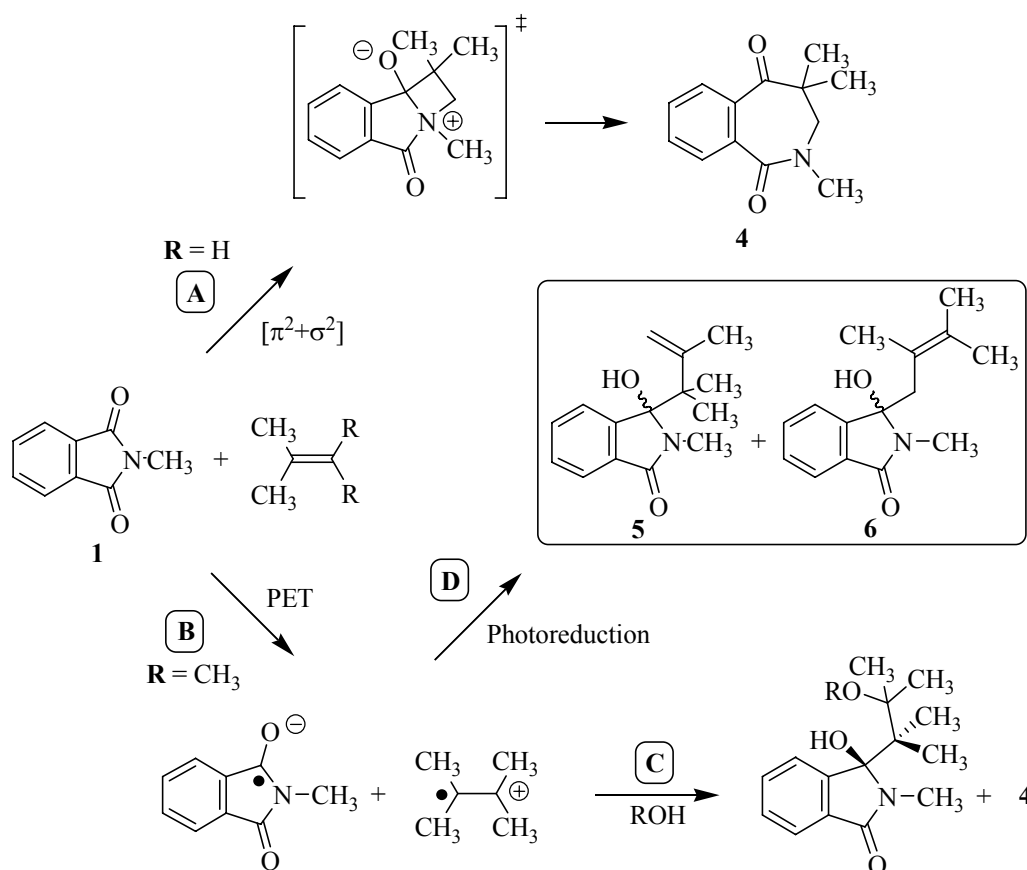
Five major processes²⁰ dominate photoadditions of alkenes to phthalimides. Due to their relevance to this work, only photoreductions will be described in detail:

1. $[\pi^2+\sigma^2]$ Addition to the C(O)-N bond and formation of ring expanded benzazepinediones
2. Electron transfer leading to photoreduction to the corresponding carbinols
3. Electron transfer to the corresponding radical ion pair which is trapped by alcohols

- Cycloaddition to the carbonyl bond and formation of oxetanes, (Paternò-Büchi), and
- Cycloaddition to the aromatic ring and formation of [4+2] photocycloaddition products

The outcome of photoreactions of phthalimides with alkenes is, as a rule, determined by the irradiation conditions and the oxidation potential of the C=C double bond in particular, and numerous studies have been reported separately by the groups of Mazzocchi²¹ and Kubo.²²

The Rehm-Weller equation^{4,5} can estimate the viability of an electron transfer process between the alkene and the phthalimide. In cases where an electron transfer was *endergonic* with $\Delta G_{ET} > 5$ kcal/mol, $[\pi^2+\sigma^2]$ addition reactions to benzazepinediones were observed (**Scheme 1.4; path A**).¹⁹

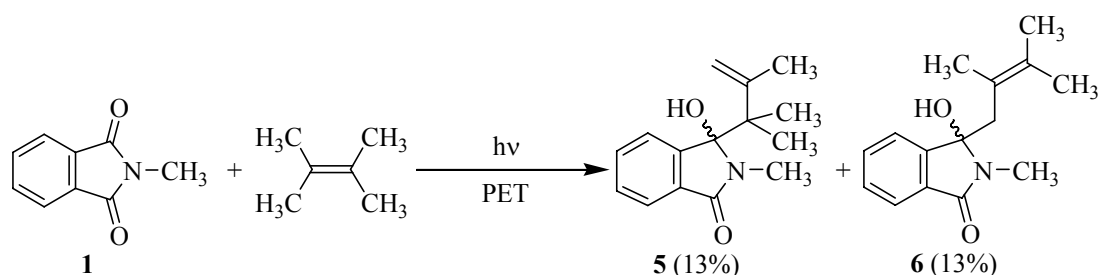


Scheme 1.4 Reaction scheme of **1** and various alkenes.

When the electron transfer became more and more exergonic, electron transfer started to dominate (**Scheme 1.4**; path **B**). In the presence of suitable nucleophiles, *e.g.* alcohols, the intermediate formed, a radical ionic pair, was trapped in an *anti*-Markovnikov fashion (**Scheme 1.4**; path **C**). In the absence of suitable trapping agents, back electron transfer (BET, which regenerated the starting materials) efficiently competed with proton transfer and radical combination to carbinols (**Scheme 1.4**; path **D**). In cases where the ET was only slightly endergonic, both pathways competed and mixtures of $[\pi^2+\sigma^2]$ addition and PET products were obtained.

1.3.2.1 Photoreductions

Mazzocchi and Klinger studied extensively the photoreaction of **1** with 2,3-dimethyl-2-butene in acetonitrile.^{21b} Prolonged irradiation was necessary to obtain high conversion rates and a pair of the photoreduction products **5** and **6** were isolated in equal yields of 13% each (**Scheme 1.5**). A third product was also obtained in 4% yield, which was identified as an oxetane made from a competing Paternò-Büchi reaction. An initial electron transfer was suggested as the key-step in the mechanism. BET, regenerating the starting materials, competed efficiently with follow-up reactions, as evident from the required irradiation time. Sensitization and quenching studies with indanone and fluorene suggested that the carbinol products arise from the singlet state of **1**,^{21b} and not from the triplet state as was previously suggested.²³

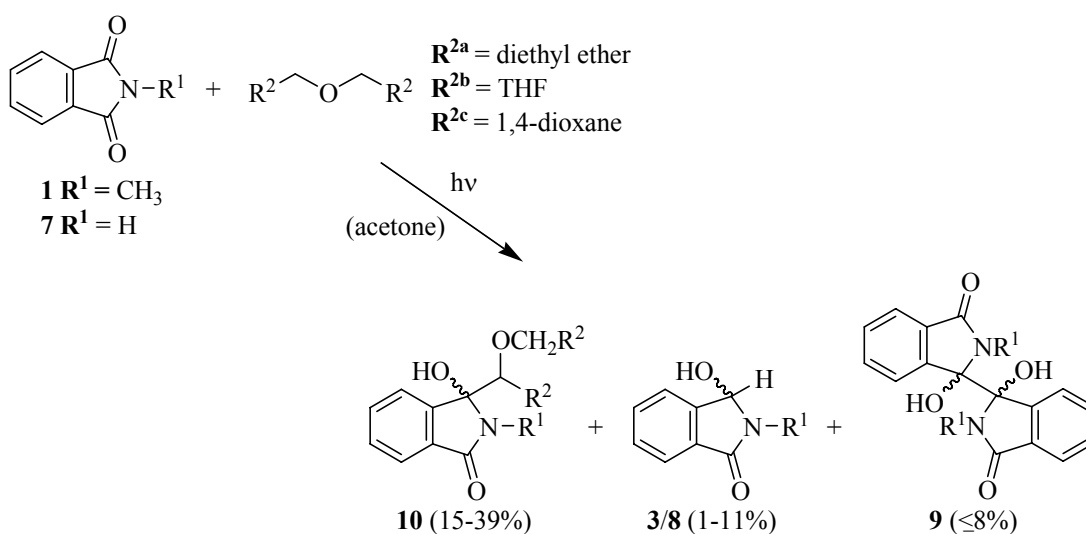


Scheme 1.5 Reaction scheme of **1** and 2,3-dimethyl-2-butene.

1.3.3 Photoadditions of oxygen containing compounds

1.3.3.1 Photoadditions of ethers

Kanaoka²⁴ found that diethyl ether, THF and 1,4-dioxane added to **1**, while Roth^{25, 26} and Tanabe²⁷ independently reported on the photoadditions of ethers to phthalimide **7** and other *N*-substituted phthalimides. Acyclic (*e.g.* diethyl ether) as well as cyclic (*e.g.* THF, 1,4-dioxane) ethers gave the corresponding α -addition products **10** in modest yields of 15-39% (**Scheme 1.6**).



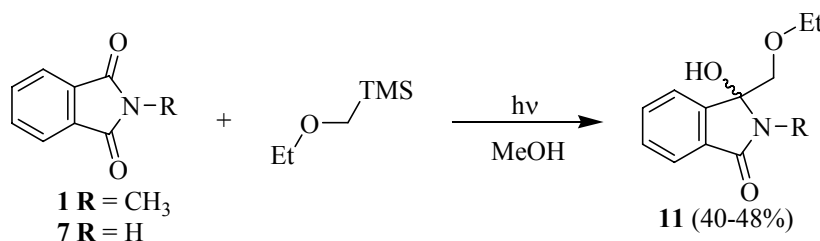
Scheme 1.6 General reaction scheme of **1** and **7** with various ethers.

In some cases, small amounts of the corresponding reduction, **3** and **8**, and dimerisation products **9** were isolated, and these side reactions were especially pronounced for **7**. When acetone was used as solvent, its trapping product was additionally isolated as a minor product in a yield of 5% for the phthalimide/dioxane pair.²⁵ While Thalidomide solely underwent photoreduction in the presence of THF,²⁵ the pesticide Imidan exclusively showed fragmentation of the side-chain when irradiated in diethylether.²⁷

1.3.3.2 Photoadditions of α -trialkylsilylmethyl-substituted ethers

Intra- and *intermolecular* PET reactions of α -trialkylsilyl (TMS) methoxy-substituted phthalimides were investigated by Yoon and Mariano.²⁸ The α -TMS group has a profound effect on the oxidation potential of the ether oxygen, which is lowered by about 0.5 V.²⁹ As a result of this, electron transfer from the heteroatom to the electronically excited phthalimide becomes energetically feasible. In addition, the presence of the silyl group furthermore enhances the efficiency and selectivity of the subsequent photoaddition.

As an example, trimethylsilylmethyl ethyl ether yielded the related addition products **11** in satisfactory yields when irradiated in methanol (**Scheme 1.7**).³⁰ However, the photoreaction was less efficient in acetonitrile where, in an extreme case, **7** showed no reaction at all.

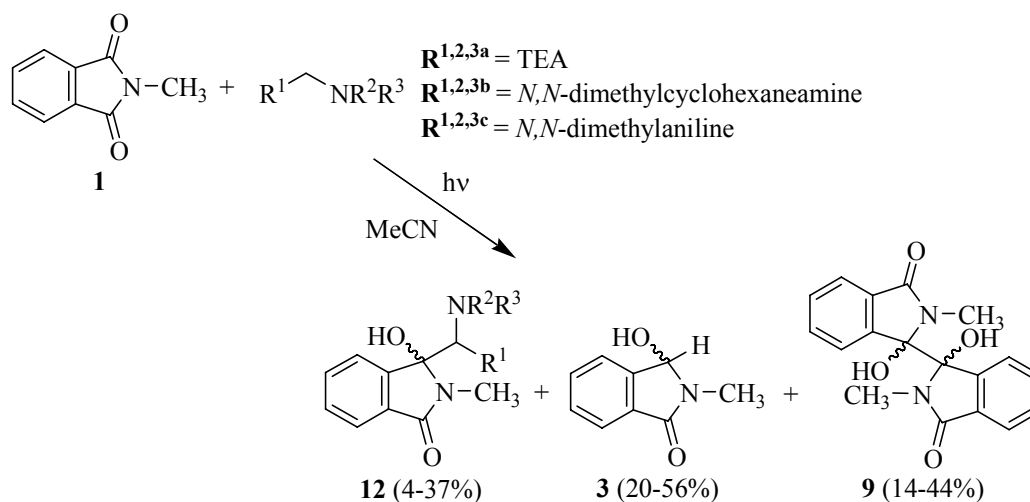


Scheme 1.7 Reaction scheme of **1** and **7** with trimethylsilylmethyl ethyl ether.

1.3.4 Photoadditions of nitrogen containing compounds

1.3.4.1 Photoadditions of amines

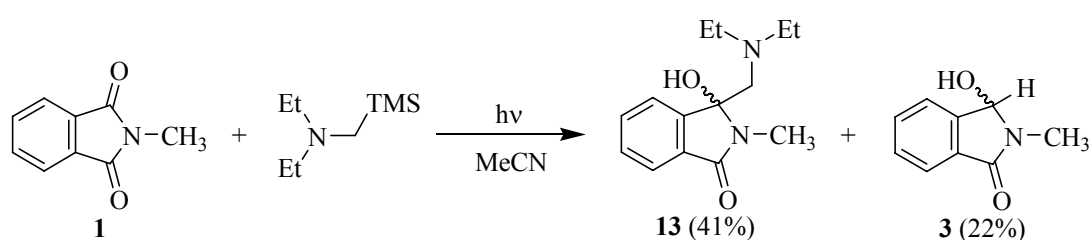
The addition of triethylamine, *N,N*-dimethylcyclohexanamine and *N,N*-dimethylaniline to **1** gives the aminocarbinals **12** in low to moderate yields (**Scheme 1.8**)²⁵ (each of these amines are known to be efficient photoreducing agents for aromatic ketones³¹). However, the photoadditions proceeded quite slowly in general and larger amounts of photoreduction **3** or dimerisation products **9** ($R^1 = CH_3$) were observed.



Scheme 1.8 General reaction scheme of **1** with various amines.

1.3.4.2 Photoadditions of α -trialkylsilylmethyl-substituted amines

Yoon and Mariano studied PET reactions of *N*-trimethylsilylmethyl-*N,N*-diethylamine with phthalimides.³⁰ The outcome of the photoaddition showed a notable solvent dependency. In acetonitrile or dichloromethane, **1** gave mixtures of the corresponding addition product **13** and the reduced hydroxyphthalimidine **3**, whereas irradiations in methanol or *n*-hexane only resulted in the formation of **3** (**Scheme 1.9**). In comparison **7** underwent reductive dimerisation to **9** ($\text{R}^1 = \text{H}$) in both methanol and acetonitrile.³⁰

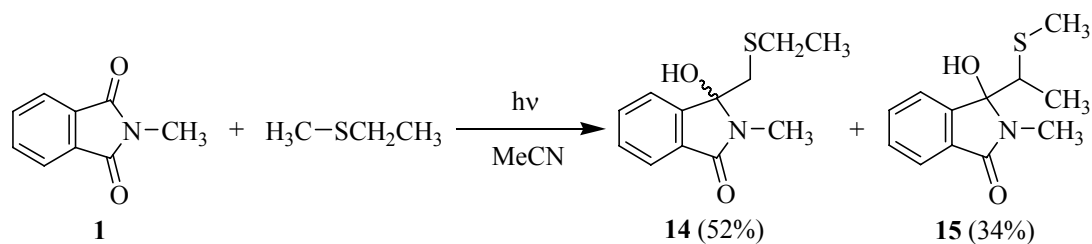


Scheme 1.9 Reaction scheme of **1** with *N*-trimethylsilylmethyl-*N,N*-diethylamine.

1.3.5 Photoadditions of sulfur containing compounds

1.3.5.1 Photoadditions of thioethers

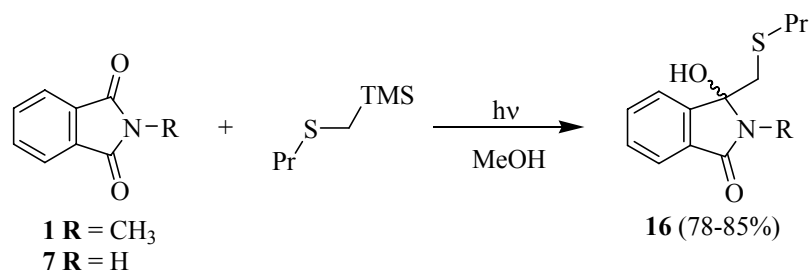
The photoaddition of some sulfides to **1** has been described by Kanaoka and coworkers.³² In methanol, acetone and acetonitrile, a 1:2 ratio of **1** to dimethyl sulfide gave **14** in yields of 16, 69 and 80% respectively. Using a 1:10 ratio of **1** vs. sulfide, the yield in acetone was increased to 79%, while yields in acetonitrile were improved to 87% when a more powerful lamp was used. A 1:2 ratio of **1** and ethyl methyl sulfide in acetonitrile gave **14** in 52% yield, along with *threo*- and *erythro*-**15** in 19% and 15% yields (**Scheme 1.10**) respectively. The quantum yields of the product formation in acetonitrile were determined as $\Phi = 0.06$ (Me_2S) and 0.05 (MeSEt), respectively.



Scheme 1.10 Reaction scheme of **1** with ethyl methyl sulfide.

1.3.5.2 Photoadditions of α -trialkylsilylmethyl-substituted thioethers

Yoon and Mariano described photoadditions of trimethylsilylmethyl *n*-propyl thioether with **1** and **7**.³⁰ The corresponding products **16** were isolated in yields of 78-85% when irradiated in methanol (**Scheme 1.11**). In acetonitrile, the reaction proceeded with much lower conversions, while larger amounts of the corresponding dehydration products were also obtained.

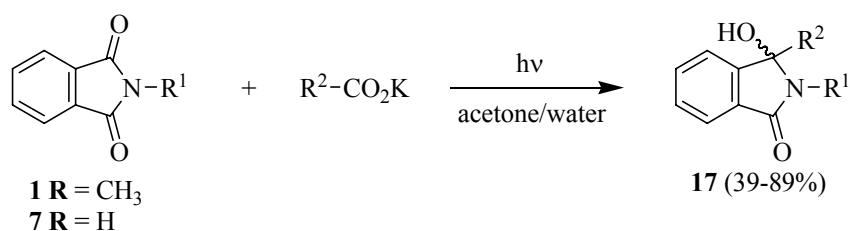


Scheme 1.11 Reaction scheme of **1** and **7** with trimethylsilylmethyl *n*-propyl thioether.

1.3.6 Photoadditions of carboxylates

1.3.6.1 Photoadditions of alkyl carboxylates

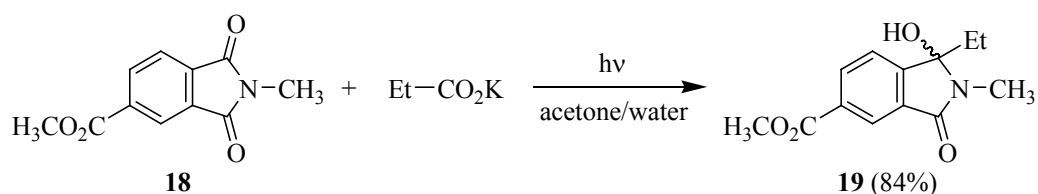
Griesbeck and coworkers established the photodecarboxylation of ω -phthalimido carboxylates as a versatile method for the synthesis of medium to macrocyclic ring systems.³³ Similarly, alkyl carboxylates underwent *intermolecular* addition reactions to the corresponding alkyl hydroxyphthalimidines **17** in good to excellent yields (**Scheme 1.12**).³⁴ The reaction was also applied to large multigram scales using a 308 nm XeCl excimer light source.^{34b,35} As a result, this method represents a mild and convenient alternative to thermal procedures.



Scheme 1.12 General reaction scheme of **1** with various alkyl carboxylates.

A highly regioselective alkylation of *N*-methyltrimellitic acid imide **18** has been described.³⁶ Photolysis in the presence of potassium propionate gave solely the *para*-addition product **19** in 84% yield (**Scheme 1.13**). This preferred formation was explained by exploring the differences in spin densities in the corresponding imide radical anions. For the radical anion of **18**, the spin densities were significantly higher for the imido *para*-carbon atom than for the *meta*-carbon atom thus signifying

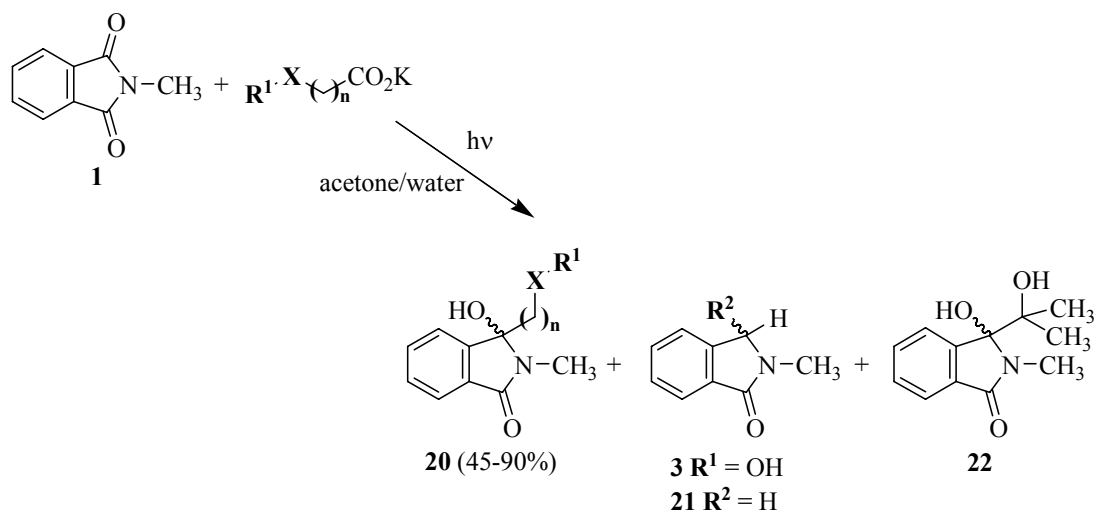
preferential *para* coupling. In contrast, *N*-methylquinolinic acid imide only showed a slight preference for formation of its *ortho* isomer.



Scheme 1.13 Reaction scheme of **18** with potassium propionate.

1.3.6.2 Photoadditions of heteroatom substituted carboxylates

The incorporation of additional heteroatoms in the alkylcarboxylate affected the respective electron donor capacity,³⁷ and either strongly increased or decreased the addition efficiency.³⁸ α -Thioalkyl- and α -oxoalkyl-substituted carboxylates readily gave the corresponding addition products **20** in modest to high yields of 51-90% from **1**. In comparison, the β -thioalkyl-substituted carboxylate remained inert, whereas the corresponding β - to ω -oxoalkyl carboxylate reacted efficiently to give the addition products in 45-76% yield (**Scheme 1.14; Table 1.1**).³⁸ As an explanation for the different reactivity of sulfur- vs. oxygen-substituted carboxylates, it was concluded that oxidation of the heteroatom is dominant for thioethers. In the case of the β -thioalkyl substrate, the sulfur atom acts as a “hole trap” due to fast non-productive BET³⁹ and prevents oxidation of the carboxylate. The photoreactions involving alkylamino-substituted carboxylates gave exclusively photoreduction to **21** ($R^1 = H$) or trapping of the solvent, acetone, leading to the formation of **22**.^{38a}



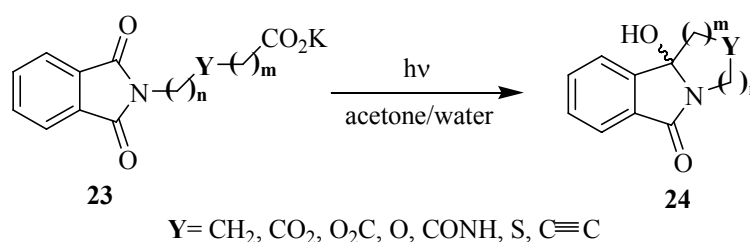
Scheme 1.14 General reaction scheme of **1** with various heteroatom substituted carboxylates.

Table 1.1 Photoadditions of heteroatom substituted carboxylates to **1**.

carboxylate			yield		
X	n	R	20 [%]	3/21 [%]	22 [%]
S	1	CH ₃	90	—	—
S	1	Ph	57	—	—
S	2	CH ₃	—	—	—
O	1	CH ₃	57	—	—
O	1	Ph	73	—	—
O	1	2,4-Cl ₂ C ₆ H ₃	76	—	—
O	2	CH ₃	51	—	—
O	2	Ph	65	—	—
O	3	Ph	55	—	—
O	4	Ph	45	—	—
O	9	Ph	47	—	—
O	10	Ph	49	—	—
O	1	H	57	<5 (3)	—
NCH ₃	1	CH ₃	—	21 (21)	—
NCH ₃	2	CH ₃	—	57 (21)	36

1.3.6.3 Intramolecular decarboxylative cyclisation reactions

N-Phthaloyl-activated α -amino acids give clean and efficient α -photodecarboxylations (PDC) when irradiated in organic solvents.⁴⁰ Remote carboxylic acid groups could be activated for photodecarboxylation *via* their corresponding carboxylates. Using the decarboxylative photocyclisation, the synthesis of medium- and macrocyclic amines, lactones, polyethers, lactams as well as cycloalkynes were accessible in ring sizes up to 26 (**Scheme 1.15**)⁴¹ and even in multigram quantities.^{35a} Although the oxidation potentials of carboxylates are relatively high compared to other electron donor groups (*e.g.*, acetate: $E_{Ox} = 1.54$ V in MeCN, 2.65 V in H₂O vs. SCE),⁴² the decarboxylative cyclisation proceeds very efficiently and many functional groups are tolerated. As the key step in the reaction, rapid *intramolecular* photoinduced electron transfer proceeds via the $^3\pi,\pi^*$ state or the higher excited $^3n,\pi^*$ triplet state in the nanosecond time regime.⁴³



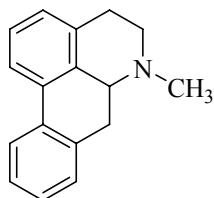
Scheme 1.15 General reaction scheme of various *intramolecular* decarboxylative cyclisation reactions.

1.4 Aristolactams

1.4.1 Naturally occurring aristolactams and their biological activity

Aristolactams⁴⁴ are a small family of compounds which have a phenanthrene chromophore (**Figure 1.9**) and are mainly found in the plant species Aristolochiaceae, together with the aristolochic acids and 4,5-dioxoaporphines.⁴⁵ Several aristolactams and 4,5-dioxoaporphines have been isolated from *P. wightii*, *P. argyrophyllum*, *P. schmidtii*, *P. acutisleginum*, and *P. betel*.^{46,47} Aristolochic acids and aristolactams are non-basic, however they are classified as aporphinoids since

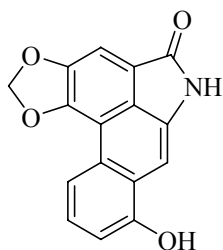
their skeletons bear a distinct similarity to that of the aporphines. Based on their structural relationship, it is suggested that aristolochic acids are derived from aristolactams rather than directly from quaternary aporphine alkaloids.



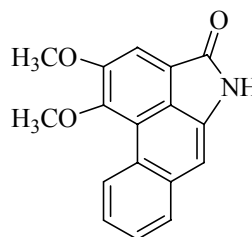
Aporphine

Figure 1.8 Structure of aporphine.

An alcoholic extract of *Aristolochia indica*, commonly known as “Indian birthwort” and which is reputedly used in Indian folk medicine as an emmenagogue and as an abortifacient, was found to show reproducible tumour inhibitory activity against the adenocarcinoma 755-test system in mice.⁴⁸ Aristolactams are also potent inhibitors of platelet aggregation.



Aristolactam Ia



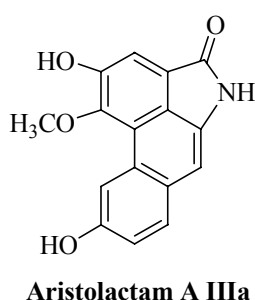
Taliscanine

Figure 1.9 Examples of aristolactams.

Many aristolactams have been discovered to be biologically active, for example aristolactam Ia, (**Figure 1.9**) which has shown *in vitro* cytotoxicity against P-388 lymphocytic leukaemia and N S C L C N 6 (bronchial epidermoid carcinoma of human origin), and taliscanine, (**Figure 1.9**) which has activity against neurological disorders, especially Parkinson’s disease.⁴⁴

More recently, aristolactams have been reported to have been isolated from the stem of *Fissistigma oldhamii*,⁴⁹ a herb which was used in a traditional Chinese herbal

formula for the purpose of treatment of rheumatoid arthritis. It has been shown that T and B cells⁵⁰⁻⁵² play a vital role in the function of this autoimmune disease⁵³ and several aristolactams were shown to have immunosuppressive abilities, by exhibiting strong activities in the inhibition of T and B cell proliferation. The plant *Aristolochia manshuriensis* has also been found to contain aristolactam derivatives of which aristolactam A IIIa, (**Figure 1.10**) was found to be a potent inhibitor of the CDK2 enzyme with an IC₅₀ value of 140nM.⁵⁴ In the cell cycle CDK2 was found to have a rate-limiting role, which led it to be considered as a potential target for antitumour drug design.⁵⁵



Aristolactam A IIIa

Figure 1.10 Structure of aristolactam A IIIa.

1.4.1.1 Examples of related derivatives

Alkyl- or arylmethylidene isoindolinones are known to possess a broad range of bioactivities. The compound AKS 186, (**Figure 1.11**) for example, has been reported to inhibit vasoconstriction induced by the thromboxane A₂ analogue (U-46619)⁵⁶ and the 4-acetoxyphenylmethylidene derivative (**Figure 1.11**) has been claimed to exhibit local anaesthetic activity superior to that of procaine.⁵⁷

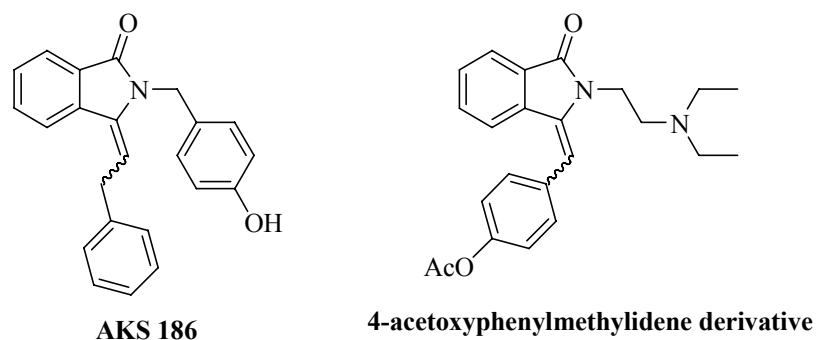


Figure 1.11 Examples of aristolactam derivatives.

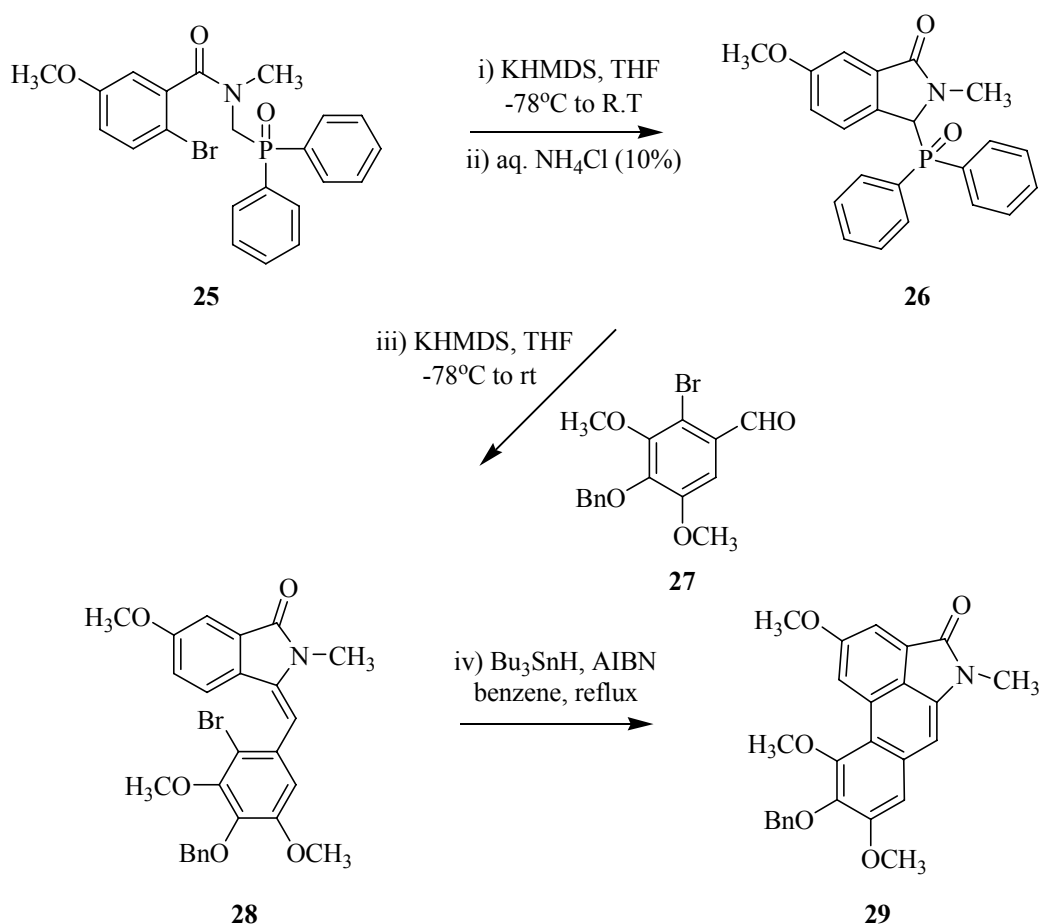
1.4.1.2 Isolation of natural aristolactams

At present, classical separation methods such as low-pressure column chromatography and thin layer chromatography (TLC) are used in the purification of aristolactams and their related aristolochic acids.^{58,59} While these methods produce results, there are disadvantages such as poor separation with selective separation being difficult to achieve. Recently, an efficient method for the preparative isolation and purification of aristolactams and aristolochic acids from *Aristolochia* plants has been reported.⁶⁰ An oligo (ethylene glycol) separation column possessing a “clustering function” was used to produce fractions containing similar structures which were then further separated by preparative HPLC. This advancement enabled target compounds with similar structures to be separated and purified selectively.

Even though developments are being made in the direct isolation of natural aristolactams, studies are ongoing on the synthesis of these compounds and with good reason. The examples shown previously illustrate that the aristolactam family possesses a wide variety of biological activity. There is continuing interest in developing further compounds in this class, as they may be useful as pharmaceuticals such as immunostimulants and anticancer agents among many more.

1.4.2 Synthesis of aristolactams

Little is known about the biosynthesis of aristolactams, however, it is assumed they are derived from aporphine alkaloids as they are biogenetically related. Aristolactams can be synthesised thermally by the general synthetic methodology used by Couture *et al.*⁶¹ Although this method is successful, there are a number of complicated steps needed to achieve the desired compounds as shown in (Scheme 1.16) below.

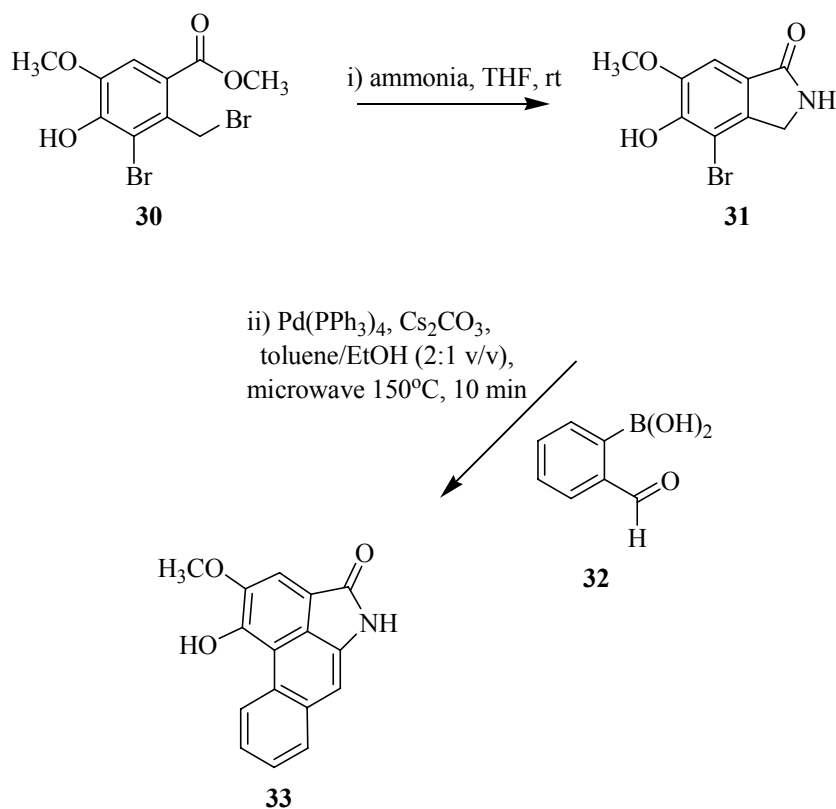


Scheme 1.16 An example of thermal synthesis of aristolactams by Couture *et al.*

Following the synthesis of halogeno-*N*-(diphenylphosphinoylmethyl) benzamide derivatives **25**, either by the reaction of differently substituted 2-halogenobenzoic acid or benzaldehyde and phosphorylated amine in the presence of DCC and dimethylaminopyridine,⁶² they were then exposed to potassium bis(trimethylsilyl)amide and subsequently treated with acid to give the phosphorylated lactams **26**. A Horner reaction with the appropriate

bromobenzaldehyde **27** gave the arylmethyleisoindolinones **28** which, when reacted with tributyltin hydride and AIBN resulted in the corresponding aristolactams **29**.

Another method, employed by Y. L. Choi *et al.*⁶³, showed the preparation of isoindolin-1-ones **31** by reacting 2-bromomethylbenzoates **30** with various aliphatic and aromatic amines. These were then used in a one pot synthesis of aristolactam analogues **33** (the example shown is the formation of piperolactam A) with a number of 2-formylphenylboronic acids **32**. Interestingly, this second step took only 10 minutes to complete by performing the reaction in a microwave reactor. The reaction proceeds via Suzuki-Miyaura coupling/aldol condensation cascade sequence. This method is impressive but when the synthesis of **30** is taken into account, the result is an overall seven-step procedure.⁶⁴



Scheme 1.17 Thermal synthesis of piperolactam A (**33**) by Choi *et al.*

Griesbeck and coworkers used the photodecarboxylative benzylation of phthalimides (achieved by the same method as described previously in Section 1.3.6; **Scheme**

1.12) as a concise route to open *Aristolactam* analogues.⁶⁵ However, the necessary final electrocyclisation step appears problematic.⁶⁶

1.5 Phthalonitriles and phthalocyanines

1.5.1 General structure and properties

Phthalocyanines (Pcs) are one of the most studied classes of functional organic materials. It is a planar, aromatic macrocycle comprised of four iminoisoindole units that can play host to ions derived from over 70 elements. The coordination chemistry of the Pc ligand, which usually possesses a formal charge of 2^- , is a rich and extensive subject. Without the intervention of a metal ion, only the simple tetraiminoisoindoline ligand exists. The general structure of a metal-free phthalocyanine **34** and a metallo phthalocyanine (MPc) **35** are shown in (Figure 1.12).

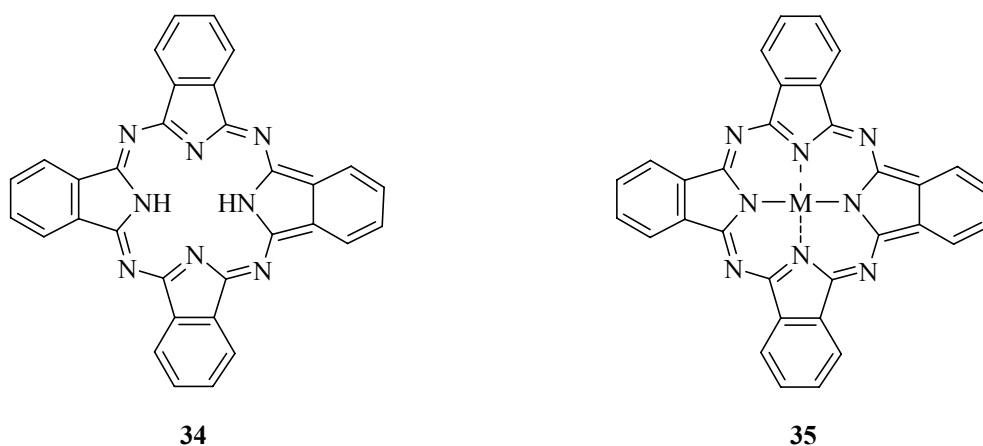


Figure 1.12 General structure of metal-free phthalocyanine **34** and metallo phthalocyanine **35**.

The diverse and useful functionality of the Pc macrocycle originates from its 18- π -electron aromatic system, which is closely related to that of the naturally occurring porphyrin ring. The additional π -orbital conjugation afforded by the four benzo-

moieties, and the orbital disruption caused by the nitrogen atoms at the four meso-positions, have a profound effect on the molecular orbital structure of the porphyrin chromophore. The result is a bathochromic shift of the lowest-energy absorption band (the Q-band) in the visible region of the spectrum, and a strong enhancement of its intensity (typically $\lambda = 680 \text{ nm}$, $\epsilon = \sim 2 \times 10^5 \text{ cm}^2 \text{ mol}^{-1}$).⁶⁷

1.5.2 Photodynamic therapy and phthalocyanines

Pcs are perhaps most well known for their commercial use as dyes and pigments due to their bright blue or green colours. Owing to their renowned chemical and thermal stability, they have also been investigated in a number of other fields including information storage (CD's), catalysis,⁶⁸ chemical sensors, non-linear optical materials⁶⁹, ink-jet printing and electrophotography. They are also important sensitisers in the application of Photodynamic Therapy (PDT)⁷⁰ owing to their good singlet oxygen generation ability.

PDT requires three basic elements: a photosensitiser, oxygen and visible light. While separately, these elements have no effect on cancer cells, when combined they generate singlet oxygen which destroys the targeted cancer cells. This technique involves the topical or systemic administration of a photosensitising agent, which is preferentially accumulated or retained by the tumour tissue, followed by illumination of the neoplastic area with light wavelengths specifically absorbed by the photosensitiser. The reasons for some photosensitisers localising selectively in tumours is thought to be due to the differences in physiology of normal tissue and tumours such as the larger interstitial volume of tumours, their poor lymphatic drainage and the fact that tumour tissue contains many receptors for lipoproteins.⁷¹

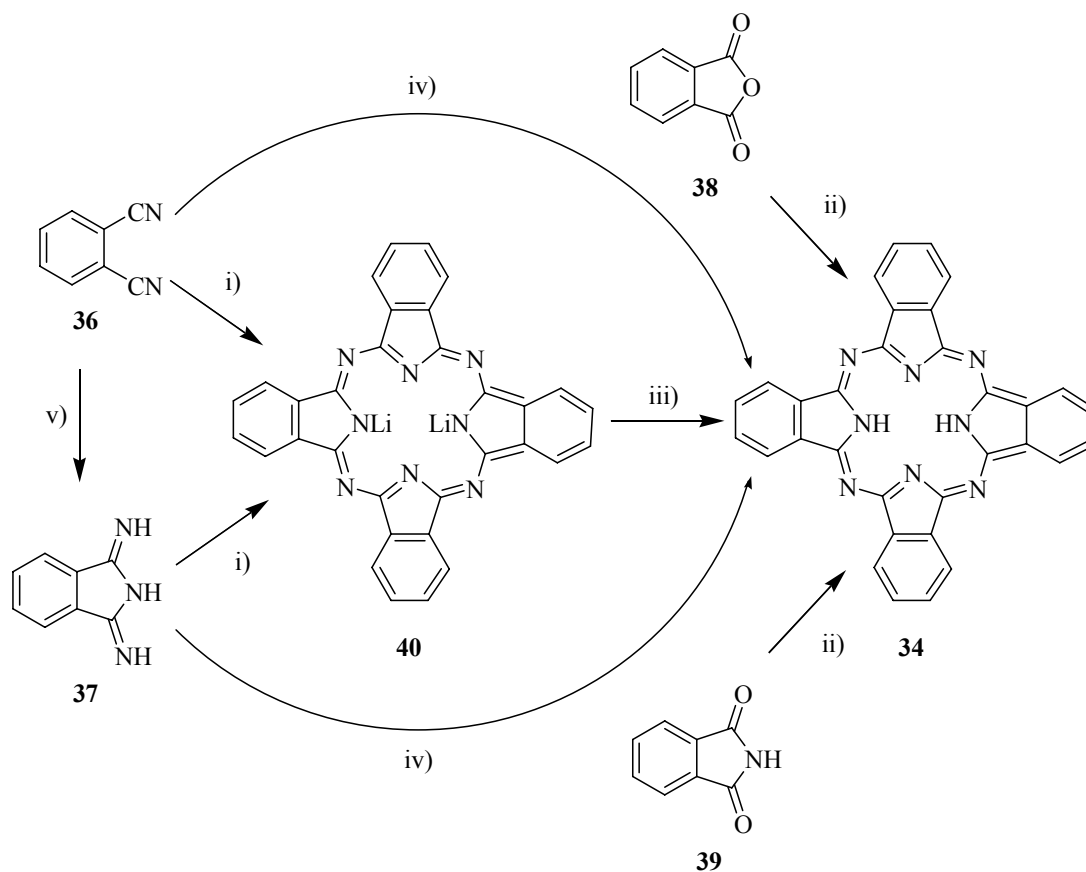
The first generation of photosensitisers were mainly haematoporphyrin derivatives. For example, Photofrin II,⁷² used in the treatment of specific tumours at a clinical level, is a complex mixture of porphyrins originated from the chemical modification of haematoporphyrin. It exhibits important limitations, including the low molar extinction coefficient in the clinically useful red spectral region, which limits the efficiency of its activation by light. The compound can also be retained by cutaneous tissue for extended periods of time meaning patients would have to avoid bright

sunlight as this causes a marked skin photosensitivity. Additionally, the red absorption maximum of Photofrin corresponds to a wavelength of 630 nm which has reduced penetration power within most human tissues. For these reasons it is often necessary to have repeated PDT treatments.⁷³

It was therefore apparent that second generation photosensitisers were needed and Pcs have been found to be excellent candidates for PDT. Their absorption wavelength of 680 nm has the advantage of having a high penetration power into human tissue⁷⁴ while still being energetic enough to produce singlet oxygen, and is not absorbed by the endogenous constituents of cells, thereby minimising the risk of general photodamaging effects. Also Pcs or MPcs possess higher extinction coefficients than porphyrins, selectively accumulate in tumour cells and can be prepared in their pure state, which are all desirable characteristics for photosensitisers used in PDT applications. It has been reported that fluorinated MPcs have been shown to have several advantages over non-fluorinated derivatives as photosensitisers for PDT.⁷⁵ Zinc tetracarboxy-octafluorophthalocyanine (ZnC_4F_8Pc) was shown to have a remarkable photodynamic effect, due to the fact that the Pc was mainly accumulated in the hydrophobic lipid membrane in its photoactive monomer form. As fluorinated Pcs are hydrophobic compounds they may favour the hydrophobic environment.

1.5.3 Synthesis of phthalocyanines

Pcs can be synthesised from a number of benzene derivatives including phthalimides, phthalonitriles, phthalic anhydride and 1,3-diiminoisoindoline. Phthalonitrile **36** and 1,3-diiminoisoindoline **37** are two starting materials frequently used to prepare metal free Pcs. The most common method involves the condensation of **36** to dilithium Pc ($PcLi_2$) **40** by refluxing **36** and lithium metal in pentanol. When **40** is treated with dilute acid this results in the formation of **34**. Another route for the synthesis of **37**, is by reacting **36** with ammonia and sodium metal in methanol under mild conditions (Scheme 1.18).⁷⁶



Scheme 1.18 i) Lithium, reflux, pentanol. ii) Heat in a high boiling point solvent with urea. iii) Treat with acid. iv) Heat; 1,8-diazabicyclonon-5-ene (DBN) or dimethylaminoethanol (DMAE), pentanol. v) Sodium, ammonium, methanol.

Most MPCs can be synthesised using the same methods and starting materials, with the sole variation of including the desired M^{+2} salt during the condensation reactions.

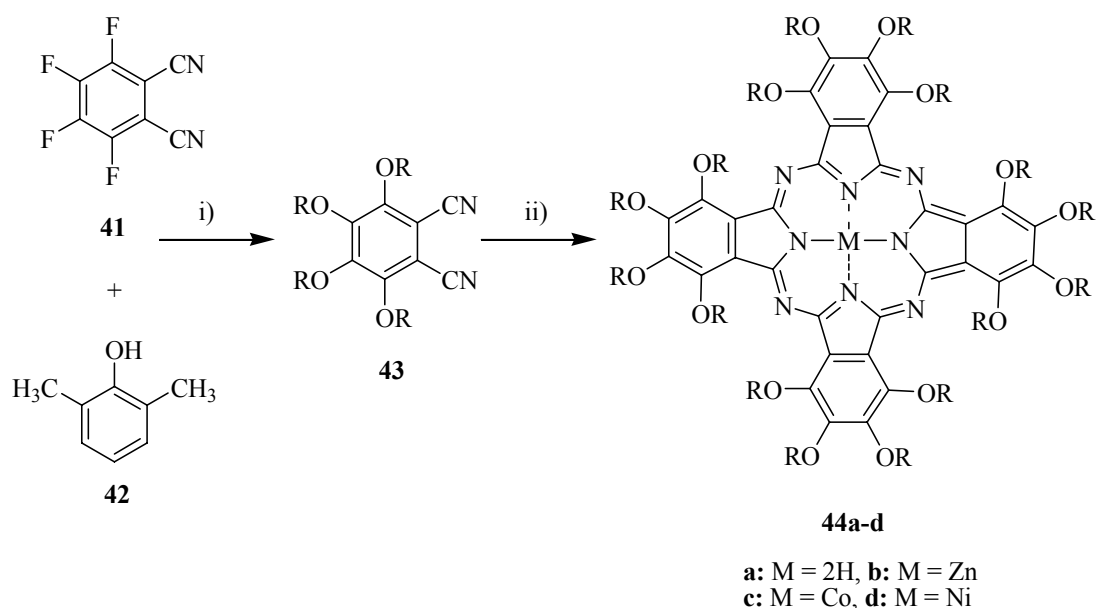
1.5.4 Solubility of phthalocyanines

The fundamental structure of Pcs makes them, when unsubstituted, insoluble in nearly all solvents. Due to their extended planar hydrophobic aromatic surface, Pc molecules can interact with each other by $\pi - \pi$ stacking interactions. The $\pi - \pi$ stacking interactions of Pcs affect aggregation and solubility tendencies both in solution and in the solid state. Specifically, the aggregation behaviour of Pcs can cause a drastic decay of the photodynamic activity and nonlinear optical properties through reducing the active absorbing excited-state lifetime which limits their applications in many fields⁷⁷.

Water-solubility is necessary, not only to determine their physical and chemical properties, but is also a desirable quality for various applications of Pcs, including biological and medical applications such as PDT. Catalysis of reactions in aqueous media, mainly the degradation of pollutants, is currently experiencing a surge in interest,⁷⁸ and this is another area where water-soluble Pcs are required.

The properties of Pcs are not only decided by the nature of their substituents on the ligand but are also affected by the metal ion located at the core of the ligand. The solubility can be improved significantly by introducing electron-withdrawing (-F, -Cl, -Br, -NO₂, etc.) and electron-donating (-NH₂, -Ar-S-, RO-, etc.) bulky or long chain groups.⁷⁹

It has been reported that when bulky phenoxy substituents are located on the peripheral position of the Pc core, this prohibits close self-association of the macrocycle and can result in the formation of cubic crystals containing substantial solvent-filled voids.⁸⁰ An example of this is shown in (**Scheme 1.19**).



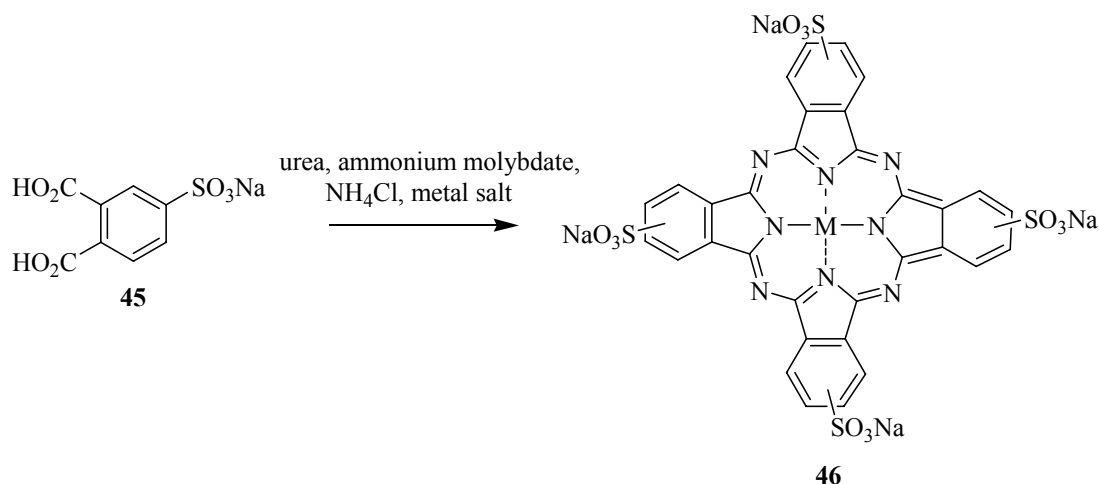
Scheme 1.19 i) anhydrous K_2CO_3 , DMF, 120°C , 72 hr; ii) microwave irradiation, 350 W, hydroquinone, appropriate metal salt, hexanol/DBU, 160°C , 10 min.

The aromatic nucleophilic substitution reaction between the anion of 2,6-dimethylphenol **42** and tetrafluorophthalonitrile **41** resulted in the formation of 2,3,4,5-tetrakis(2,6-dimethylphenoxy)phthalonitrile **43**. The most common condensation procedure mentioned previously (lithium/pentanol) was attempted, however this gave poor results. Microwave-assisted synthesis was then applied, which gave the desired Pcs in high yields and purities. The metal-free Pc **44a** and three MPcs **44b-d** (M = Zn, Co and Ni) were synthesised using this method.

1.5.5 Sulfonated phthalocyanines

Anionic substituents such as sulfonate, carboxylate and phosphorus-based functions are commonly used to bestow Pcs with water-solubility, however, most of the reported anionic Pcs contain sulfonate or sulphonic acid groups.⁸¹ These functional groups are either attached directly to the macrocycle or linked by various spacers. The synthesis of these compounds can be achieved by using sulfonated precursors or

by introducing the sulfonate function after the Pc has been formed. An example of the former method is shown in (Scheme 1.20) below.



Scheme 1.20 Synthesis of sulfonated Pcs from sulfonated Pc precursors.

The desired sulfonated Pc **46** is achieved by adding the monosodium salt of 4-sulpho phthalic acid **45** to a mixture of the appropriate metal salt, urea, ammonium molybdate, NH_4Cl and heating in nitrobenzene at 180°C . Microwave-assisted synthesis of **46**, using the same precursors, with various metals at the core of the Pc has also been accomplished.⁸²

Other sulfonated Pc precursors have been reported such as substituted phthalonitriles in which the sulphonic acid function is introduced with additional aromatic rings **47-49** as shown in (Figure 1.13) below.

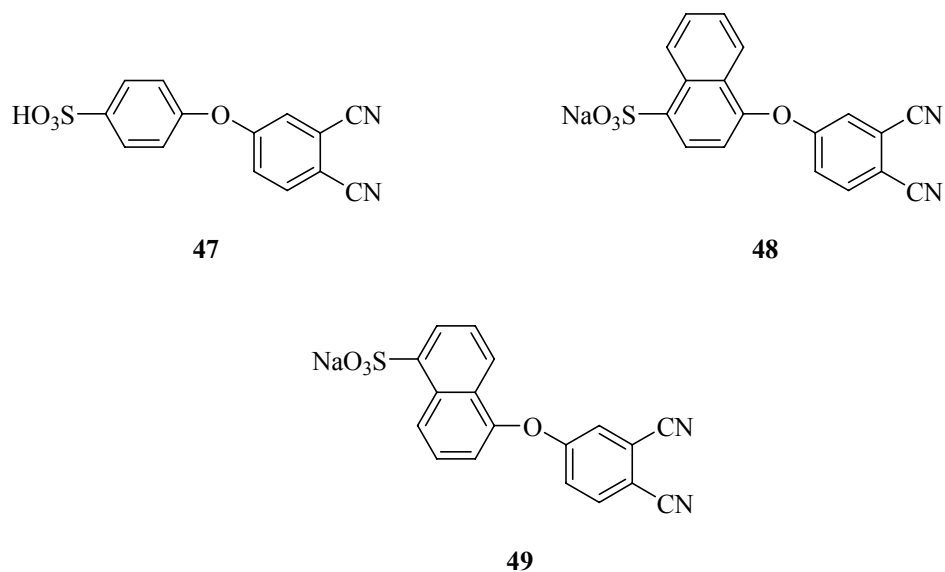
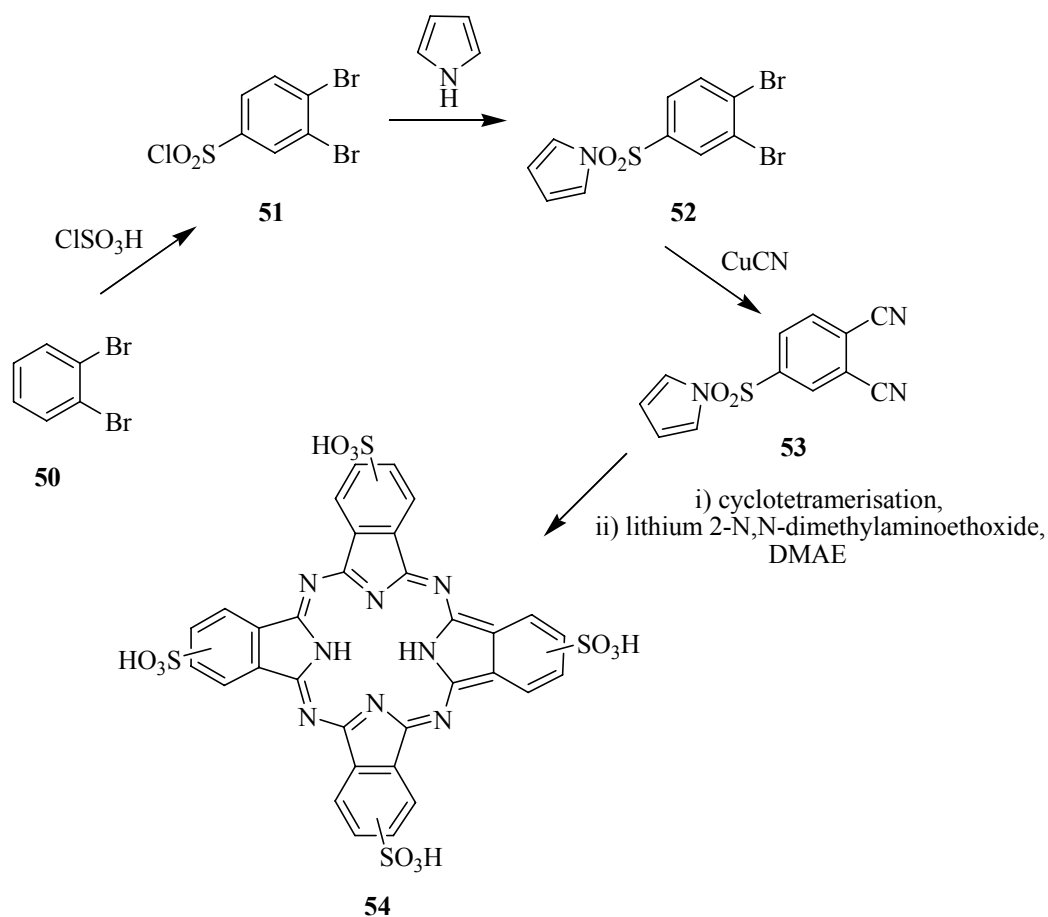


Figure 1.13 Examples of sulfonated Pc precursors.

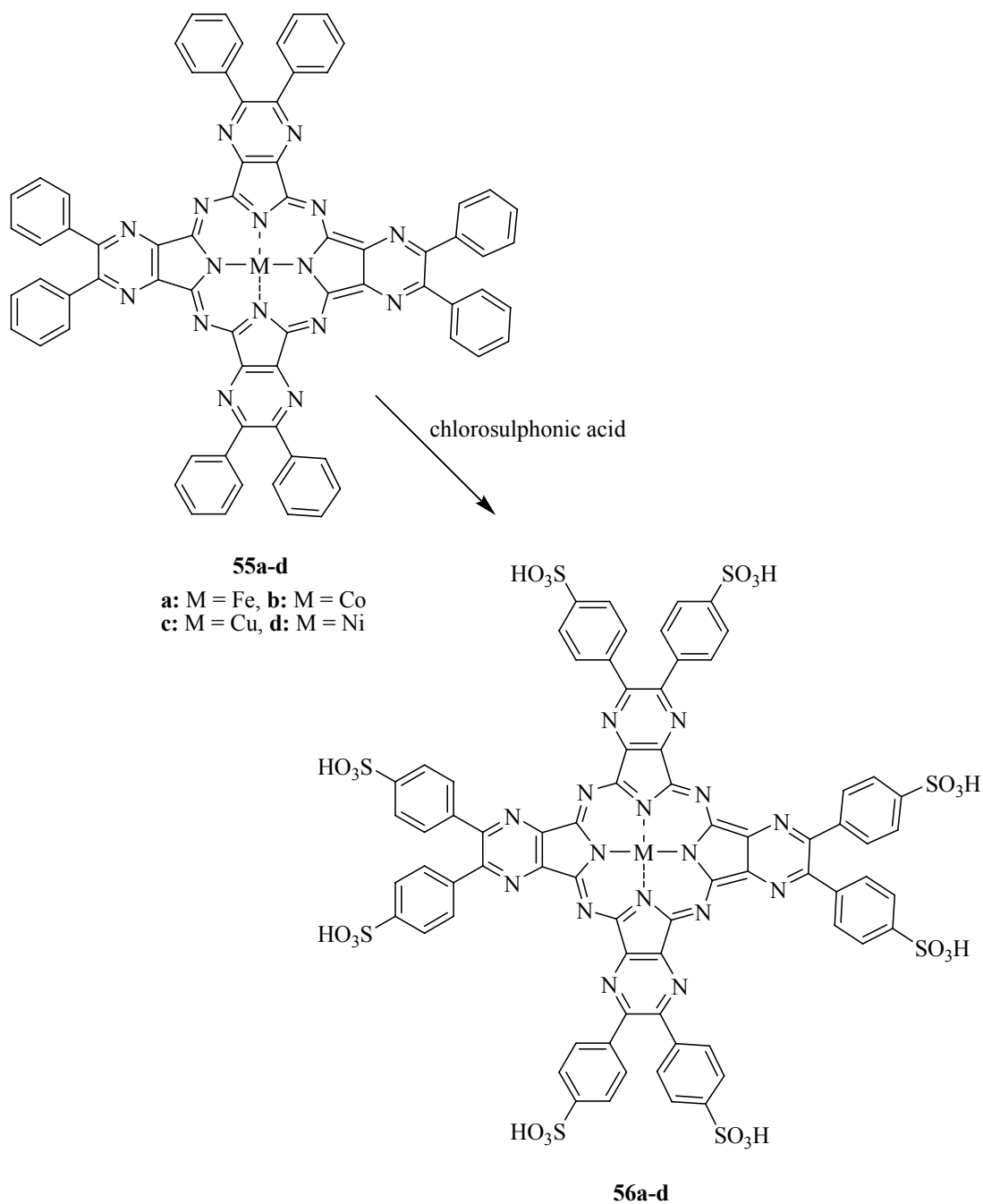
They are prepared by the condensation of 4-nitrophthalonitrile with 4-hydroxybenzene sulphonic acid, monosulfonated naphthol sodium salt and its isomer: 5-hydroxy-1-naphthalene sulphonic acid respectively.⁸¹ These precursors have been condensed by a variety of methods with a range of metal salts to give the corresponding sulfonated MPcs.

Protected sulphophthalonitriles, an example of which is shown in (**Scheme 1.21**) can also be used in the formation of sulfonated Pcs. While these precursors involve a more complex synthesis they have proved to be quite versatile.⁸³ They are prepared by the chlorosulfonation of 1,2-dibromobenzene **50** and subsequent reaction with pyrrole, the sulfonate being protected by a heterocyclic amide function before undergoing the Rosenmund-von Braun dinitration to form **53**. After formation of the Pc, the protecting groups were removed by lithium 2-N, N'-dimethylaminoethoxide in DMAE, yielding **54**.



Scheme 1.21 Synthesis of sulfonated Pc from protected sulphophthalonitrile.

The traditional industrial approach to sulfonated Pcs is electrophilic sulfonation. Metal-free or metallated unsubstituted Pcs are sulfonated when treated with concentrated sulfuric acid at 80-100°C. A mixture of mono-, di-, tri- and tetrasulfonated Pcs is usually obtained, with the degree of sulfonation determined by high performance liquid chromatography (HPLC). Attempts to control the sulfonation process have been made⁸⁴ but after laborious experiments adjusting the reaction conditions it was concluded that a process to target the formation of specific sulfonated products could not be found. An example of a selective sulfonation can be seen in (Scheme 1.22).



Scheme 1.22 Example of selective sulfonation.

Metallated octaphenyltetrapyrazinoporphyrazines **55a-d** (M = Fe, Co, Cu and Ni) underwent selective sulfonation at the *para* position of each of the eight phenyl groups resulting in the formation of the water soluble derivatives **56a-d**.⁸⁵

1.6 Microphotochemistry

It is becoming apparent that the time-honoured methods for practicing organic chemistry are not sustainable and must be changed. While traditional synthesis has been extremely successful, it is by nature wasteful, and as raw materials become more limited, it is essential that we endeavour to make synthetic organic chemistry more efficient.⁸⁶ Despite the fact that light is regarded as a *clean reagent*,⁸⁷ the photochemical production of chemicals on an industrial scale remains rare, and although organic chemists have not yet fully embraced microphotochemistry, *i.e.* photochemistry in microstructured reactors, there has been increased interest shown in this area as it is proving to have many advantages over conventional methods. Some of these advantages include shorter irradiation time, fewer side-reactions, lower quantities of reactants and solvents required which all demonstrate a more desirable, “greener” process.

1.6.1 Examples of microstructured reactors

The term ‘(Molecular) microreactor’ refers to a confined space in which a chemical reaction can occur and has been used in reference to micelles, zeolites, supramolecular systems and nanoparticles.^{88- 94} However, it also refers to microstructured reactors, otherwise known as microchannelled reactors. Microstructured reactors have demonstrated significant promise in the area of synthetic organic chemistry, including photochemical transformations.^{95- 106} In general, microstructured reactors consist of a solid support with channels of only several micrometres in width and depth (10-1000 μm). The narrow channel dimensions promote millisecond mixing times, while their small size also prevents “hot spots” which usually occur in batch reactors, offering better selectivity and yields for many organic reactions. These features of rapid mixing and heat transfer allow the use of highly concentrated reagent solutions, meaning reactions can be run with minimal waste.

Microreactors also facilitate both process optimisation and library generation to be done rapidly on a small scale, further reducing waste. More significant, however, is

the fact that microreactors effectively eliminate scale-up, opting instead for “numbering up” with many reactors to increase output. Safety is increased and production enhanced by avoiding larger reactors.¹⁰⁷ As photochemistry is limited in the development of drug candidates due to the problems associated with scale-up, in particular with the scale-up of the light source, microreactors offer a solution to this as large volumes of materials can be synthesised using commercially available light sources.

Many research groups custom build microreactors for their own use. This enables them to choose the solid substrate and glass used, as well as optimisation of path length and depth to suit their particular needs. An example of a microchip reactor in combination with a UV-LED-array is shown in **Figure 1.14**.

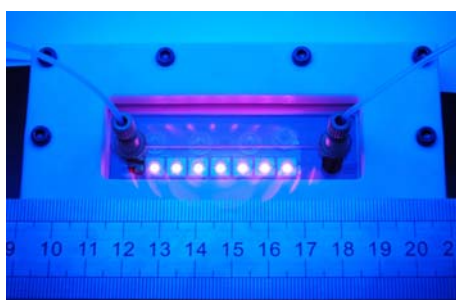


Figure 1.14 Quartz microchip design with 365 nm/500 mV UV-LED-array.¹⁰⁸

Engineering of microreactors is, in itself, a significant research area, with many groups using photochemical processes as model reactions to optimise reactor design. The engineering of a microstructured reactor may be done using a variety of techniques.¹⁰⁹ The solid support used may be glass, silicon, metal, ceramic or polymeric in nature. The choice of solid may depend on the reaction to be carried out, for example, some polymers are not stable in all solvents. For photochemical reactions use of glass as the solid substrate is ideal, as a transparent ‘window’ through which the reaction mixture can be irradiated is required. The channels are created using photolithography, hot embossing, microlamination and other microfabrication techniques.

Commercial microstructured reactors are also available and have been commonly adopted for photochemical applications, particularly serpentine channel and the

falling film type reactor (FFMR). In the case of the FFMR, which utilises a multitude of microstructured channels, the reagent solution is pumped into the microreactor where the liquid spills over the top creating a thin film as it moves by the force of gravity down the parallel microstructured channels. This microreactor is specifically designed for gas-liquid reactions, *e.g.* oxidations and hydrogenations, where the gas flows against the film of liquid. The high specific interface area (up to 20.000 m²/m³) enables sufficient saturation of the film with reactant gas. This reactor type is thus more efficient than closed channel devices, which require pre-saturation of the reactant solution with reagent gas. Scale-up can be achieved using cylindrical reactor models.



Figure 1.15 Cylindrical Falling Film Micro Reactor (Cyl-FFMR) for 10-fold scale-up and the Standard version FFMR.

One of the main qualities of the serpentine reactor is its long path length, which may range from several centimetres up to a metre or more. The *dwell-reactor* produced by Mikrogilas (**Figure 1.16**), for example, has a total path length of 1.15 m (20 turns) on a 118 mm x 73 mm aperture. This reactor consisted of a (bottom) serpentine channel with a second (top), heat-exchanging channel through which water is passed in order to control the reactor temperature. The longer path length can be used to increase residence time, and is therefore suited to reactions which require longer periods of irradiation. In the serpentine reactor the reagents may be either pre-mixed, as in the case of the *dwell-device*, or mixed “on-chip” in cases with two separate inlets leading into a single channel in either a “T” or “Y” shape.

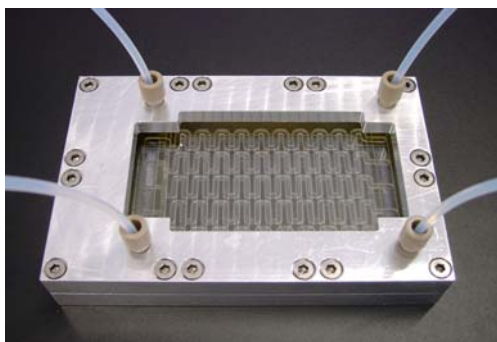


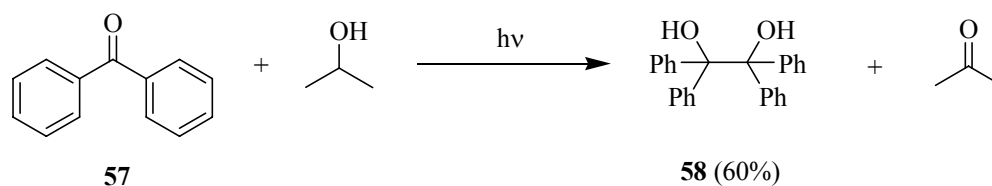
Figure 1.16 *Dwell Device* (Mikroglas).

The photochemical reactions carried out in microstructured reactors can be split into three categories. Firstly, homogeneous reactions (such as photocyanation,¹¹⁰ [2+2]-cycloadditions,^{111,112} the Barton reaction,¹¹³ photochemical pinacolisation¹¹⁴), secondly, heterogeneous reactions between liquid and gaseous reagents, as carried out in the FFMR, (e.g. [4+2]-cycloadditions of singlet oxygen^{115,116}) and lastly as catalytic processes using semiconductors (such as catalytic reactions using titanium dioxide¹¹⁷⁻¹¹⁹). A review of these categories of organic photochemistry has been published¹²⁰ and isolated examples of *homogenous* reactions will be presented here.

1.6.2 Selected examples of micro-photochemical reactions

In these reactions the reagents are all in the same phase, *i.e.* all in solution. Therefore there are few additional requirements for the microstructured reactor beyond the ability to pump the reagents in solution through the reactor. One of the earliest reported photochemical reactions in a microstructured reactor was the photo-pinacolisation of benzophenone **57** in isopropanol (**Scheme 1.23**).¹¹⁴ The microstructured reactor was fabricated in-house by bonding a patterned silicon wafer to a quartz wafer, the advantage of this technique being that the quartz substrate allows reaction and detection using UV light of lower wavelengths than permitted by glass substrates such as Pyrex.¹²¹ The light source used was a mini UV lamp, which provided light of 365 nm. The typical concentration of the benzophenone solution was 0.5 M. The use of a concentrated solution effectively demonstrated the advantage of a microstructured reactor, as the shallow channel depth ensured complete irradiation of the reaction mixture which would not have been possible

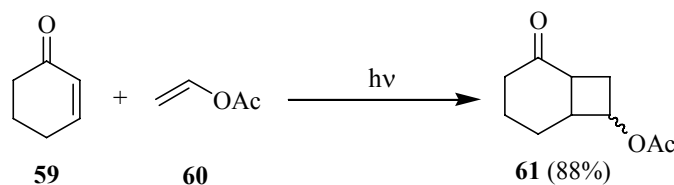
under conventional photochemical set ups. The progress of the transformation was monitored off-chip using HPLC and on-line using UV-spectroscopy.



Scheme 1.23 Reaction scheme of the photo-pinacolisation of **57**.

The authors reported that this reaction required flow rates of less than $10 \mu\text{l min}^{-1}$ to ensure adequate residence time on the chip. The reaction is known to follow a radical reaction pathway and it is reported that the longer the residence time of the reaction, the greater the conversion to benzopinacol **58**. This is because the longer residence time results in the increased absorbance of light and provides sufficient time for the excited species to diffuse and react with **57**, although flow rates above $3 \mu\text{l min}^{-1}$ were used to avoid precipitation of product **58** in the microstructured reactor. Above this threshold, crystallisation of the product was observed in the effluent storage device instead. At a flow rate of $4 \mu\text{l min}^{-1}$ conversions of up to 60% were achieved.

Fukuyama *et al.* carried out an investigation into the use of microstructured reactor technology for photochemical [2+2]-cycloadditions (**Scheme 1.24**).¹¹² This study demonstrates the application of the previously mentioned *dwell device* (**Figure 1.16**) for a range of substrates using a common high pressure mercury lamp (300 W) as the light source. The model reaction examined was the reaction of cyclohex-2-enone **59** with vinyl acetate **60**.

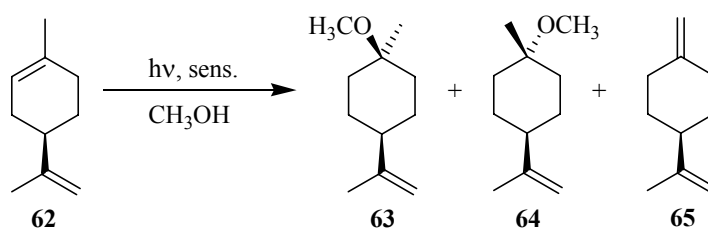


Scheme 1.24 Reaction scheme of a photochemical [2+2]-cycloaddition.

At a flow rate of 0.5 ml/hr, which corresponds to a residence time of 2 hours, **61** was obtained in a yield of 88%. This was compared to a batch reactor (10 ml) irradiated

using the same light source for 2 hours, which yielded only 8% of **61**. This demonstrates clearly that the use of microstructured reactor technology can both shorten irradiation times and increase yield. The reaction was repeated with two reactors in series at a flow rate of 1 ml/hr, which resulted in a similar yield of 85%.

The use of microstructured reactors can decrease or even eliminate unwanted side reactions as rapid flow rates decrease the residence time of the substrates and can ensure that the products are rapidly removed from the reactor. Sakeda *et al.* have demonstrated this theory using the asymmetric photosensitised addition of methanol to (R)-(+)-(Z)-limonene **62** as a model reaction (Scheme 1.25).¹²²



Scheme 1.25 Reaction scheme of **62** and methanol.

Three microstructured reactors of different dimensions were made from quartz and a low-pressure mercury lamp (40 W) was used as the light source. A study of the effect of channel size on photon efficiency was carried out. With decreasing channel size, photon efficiency was shown to increase and was significantly greater for microstructured reactors than batch conditions. The reason for this was attributed to high spatial illumination homogeneity, excellent light penetration and short exposure times. In addition, the diastereomeric excess (*d.e.*) of the photoproduct was found to be slightly larger than that obtained under batch conditions. This was explained by suppression of side reactions in the microstructured reactors as, due to the short space of time the reactants and products spend under irradiation, there is less chance of either a secondary product being formed or of the product being converted to another compound.

Thesis proposal

Microchemistry is an emerging area of interest, as described in the literature review (Chapter 1). Microreactors are known to use less solvent, be more energy-efficient and result in less side-reactions making them attractive as a prospective method for organic synthesis. With this in mind, we decided to investigate the potential of performing various photochemical reactions in a microreactor.

Investigating the feasibility of microreactors in organic photochemistry:

To do this, we will first need to acquire results from a “conventional” method and then perform the same reactions in a microreactor and finally compare both sets of results for any similarities or improvements.

Phthalimide chemistry:

As phthalimide chemistry was a focus for our group, particularly photodecarboxylative (PDC) additions of carboxylates to phthalimides, several of these reactions will be used as model reactions, to both optimise the microreactor set-up and use as comparison reactions.

Aristolactam synthesis:

Aristolactams are an important family of compounds possessing a wide variety of biological activity. Continuing on from the phthalimide chemistry, it will be investigated whether aristolactams can be synthesised from the PDC addition products *via* an efficient photochemical method. We wish to optimise this chemistry first by conventional methods and then determine if it can be transferred to a microreactor. If successfully transferred, then the value of microphotochemistry could be demonstrated for compound libraries.

Phthalonitriles and phthalocyanines:

Another focus of our group is phthalocyanine (Pc) chemistry. Although it is possible to synthesise Pcs from phthalimides, in this case we will explore the option of using phthalonitriles as the precursors. The application of synthetic organic photochemistry for the preparation of new sulfonated phthalonitrile derivatives will be investigated,

as water solubility is a desirable feature of Pcs for application in PDT and cell imaging. The phthalonitrile chemistry will also be performed in a microreactor and compared to conventional methods.

Ultimately we wished to demonstrate that microphotochemistry can be used as an efficient tool in organic synthesis.

Chapter 2

2 Photoaddition reactions of NMP and phthalimide

2.1 Introduction

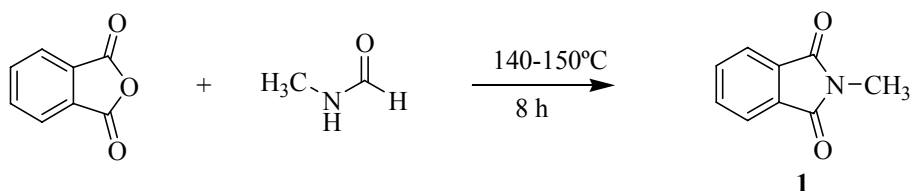
In this chapter photoaddition reactions are introduced. NMP is the starting material of choice which will be synthesised and then reacted with a number of addition partners such as alkyl carboxylates, phenyl acetates and α -keto carboxylates. PET will be introduced and the mechanisms of these reactions will be discussed. A variety of photoaddition reactions with phenyl acetates will also be performed using phthalimide as the starting material and any differences in the results obtained discussed.

Several photoaddition products will then be dehydrated to form the related arylmethylenesioindolin-1-ones, which have the general structure of the open analogues of aristolactams which were discussed in Chapter 1 and will be dealt with in Chapter 4.

2.2 Synthesis of starting material

2.2.1 Synthesis of *N*-methylphthalimide

N-Methylphthalimide (NMP) **1** was the starting material of choice used for most of the reactions described in this and subsequent chapters. It is available commercially, however it is possible to synthesise it quite easily from phthalic anhydride and *N*-methylformamide according to a method described by Schindlbauer¹²³ (**Scheme 2.1**). The pure product (**1**) was afforded in a yield of 71% and the ¹H-NMR revealed the presence of the NCH₃ group at 3.11 ppm in CDCl₃.



Scheme 2.1 Experiment 1.

2.3 Photoaddition reactions in solution

2.3.1 Experimental set-up

For the irradiation experiments a Rayonet photochemical chamber reactor was used (**Figure 2.1** and **Figure 2.2**). The reactor was fitted with 16 RPR-3000 Å lamps ($\lambda = 300 \pm 20$ nm). Schlenk flasks ($\lambda \geq 300$ nm) were used and the reaction mixture was constantly purged with a slow stream of N₂. To avoid overheating, a cold finger was used. A short Teflon tube was inserted into the second Suba Seal to act as an outlet for the gas to prevent pressure build up. The progress of the reaction was monitored by TLC analysis, or by connecting a bubbler to the Schlenk flask containing a saturated solution of barium hydroxide, used to detect the presence of carbon dioxide which is only formed when the reaction is in progress.

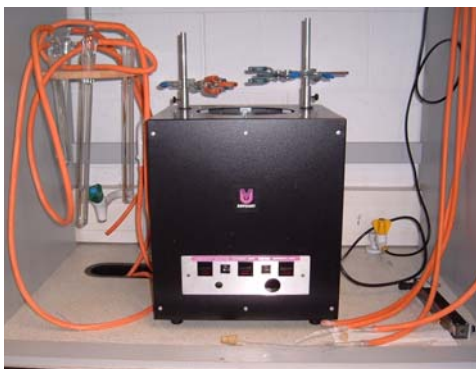


Figure 2.1: Rayonet photoreactor.

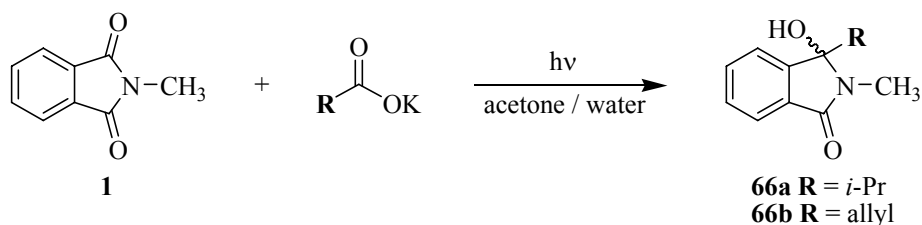


Figure 2.2: Experimental set-up.

Figure 2.2 1: Pyrex tube containing reaction mixture, 2: Cold finger to keep reaction cool, 3: Outlet to prevent pressure build-up, 4: Inlet for N₂.

2.3.2 Reactions of alkyl carboxylates and phenylacetates with NMP

In general, **1** was irradiated in the presence of 3 equivalents of a potassium carboxylate, the latter which was generated *in situ* from the carboxylic acid and K₂CO₃, resulting in the formation of the desired photoproducts (**Scheme 2.2**). In experiment 2, *i*-butyric acid was used as the addition partner and, following 7 hours of irradiation, the product **66a** was obtained in a yield of 74%. In experiment 3, vinyl acetic acid was the reagent of choice. After irradiating for 5 hours, the yield was found to be 24% despite complete conversion of **1** being achieved (**Table 2.1**). The C-OH peak for both products was found around 90 ppm in the ¹³C NMR spectra, in C₂D₆CO and CDCl₃ respectively.



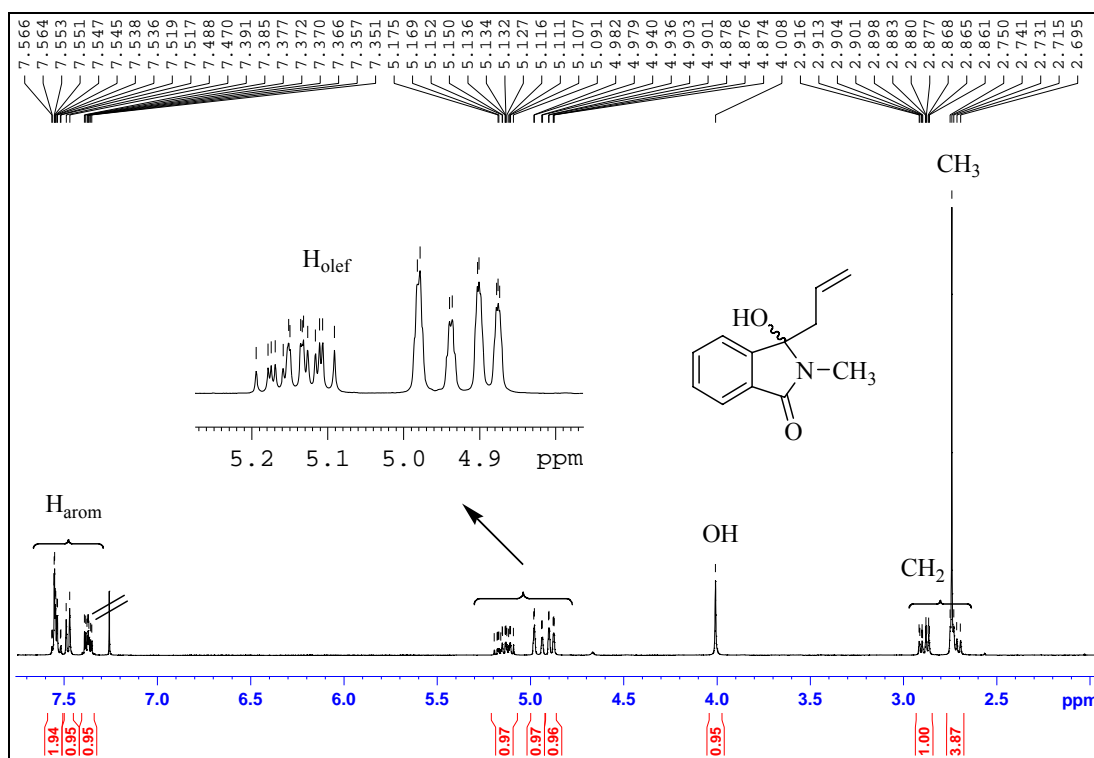
Scheme 2.2: Experiments 2 and 3.

Table 2.1: Photoadditions involving **1**.

compound	R	time [hr]	yield [%]	¹³ C-NMR [ppm] C-OH
66a	<i>i</i> -Pr	7	74	93.2 ^a
66b	allyl	5	24	90 ^b

^a in acetone-d₆, ^b in CDCl₃

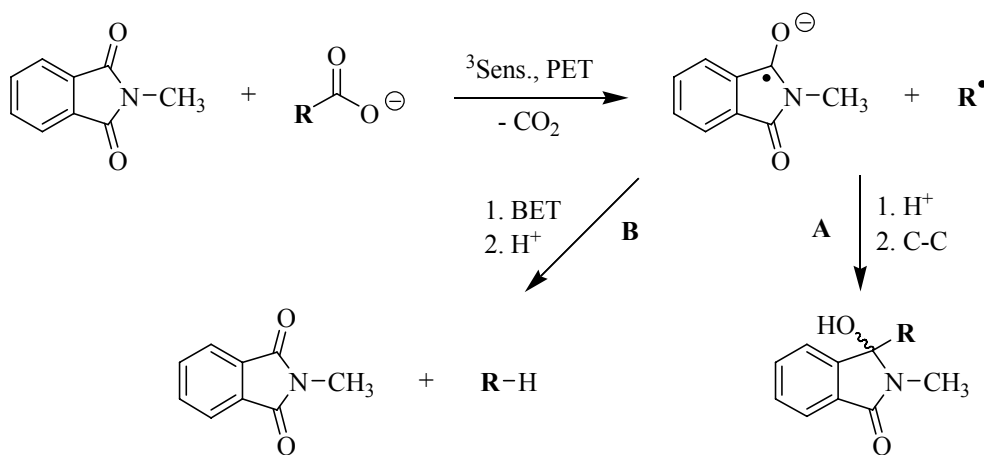
In the ¹H-NMR spectrum of **66b** (**Figure 2.3**), the *N*-methyl group and one of the peaks corresponding to the CH₂ group overlap at around 2.75 ppm. The peak representing the OH group is found at 4.0 ppm as a sharp singlet, and in the olefinic region, peaks were observed between 4.8 and 5.3 ppm. In the aromatic region the characteristic peaks representing the four aromatic protons were found.

**Figure 2.3** ¹H-NMR spectrum of **66b** in CDCl₃.

Both photoadditions of alkyl carboxylates to *N*-methylphthalimide **1** resulted in the formation of alkylphthalimidines as the only products. As mentioned previously, in experiment 2, the addition of *iso*-butyric acid to NMP resulted in a 74% yield after 7 hours irradiation. In experiment 3 however, the addition of vinyl acetic acid to NMP

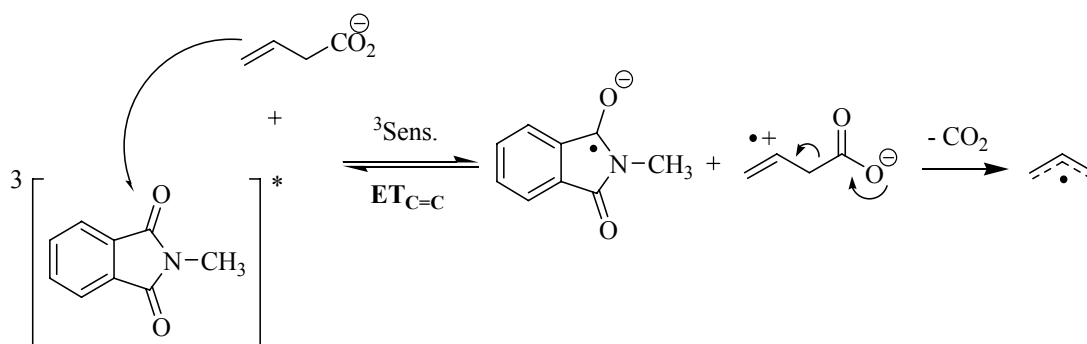
only resulted in a yield of 24% after 5 hours irradiation. It was assumed, due to the stability of the corresponding allyl radical, that this reaction would proceed readily even with a short irradiation time. Alternative reactions involving the C=C double bond, for example Paternò-Büchi reactions or photoadditions via C-H activation, might have successfully competed with the desired photodecarboxylation in this case.¹²⁴ No evidence of these proposed side-reactions was found although, as a consequence of their carboxylic acid functionalities, the resulting products would have been water soluble and extracted during work-up.

The proposed mechanism for the photodecarboxylative addition is illustrated in **Scheme 2.3**.^{125,126} Triplet sensitisation by acetone is followed by single electron transfer (SET) from the carboxylate to the triplet excited phthalimide. Although the oxidation potentials of carboxylates are relatively high compared to other electron donor groups (*e.g.* acetate: $E_{\text{Ox.}} = 1.54 \text{ V}$ in MeCN, 2.65 V in H_2O vs. SCE¹²⁷) *intramolecular* electron transfer *via* the excited $^3\pi,\pi^*$ triplet state ($E_{00} = 3.1 \text{ eV}$) or the higher $^3n,\pi^*$ state ($E_{00} \approx 3.6 \text{ eV}$) are both energetically feasible. Subsequent decarboxylation of the carboxy radical yields the corresponding C-radical. The rate for CO_2 loss is controlled by the stability of the corresponding alkyl radical and is estimated to be in the range of 10^9 - 10^{10} s^{-1} for simple alkyl acyloxy radicals.¹²⁸ Protonation, intersystem crossing and C-C bond formation result in the desired photoaddition products (path **A**). Alternatively, BET generates the corresponding carbanions, which are protonated by water (path **B**).¹²⁹



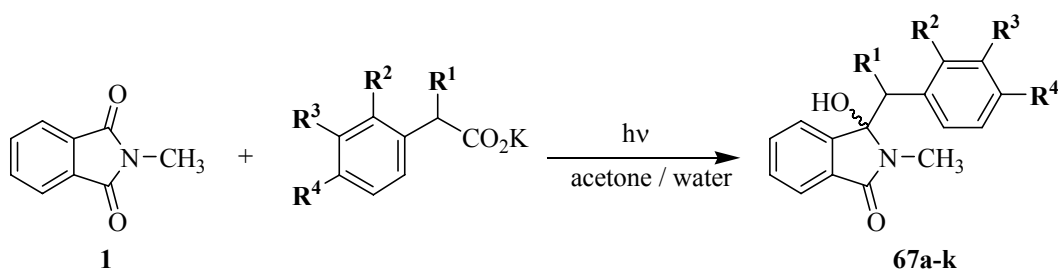
Scheme 2.3 Mechanism of photodecarboxylative addition of carboxylates to phthalimide.

For vinyl acetate, an alternative mechanism involving electron transfer from the C=C double bond can be postulated (**Scheme 2.4**). Subsequent α -decarboxylation leads to the common allyl radical. A similar competitive mechanism has been described by Kurauchi and co-workers for the decarboxylative addition to 1-methyl-2-phenyl-1-pyrrolinium perchlorate.¹³⁰ Based on fluorescence quenching experiments the authors concluded that electron transfer proceeded from both donor sides yielding the same final product. A similar behaviour might be operating here as well.



Scheme 2.4: Alternative mechanism of allylation.

As seen in **Scheme 2.5** and summarised in **Table 2.2**, NMP in the presence of 1.5 equivalents of different potassium phenyl acetates in acetone-water (50:50), for 1–5 hours gave addition products **67a-i** in yields of 18–78%. The characteristic C-OH signals in the ^{13}C -NMR spectra were found around 90 ppm for all compounds. For **67b**, it was calculated from the crude NMR that only 52% of the starting material had reacted, and therefore the % yield was calculated based on conversion as 56%.



Scheme 2.5: Experiments 4-14.

Table 2.2: Photoadditions of phenyl acetates to **1**.

compound	R ¹	R ²	R ³	R ⁴	time [hr]	yield [%]	¹³ C-NMR [ppm] C-OH
67a	H	H	H	H	1	54	90.7 ^b
67b	H	H	H	CH ₃	2	53	90.9 ^c
67c	H	H	H	OH	5	18	91.1 ^c
67d	H	H	H	OCH ₃	4	78	91.3 ^c
67e	H	H	H	F	2	36	91.8 ^c
67f	H	H	H	Cl	5	29 (56) ^a	90.5 ^b
67g	H	H	Cl	Cl	3	53	90.1 ^b
67h	H	Br	H	H	5	35	90.3 ^c
67i	Ph	H	H	H	3.5	76	92.2 ^c
67j	H	CH ₃	H	H	3	63	90.4 ^c
67k	H	CF ₃	H	H	7	46	90.2 ^c

^a yield based on conversion, ^b in CDCl₃, ^c in C₂D₆CO.

A representative ¹H-NMR spectra of photoaddition product **67a** is shown in **Figure 2.4**. The methyl group at the *N*-terminus is found as a singlet at 2.88 ppm. The two doublets at 3.09 and 3.46 ppm represent the bridging CH₂ group between the original isoindolinone and the newly introduced phenyl ring. These two hydrogens are chemically inequivalent, which is why they appear as two doublets and not as a single peak. The OH group was found as a broad peak at 3.7 ppm. In the aromatic region the peaks representing the nine aromatic protons can be found between 6.8-7.5 ppm. Four of these protons can be assigned to the aromatic ring of the original isoindolinone and five to the newly introduced phenyl ring.

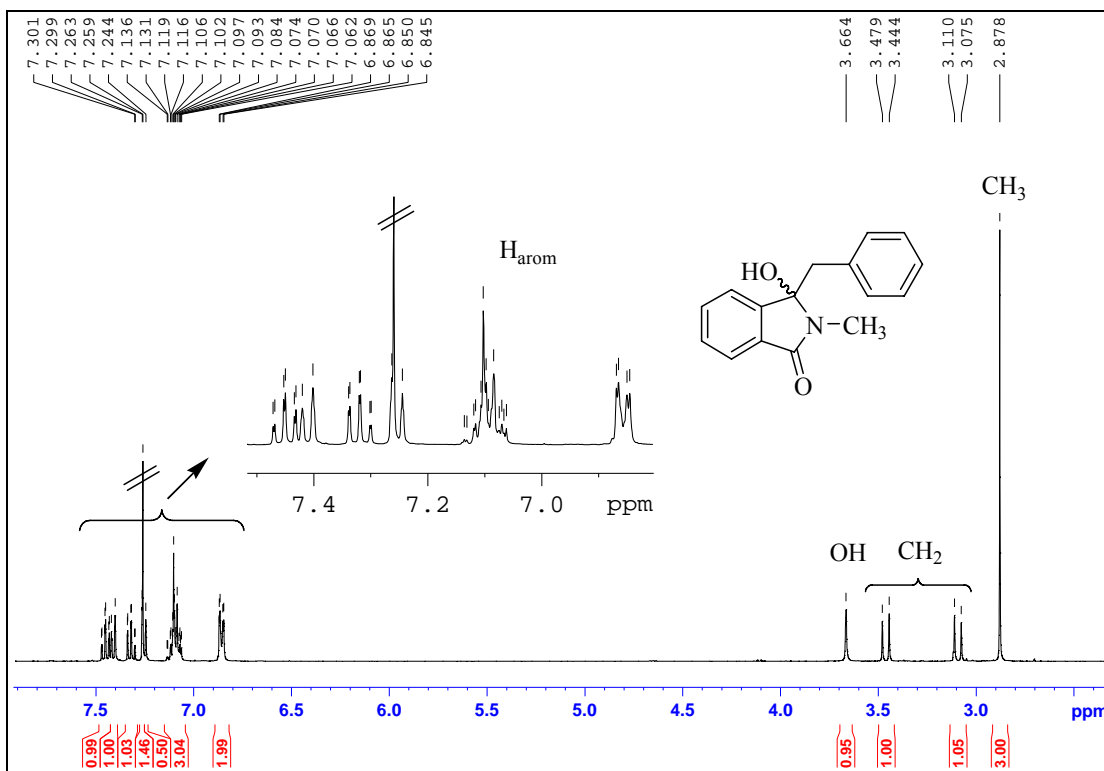
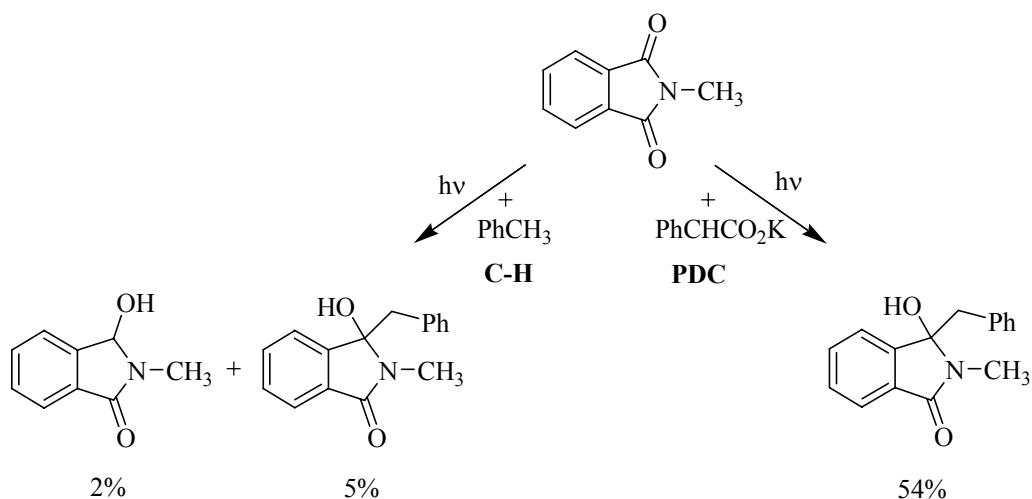


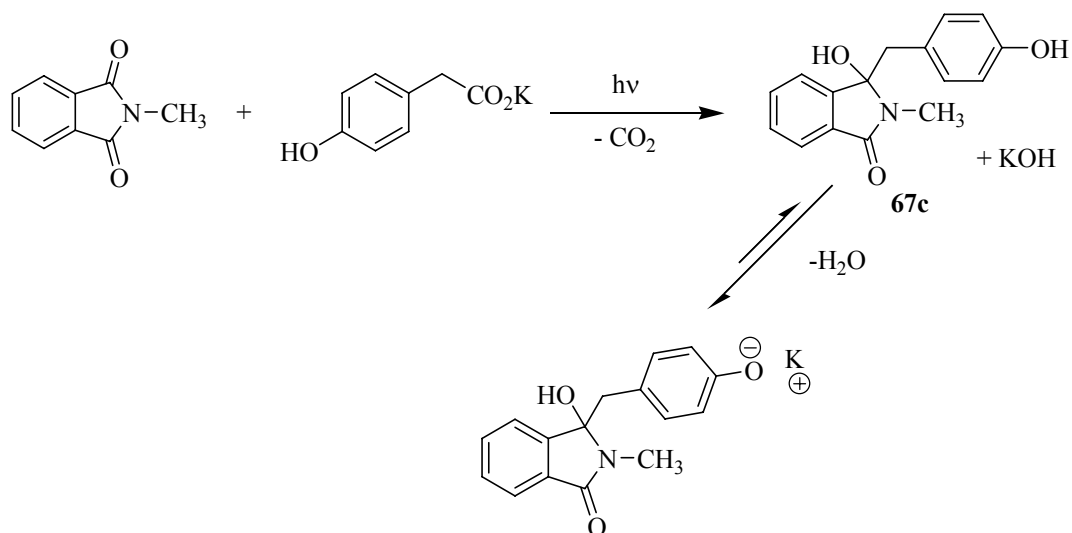
Figure 2.4 Representative ¹H-NMR of **67a** in CDCl₃.

Major advantages of the photodecarboxylation protocol are its simple procedure and the usage of carboxylic acids. These starting materials are readily accessible in large quantities with broad structural diversity, and are additionally stable in comparison to other thermal methods *e.g.* SmI₂-mediated coupling of organic halides (SmI₂/R-X),^{131a} addition of organometallic compounds (R-Mg-X or R-Li),^{131b-d} or alkylation with organic halides using lithium in liquid ammonia (Li/NH₃/R-X),^{131e} respectively. The efficiency of the PDC approach becomes especially apparent when comparing the benzylation of *N*-methylphthalimide with toluene or phenyl acetate (**Scheme 2.6**). As reported by Kanaoka and co-workers, simple hydrogen abstraction gives the corresponding benzylated product in low yield (5%) and with poor selectivity and conversion (30%).¹⁸ In contrast, PDC exclusively yields the benzylated product in high yield and purity.



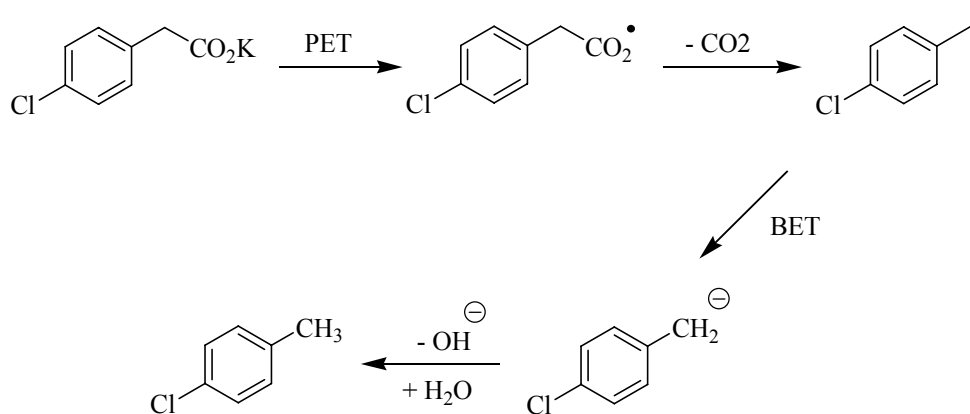
Scheme 2.6: Alternative benzylation procedures.

In the case of **67c** the product is obtained in a low yield of 18%, even though complete conversion of starting material occurs as was evident by TLC. This is probably due to the formation of the potassium salt (phenolate) of the desired product (**Scheme 2.7**) which should be water soluble and so remains in the aqueous layer during work-up. This occurs because the pH of the reaction solution rises during irradiation due to the formation of KOH. No attempt was made to recover this product.



Scheme 2.7 Formation of potassium salt (phenolate) of **67c**.

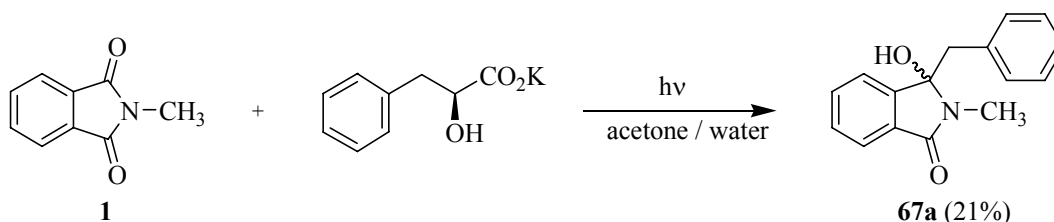
In the case of **67f** the conversion was calculated from the $^1\text{H-NMR}$ to be 52% after a total of 5 hr irradiation. This may be due to a competitive reaction taking place in which the simple PDC product is formed (**Scheme 2.8**).



Scheme 2.8 Formation of simple PDC product for experiment 9.

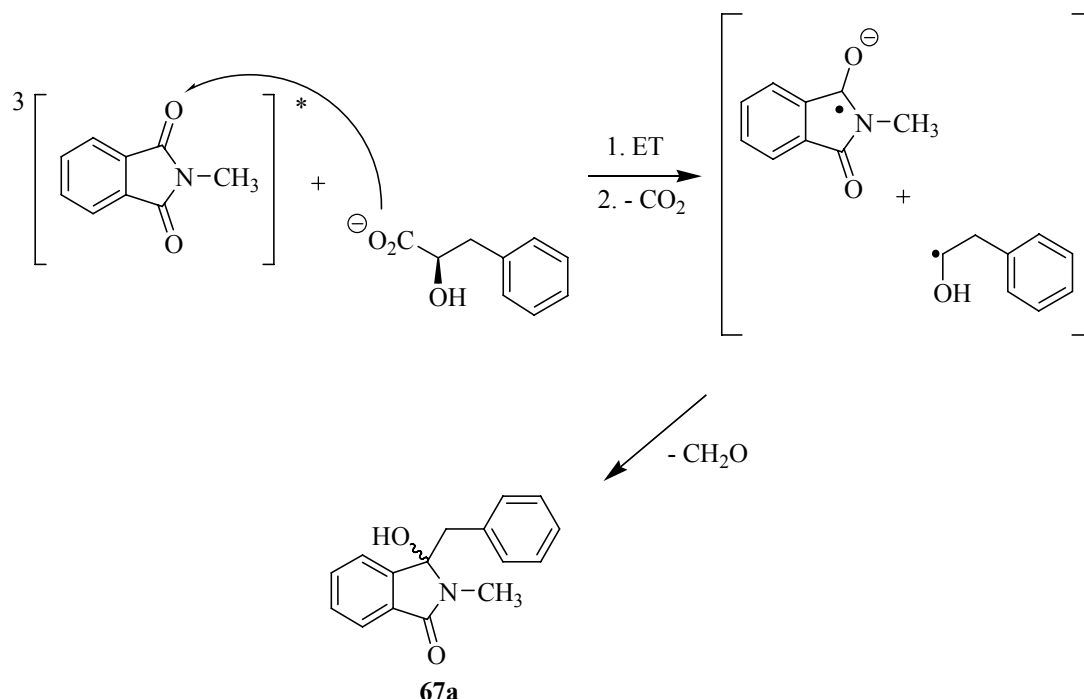
As seen in **Scheme 2.3**, path B results in the formation of the simple decarboxylation products ($-\text{CO}_2\text{H} \leftrightarrow -\text{H}$ exchange). Although these simple decarboxylation products were sometimes detected by TLC or in the crude NMR spectra, no attempt was made to isolate these compounds. In most cases, they were removed during drying under vacuum due to their volatility. For **67f**, as the conversion was so low, simple PDC might be more pronounced.

The reaction of **1** with potassium *L*-3-phenyllactate also resulted in the formation of **67a** (**Scheme 2.9**) with a yield of 21% after 4 hours irradiation. As previously mentioned, the yield obtained with potassium phenylacetate as the addition partner was found to be 54% after only 1 hour of irradiation.



Scheme 2.9 Experiment 15.

The differences in yield can be explained by the differences in mechanism of both reactions. While both mechanisms are similar, in the case of potassium *L*-3-phenyllactate an extra step is needed. Decarboxylation is followed by the loss of formaldehyde before C-C bond formation can afford the desired photoproduct as depicted in **Scheme 2.10**. This means that the reaction will take longer to complete and hence requires a longer irradiation period.



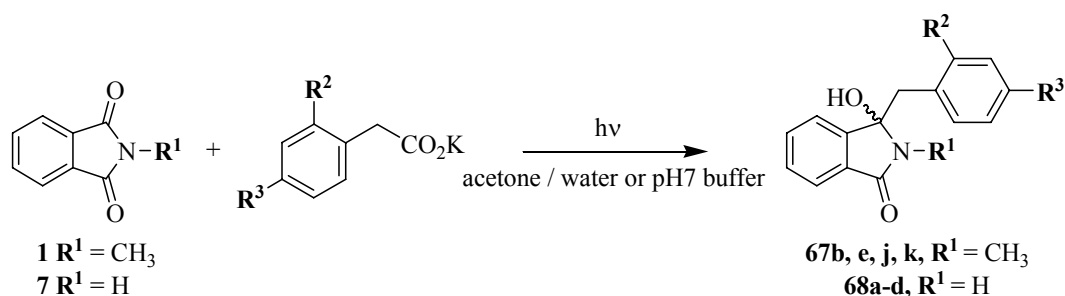
Scheme 2.10 Mechanism of **1** and potassium *L*-3-phenyllactate.

2.3.3 Reactions of phthalimide with phenylacetates

A major shortcoming of the original PDC procedure is the need to have *N*-substituents on the phthalimide due to the rising pH during irradiation (final pH ~9-10). With “free” phthalimide the initially formed benzylated-hydroxyphthalimidines are consequently obtained as their potassium salts and cannot be isolated easily. Early attempts to convert these salts directly to the corresponding arylmethyleneisindolin-1-ones by means of an acidic work-up and subsequent extraction, resulted in complex mixtures with unreacted starting materials. Since the acidity of phthalimide ($pK_a = 8.3$) differs considerably from that of common

carboxylic acids ($pK_a = 5-6$), a mixture of acetone and pH 7 buffer solution was therefore applied for the irradiation reactions.

A number of reactions were performed using phthalimide as the starting material and acetone/pH 7 buffer (1:1) as the solvent, as shown in **Scheme 2.11**. In most cases the results obtained showed greater yields with shorter irradiation times than the related reactions using **1** as the starting material (**Table 2.3**).



Scheme 2.11 Reaction of **1** and **7** with various phenylacetates.

Table 2.3 Results obtained for photoproducts from both **1** and **7**.

compound	R ¹	R ²	R ³	time [hr]	yield [%]
67b	CH ₃	H	CH ₃	4	47
68a	H			3	92
67e	CH ₃	H	F	4	39
68b	H			3	85
67j	CH ₃	CH ₃	H	3	63
68c	H			3	57
67k	CH ₃	CF ₃	H	7	46
68d	H			6	63

The only exception to this was experiment 20 which, after the same irradiation period of 3 hours, gave **68c** in a yield of 57% which was comparable to **67j** (63% yield).

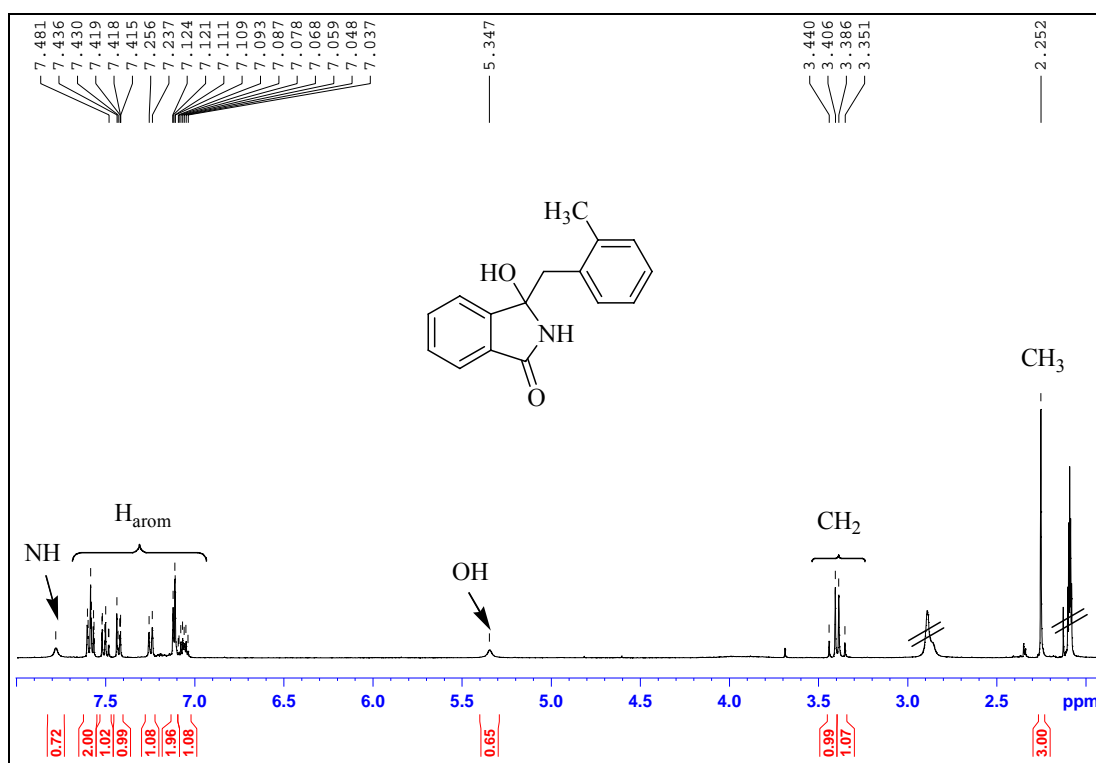
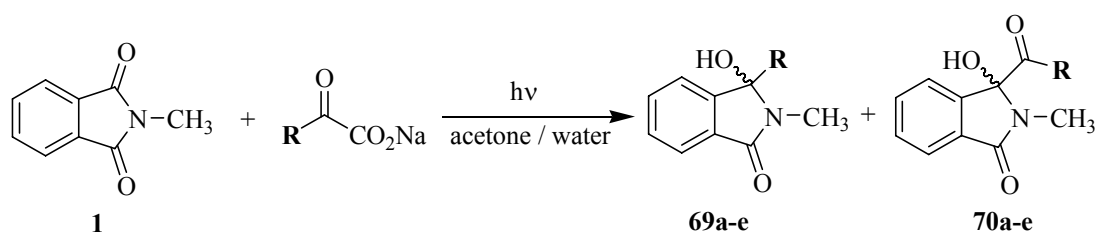


Figure 2.5 Representative ¹H-NMR of **68c** in C₂D₆CO.

A representative ¹H-NMR of **68c** is shown in **Figure 2.5**. Obviously the main difference from the previous representative ¹H-NMR spectra is the absence of the N-CH₃ peak ~3 ppm and the presence of the NH peak found as a broad singlet at 7.8 ppm. The doublets representing the bridging CH₂ group were found at 3.3 and 3.4 ppm, while the methyl group appeared as a singlet at 2.3 ppm. In the aromatic region, the peaks representing the 8 aromatic protons were found between 7.0 and 7.6 ppm, four representing the newly introduced aryl ring and the remaining four representing the aromatic ring of the original isoindolinone. The broad peak found at 5.3 ppm corresponded to the OH group.

2.3.4 Reactions of NMP with α -keto carboxylates

Following the general procedure described previously, **1** was irradiated in the presence of the sodium salts of α -keto acids. Upon irradiation, either the alkylated or acylated photoproducts were obtained in yields of 26-69%.



Scheme 2.12 Experiments 22-26.

Table 2.4 Photoadditions of α -keto carboxylates to **1**.

compound	R	time [hr]	yield [%]	
			69	70
a	<i>i</i> -Pr	3	29	-
b	<i>i</i> -Bu	4.5	-	26
c	<i>t</i> -Bu	2.5	69	-
d	<i>s</i> -Bu	3	39	-
e	CH ₂ Ph	6.5	52	-

As we can see from **Table 2.4**, experiment 23 resulted in the acylation product **70b** being formed in a yield of 26%. In all other cases, the alkylation product was formed. In experiment 25, as there are two chiral centres present, a diastereomeric mixture of *like*- and *unlike*-**69d** (*like* = R,R / S,S and *unlike* = R,S) was formed in a ratio of 58:42, (d.e. = 16%), however despite column chromatography they could not be separated.

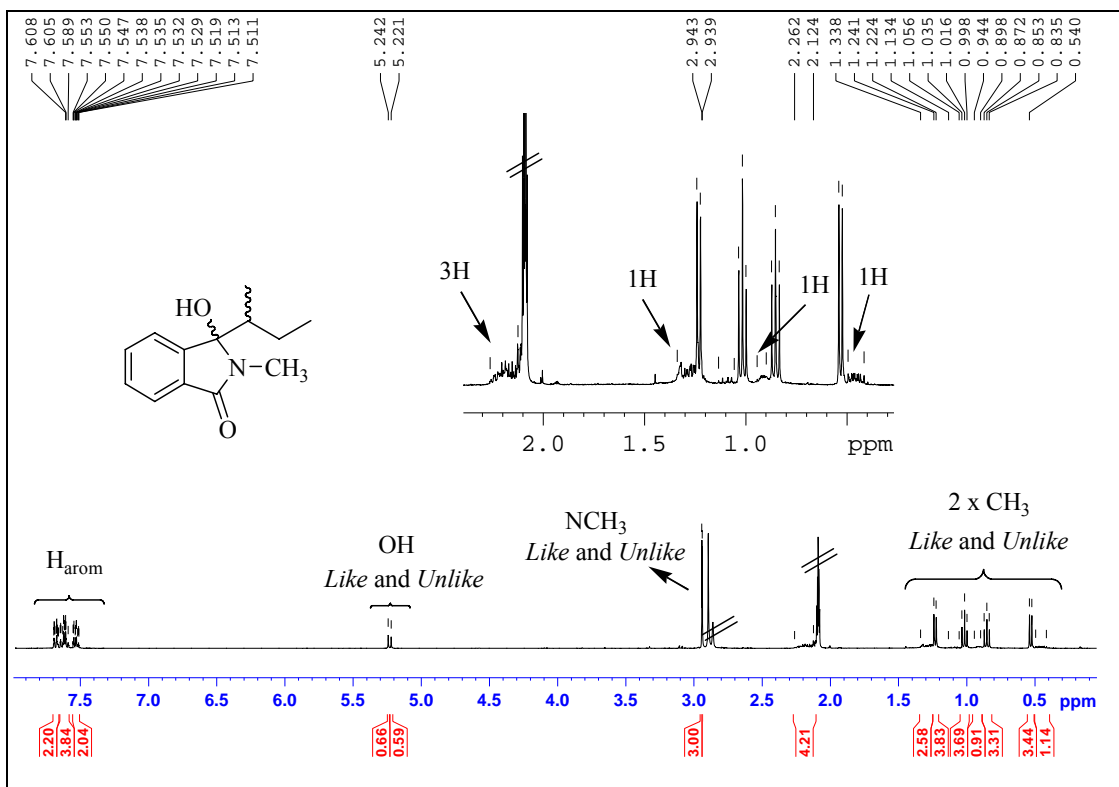


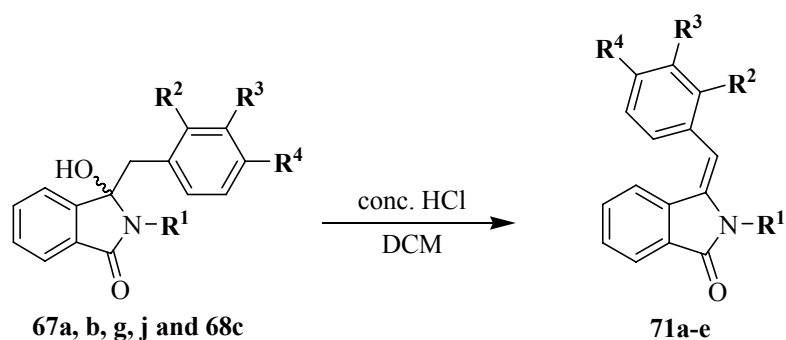
Figure 2.6 Representative $^1\text{H-NMR}$ spectrum of **69d** in $\text{C}_2\text{D}_6\text{CO}$.

The $^1\text{H-NMR}$ spectrum of photoaddition product **69d** is shown in **Figure 2.6**. It could not be determined which diastereoisomer (*like* or *unlike*) was the major/minor component. The *N*-terminus methyl groups were found as singlets at 2.94 ppm. Two doublets representing the $\text{CH}_3(\text{CH})$ groups were found at 0.53 and 1.23 ppm respectively. Two triplets representing the $\text{CH}_3(\text{CH}_2)$ groups were found at 0.85 and 1.02 ppm respectively. The CH_2 and CH groups for both were found as multiplets between 0.46 and 2.26 ppm. The OH groups were found as broad singlet peaks at 5.22 and 5.24 ppm. In the aromatic region the peaks representing the eight aromatic protons can be found between 7.51 and 7.70 ppm.

Out of experiments 22-26 only one of them (experiment 23) yielded the acylation product **70b**. This is in line with the literature results.¹³² For the other reactions, the alkylation product is obtained in moderate to good yields. The reaction cascade is initiated by electron transfer (ET) from the α -keto carboxylate to the triplet excited phthalimides (**Scheme 2.13**).

2.4 Dehydration of photoaddition products

A selection of previously synthesised photoaddition products, including four aryl-*N*-methylisindolin-1-ones and one arylisindolin-1-one, were dehydrated to the corresponding arylmethylenisindolin-1-ones as shown in **Scheme 2.14**. They were obtained in moderate to good yields via acid-catalysed dehydration in DCM. In almost all cases, high *E*-selectivities were obtained as confirmed by ¹H-NMR spectroscopy. The results are summarised in **Table 2.5**.



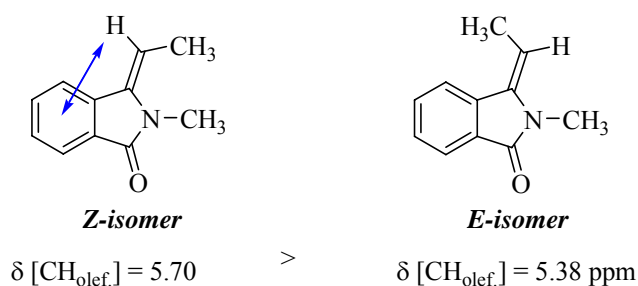
Scheme 2.14 Experiments 27-31.

Table 2.5 Dehydration reactions of previously made photoproducts.

compound	R ¹	R ²	R ³	R ⁴	¹ H-NMR [ppm] CH _{olef} ^a (<i>E</i>)	yield [%]	d.e. [%]
71a	CH ₃	H	H	H	6.5 ^b	68 <i>E/Z</i>	80
71b	CH ₃	H	H	CH ₃	6.5 ^b	62 <i>E/Z</i>	82
71c	CH ₃	H	Cl	Cl	5.9 ^b	74 <i>E/Z</i>	64
71d	CH ₃	CH ₃	H	H	6.7 ^c	58 <i>E</i>	68
71e	H	CH ₃	H	H	6.7 ^c	67 <i>Z</i>	52

^a determined from integration of H_{olef} peaks in ¹H-NMR spectra, ^b in CDCl₃, ^c in C₂D₆CO.

The configurations of the two isomers (*E/Z*) were assigned by comparison with known analogues reported by Ang and Halton.¹³⁴



Scheme 2.15 Assignment of *Z*- and *E*-isomers according to Ang and Halton.

The olefinic hydrogen of the *Z*-isomer is influenced by the anisotropic effect of the aromatic ring (indicated as blue arrow in **Scheme 2.15**) and is found at higher chemical shifts than its *E*-counterpart. This general trend was applied when assigning all subsequent isomers of compounds prepared.

In experiments 27-29, the most abundant isomer was found to be the *E*-isomer. The highest *d.e* of 82% was obtained for **71b**. Purification was carried out by column chromatography, however this failed to separate the isomers. In experiment 30, **71d** was also found to contain a majority of the *E*-isomer and this was successfully isolated by washing the product with a little acetone. The *Z*-isomer was removed along with the impurities. In experiment 31, which was the sole example of a photoproduct using phthalimide (**7**) as the starting material, **71e** was found to contain a majority of the *Z*-isomer. This was also successfully isolated by the same purification method as in experiment 30. For comparison, the $^1\text{H-NMR}$ spectra of both **71d** and **71e** are shown below in **Figure 2.7** and **Figure 2.8** respectively.

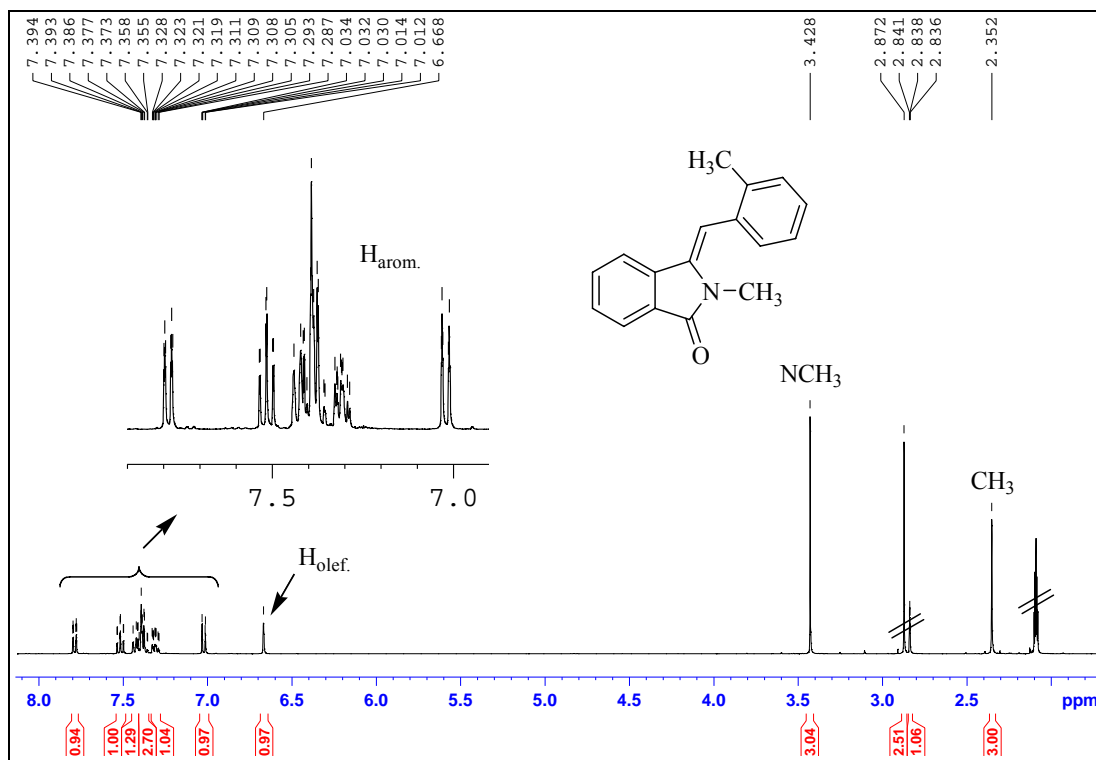


Figure 2.7 $^1\text{H-NMR}$ spectrum of **71d** in $\text{C}_2\text{D}_6\text{CO}$.

The *N*-methyl group of **71d** was found as a singlet at 3.4 ppm, while the methyl peak also appeared as a singlet at 2.4 ppm. The characteristic H_{olef} peak was found at 6.7 ppm. The peaks representing the aromatic protons were found between 7.0 and 7.8 ppm.

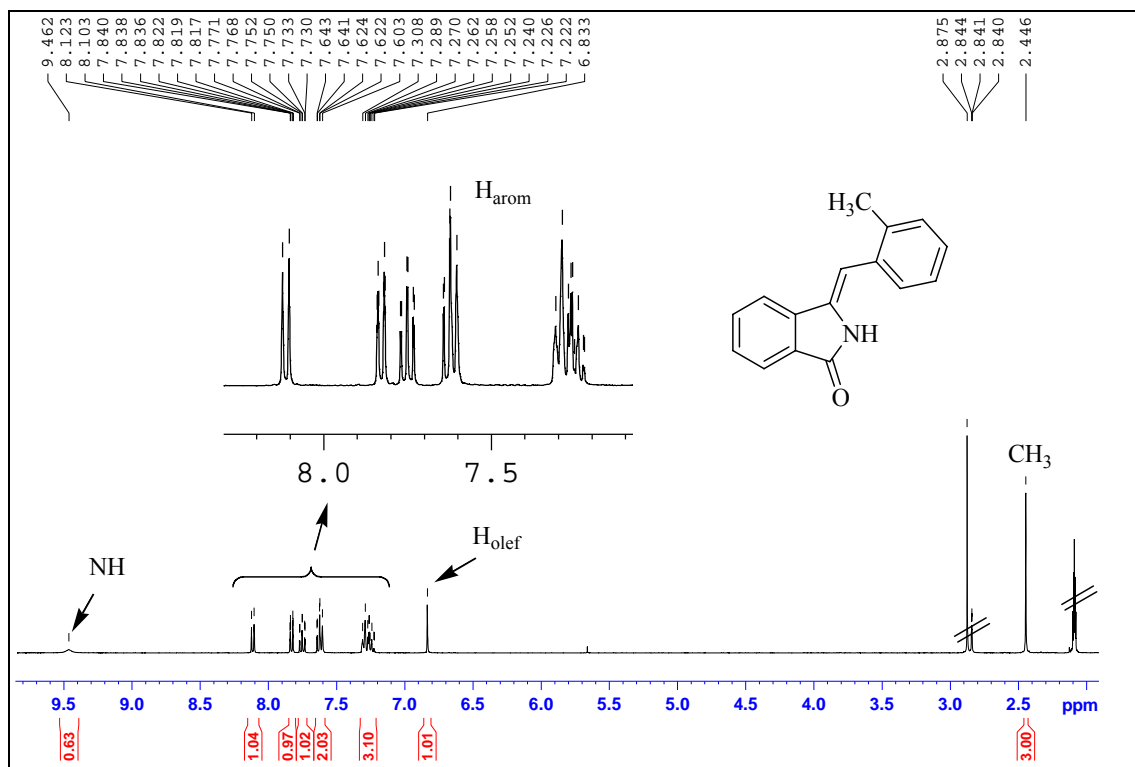


Figure 2.8 $^1\text{H-NMR}$ spectrum of **71e** in $\text{C}_2\text{D}_6\text{CO}$.

The $^1\text{H-NMR}$ of **71e** showed the characteristic H_{olef} peak at 6.8 ppm, while the peak representing the methyl group was found to be at 2.4 ppm. The broad peak corresponding to the NH group appeared at 9.5 ppm. The peaks representing the aromatic protons were found between 7.2 and 8.1 ppm.

2.5 Summary

In this chapter, starting material **1** was synthesised and photoaddition reactions were introduced. The reactions of **1** with alkyl carboxylates, phenyl acetates and α -keto carboxylates were all performed in a solvent mixture of acetone:water. All these reactions were successful and resulted in moderate to good yields. These reactions were all acetone-sensitised reactions, involving triplet sensitisation by acetone followed by PET from the carboxylate to the triplet excited phthalimide. Subsequent decarboxylation of the carboxy radical yields the corresponding C-radical while protonation, intersystem crossing and C-C bond formation result in the desired photoaddition products.

A variety of photoaddition reactions with phenyl acetates were also performed using phthalimide as the starting material. The solvent system acetone:pH 7 buffer was used in these cases to inhibit the natural rise in pH during irradiation, which results in the initially formed benzylated-hydroxyphthalimidines being converted to their potassium salts and therefore making them difficult to isolate. Using the buffered solution it was found that the yields obtained were higher than those using **1** as starting material.

A selection of these reactions will be used to make a comparison between the Rayonet reactor and the microreactor, to be discussed in Chapter 6.

Several photoaddition products were then dehydrated to form the related arylmethylenesioindolin-1-ones in good yields, which have the general structure of the open analogues of aristolactams and will be dealt with in more detail in Chapter 4.

Chapter 3

3 Photoaddition reactions of NMP with heteratom-containing addition partners

3.1 Introduction

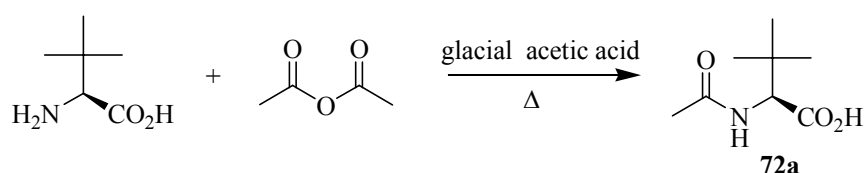
This chapter deals with the reactions of **1** and substituted phthalimides with heteroatom substituted addition partners. A series of reactions will be performed under the conditions described in Chapter 2, including examples of sulfur-containing addition partners and oxygen-containing addition partners. The different mechanisms will be discussed.

A variety of *N*-acetylated amino acids will be synthesised and subsequently reacted with **1**, and this reaction mechanism will also be discussed. The yields and *d.e*'s will be recorded, then a selection of these reactions will also be performed using acetone/pH 7 buffer as the solvent.

3.2 Synthesis of starting materials

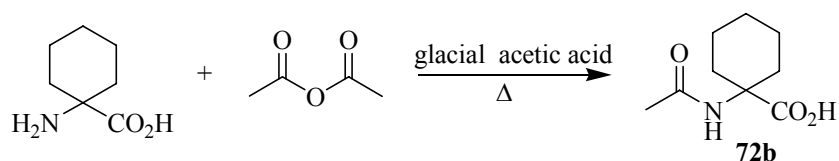
3.2.1 Synthesis of *N*-acetylated amino acids

Four acetyl amino acids and one acetyl dipeptide were synthesised by modifying a procedure according to Paulmann¹³⁵ by heating the desired reactant under reflux, with acetic anhydride, in glacial acetic acid over a 3 day period. Acetyl *L*-*t*-leucine **72a** was obtained in a yield of 40% following purification (**Scheme 3.1**). The characteristic methyl group of the added acetyl group was found at 2.18 ppm in the ¹H NMR spectrum, using CDCl₃ as solvent.



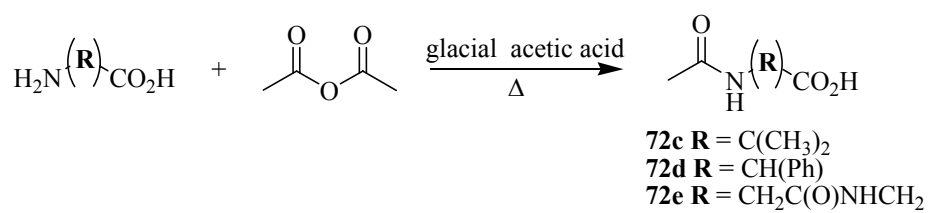
Scheme 3.1 Experiment 32.

The same procedure was carried out using 1-aminocyclohexane carboxylic acid (**Scheme 3.2**) and **72b** was obtained in a yield of 95%. No purification was necessary and the characteristic methyl group of the added acetyl group was found at 2.22 ppm in the ¹H NMR spectrum.



Scheme 3.2 Experiment 33.

The final two amino acids used were 2-amino-2-methylpropanoic acid and 2-amino-2-phenylacetic acid. Experiment 36 was carried out in the same way using the dipeptide glycyl-glycine (**Scheme 3.3**). The preparation of **72e** was problematic. Previous experiments resulted in a mixture of the desired product and acetyl glycine. It appeared the product was being cleaved due to the high temperature used (145°C), thus resulting in the formation of acetyl glycine. This was rectified by heating gently to 120°C for a short period of time rather than heating under reflux constantly.



Scheme 3.3 Experiments 34-36.

All the acetylated products were obtained in good yields, and the CH₃CO peak for each product appeared at around 2.2 ppm in the ¹H-NMR spectra, as shown in **Table 3.1**.

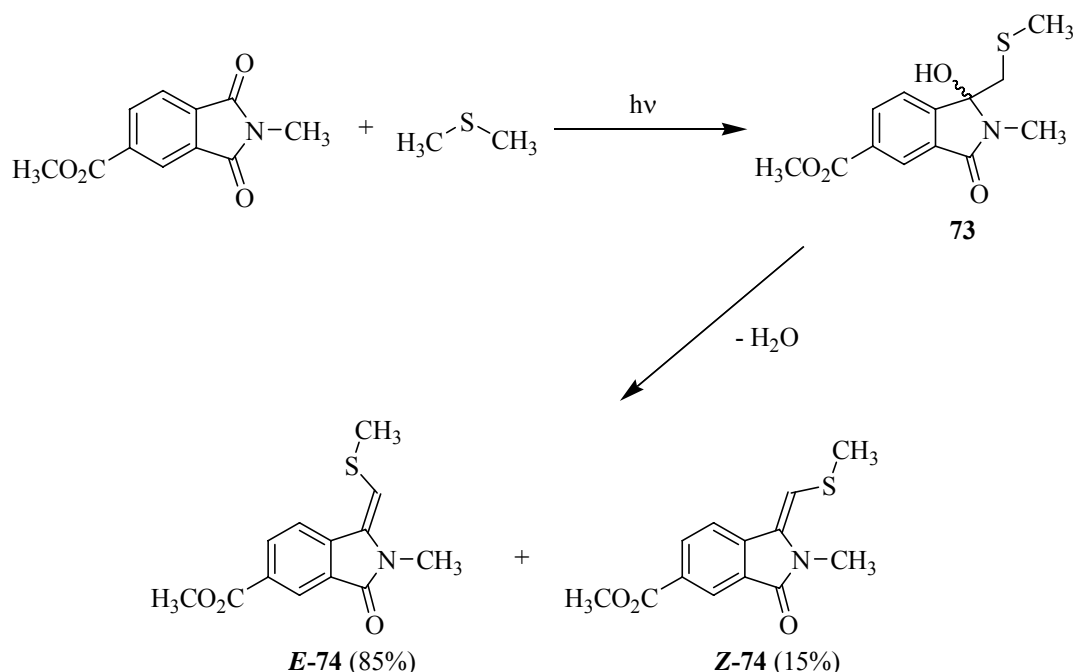
Table 3.1 Synthesis of *N*-acylated amino acids.

compound	amino acid	¹ H-NMR [ppm] CH ₃ CO ^a	yield [%]
72a	<i>L</i> - <i>t</i> -leucine	2.18	40
72b	1-aminocyclohexane carboxylic acid	2.22	95
72c	2-amino-2- methylpropanoic acid	2.19	89
72d	2-amino-2-phenylacetic acid	2.26	79
72e	glycyl-glycine	2.24	96

^a in CDCl₃/TFA

3.2.2 Reactions of phthalimides with sulfur-containing addition partners

N-methyl trimellitic acid imide methyl ester and dimethylsulfide were irradiated at a wavelength of 300nm, in the previously described set-up in the Rayonet reactor (Chapter 2), resulting in the regioselective formation of the photoproduct **73**. However, this primary product was sensitive towards dehydration and the corresponding olefins *E*- and *Z*-**74** were obtained, with the *E* isomer being the predominant product.



Scheme 3.4 Experiment 37.

In the $^1\text{H-NMR}$ spectrum, a mixture of the *E* and *Z* isomers were present. Since the R_f value determined by TLC analysis matched those typical for the photoaddition products, it was concluded that **73** was formed as expected and dehydration only occurred in the NMR tube upon standing in CDCl_3 . The *E*-**74**:*Z*-**74** ratio was determined by the $^1\text{H-NMR}$ as 85:15.

The first peaks again represent the methyl group bound to the *N*-terminus. Next the singlets representing the methyl group bound to the sulfur are observed, followed by those representing the methoxy group. In the olefinic region the signals representing the olefinic protons were found for both isomers. Finally in the aromatic region, the three hydrogens from the aryl ring are accounted for.

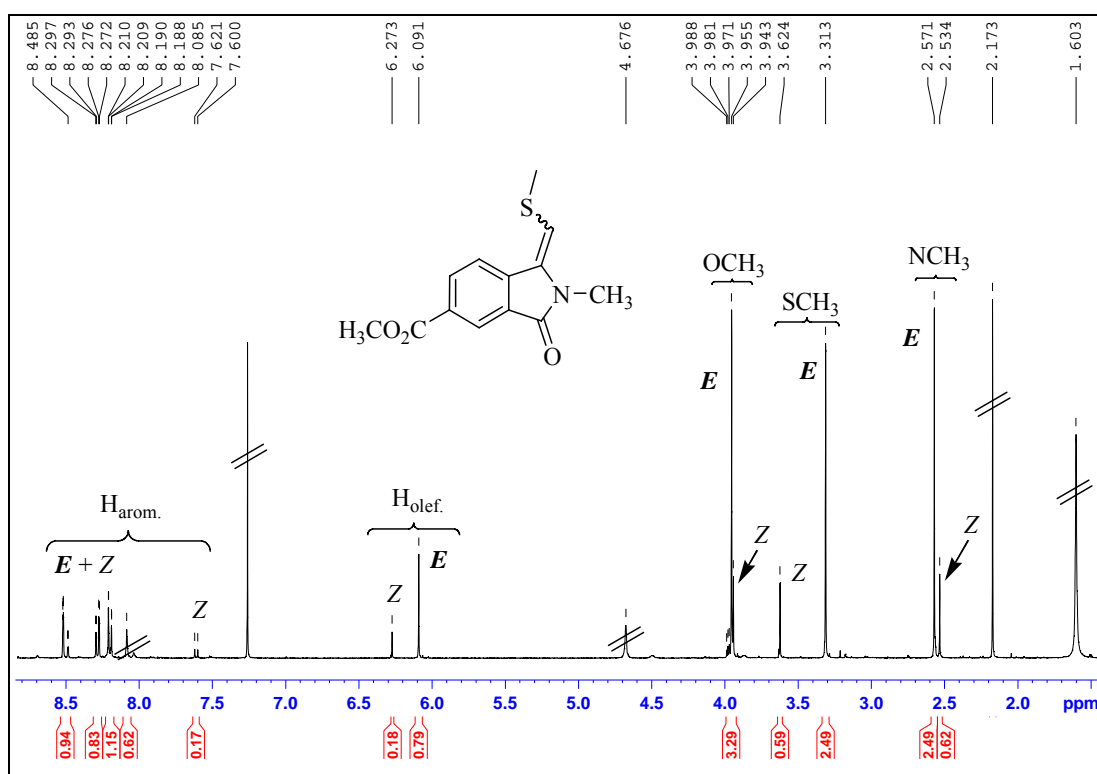
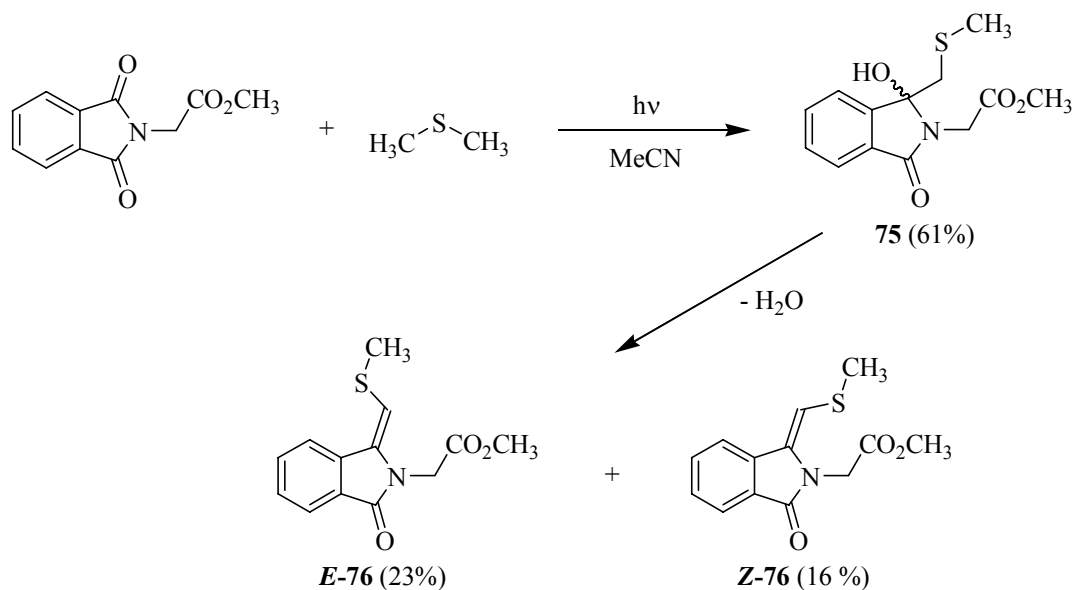


Figure 3.1: ¹H-NMR spectrum of *E*- and *Z*-74 in CDCl₃.

Additionally, *N*-phthalimido-glycine methyl ester was reacted with dimethylsulfide by irradiating at 300nm, resulting in the formation of **75** (Scheme 3.5). Again, the primary product **75** was sensitive to dehydration and as a result, **75** was isolated with the dehydration products **76**. The *E* isomer was again found to be the main isomer for the dehydration products. The **75**:*E*-**76**:*Z*-**76** ratio was determined by ¹H-NMR as 61:23:16.



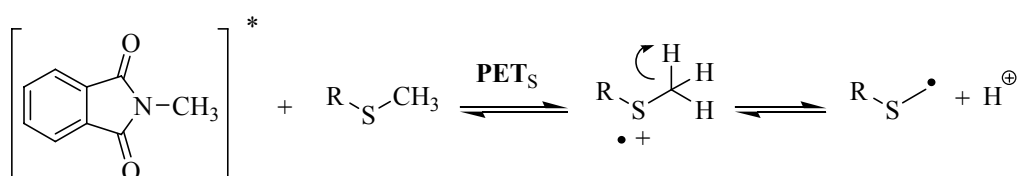
Scheme 3.5: Experiment 38.

Table 3.2: Photoadditions of dimethylsulfide to *N*-methyl trimellitic acid imide methyl ester and *N*-phthalimido-glycine methyl ester.

compound	time [hr]	conversion [%]	yield [%]	composition ^b		
73/74 ^a	24	100	47	73 = 0	E-74 = 85	Z-74 = 15
75/76 ^a	4.5	100	74	75 = 61	E-76 = 23	Z-76 = 16

^a identified as corresponding olefin pair in the ¹H-NMR, ^b determined by ¹H-NMR integration.

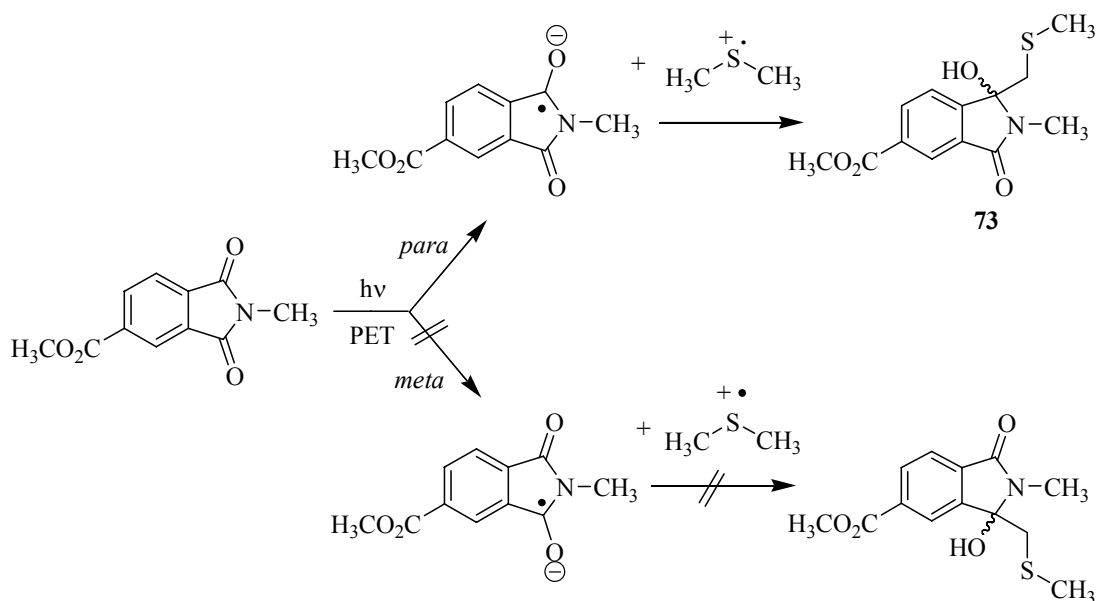
In the case of thioethers (**Scheme 3.6**), both electron transfer and deprotonation are reversible and as a consequence, a quantity of the starting materials are regenerated before they can undergo addition. Because of this, prolonged irradiation times are required for the reaction to go to completion.



Scheme 3.6 Mechanistic key-steps for the addition of thioethers.

In experiment 37, *N*-methyl trimellitic acid imide methyl ester was reacted with dimethylsulfide resulting in the formation of the photoproduct **73**. This reaction was regioselective as addition exclusively occurred at the carbonyl group *para* to the

CO₂Me group. Its preferred formation over the *meta*-product is in line with the literature,³⁶ which offers an explanation on the basis of the differences in spin densities in the corresponding imide radical anions. The spin density is significantly higher at the imide *para*-carbon atom than for the *meta*-carbon atom, so the chance of *para*-coupling is therefore much higher.



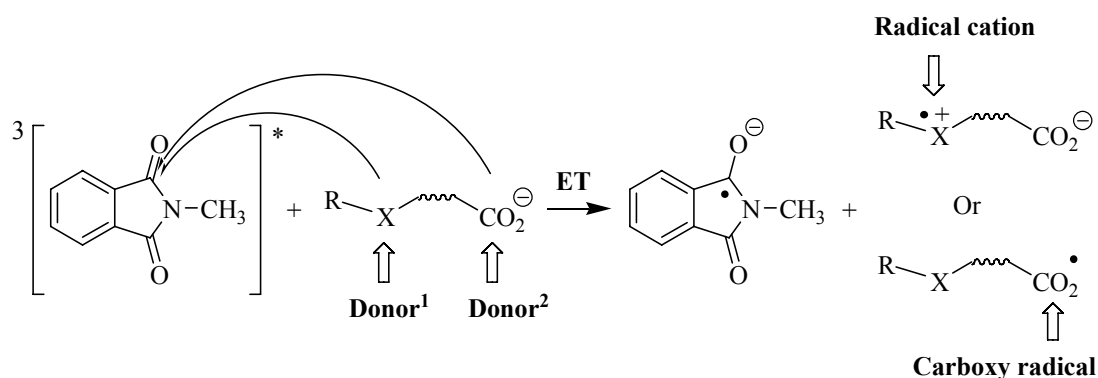
Scheme 3.7 Proposed mechanism for experiment 37.

Also mentioned previously is the fact that a mixture of the *E* and *Z* isomers for **74** were formed, as determined by ¹H-NMR. This dehydration must have occurred in the NMR tube, as CDCl₃ was used as the solvent, which becomes slightly acidic due to the formation of DCl. Photoaddition products are known to be sensitive towards hydrolysis, as the driving force of this reaction is the potential gain in conjugation with the aromatic ring. In experiment 38, the photoproduct **75** also underwent dehydration in the NMR tube to give a mixture of *E* and *Z* olefins **76**.

For photoadditions involving heteroatom-substituted carboxylates, two mechanistic pathways are possible (**Scheme 3.8**):

1. Electron transfer from the carboxylate anion to the excited phthalimide yielding unstable carboxy radicals and
2. Electron transfer from the neutral heteroatom resulting in the formation of its radical cation. This mechanism is known for α -trimethylsilylmethyl-

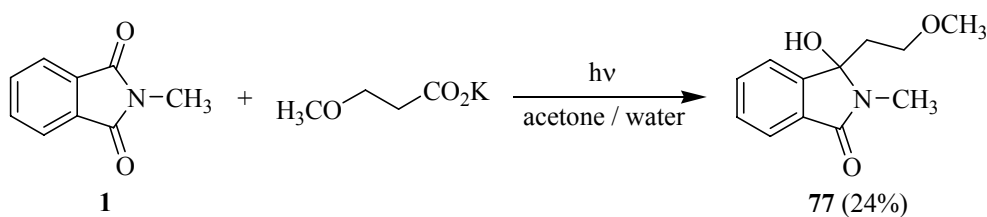
substituted analogues where the TMS-cation functions as activating and leaving group.^{28c}



Scheme 3.8 Competitive scenario for heteroatom substituted carboxylates.

3.2.3 Reaction of NMP with oxygen-containing addition partner

As an example of a reaction of NMP with an oxygen-containing addition partner, in experiment 31 a methoxy-ethylene group was introduced (**Scheme 3.9**), but even after prolonged irradiation of 16 hours a conversion of just 33% was achieved. Based on the conversion the yield was found to be 24%.



Scheme 3.9 Experiment 39.

In the ¹H-NMR of **77** (**Figure 3.2**), the CH₂ bridge is found between 2.20 and 2.48 ppm. The two hydrogens are split by each other and by the neighbouring CH₂O group. The singlet representing the *N*-methyl group was found at 2.85 ppm. The triplet at 3.0 ppm represents the CH₂ group bound to the methoxy group. The methoxy group was observed as a singlet at 3.16 ppm, the OH group at 4.14 ppm as a sharp singlet. The four aromatic protons were found between 7.4 and 7.6 ppm.

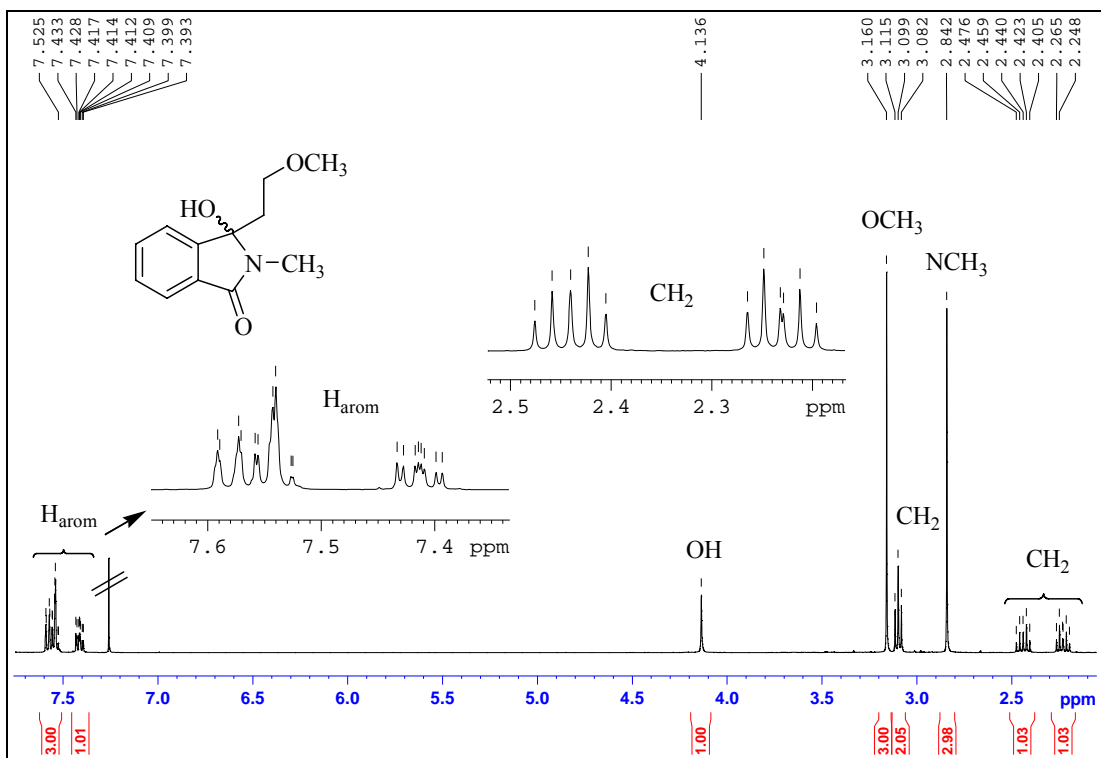
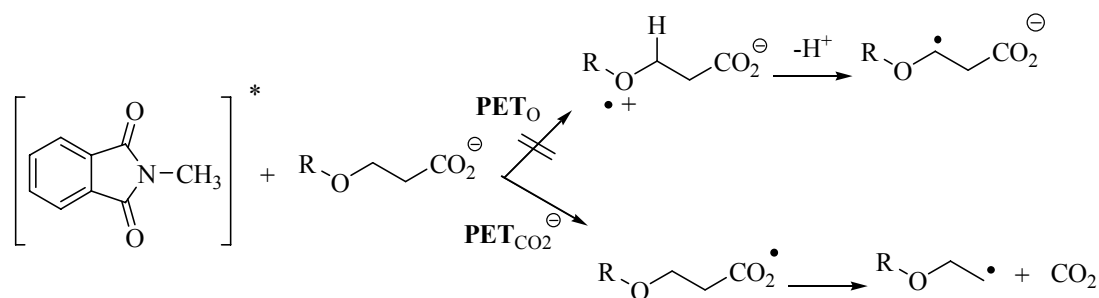


Figure 3.2 ¹H-NMR spectrum of **77** in CDCl₃.

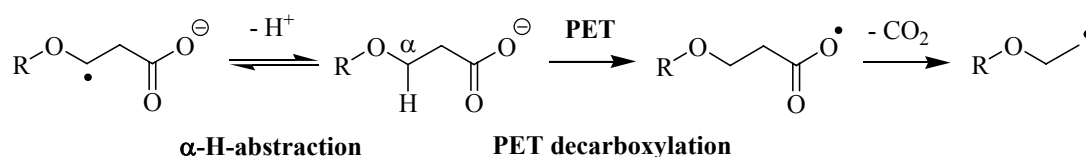
Due to the low conversion of starting material (**1**) of only 33% after 16 hours irradiation, it was assumed, that in the particular case of **77**, an alternative simple decarboxylation pathway (CO₂H/H exchange) dominated in which the NMP acted as a catalyst.^{34b} Alternatively, a non-productive electron transfer from the ether-group may have caused this drop in conversion.^{38a}

The proposed mechanism for β-oxoalkyl-substituted carboxylates is depicted in **Scheme 3.10**. Product formation can only be explained by electron transfer from the carboxylic acid function to the excited phthalimide chromophore. Subsequent decarboxylation and C-C formation yields the observed addition products. This crucial key-step is in agreement with the lower oxidation potential of carboxylates compared to the ether oxygen.



Scheme 3.10 Mechanism of addition of β -substituted heteroatom in the oxygen case.

Although reactivity prevailed for the β -oxoalkyl-substituted carboxylate, the efficiency of this reaction was very low, based on both the yield and required irradiation time. Possibly, hydrogen abstraction from the α -position of the oxygen atom may compete with electron transfer mediated decarboxylation (**Scheme 3.11**). Similar hydrogen-abstractions are known for irradiations involving simple dialkylethers.^{24,26}



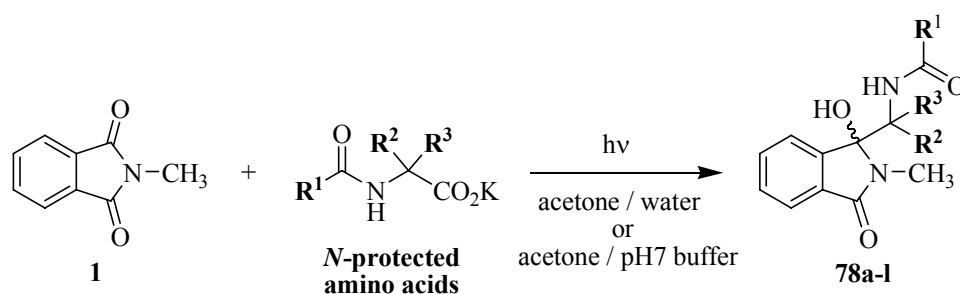
Scheme 3.11 Alternative mechanisms for the β -oxoalkyl-substituted carboxylates.

It should be noted here that despite their low yields the β -oxoalkyl-based photoaddition products are only available *via* the photodecarboxylative addition protocol. Neither dialkylethers nor trimethylsilylalkyl ethers yield similar products.

3.2.4 Photodecarboxylative addition of *N*-protected amino acids to NMP

NMP (**1**) was reacted with twelve *N*-protected amino acids as shown in **Scheme 3.12**. These reactions were performed over a period of 1-8.5 hr and gave yields ranging from 6-92%. Compounds **78c, d, f, g, i, and j** gave diastereoisomeric mixtures with *d.e.*'s ranging from 8-56%, which are shown in **Table 3.3**.

A selection of these reactions were also performed in acetone/pH 7 buffer to investigate the effect, if any, this had on the reactions with particular interest in the *d.e.*'s obtained. This solvent mixture was known to clean up reactions as demonstrated in our research group.¹³⁶ The results are also shown in **Table 3.3** below.



Scheme 3.12 Experiments 40-56.

Table 3.3 Photoadditions of *N*-protected amino acids to **1**.

compound	R ¹	R ²	R ³	time [hr]	yield [%]	d.e. [%]
78a	CH ₃	H	H	3.5	19	
78b	CH ₃	CH ₃	CH ₃	4.5	83	
78c	CH ₃	<i>i</i> -Pr	H	3.5	52	52
				5 ^a	32 ^a	24 ^a
78d	CH ₃	<i>i</i> -Bu	H	3	26	24
				4 ^a	36 ^a	22 ^a
78e	CH ₃	<i>s</i> -Bu	H	3	78	See below
78f	CH ₃	<i>t</i> -Bu	H	8.5	6	48
78g	CH ₃	Ph	H	2	92	8
78h	<i>t</i> -BuCO	H	H	1	74	
78i	<i>t</i> -BuCO	CH ₃	H	2	65	34
				4 ^a	81 ^a	10 ^a
78j	<i>t</i> -BuCO	PhCH ₂	H	3	34	36
				4 ^a	36 ^a	30 ^a
78k	CH ₃	C ₅ H ₁₀		3	80	
78l	(C ₁₃ H ₁₀)CH ₂ O	H	H	1.5	19	
				3 ^a	20 ^a	

^a reaction performed in acetone / pH7 buffer

In experiment 46, a total of four stereoisomers of the product **78e** were obtained as there are three chiral centres present. One chiral centre is fixed due to the addition partner used, while the other two are determined by the C-C bond formation, which results in four different isomers and their respective enantiomers being formed in ratios of 11:12:25:52 (see experimental section). Three products **78a,b** and **h** showed no visible formation of isomers in the resulting $^1\text{H-NMRs}$. For the remaining products, the d.e. ranged from 6-50%.

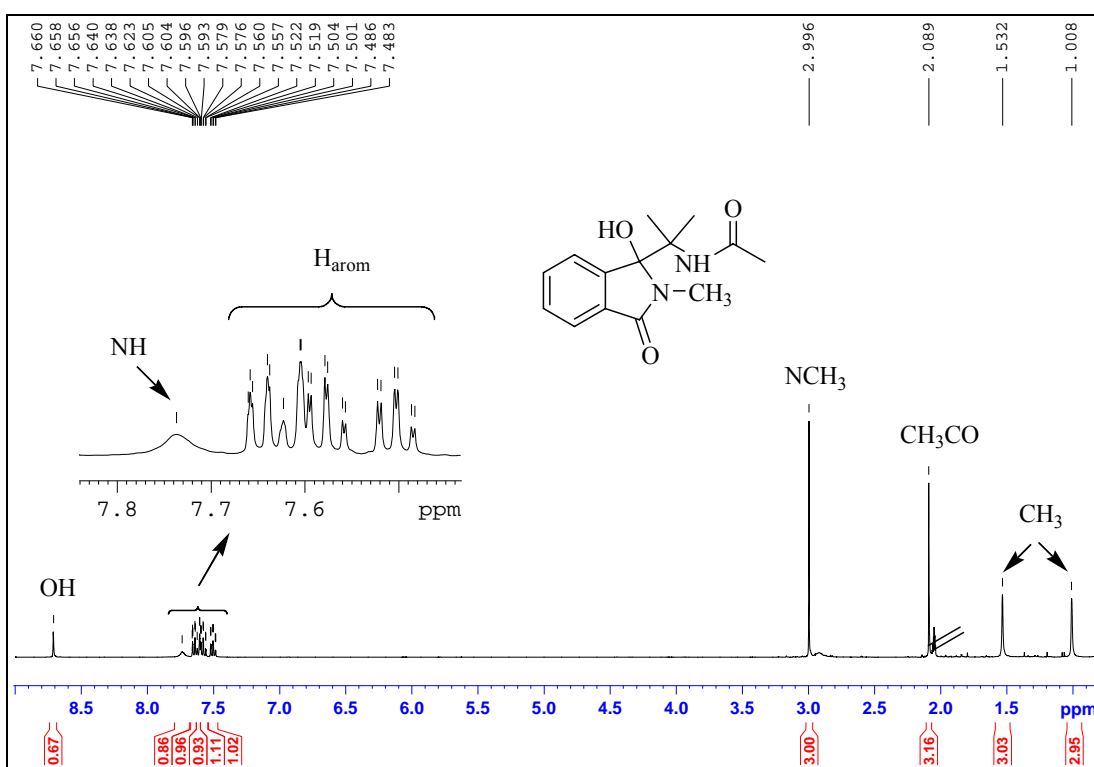


Figure 3.3 $^1\text{H-NMR}$ spectrum of **78b** in $\text{C}_2\text{D}_6\text{CO}$.

A representative $^1\text{H-NMR}$ spectrum for *N*-acetylated photoaddition products is shown using photoaddition product **78b** as an example in **Figure 3.3**. The methyl group at the *N*-terminus is found as a singlet at 3.00 ppm. The two singlets at 1.00 and 1.53 ppm represent the two methyl groups at the bridge between the former phthalimide and the addition partner. The acetyl group is found as a singlet at 2.09 ppm. The OH group was found as a broad peak at ~8.7 ppm, while the NH group was found at 7.7 ppm. In the aromatic region the peaks representing the four aromatic protons can be found between 7.5-7.7 ppm.

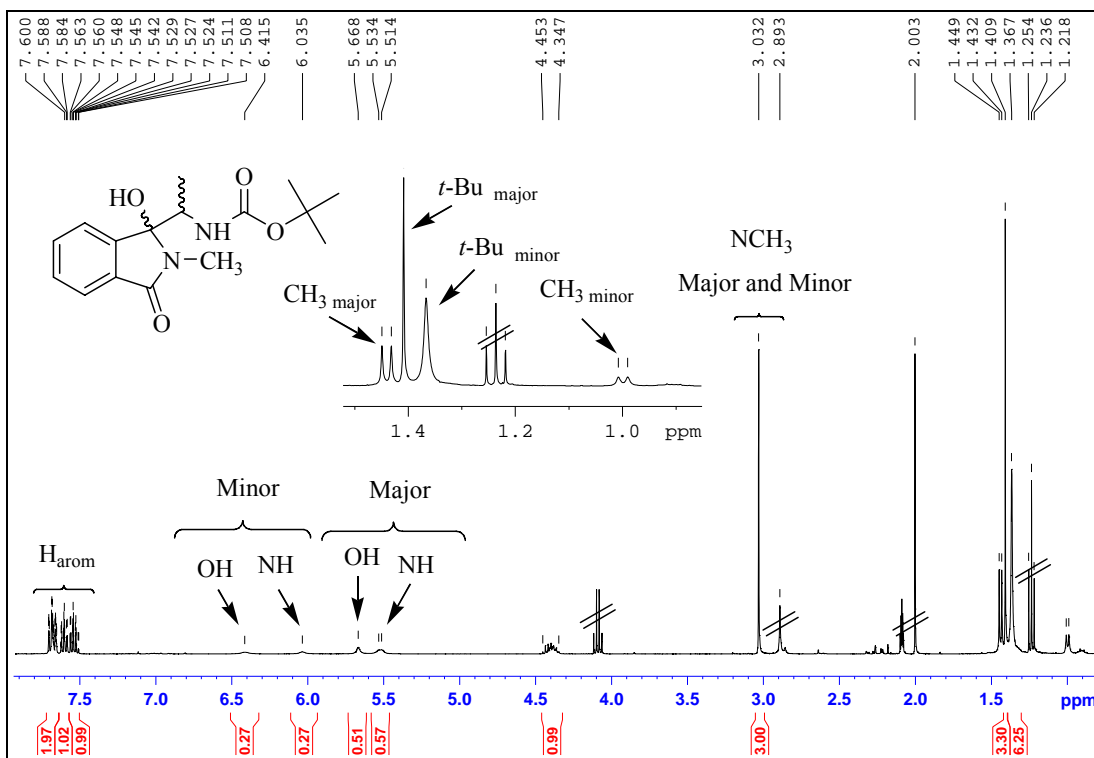


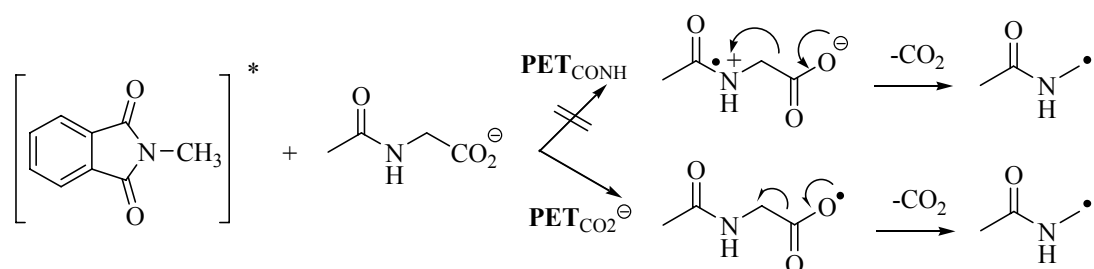
Figure 3.4 ¹H-NMR spectrum of **78i** in C₂D₆CO.

A representative ¹H-NMR spectra for *N*-BOC-protected photoaddition product **78i** is shown in **Figure 3.4**. It could not be determined which diastereoisomer (*like* or *unlike*) was the major/minor component. The *N*-terminus methyl groups were found as singlets at 3.03 ppm. Two doublets representing the CH₃(CH) groups were found at 1.00 and 1.44 ppm respectively. Two singlets representing the *t*-Bu groups were found at 1.37 and 1.41 ppm respectively. The CH groups for both appeared as a multiplet at 4.4 ppm. The OH groups were found as singlet peaks at ~5.7 and 6.4 ppm. The NH groups were also found in that region at ~5.5 and 6.0 ppm. In the aromatic region the peaks representing the eight aromatic protons can be found between 7.51 and 7.71 ppm.

In contrast to irradiations involving *N,N*-dialkylated amino acids, which solely give photoreduction or solvent-trapping, *N*-acylation of amino acids restored photoreactivity and the corresponding addition products were obtained in moderate to high yields after short irradiation times. This suggests that the crucial electron transfer step occurs primarily from the carboxylate function as supported by the oxidation potentials ($E_{\text{Ox. CONR}} \geq E_{\text{Ox. CO}_2^-}$). The difference of the oxidation

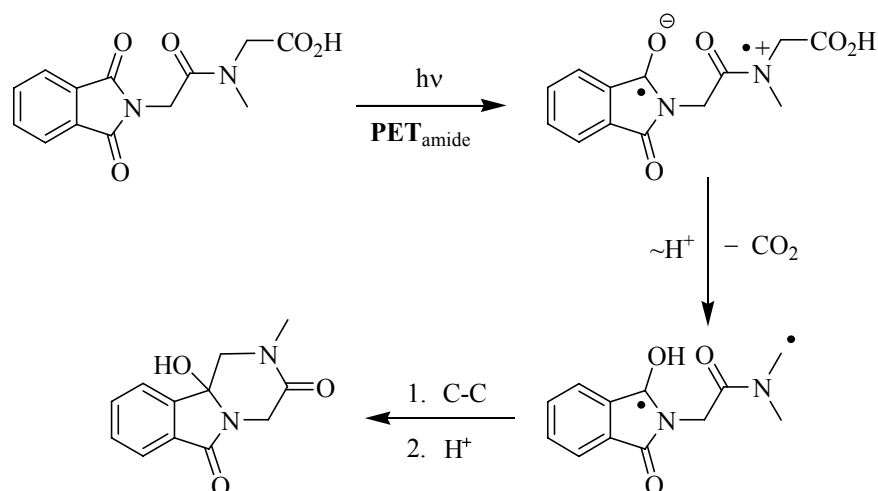
potentials of the competing donors is, however, rather small (*N*-methylacetamide: $E_{\text{Ox.}} = 1.81 \text{ V}$ in MeCN¹³⁷ and acetate: $E_{\text{Ox.}} = 1.54 \text{ V}$ in MeCN vs. SCE¹²⁷).

As for simple alkyl and oxygen-containing carboxylates, photoinduced electron transfer from the carboxylate function to the excited phthalimide yields an unstable carboxy radical, which rapidly undergoes decarboxylation to the corresponding carbon centred radical (**Scheme 3.13**). Subsequent C-C bond formation yields the isolated photoproducts.

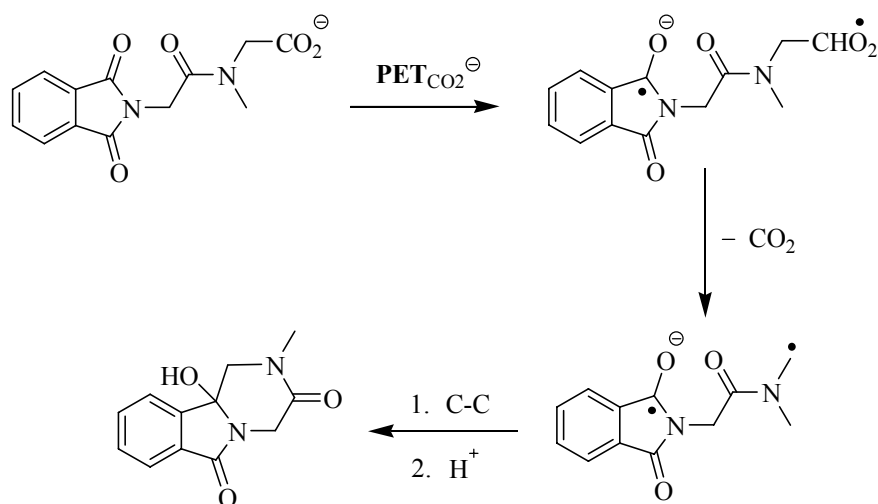


Scheme 3.13 Mechanism of amide-containing carboxylates.

Analogue photocyclisations of phthaloyl dipeptides have been described by the groups of Yoon/Mariano¹³⁸ and Griesbeck/Oelgemöller.¹³⁹ Both groups favour different PET scenarios. Whereas Yoon and Mariano postulated electron transfer from the amide linker (**Scheme 3.14**), Griesbeck and Oelgemöller suggested electron transfer from the carboxylate function instead (**Scheme 3.15**). The latter scenario is supported by successful macrocyclisation of dipeptides with terminal ω -amino acid. In those cases, the remote position of the amide group would not allow rapid elimination of carbon dioxide.



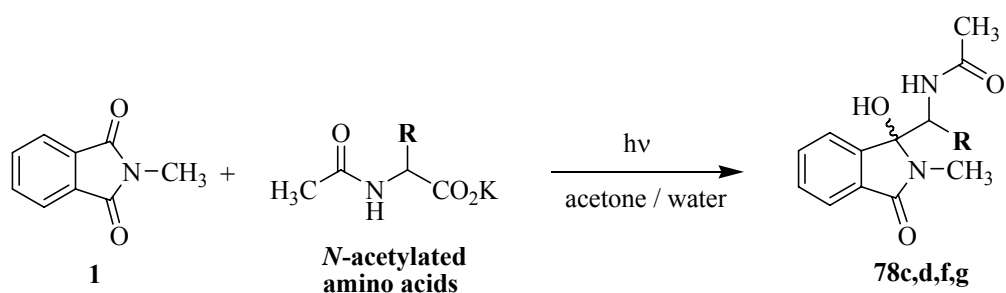
Scheme 3.14 Proposed mechanism for the photocyclisation of *N*-phthalimidoglycine sarcosine by Yoon and Mariano



Scheme 3.15 Proposed mechanism for the photocyclisation of *N*-phthalimidoglycine sarcosine by Griesbeck and Oelgemöller

By comparing the crude $^1\text{H-NMR}$ spectra, the products formed in experiments 43, 45, 51, 53 and 56, performed in acetone/pH 7 buffer, were shown in general to have no significant improvement on the previous reactions in terms of purity. In the case of **78i**, the yield was improved considerably, from 65% to 81%, however the *d.e.* was found to decrease from 34% to 10%. In fact the resulting products all had lower *d.e.*'s than the previous products obtained.

Using Ligand Repulsive Energies, E_R , (in kcal mol⁻¹)¹⁴⁰ it was attempted to explain the diastereoselectivity obtained in products **78c**, **d**, **f** and **g**. In contrast to other steric parameters, these E_R values are free of any resonance effects and have been demonstrated to provide reliable steric parameters for ligands in organometallic systems. They have been used in this case as it was found that they provide the most consistent and generally useful measures of relative steric sizes.¹⁴⁰ Results are shown in **Table 3.4** below.



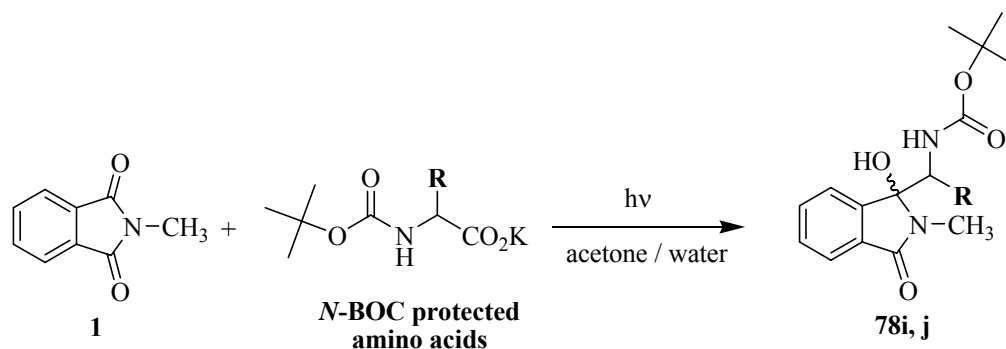
Scheme 3.16 Reaction of **1** with *N*-acetylated amino acids.

Table 3.4 Comparison of E_R values and *d.e.*'s obtained for **78c**, **d**, **f** and **g**.

compound	R	E_R [kcal/mol]	<i>d.e.</i> [%]
78g	Ph	33	8
78d	<i>i</i> -Bu	44	24
78c	<i>i</i> -Pr	57	52
78f	<i>t</i> -Bu	59	48

It is clear there is indeed correlation between increased steric bulk and a higher *d.e.* value, despite the minor anomaly between the *i*-Pr and *t*-Bu groups. As there is only a slight difference between their respective E_R values, it is not surprising that the *d.e.* values would also be similar. These results imply that anything larger than an *i*-Pr group, such as a *t*-butyl group, has no further effect on the *d.e.* values.

The same was attempted for both *N*-BOC protected amino acids, **78i** and **j** (Scheme 3.17), and the results are shown in Table 3.5.



Scheme 3.17 Reaction of **1** with *N*-BOC protected amino acids.

Table 3.5 Comparison of E_R values and *d.e.*'s obtained for **78i** and **j**.

compound	R	E_R [kcal/mol]	<i>d.e.</i> [%]
78i	CH ₃	17	34
78j	PhCH ₂	42	36

Although the difference in the *d.e.*'s obtained was only marginal, whereas the difference in the E_R values was quite significant, it did however follow the trend *i.e.* the lower the E_R value, the lower the *d.e.* value. It can therefore be concluded that the Ligand Repulsive Energies can in fact be used as a guide in determining the expected *d.e.*'s of the desired products.

3.3 Summary

In this chapter, reactions of **1** and substituted phthalimides with heteroatom with heteroatom-containing addition partners were investigated. Following the successful reactions of substituted phthalimides *N*-methyl trimellitic acid imide methyl ester and *N*-phthalimido-glycine methyl ester with dimethylsulfide, **1** was successfully reacted with 3-methoxypropanoic acid.

A variety of *N*-acetylated amino acids were successfully synthesised and subsequently reacted with **1**, with low to moderate *d.e*'s obtained. Performing the selected reactions of **1** with *N*-acetylated amino acids in solvent system acetone:pH 7 buffer seemed to slightly lower the *d.e* values obtained. Ligand Repulsive Energies were also used to discuss the *d.e*'s obtained, and a correlation was found between the bulk of the substituent groups on the *N*-acetylated amino acids and size of the *d.e* values obtained.

These reactions will also be used to make a comparison between the Rayonet reactor and the microreactor as a selection of these will be performed in the microreactor and discussed in Chapter 6.

Chapter 4

4 Synthesis of aristolactams using phthalimide derivatives as precursors

4.1 Introduction

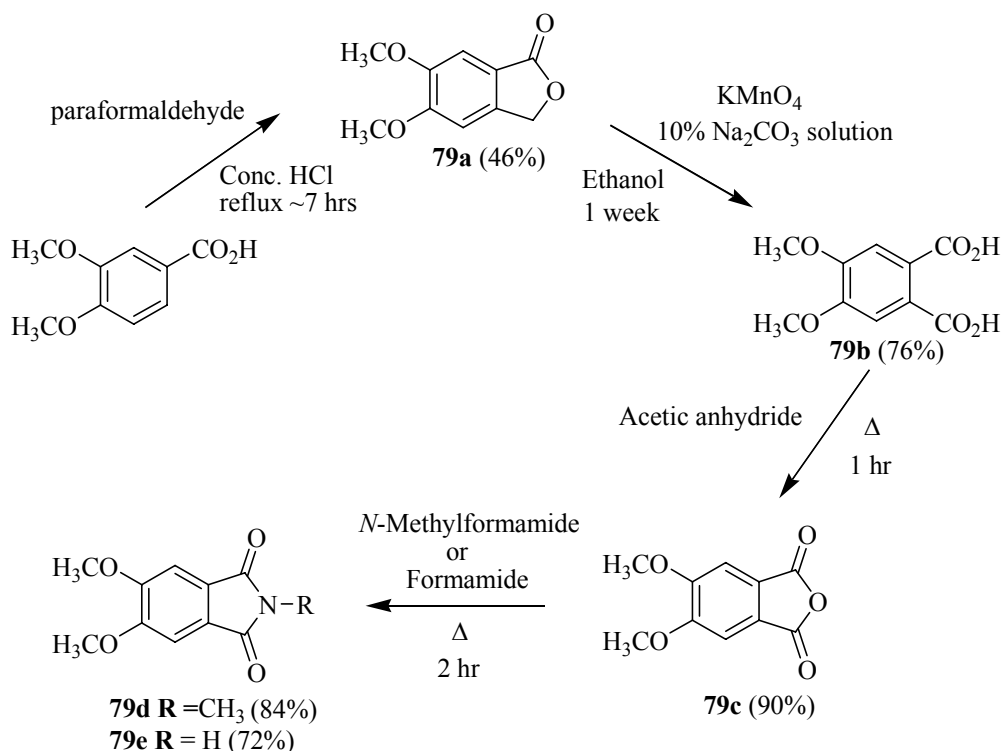
Aristolactams are a family of naturally occurring compounds possessing a phenanthrene chromophore, and are known to possess a wide variety of biological activity. For example, aristolactams and related compounds act as antibacterial agents, immunostimulants and display cytotoxic activity against various cancer cell lines and so may be useful for further development as pharmaceuticals, as outlined in Chapter 1.

Several compounds have been synthesised thermally by Couture *et al.*, however in this chapter, an attempt to synthesise aristolactams by photochemical means is discussed. One of the benefits of this method, if successful, is the availability of a vast array of cheap starting materials possessing a wide range of substituents, ideal for constructing structurally diverse derivatives. A three-step procedure will be used, which involves an initial photoaddition reaction, dehydration of the resulting photoproduct and eventual ring closure by irradiation in benzene.

4.2 Synthesis of starting materials

4.2.1 Synthesis of dimethoxy-*N*-methylphthalimide and its precursors

The synthesis of dimethoxy-NMP **79d** and dimethoxyphthalimide **79e** were realised in a four-step procedure (**Scheme 4.1**).



Scheme 4.1 Experiments 57-61.

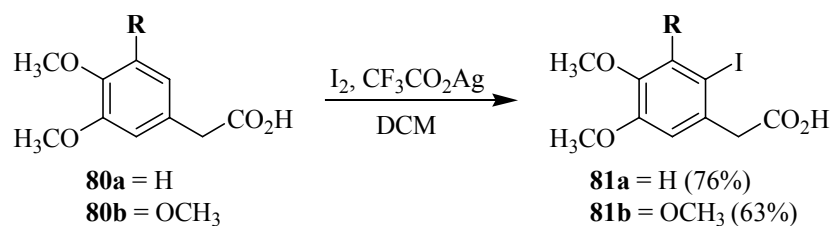
In the first step, **79a** is synthesised by heating paraformaldehyde and veratric acid under reflux in concentrated HCl for 6 hr. When the pH of the solution was adjusted to pH 7 the product formed as a precipitate (46% yield). **79a** was then stirred for a week at r.t. with 1.1 equivalents of KMnO₄ and 2.2 equivalents of a 10% Na₂CO₃ solution. Following work-up, the precursor **79b** was obtained in a yield of 76%. In the second step **79b** was heated under reflux in acetic anhydride for 1 hr, after which time the solvent was removed by distillation and the anhydride **79c** was obtained in a yield of 90%. This was then used in the final step of the synthesis of **79d**, which involved heating **79c** under reflux in *N*-methylformamide for 2 hr, resulting in crystals being formed upon cooling, which were filtered to give **79d** in 84% yield.

The overall yield, throughout the final three steps, was calculated to be 40%. The characteristic *N*-methyl group was found at 3.14 ppm in the ¹H NMR spectrum in CDCl₃.

For the synthesis of **79e**, the first three steps of the procedure were repeated, while the last step consisted of heating **79c** under reflux in formamide. The final step produced **79e** in a pure yield of 72%.

4.2.2 Iodination of di- and trimethoxyphenylacetic acids

The synthesis of iodo-dimethoxyphenylacetic acid **81a** and iodo-trimethoxyphenylacetic acid **81b** were achieved with a straightforward one step procedure (**Scheme 4.2**).



Scheme 4.2 Reaction scheme for synthesis of **81a** and **81b**.

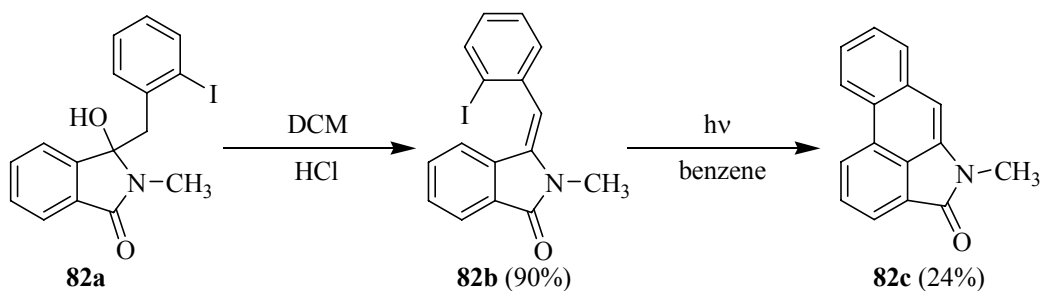
Following a method by Janssen and Wilson,¹⁴¹ the iodination of both **80a** and **80b** was performed by stirring the desired acid with silver trifluoroacetate (1 equiv.) and iodine (1 equiv.) in chloroform overnight. Following recrystallisation the pure yield for **81a** was found to be 76% and in the case of **81b** the yield was 63%.

4.3 Formation of aristolactams

4.3.1 Formation of aristolactam skeleton

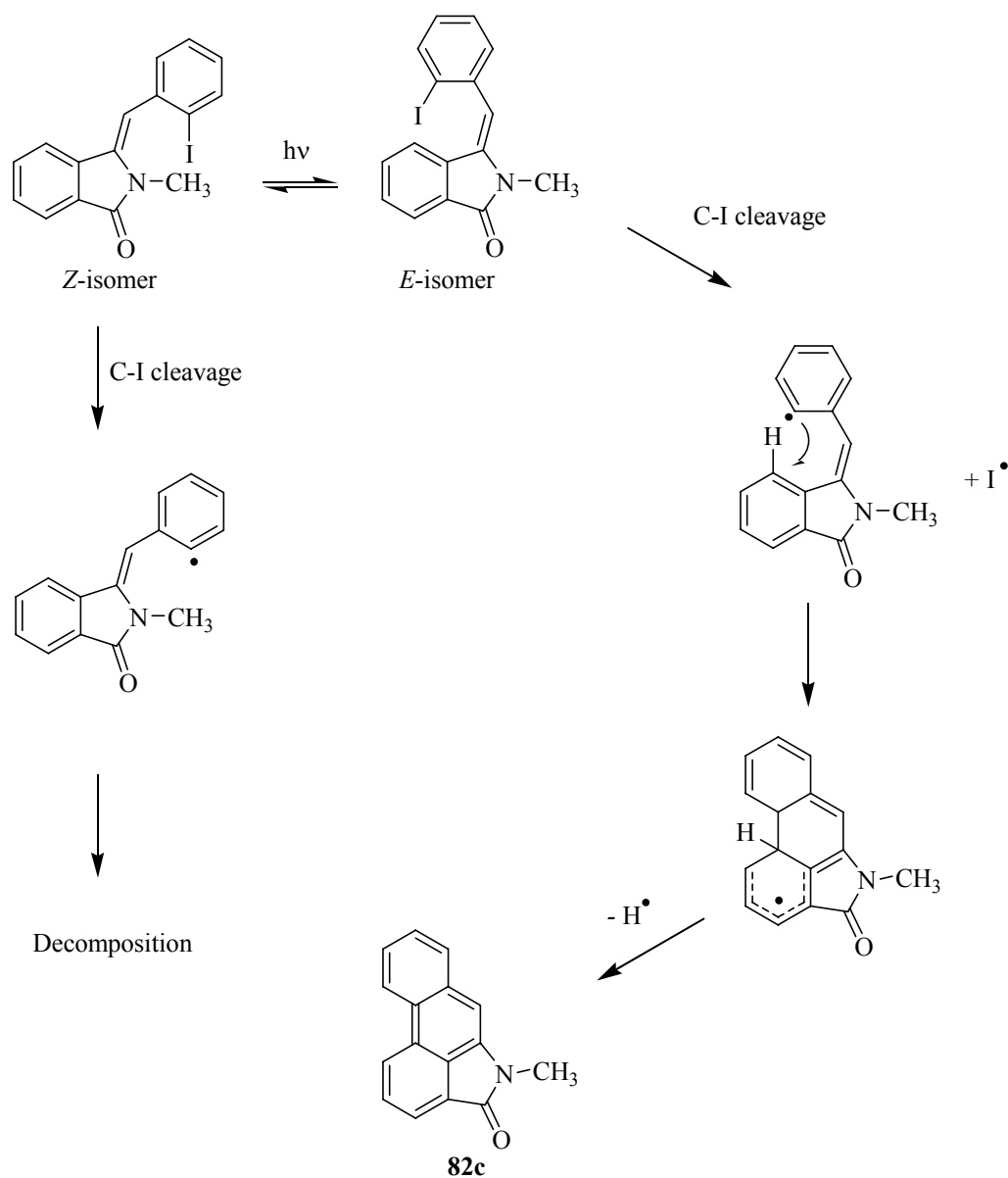
As an alternative to thermal methods, the aristolactam skeleton **82c** was successfully formed in a three-step procedure using PDC addition (as seen in Chapter 2) of 2-

iodophenylacetic acid to **1** as the first step. This resulted in **82a** being obtained in a yield of 51%.



Scheme 4.3 Experiments 64-66.

The second step involved **82a** undergoing a dehydration reaction to form **82b** which was obtained in a yield of 90% as the single *Z*-isomer. The final step was an oxidative dehydrohalogenation using benzene as the solvent. The iodo group was cleaved during irradiation which effected the formation of the aristolactam skeleton **82c** which was obtained in a yield of 24% after performing column chromatography. Interestingly, the crude $^1\text{H-NMR}$ showed the presence of both isomers. As the intermediate **82b**, formed by hydrolysis resulted in solely the *E*-isomer being formed, which is the “reactive geometry” needed, *E-Z* isomerisation (**Scheme 4.4**) must have occurred during the final step. This could explain the low yield of the desired product.



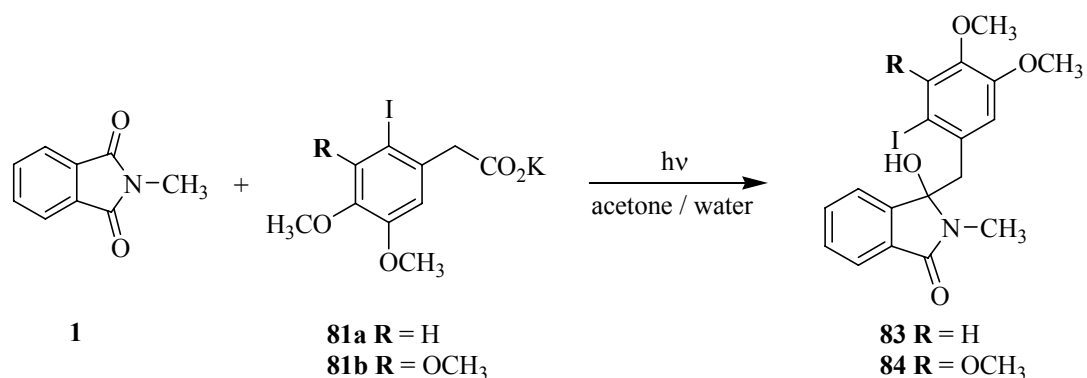
Scheme 4.4 *E-Z* isomerisation of **82b** resulting in the formation of **82c**.

The isomerisation competes with the cyclisation reaction, generating a radical which results in the eventual ring closure forming the aristolactam skeleton.

Having successfully synthesised the skeleton, the next step was to attempt to synthesise several substituted aristolactams.

4.3.2 Formation of substituted aristolactams with iodo-precursors

In experiments 67 and 70, **1** was irradiated in the presence of both **81a** and **81b** to form **83** and **84** in yields of 8% and 33% respectively. In both cases, even after prolonged irradiation, both **1** and the acid partner were still present in the crude ^1H -NMR spectrum.



Scheme 4.5 Experiments 67-72.

Following purification, the products were successfully isolated. To ensure that the irradiation period was not the problem, both reactions were repeated twice with longer irradiation periods and, as seen in **Table 4.1** below, extending the irradiation time did little to improve the overall yields obtained for either **83** or **84**.

Table 4.1 Varying irradiation times for the synthesis of **83** and **84**.

compound	R	time [hr]	yield [%]
83	H	8	8
83	H	16.5	9
83	H	31	11
84	OCH_3	13	33
84	OCH_3	16.5	35
84	OCH_3	31	35

A potential reason for the low yields could be that the bulky iodo group is simply blocking the C-C bond formation. Taking the iodo acid **81b** as an example, shown in **Figure 4.1** as a “ball and stick” model for comparison, this idea is investigated.

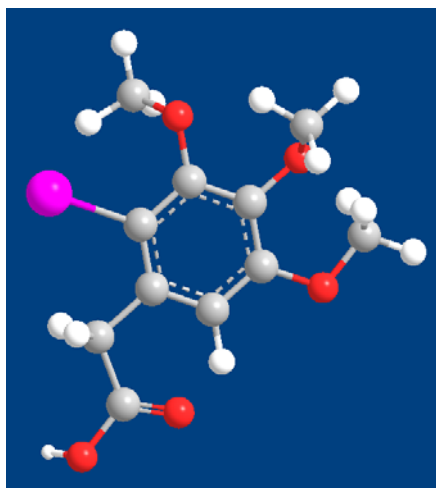


Figure 4.1 “Ball and stick” model of **81b** created using Chem3D Ultra 8.0 software.

As seen from the “space filling” model of **81b** shown in **Figure 4.2**, the iodo substituent (shown in pink) is a very large group which may, due to its sheer size, simply not allow the two newly formed radicals to come into contact because of steric hindrance. For both **81a** and **81b**, the iodo group is located beside the carboxylic acid substituent which undergoes the required PDC process, and hence the radical is subsequently in close proximity to the bulky iodo function.

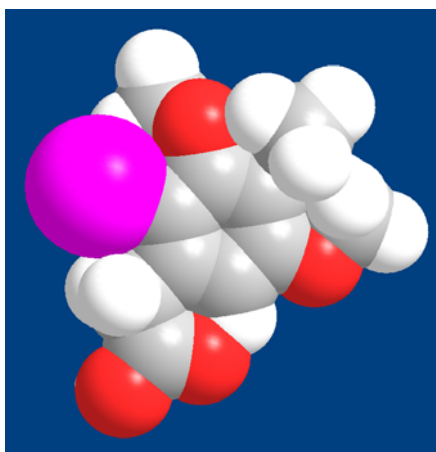
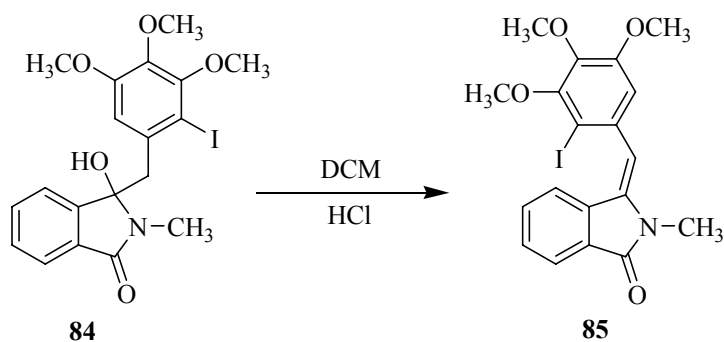


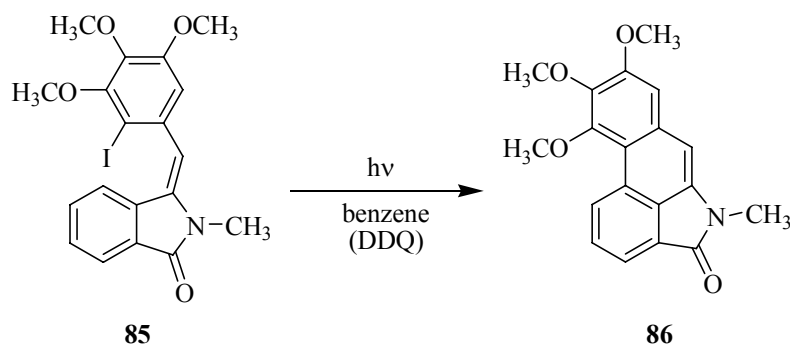
Figure 4.2 “Space filling” model of **81b** created using Chem3D Ultra 8.0 software.

The second dehydration step was performed with **84** as shown in (Scheme 4.6) below.



Scheme 4.6 Experiment 73.

In experiment 73, the starting material **84** was converted by dehydration to **85**. Following work-up, both isomers were formed as seen in the $^1\text{H-NMR}$ and the ratio calculated from the integration of the olefinic peaks to be 17:83, with the *E*-isomer found to be the major isomer. This product was then used in the final step to make the desired aristolactam as seen below in (Scheme 4.7).



Scheme 4.7 Experiments 74 and 75.

As an investigative monitoring study, **85** was dissolved in benzene- d_6 and placed in an NMR tube which was then set up in the Rayonet reactor and irradiated. For the first hour $^1\text{H-NMR}$ spectra were obtained every 15 min by stopping the reaction, obtaining the $^1\text{H-NMR}$, returning the NMR tube to the Rayonet reactor and then commencing irradiation. From then on, $^1\text{H-NMR}$'s were continued to be obtained hourly up until 19 hr, when the reaction was undisturbed until 36 hr and a final $^1\text{H-NMR}$ obtained. In the first few hours, *E-Z* isomerisation was clearly occurring as indicated by $^1\text{H-NMR}$ (**Figure 4.3** and **Figure 4.4**).

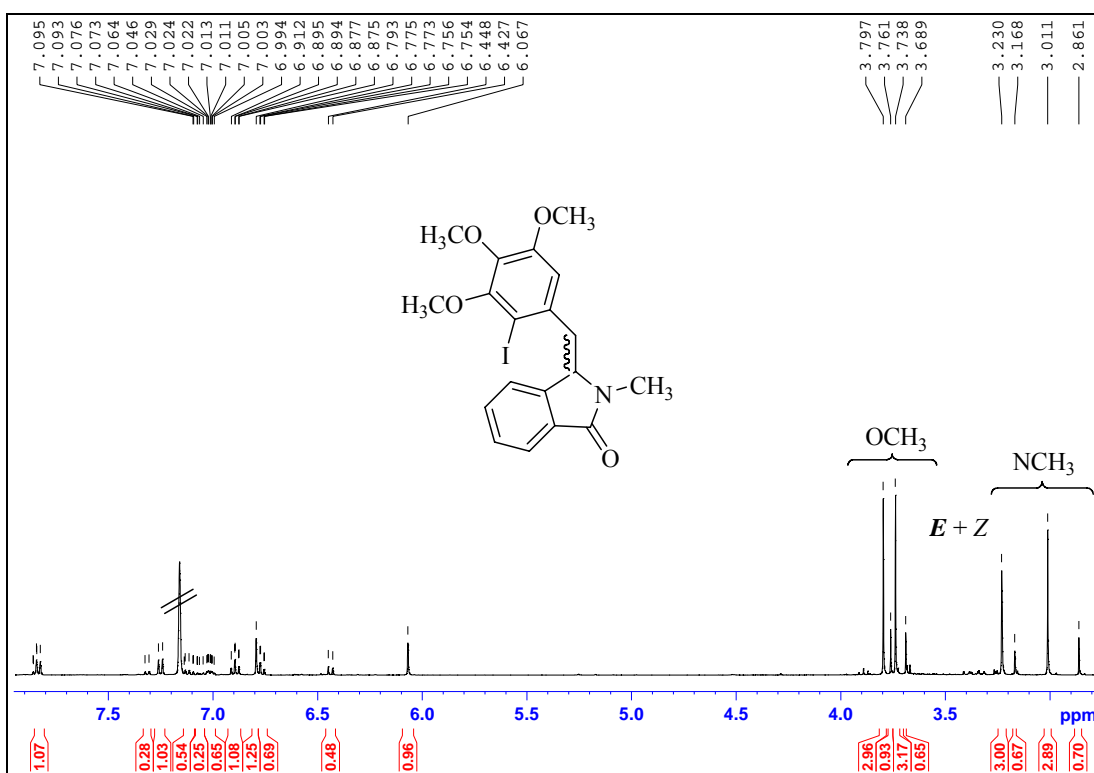


Figure 4.3 Initial $^1\text{H-NMR}$ of experiment 74 obtained at 0 hr.

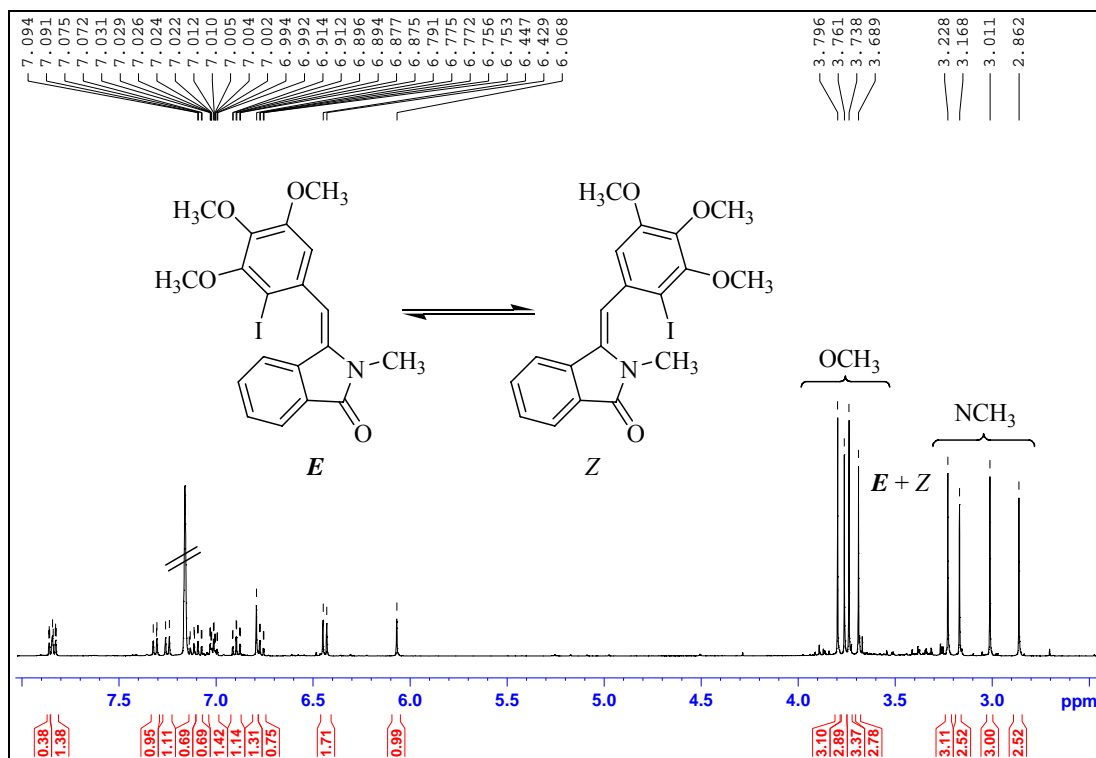


Figure 4.4 ¹H-NMR of experiment 74 obtained after 15 min.

The first signs of the aristolactam being formed occurred after 3 hr (**Figure 4.5**) and in the final ¹H-NMR (**Figure 4.6**) the distinctive aromatic protons of the product can clearly be seen although it is not entirely pure.

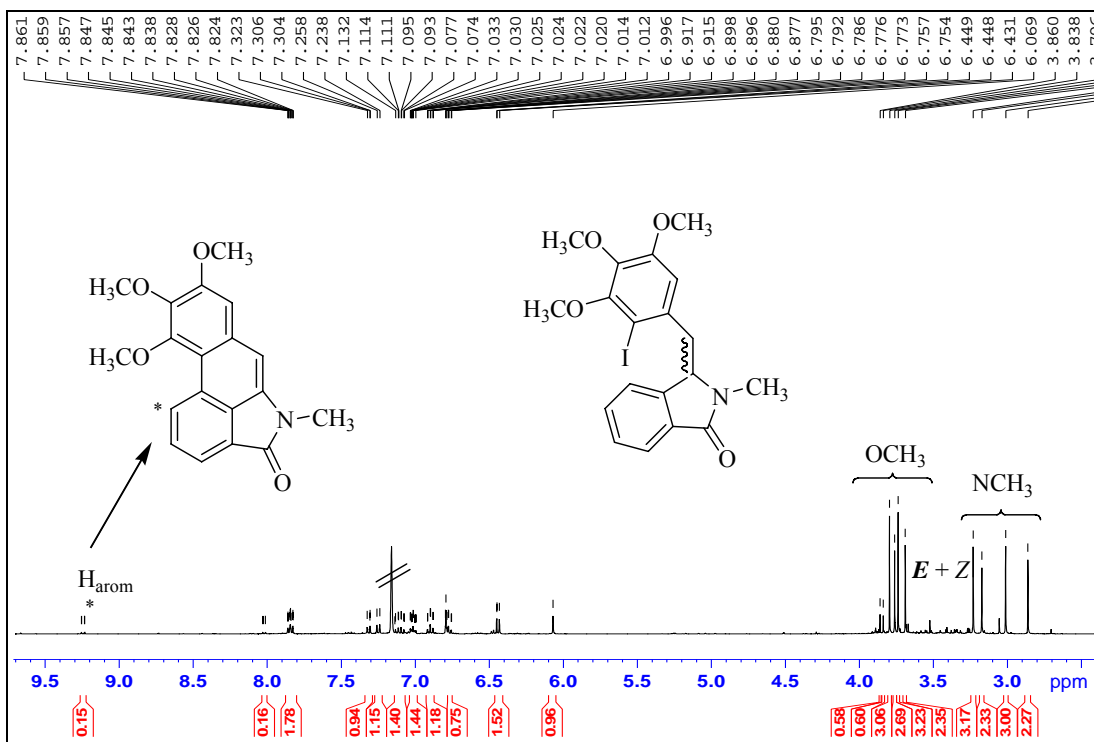


Figure 4.5 $^1\text{H-NMR}$ of experiment 74 obtained after 3 hr.

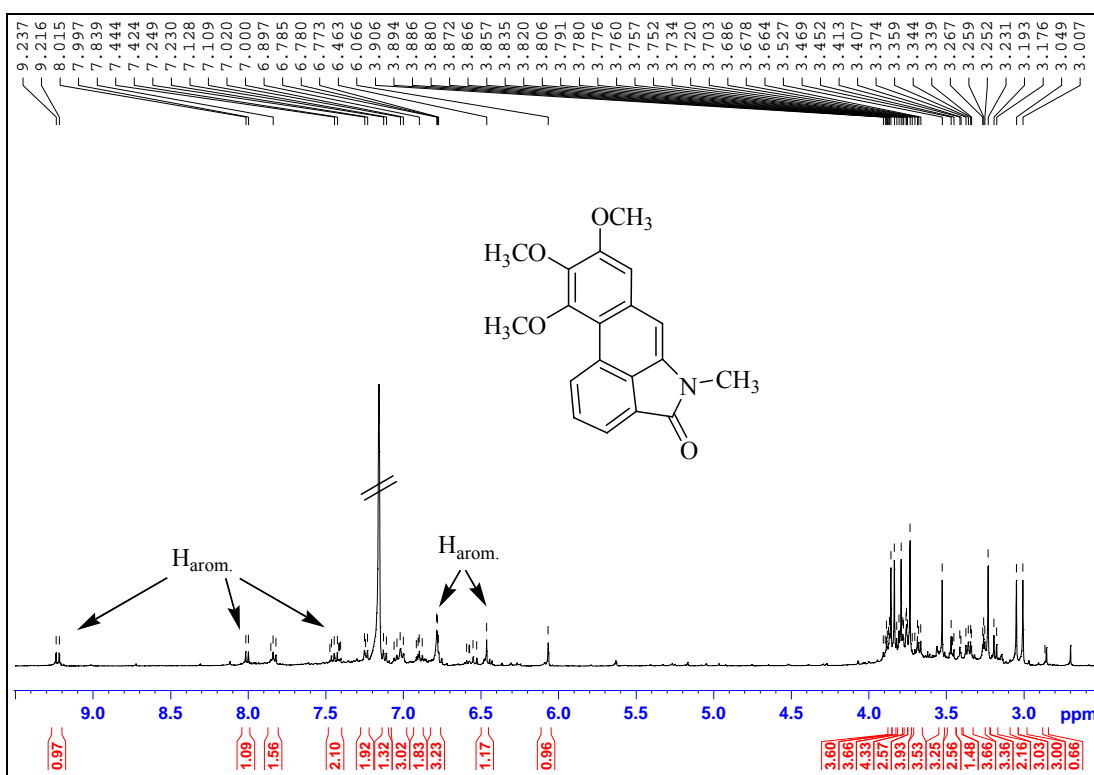


Figure 4.6 Final $^1\text{H-NMR}$ of experiment 74 obtained after 36 hr.

In an attempt to improve the purity of the aristolactam, in a second monitoring study, **85** was again placed in an NMR tube in solvent benzene- d_6 , and to encourage ring closure the oxidant DDQ was added periodically throughout the reaction. Again a $^1\text{H-NMR}$ was obtained after the first and second hour, and then for every 2nd hour until 22 hr, the final $^1\text{H-NMR}$ was obtained after 25 hr.

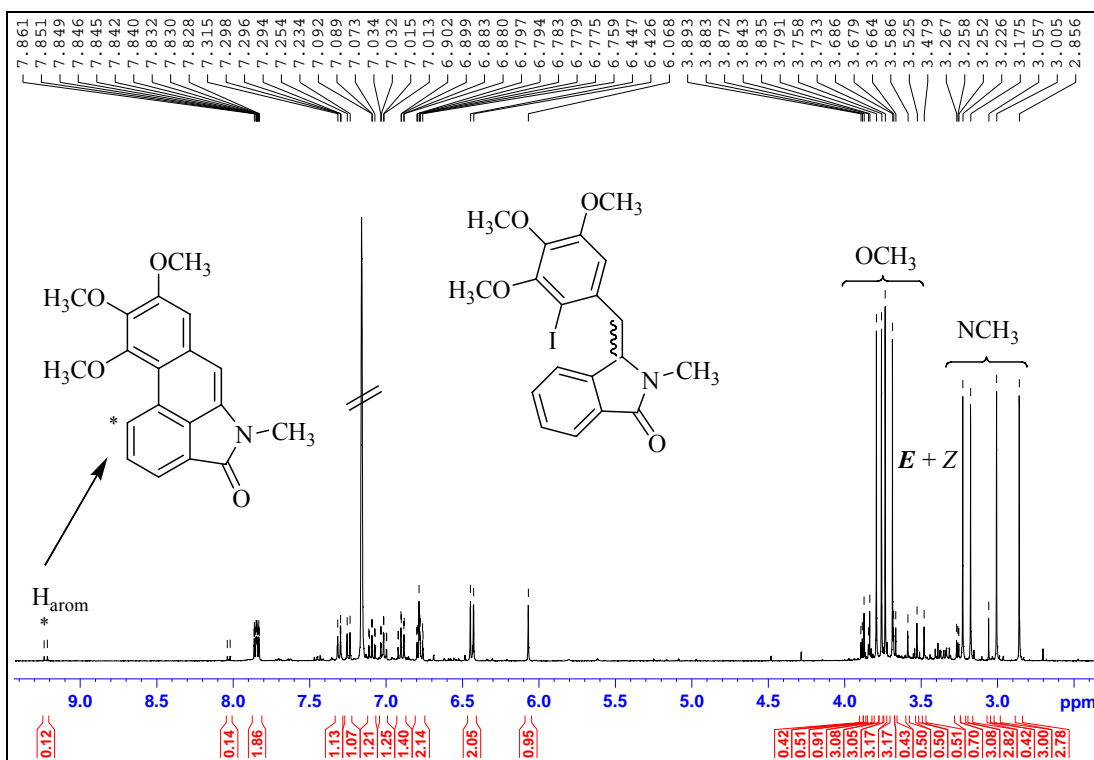


Figure 4.7 $^1\text{H-NMR}$ of experiment 75 after 1 hr with desired product **86** visible.

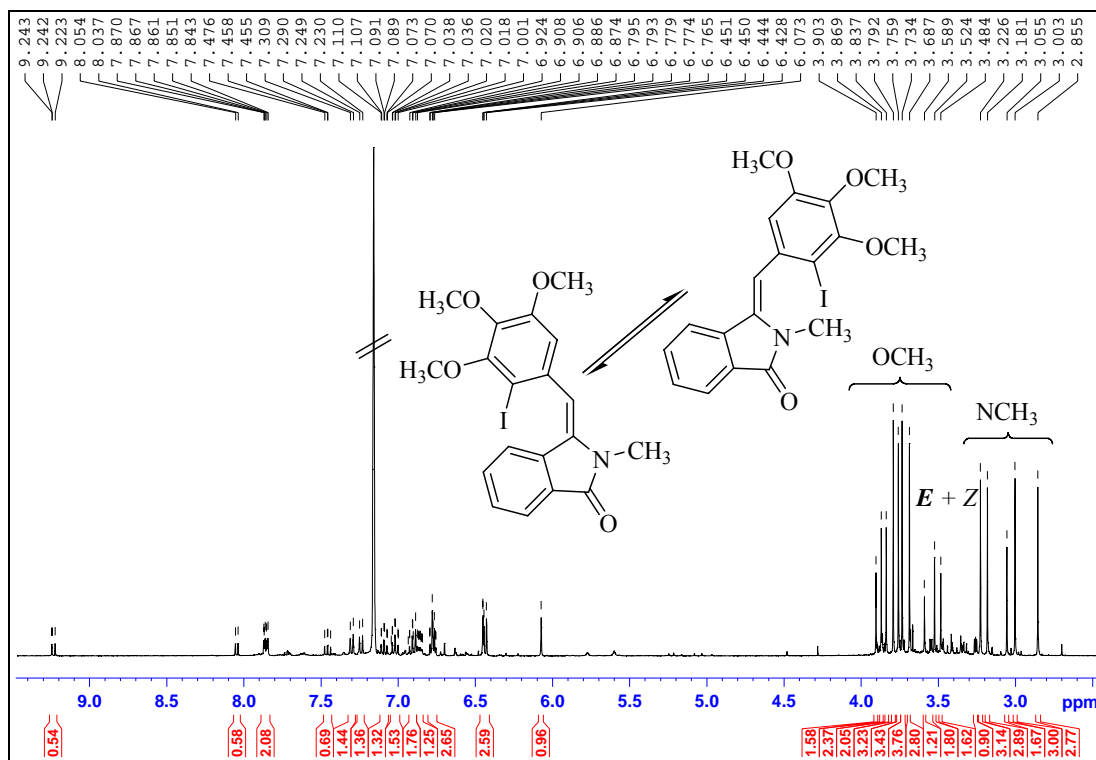


Figure 4.8 $^1\text{H-NMR}$ of experiment 75 after 4 hr.

E-Z isomerisation was also seen to occur during this reaction, as illustrated in **Figure 4.7** and **Figure 4.8**, however this reaction progressed more efficiently with the desired product being visible after 1 hr (**Figure 4.7**). After 25 hr the aristolactam was found to be quite pure albeit with a small amount of starting material still visible (**Figure 4.9**).

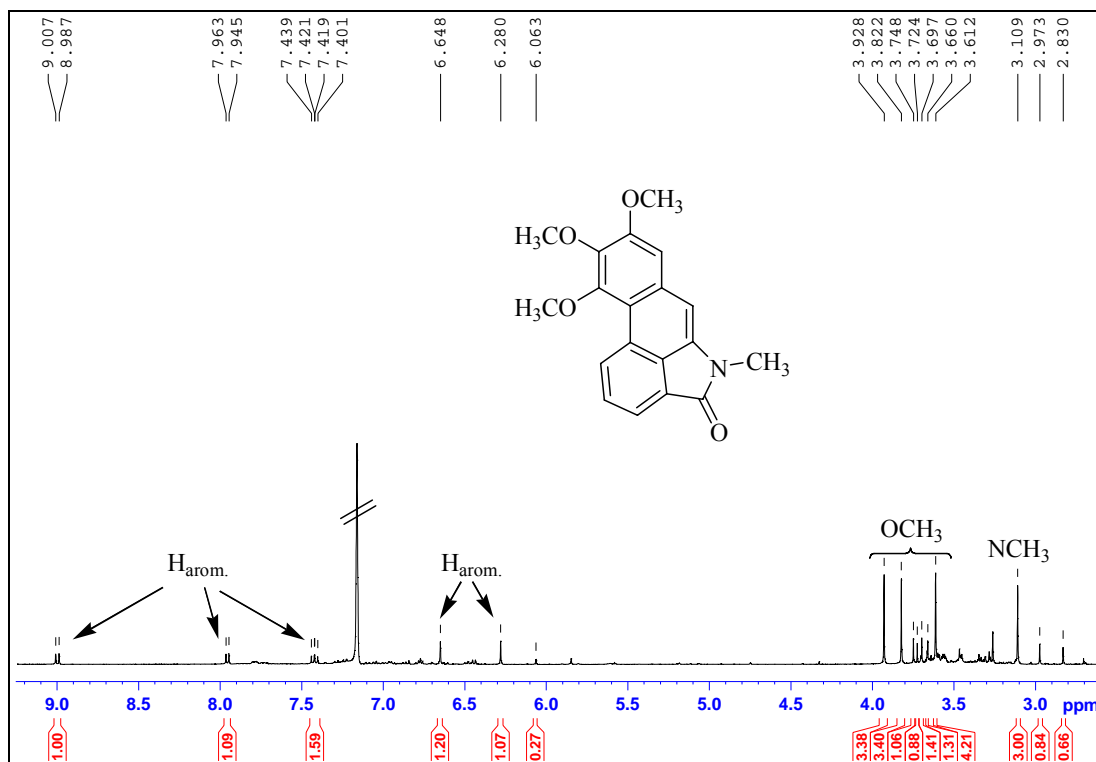


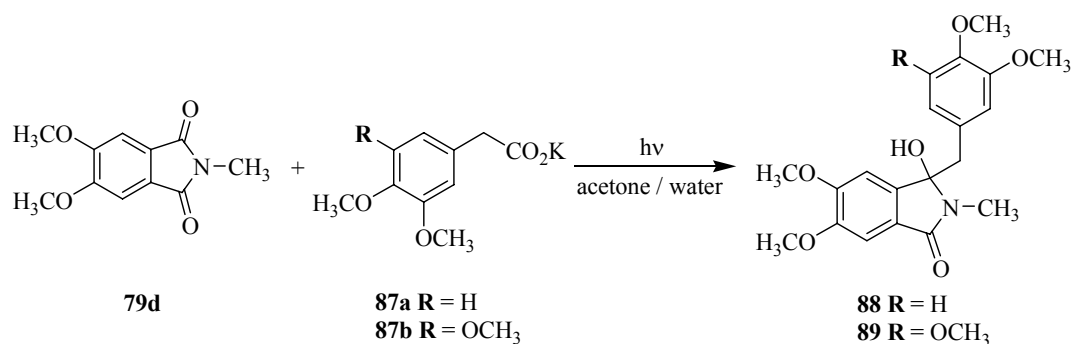
Figure 4.9 Final ¹H-NMR of experiment 75 obtained after 25 hr showing formation of **86**.

The iodinated addition partners **81a** and **81b** were chosen specifically with the final step of the procedure in mind. The iodo group is known to act as a very good leaving group which should guarantee ring closure occurring. Paradoxically, the iodo group seemed to be preventing the initial photoaddition reaction from proceeding.

The result obtained in experiment 75 was therefore very exciting as it was hoped that DDQ could be used to drive the reaction forward in the final cyclisation step without the presence of the bulky iodo group which seemed to be causing the insolubility issues. Electrocyclisation does not occur without the iodo being present, as the positions are too far away from each other due to ineffective overlapping of the extremes of the hexatriene system as postulated by Castedo *et.al.*⁶⁶ It was thought that DDQ, as a powerful oxidising agent, might help to overcome this.

4.3.3 Formation of substituted aristolactams with non-iodo-precursors

To investigate whether the initial photoaddition reactions would go to completion more readily without the presence of the iodo group, photoaddition reactions of **79d** and commercially available potassium di-/trimethoxyphenylacetates **87a,b** were performed as outlined in **Scheme 4.8** below.



Scheme 4.8 Experiments 76 and 77.

While there were some further solubility issues with the starting material **79d** in experiment 76, the results as shown in **Table 4.2** were far superior to those obtained previously with the starting material **1** and the related iodo-compounds.

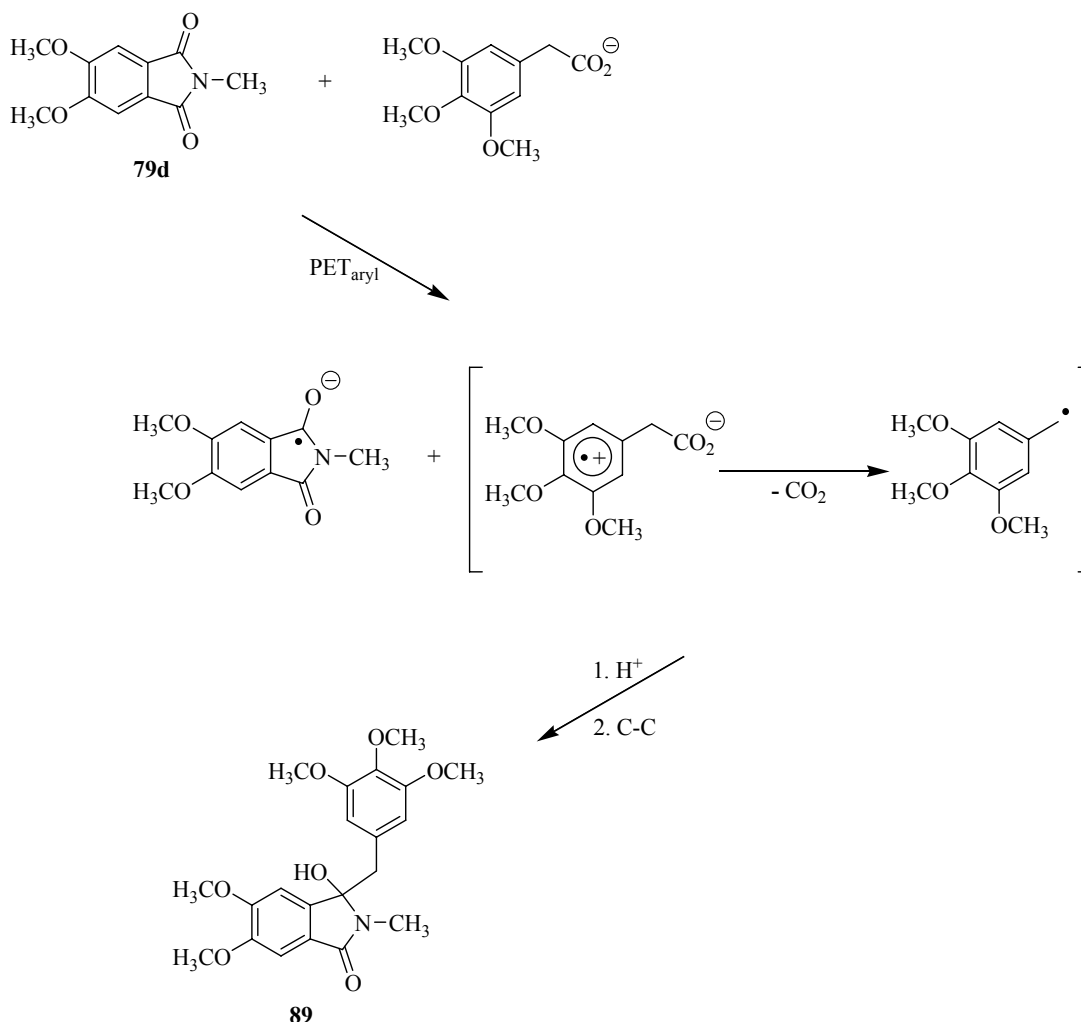
Table 4.2 Yields for experiments 76 and 77.

compound	R	time [hr]	yield [%]
88	H	8	21
89	OCH ₃	8	97

In experiment 76 the reagents, **79d** and **87a**, were initially a little difficult to dissolve, however this was solved by sonicating and heating the solution. During irradiation, a precipitate was visible throughout the reaction and after irradiating for 8 hr, the reaction was stopped and the precipitate found to be a mixture of **79d** and **87a**. This was rather disappointing, however the reaction was worked up regardless and the crude ¹H-NMR showed the desired product had been formed. Following purification, the yield for **88** was determined to be 21%.

In experiment 77, using **79d** and **87b**, there were no solvation issues with **79d** and both reagents went into solution readily. In this case, a precipitate was also visible towards the end of the 8 hr irradiation period, however when isolated, the precipitate was identified as the target product in an 89% yield. Following work-up, the crude $^1\text{H-NMR}$ also showed the presence of the desired product, which after purification gave a total yield of 97%.

The photoreaction of the dimethoxy-substituted *N*-methylphthalimide **79d** with 3,4,5-trimethoxyphenyl acetate resulting in the formation of **89** illustrates another pathway that PET can occur (**Scheme 4.9**).



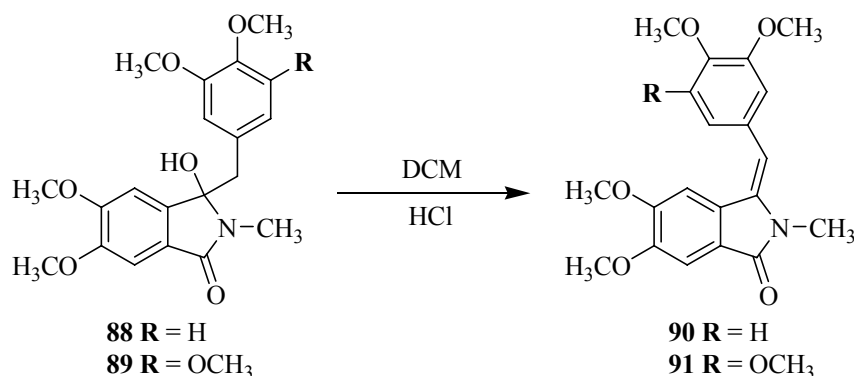
Scheme 4.9 PET-activity of dimethoxy-substituted *N*-methylphthalimide

Since the highly fluorescent singlet state of this phthalimide is not quenched by simple alkyl carboxylates, electron transfer from the carboxylate function will not

occur. The electron-rich 3,4,5-trimethoxyphenyl-group is known to function as an electron donor in the photodecarboxylative addition. The oxidation strength of the excited dimethoxylated phthalimide is thus lower than that of the excited phthalimide analogue. Based on literature data and the successful addition of the α -thioalkyl carboxylate, photoadditions to dimethoxy phthalimide do not take place for simple carboxylates and require either a heteroatom with low oxidation potential or electron-rich aryl groups in the α -position to the carboxylate.

This could explain the lower yield obtained in the reaction with the dimethoxyphenylacetic acid. Even though it differs in only one methoxy group the resulting difference in oxidation potential seems to be enough to hinder the electron transfer from the aryl group.

The dehydration reactions of both **88** and **89** were carried out resulting in the formation of **90** and **91** as shown in **Scheme 4.10**.



Scheme 4.10 Experiment 78 and 79.

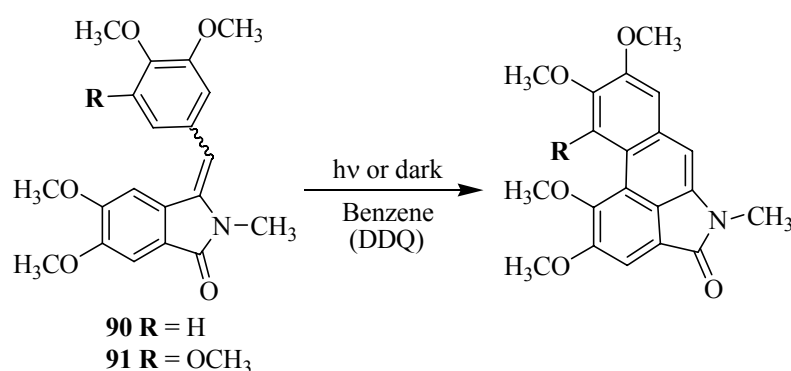
In experiment 78 (**88** \rightarrow **90**) both isomers of the desired product were formed in a ratio of 74:26 while in experiment 79 (**89** \rightarrow **91**), both isomers of the desired product were formed in a ratio of 78:22, while the yields were 93% and 95% respectively as shown in **Table 4.3** below. In both cases the *E*-isomer was the major isomer formed.

Table 4.3 Results for experiments 78 and 79.

compound	R	yield [%]	d.e. [%]
90	H	93	48
91	OCH ₃	95	56

4.3.3.1 Attempted electrocyclic ring closure

Both **90** and **91** were used in an attempted electrocyclic ring closure reaction in the presence of DDQ (previously optimised procedure).



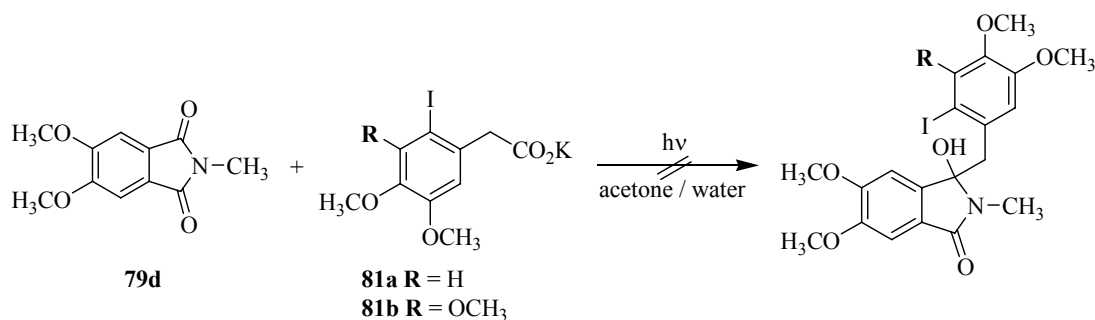
Scheme 4.11 Experiments 80-85.

All reactions were conducted in deuterated benzene, on a small scale in an NMR tube. Reactants were irradiated for up to 35 hours with DDQ present; however there was no evidence of either product in the respective ¹H-NMR's. Reference reactions were irradiated without DDQ being present simultaneously and these again showed no formation of product. Likewise, "dark reactions" were performed with DDQ present to act as controls and these reactions all resulted in no product formation.

These results prove unequivocally that ring closure will not occur without the necessary iodo group on the upper ring being present, even in the company of the oxidant DDQ. Knowing this, further reactions with iodo acids were investigated.

4.3.4 Further reactions for the synthesis of iodo precursors

Dimethoxy-NMP, **79d** was reacted with **81a** and **81b**, however these reactions were not successful as no product was formed (Scheme 4.12). It was very difficult to dissolve the starting materials in the usual solvent of acetone:water (1:1) and even when heat was applied they did not stay in solution for the duration of the irradiation period. In most cases, the starting material **79d** precipitated out and was recovered.



Scheme 4.12 Experiments 86 and 87.

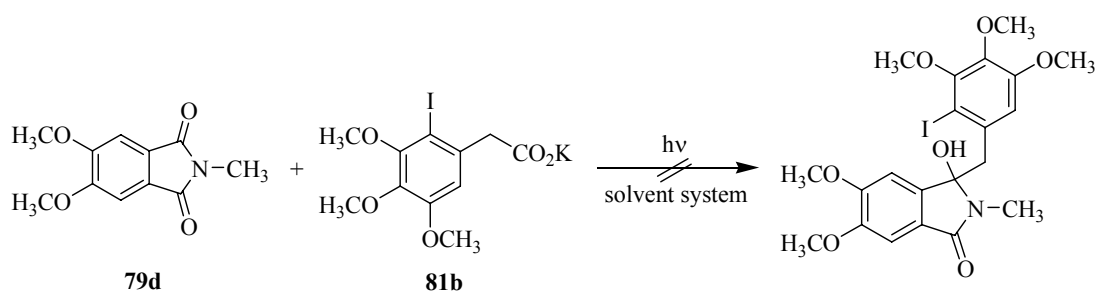
In experiment 86, **79d** was reacted with **81a** and following irradiation for a total of 32 hr **79d** precipitated almost in its entirety. The crude ¹H-NMR showed no sign of the product being formed. In experiment 87, **79d** was reacted with **81b** and even after irradiating for 53 hr the starting material was recovered. Following work-up, the crude ¹H-NMR consisted mainly of **81b** and no evidence of the photoproduct was present.

The reagent **79d** has a reduction potential of $E_{Ox} = -1.98$ V versus ferrocene/ferricenium, i.e. 100 mV more negative than that of the methoxyfree parent compound **1** and as discussed previously needs an electron rich aryl group in order for electron transfer to occur. Despite the low yield of product in the reaction of **79d** with the dimethoxyphenylacetic acid **87a**, as **79d** underwent reaction with both non-iodinated reaction partners **87a,b**, it is obvious that the iodo group is causing additional issues

As both starting materials showed solubility issues, it was thought that a change in solvent could solve this problem.

4.3.4.1 Solvent study

For this study **81b** was the acid partner selected to react with **79d** as shown in **Scheme 4.13**. Several solvent systems were applied which are shown in **Table 4.4**. Before conducting experiments with DMF as the solvent, a stability check was performed on **79d** by irradiating it in DMF overnight. The solvent was then removed, the starting material recovered and the resulting $^1\text{H-NMR}$ showed **79d** to be unchanged, therefore proving DMF was safe to use as a solvent.



Scheme 4.13 Experiments 89-95.

Table 4.4 Solvent study with **79d** and **81b**.

experiment	solvent system	ratio
89	Acetone:Water	2:1
90	Acetone:Water	4:1
91	Acetone:Water	10:1
92	Acetone:DCM	1:1
93	^a (Acetone:Water):DMF	4:1
94	^a (Acetone:Water):DMF	1:1
95	Acetone:Ethanol:microemulsion	1:1

^a (Acetone:Water) ratio is 1:1

For all these reactions, the cooling device (cold finger) was set up as usual but was not activated when the Schlenk flasks containing the reaction solutions were placed in the Rayonet reactor, as heat seemed to encourage the reactants to dissolve. In all cases, the reactants were irradiated for a period of at least 24 hr and the starting material **79d** was found to be the observed precipitate.

In experiments 89-91, by increasing the volume of acetone used in the solvent system of acetone:water, the reactants seemed to go into solution slightly more

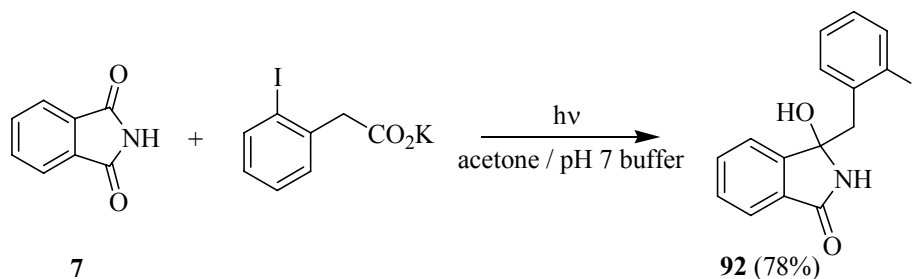
readily, however during irradiation **79d** continued to precipitate. The same occurred in experiment 92 with **79d** being recovered in a yield of 83%.

In experiments 93 and 94 using (acetone:water):DMF, despite the starting material eventually precipitating it did stay in solution for a slightly longer period of time (3-4 hr) than in the absence of DMF. Finally in experiment 95, an ethanolic microemulsion was used in conjunction with acetone, however it seemed to keep the reactants in a suspension as opposed to dissolving them. To further encourage the reaction to proceed, a more dilute solution of **79d** and **81b** was used in experiment 95. Unfortunately, the unreacted starting material **79d** was again recovered.

The fact that no photoproducts were formed, despite the reagents eventually staying in solution for a period of time while being irradiated, showed that solubility issues experienced were not the sole reason for the reactions not going to completion. Also, taking into account the fact that the reactions with **79d** and the non-iodo acid partners were successful it seems clear that the iodo function is the source of the issue. Referring back to the “space filling” model for **81d** shown earlier, the results of the solvent study seem to strengthen this postulated explanation.

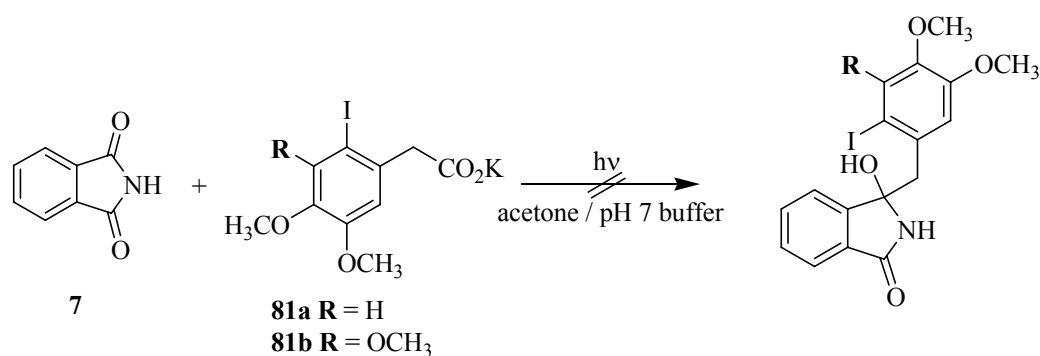
4.3.5 Reactions of phthalimide and dimethoxyphthalimide with iodo-substituted phenylacetic acids

In experiment 96, phthalimide **7** was irradiated in the presence of potassium iodo-phenylacetate for a period of 6 hr, as shown in **Scheme 4.14**, resulting in the formation of **92** in a yield of 78%.



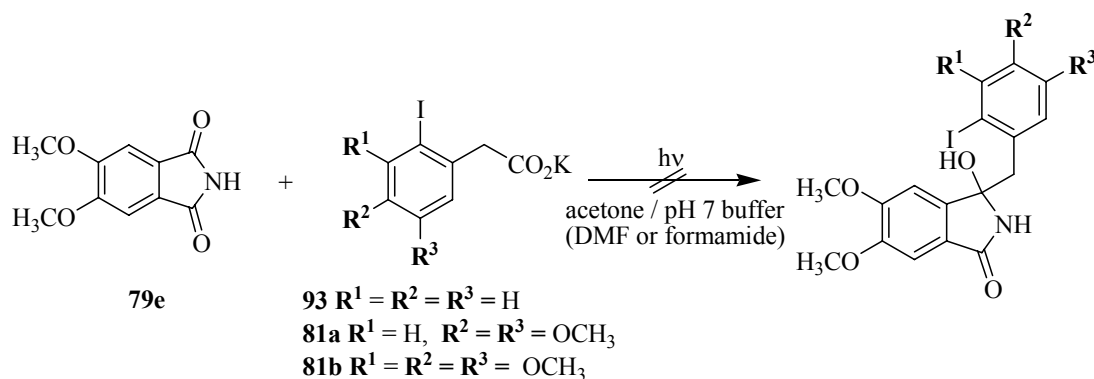
Scheme 4.14 Experiment 96.

In experiments 97 and 98, phthalimide **7** was also irradiated in the presence of **81a** and **81b** for a period of 23 hr in both cases (**Scheme 4.15**). Neither reaction was successful, and in the case of experiment 97, **81a** was recovered following purification of the crude product.



Scheme 4.15 Experiments 97 and 98.

Dimethoxyphthalimide **79e** was also reacted with all three iodo acids as shown in **Scheme 4.16**. In these cases, as seen previously when using **79d** as starting material, solubility of **79e** was also an issue so DMF or, in the case of experiment 101, formamide were added. The use of these solvents, in conjunction with the original (acetone / pH 7 buffer) solution, vastly improved the solubility of **79e**. In all cases, the desired product was not formed.



Scheme 4.16 Experiments 99-101.

The various solvent systems used are shown in **Table 4.5**. In experiments 99 and 100, the reagents stayed in solution for the entire irradiation period. Unfortunately, this did not result in product formation. In experiment 101, the starting material **79e** was seen to precipitate and was also visible in the crude $^1\text{H-NMR}$.

Table 4.5 Solvent systems for experiments 99-101.

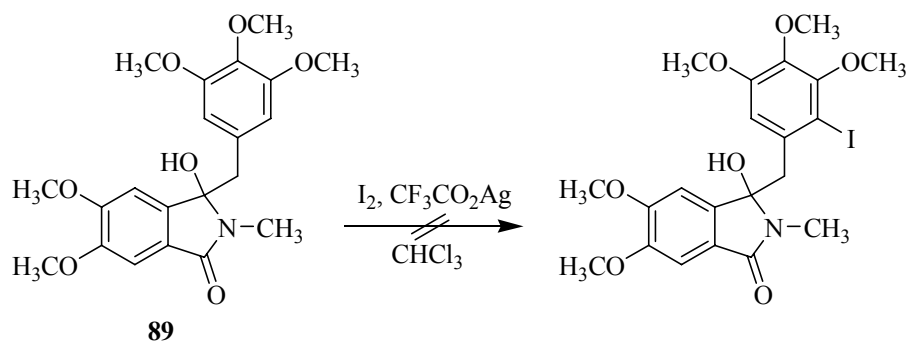
experiment	iodo acid	solvent system	ratio	time [hr]
99	93	^a (Acetone:pH 7 buffer):formamide	7:3	21
100	81a	^a (Acetone:pH 7 buffer):DMF	7:3	21
101	81b	^a (Acetone:pH 7 buffer):DMF	3:1	45.5

^a (Acetone:pH 7 buffer) ratio is 1:1

These results show that varying the starting material does little to improve the addition reactions of the iodo acids. Despite the solubility issues of **79d** and **79e**, which appear to be a separate problem, the main difficulty lies with the iodo acids and the bulkiness of the iodo substituent causing steric hindrance which, in turn, is preventing the reactions from progressing.

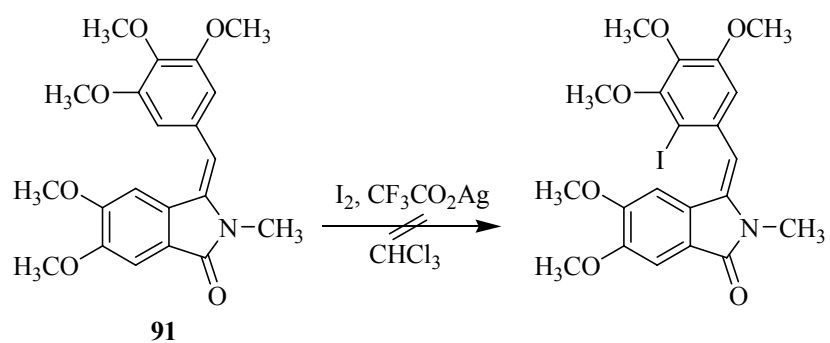
4.3.6 Attempted iodination of precursors

In a final attempt to sidestep the problems encountered previously, it was attempted to iodinate the previously formed photoproduct by the same method used to synthesise the iodo acids. This proved to be unsuccessful; the desired product was not formed.



Scheme 4.17 Experiment 102.

The same procedure was attempted with the dehydrated photoproduct **91** and regrettably, the outcome was the same.



Scheme 4.18 Experiment 103.

4.4 Summary

A three-step procedure which involved an initial photoaddition reaction, dehydration of the resulting photoproduct and eventual ring closure by irradiation in benzene, produced the unsubstituted or parent aristolactam **82c**, however substituent groups such as alkoxy or hydroxy groups, are required for a range of biological activity. After synthesising the starting materials, a number of photoaddition reactions were attempted using NMP (**1**) and Dimethoxy-NMP (**79d**) with both iodo (**81a,b**) and non-iodo di/tri-methoxyphenylacetic acids (**87a,b**). Overall, the reactions of **79d** with **81a,b** were not successful, while reactions of **1** with **81a,b** were somewhat sluggish, however did result in product formation.

The final ring closure step was attempted with both iodo (**85**) and non-iodo dehydration products (**90, 91**) and it was proved that ring closure only occurred via oxidative dehydrohalogenation as the attempted oxidative electrocyclisation was unsuccessful.

The issues associated with the initial photoaddition reactions were investigated. These were originally thought to be solubility problems, however following a solvent study, it was thought that electronic issues were also causing problems, especially with the reactions using **79e** and **81a,b**. Photoadditions were also attempted with phthalimide and dimethoxyphthalimide however there was no improvement with these reactions. Following the synthesis of the non-iodinated photoaddition product (**89**) and the non-iodinated dehydrated photoaddition product (**91**), it was finally attempted to iodinate both compounds by the same method used to synthesise the starting materials **81a,b**. This method was also revealed to be unsuccessful.

Nevertheless, the unsubstituted skeleton aristolactam and a trimethoxy-substituted aristolactam were both synthesised successfully.

Chapter 5

5 Synthesis of phthalocyanines from photochemically derived fluorinated phthalonitriles

5.1 Introduction

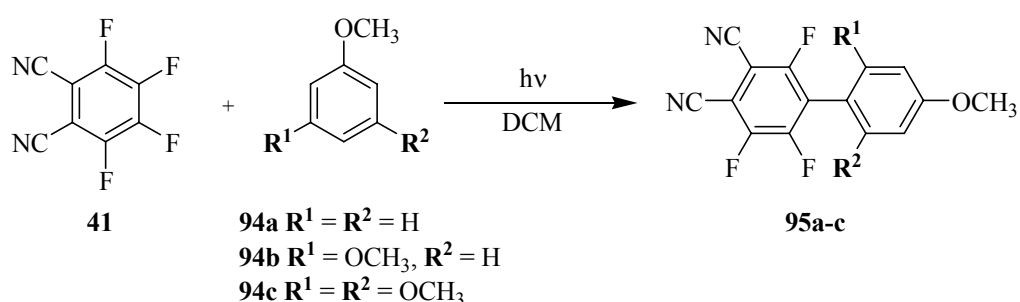
Phthalonitrile derivatives will be synthesised by photochemically reacting tetrafluorophthalonitrile (TFPN) with three different methoxy substituted benzenes. As water-solubility is a desired attribute in fluorescent compounds, meaning they can be used in cell imaging studies, it will be attempted to water-solubilise the resulting phthalonitrile derivatives by introducing water-soluble functional groups.

As phthalonitriles can be used as precursors to phthalocyanines (Pcs), it will be attempted to condense the methoxy-substituted phthalonitrile derivatives to their respective Pcs. The preparation of a water-soluble Pc will be attempted by introducing a sulfonate moiety, which would allow for enhanced solubility in alcohols and water making it a suitable sensitizer for PDT. If selective sulfonation can be achieved this would result in an exciting new sulfonated phthalocyanine, the like of which has not been seen before.

5.2 Synthesis of starting materials

5.2.1 Photochemical reactions

In experiments 104-106, shown in (Scheme 5.1) below, tetrafluorophthalonitrile **41** was irradiated with methoxy-substituted benzenes (2 equiv.) in a dilute concentration of approximately 4×10^{-3} M. All three reactions were irradiated for a period of 3 days. Following work-up, the crude product was purified by column chromatography. The results are shown in Table 5.1.^{142, 143}



Scheme 5.1 Experiments 104-106.

Table 5.1 Results for experiments 104-106.

compound	R ¹	R ²	yield [%]
95a	H	H	42
95b	OCH ₃	H	50
95c	OCH ₃	OCH ₃	47

The reason for the moderate yields after such a long irradiation period may be due to the fact that the product also absorbs light and so is in competition with the starting material. The same reactions were carried out over a shorter irradiation period of 24 hr and showed little difference in isolated yields. Therefore even after irradiating for prolonged periods of time, the improvements in the yields are minor.

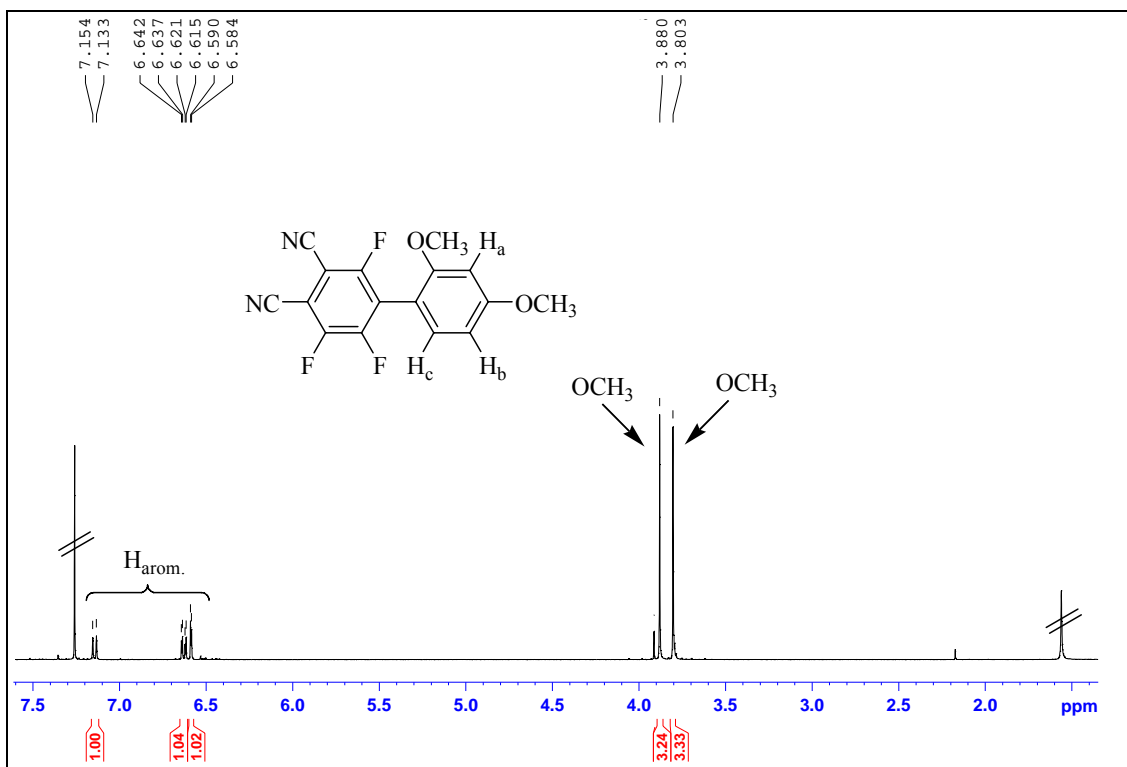
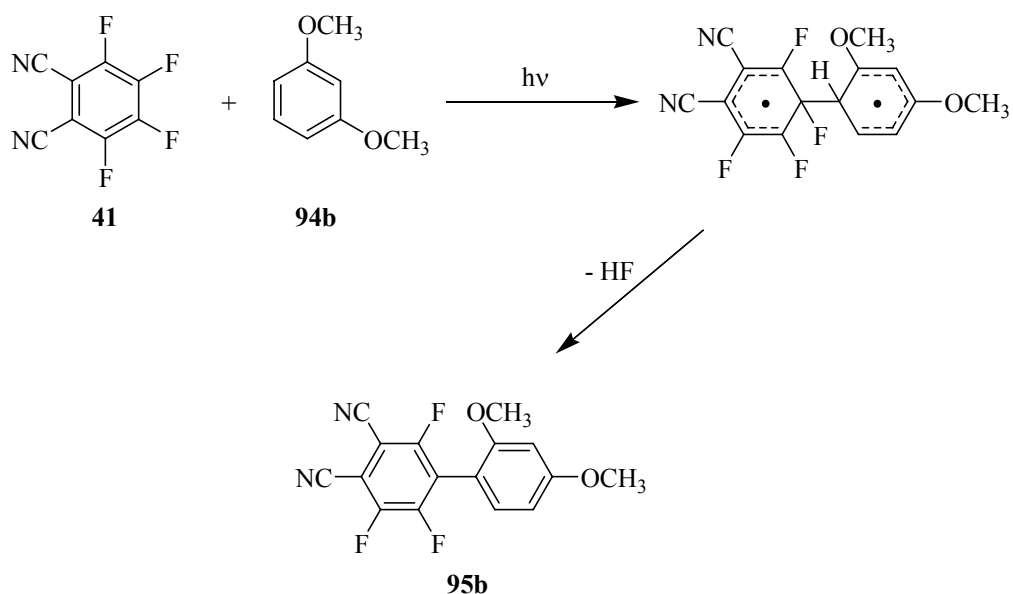


Figure 5.1 $^1\text{H-NMR}$ of **95b** in CDCl_3 .

From the $^1\text{H-NMR}$ of **95b**, shown in **Figure 5.1**, the peaks found at 3.80 ppm and 3.88 ppm represent the methoxy groups. The first of the three aromatic protons is represented by the peak found at 6.59 ppm. This corresponds to H_a , found between the two methoxy groups, and at first glance appears to be a singlet, however on closer inspection slight splitting can be seen, which is caused by 4J coupling with its nearest proton neighbour H_b . The peak found at 6.63 ppm represents H_b which is split into a doublet by H_c , while also experiencing slight splitting (4J coupling) from the previously mentioned H_a . The peak representing H_c is found at 7.14 ppm and, due to 3J coupling with H_b , appears as a doublet with no further splitting as it is too far away from the H_a for this to occur.

The $^{19}\text{F-NMR}$ proves substitution at the 4-position as three peaks are seen representing the remaining three fluorines, two of which appear as quartets and one of which appears as a triplet.



Scheme 5.2 Proposed mechanism for the synthesis of **95b**.

The proposed mechanism by Pratt *et. al.*,¹⁴² as shown in **Scheme 5.2**, describes the biaryl formation *via* a direct coupling route. Upon loss of HF from the intermediate, the product **95b** is formed. The selective coupling at the 3 or 4 position as opposed to the 2 and 5 position could be due to steric hindrance from the nitrile groups.

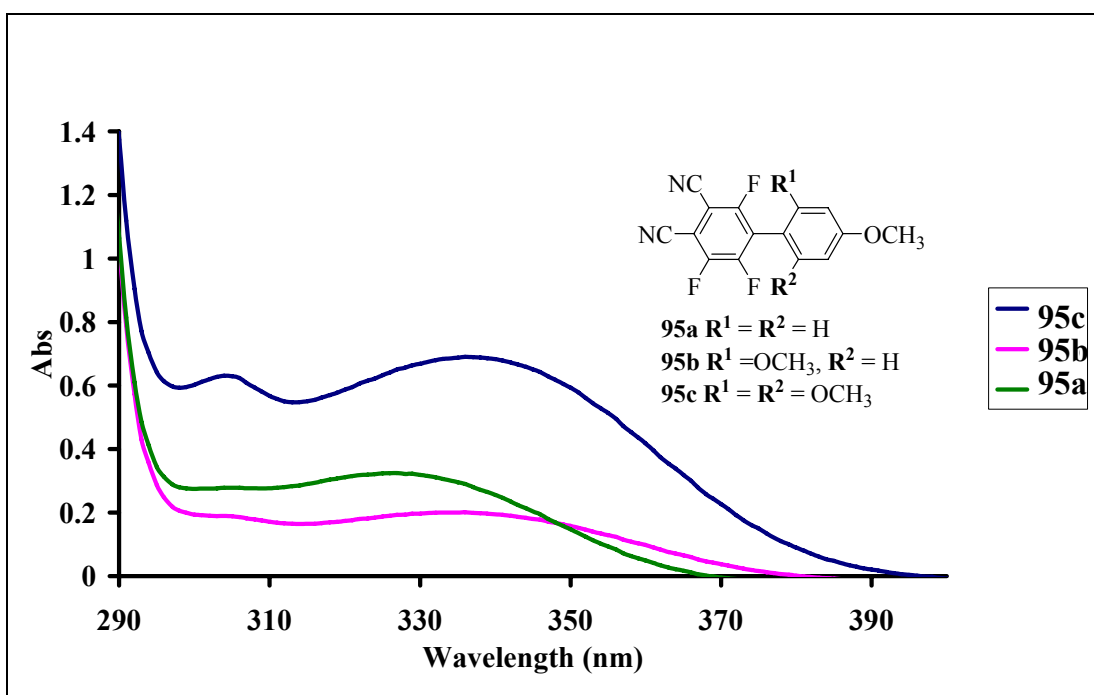


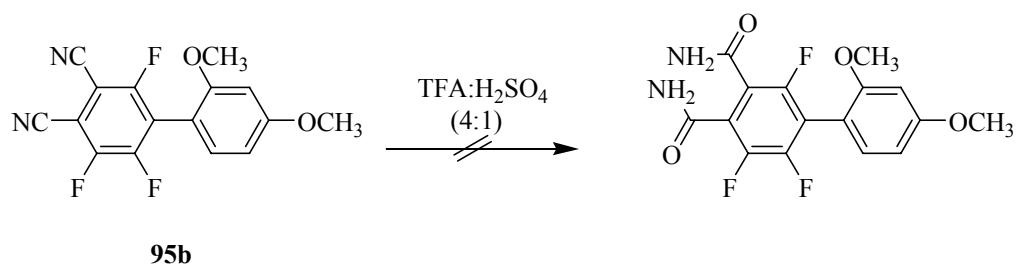
Figure 5.2 UV-Vis spectra for photoproducts **95a-c**.

The UV-Vis spectra obtained for **95a-c** are shown in **Figure 5.2**. By comparing the spectra we see that products **95b** and **95c** have similar maximum absorptions of $\lambda_{\max} = 334$ nm and $\lambda_{\max} = 336$ nm respectively. The mono-substituted methoxy photoproduct **95a** shows absorption at $\lambda_{\max} = 327$ nm.

5.3 Sulfonation of phthalonitrile derivatives

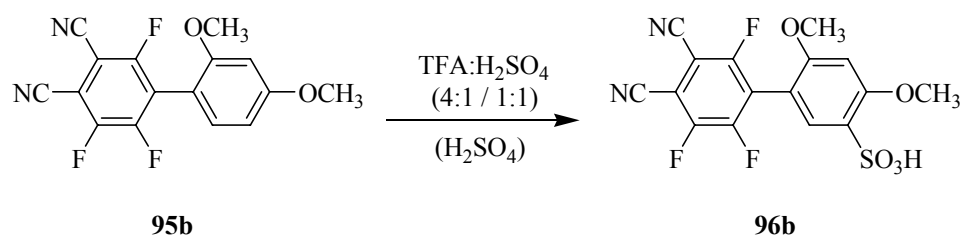
5.3.1 Synthesis of sulfonated products

Initially, it was attempted to convert the nitrile groups of the phthalonitrile derivatives into the corresponding amides. According to a method reported by Moorthy *et al.*,¹⁴⁴ **95b** was stirred in TFA:H₂SO₄ (4:1) at R.T for 2 days. This did not produce the expected product shown in **Scheme 5.3**, instead selective sulfonation was found to have taken place (**Scheme 5.4**).



Scheme 5.3 Attempted conversion of nitriles to amides using **95b** as a substrate.

In experiment 107 compound **95b** was stirred in TFA:H₂SO₄ (4:1) at R.T for 2 days. Following work-up, the crude product was purified by recrystallisation and the yield of **96b** was found to be 88%.



Scheme 5.4 Experiments 107-109.

Table 5.2 Varying solvent for sulfonation of **95b**.

experiment	solvent		time [days]	yield [%]
107	TFA:H ₂ SO ₄	4:1	2	87
108	H ₂ SO ₄		2	38
109	TFA:H ₂ SO ₄	1:1	4	29

To optimise the conditions, **95b** was dissolved in H₂SO₄ at R.T. and allowed to stir for 2 days. The sulfonated product was isolated although a lower yield of 38% was obtained. In experiment 109, **95b** was stirred at R.T. in TFA:H₂SO₄ (1:1) for a total of 4 days. The yield was found to be 29%.

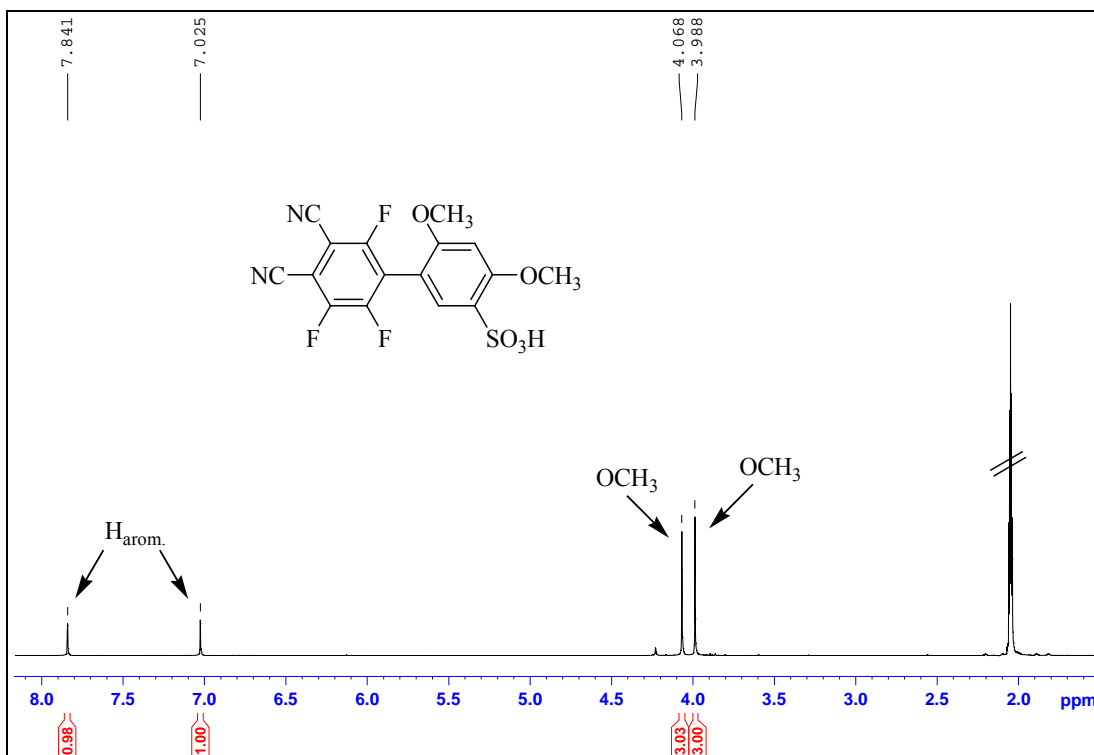


Figure 5.3 $^1\text{H-NMR}$ of **96b** in $\text{C}_2\text{D}_6\text{CO}$.

From the $^1\text{H-NMR}$ of **96b**, shown in **Figure 5.3** above, we can see that the photoproduct **95b** was selectively sulfonated in only one position. As the two remaining aromatic protons are represented by singlets at 7.03 ppm and 7.84 ppm, the *ortho*-position shown is the only possible position that could be sulfonated as the peaks would show slight splitting if sulfonation occurred at the *meta*-position. The fact that the electron-donating methoxy groups are *para*- and *ortho*-directing would further support this structure. Sulfonation does not occur at the *ortho*-position between the two methoxy groups presumably due to steric hindrance.

This was confirmed by mass spectrometry, as $[\text{M} + \text{Na}]^+$ peak was found at 421 m/z, while in the negative mode the $[\text{M}]^-$ peak was found at 397 m/z. The calculated molecular weight for **96b** was 398 g/mol.

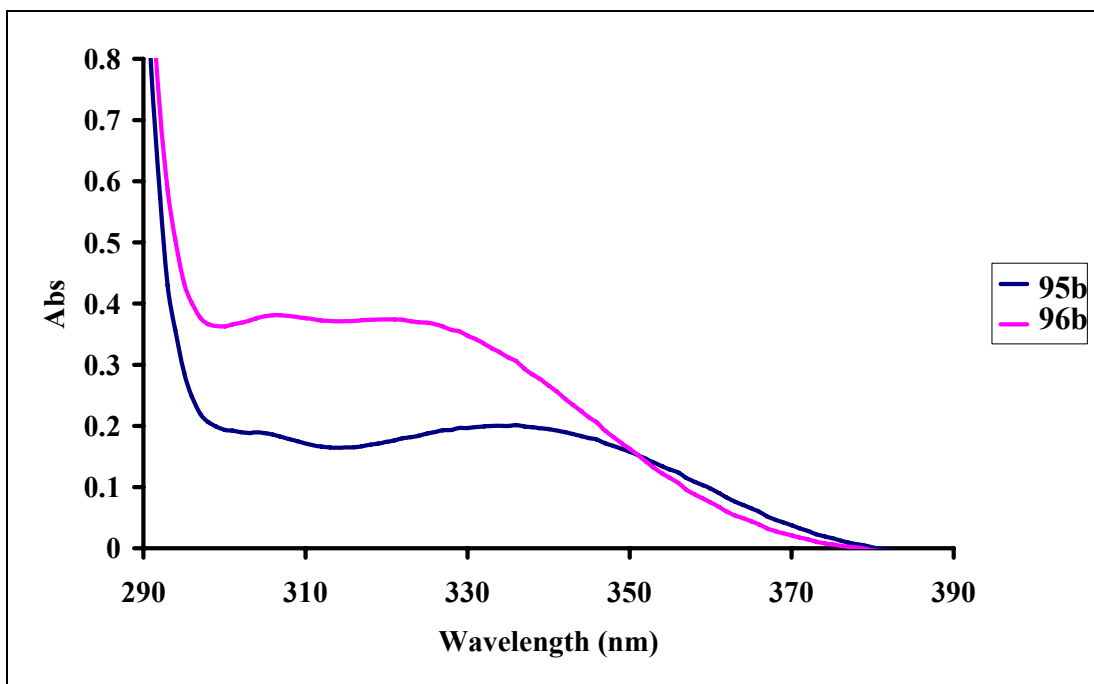
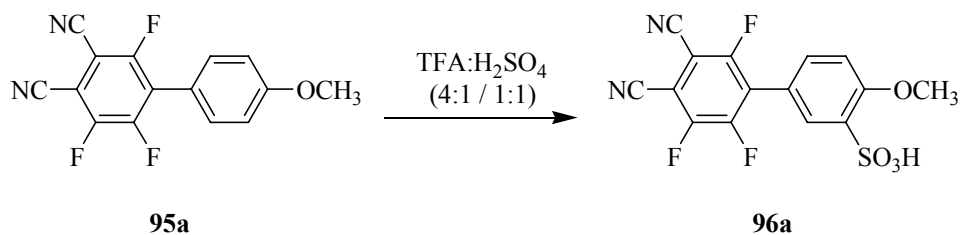


Figure 5.4 UV-Vis spectra of **95b** and its corresponding sulfonated product **96b**.

The product **96b** was examined for potential use in cell imaging using the lung adenocarcinoma cell line A549. The initial test used cells at the exponential growth phase, these were treated with a number of concentrations of the compound for 24 hours and visualised using a leica SP2 AOBS confocal. The cells were excited with a 405nm laser and scanned for excitation from 420nm to 650nm.

In a repeat experiment the cells were treated with neat compound (8 μ g/ml) for 1 hour and analysed with a flow cytometer exciting at 305nm. In both cases no fluorescence was observed.

Investigative sulfonation procedures were also carried out with the mono-substituted methoxy photoproduct **95a** and the results are summarised in **Table 5.3**.



Scheme 5.5 Experiments 110 and 111.

In experiment 110, **95a** was stirred overnight in TFA:H₂SO₄ (4:1) at R.T and upon quenching the reaction with water a precipitate was seen to form. This was isolated and found to be the starting material **95a**. From this, it was assumed the reaction was unsuccessful, however, following work-up of the filtrate, the ¹H-NMR of the crude product showed it to contain the desired sulfonated product **96a** with some starting material also present. This was purified by recrystallisation and found to have a yield of 26%.

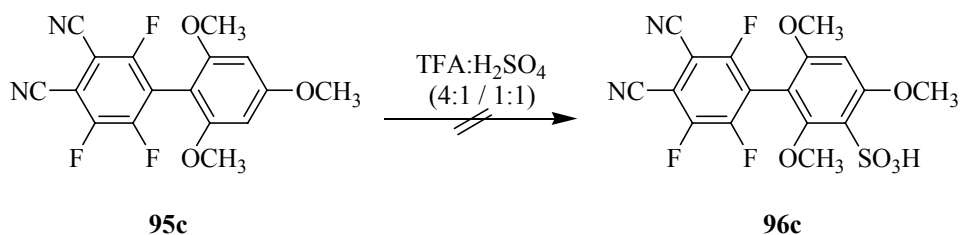
Table 5.3 Summary of results for sulfonation of **95a**.

experiment	solvent		time [days]	yield [%] ^a
110	TFA:H ₂ SO ₄	4:1	1	26
111	TFA:H ₂ SO ₄	1:1	4	73

^a Yield of **96a**.

In experiment 111, **95a** was stirred in TFA:H₂SO₄ (1:1) at R.T for a total of 4 days. Following work-up, the ¹H-NMR showed this to be the desired product in a yield of 73% with no recrystallisation necessary.

Finally, the sulfonation procedure was applied to the trimethoxy-substituted photoproduct **95c**. The results are shown in **Table 5.4**.



Scheme 5.6 Experiments 112 and 113.

Table 5.4 Results for attempted sulfonation of **95c**.

experiment	solvent		time [days]	yield [%] ^a
112	TFA:H ₂ SO ₄	4:1	1	0
113	TFA:H ₂ SO ₄	1:1	4	0

^a yield of **96c**.

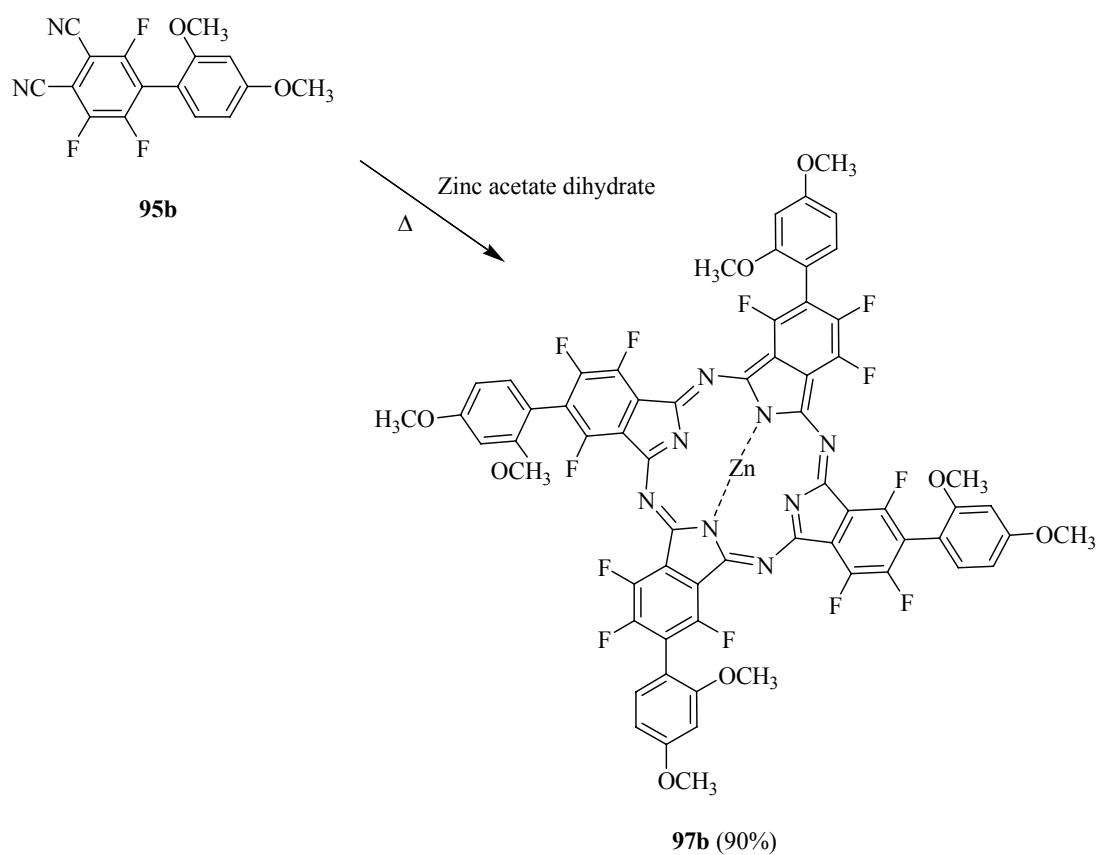
In experiment 112, **95c** was stirred in TFA:H₂SO₄ (4:1) at R.T overnight and upon quenching the reaction with water a precipitate was seen to form. This was isolated and found to be the starting material **95c**. Following work-up of the filtrate, the ¹H-NMR of the crude product confirmed it to be starting material. It was clear that sulfonation did not occur, which was further confirmed when preparing the NMR sample as the crude product dissolved in CDCl₃.

In experiment 113, **95c** was stirred in TFA:H₂SO₄ (1:1) at R.T for a total of 4 days. Following work-up, even after the extended reaction period, the sulfonated product was not formed. It is assumed sulfonation did not occur due to steric hindrance caused by the presence of three methoxy groups on the aromatic ring.

5.4 Synthesis of phthalocyanines

5.4.1 Synthesis of phthalocyanines from phthalonitrile precursors

According to a method developed by Murphy¹⁴³ the Pc **97b** was formed in a melt of **95b** with zinc acetate dihydrate. The reaction was performed on a carousel under N₂. After heating to 190°C for 1.5 hr the reaction mixture turned deep green in colour and the reaction was complete. The yield of **97b** was found to be 90%.



Scheme 5.7 Experiment 114.

A UV-Vis absorption spectrum was obtained for this product and compared with the UV-Vis spectrum of the phthalonitrile precursor **95b** (Figure 5.5). The Pc product showed a considerable shift at 693 ppm, which is red-shifted compared to unsubstituted Pcs, confirming the presence of the desired Pc.

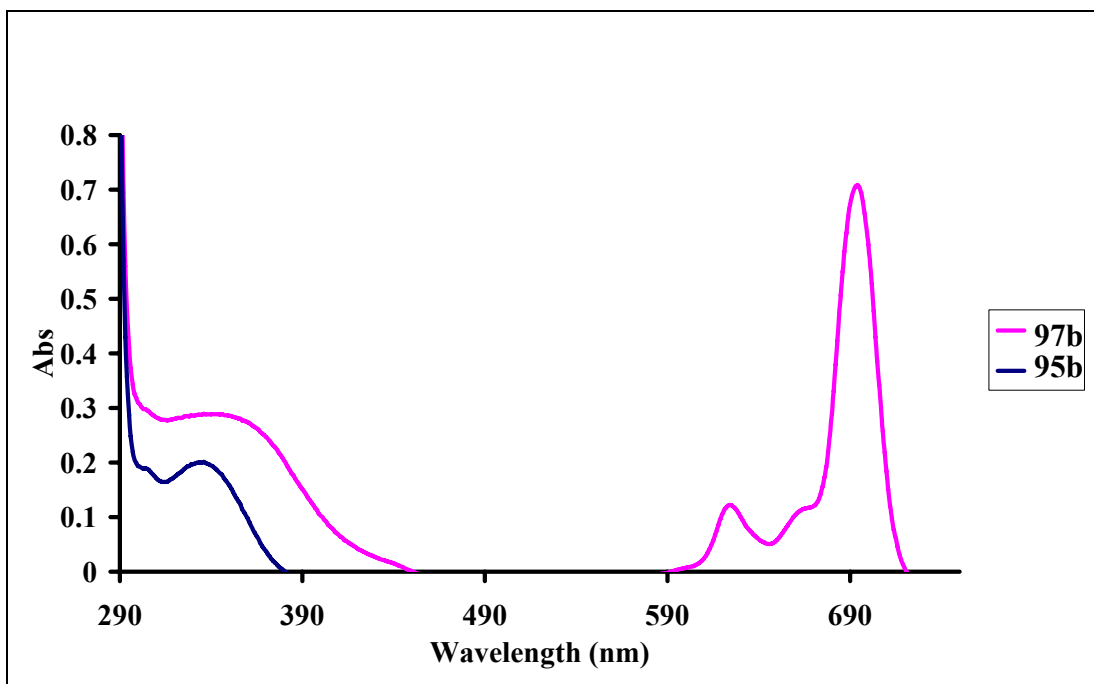
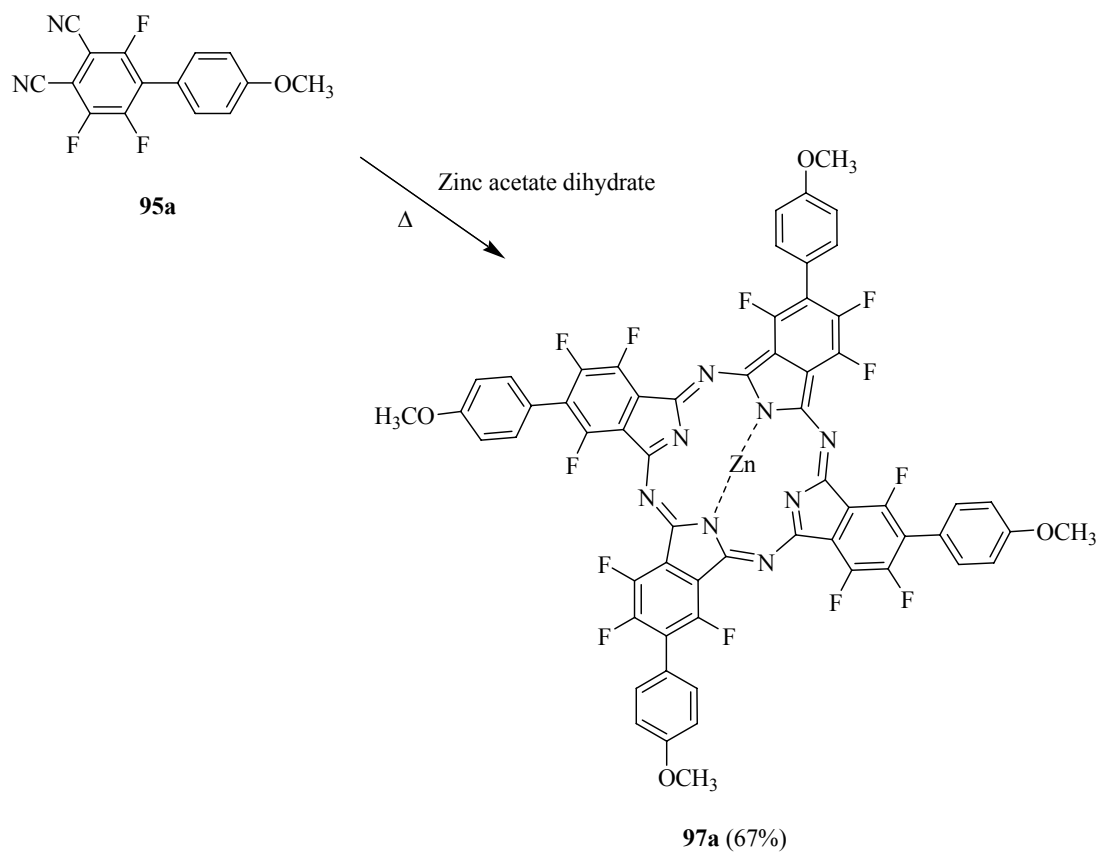


Figure 5.5 UV-Vis spectra of **95b** and **97b**.

The previous procedure was also used to convert **95a** into its corresponding Pc **97a** as shown in **Scheme 5.8**. The yield of **97a** was found to be 67%.



Scheme 5.8 Experiment 115.

A UV-Vis absorption spectrum was also obtained for this product and compared with the UV-Vis spectrum of its phthalonitrile precursor **95a** (**Figure 5.6**). The Pc product showed a considerable shift at 693 ppm confirming the presence of the desired Pc.

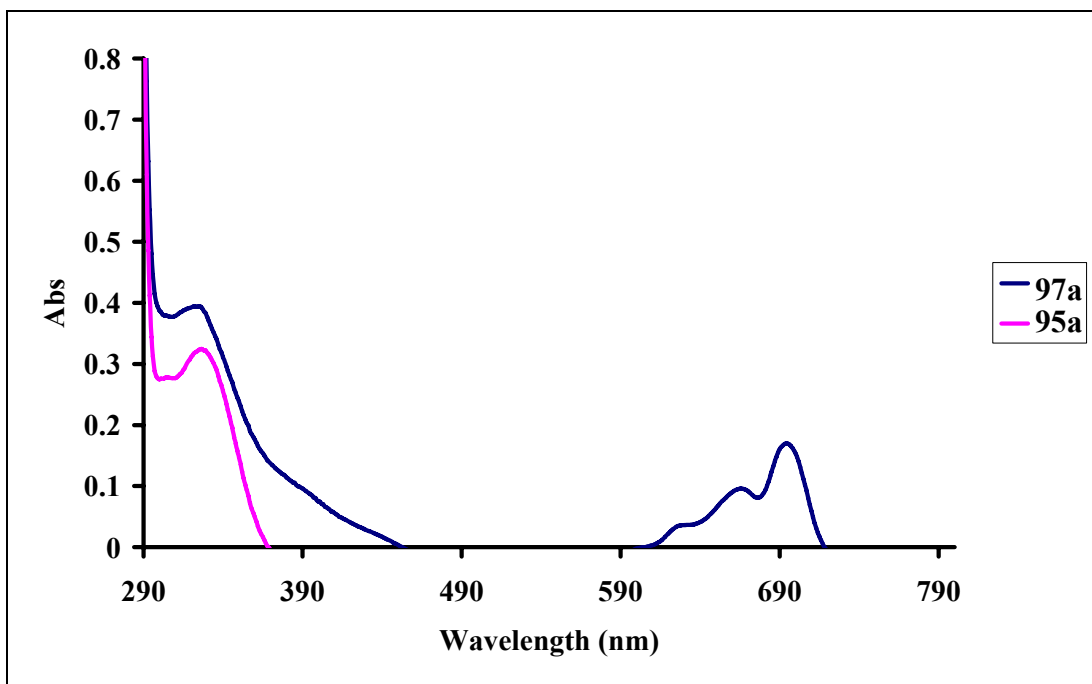
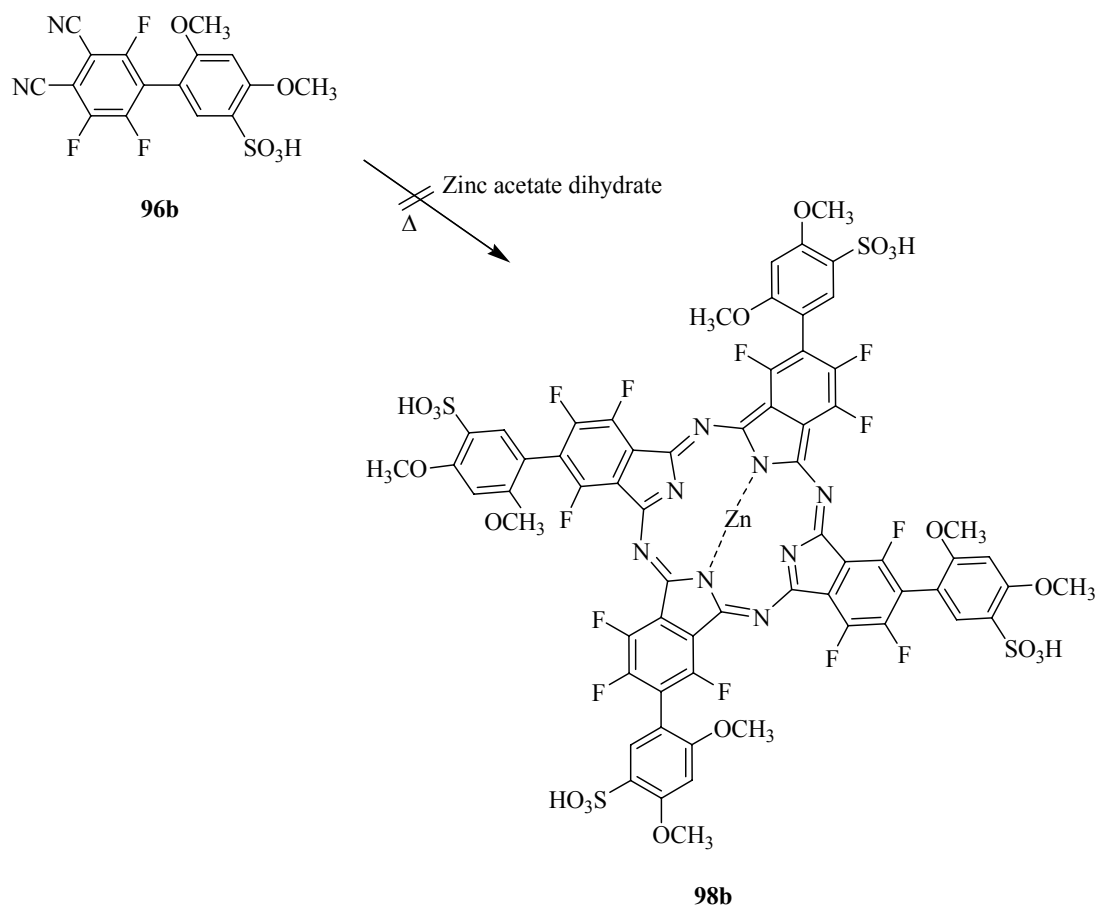


Figure 5.6 UV-Vis spectra of Pc **97a** and its precursor **95a**.

The product **97a** showed a peak at 694 ppm, once again confirming the presence of the desired Pc. These Pcs were subsequently used in an attempted sulfonation in the next section.

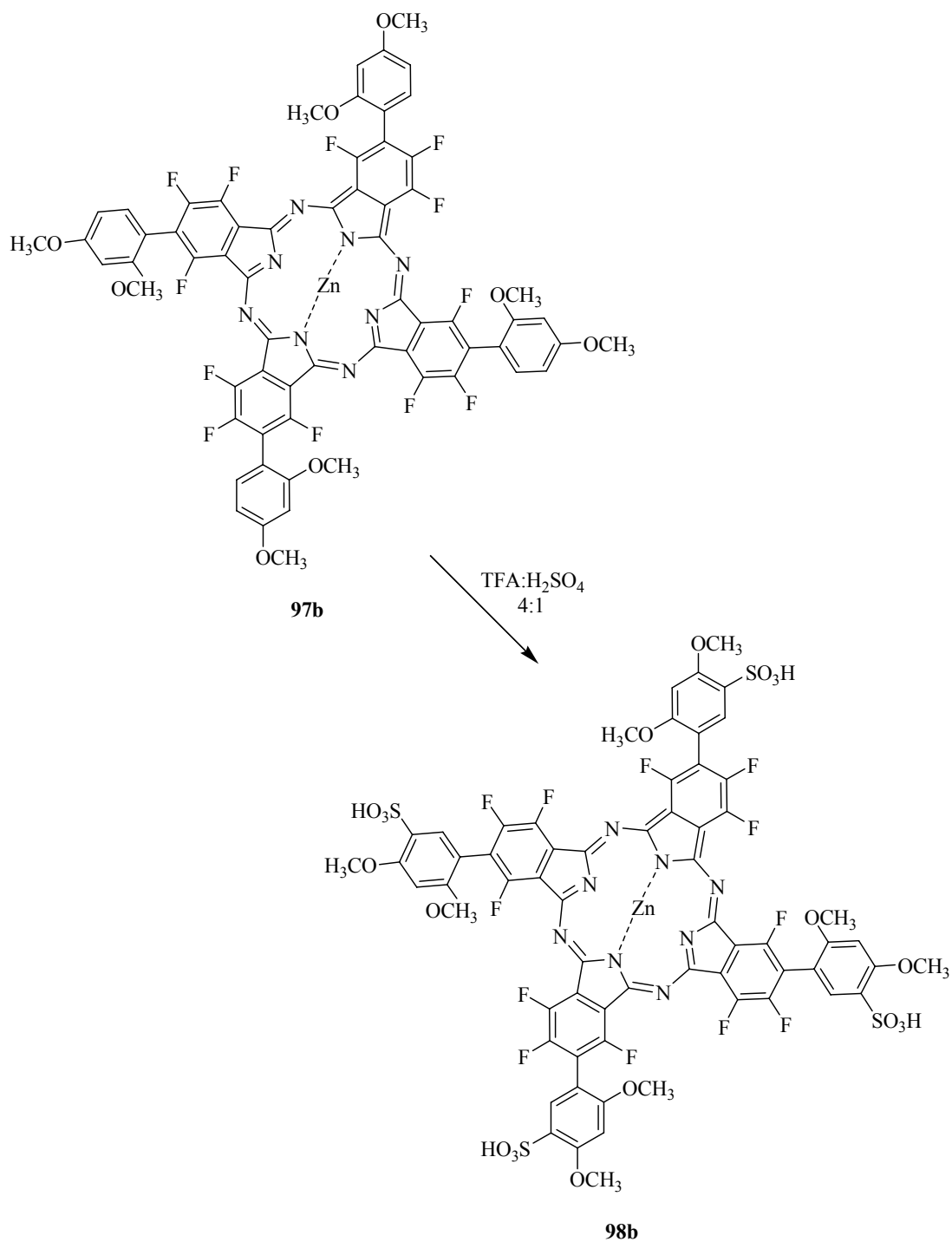
5.4.2 Synthesis of sulfonated phthalocyanines

First, it was attempted to synthesise a sulfonated Pc directly from the corresponding sulfonated precursor using **96b** as the starting material. This reaction was heated at 190°C for 2 hr and a deep green colour was seen indicating that a Pc had been formed. However when the $^1\text{H-NMR}$ was obtained, the sulfonated group seemed to cleave as there were three aromatic proton peaks seen instead of the expected two peaks for the sulfonated phthalocyanine. The reaction conditions may have been too harsh to maintain the sulfonate group.



Scheme 5.9 Experiment 116.

As preparing the sulfonated Pcs directly from the sulfonated precursors proved unsuccessful, it was then attempted, in experiment 117, to sulfonate the previously formed phthalocyanine **97b**. Following work-up, this method appeared to be successful as the $^1\text{H-NMR}$ showed there to be only two aromatic proton peaks present.



Scheme 5.10 Sulfonation of Pc **97b**.

Selective sulfonation was therefore achieved as confirmed by $^1\text{H-NMR}$ and the desired Pc **98b** obtained although was not in its pure state.

5.5 Summary

In this chapter, three methoxy-substituted (mono- **95a**, di- **95b** and tri- **95c**) phthalonitrile derivatives were synthesised. It was attempted to water-solubilise these compounds by converting the nitrile groups to amides, using **95b** as the test substrate. The resulting product **96b**, was indeed water soluble however; this was achieved due to the addition of a sulfonate group and not the converted amide as expected. The sulfonation occurred due to the use of the solvent mixture TFA:H₂SO₄, and from ¹H-NMR and MS data it was deduced that selective sulfonation had taken place at the *ortho*-position.

Several optimisation reactions were performed for the sulfonation procedure with **95b** before the procedure was applied to **95a** and **95c**. The sulfonation procedure was found to be successful only for **95a** (→**96a**). The reason the sulfonation was not successful for **95c** was thought to be due to steric hindrance.

The mono- and di-methoxy-substituted phthalonitrile derivatives (**95a** and **95b**) were successfully condensed to their related Pcs (**97a** and **97b**). In order to synthesise a selectively sulfonated Pc, two pathways were explored. It was first attempted to synthesise the sulfonated Pc directly from the sulfonated product **96b**. This method however, proved unsuccessful as the sulfonate group was removed during condensation. Sulfonation of the Pc **97b** was then attempted, using the same procedure to prepare **96b**. This method appeared to be effective judging by the ¹H-NMR and UV-Vis spectra however; the presence of the selectively sulfonated Pc **98b** has yet to be confirmed.

Chapter 6

6 Microphotochemistry performed with selected reactions

6.1 Introduction

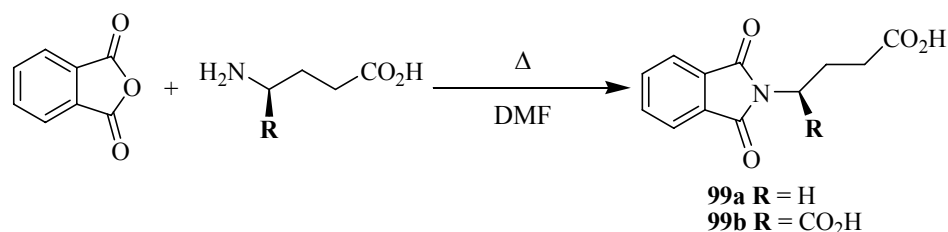
There has been increased interest over the past few years in the application of microphotochemistry as described in Chapter 1. However, there are still some doubts as to whether it is an efficient practice for organic synthesis. It will be attempted to demonstrate that microphotochemistry is a viable alternative to conventional methods. This will be done by performing several reactions using a microreactor and then comparing the results obtained with those achieved by a conventional method, namely photoreactions performed in a Rayonet reactor.

Some of the reactions chosen for comparison have already been presented in previous chapters, such as *inter*-molecular PDC additions, however some *intra*-molecular cyclisation reactions will also be attempted, and the results compared with those achieved by the conventional method. In this way, various types of photochemical reactions will be attempted in a microreactor and if successful, will demonstrate that the microreactor is an effective method for a wide range of photochemical reactions.

6.2 Synthesis of starting materials

6.2.1 Synthesis of *N*-phthalimido carboxylic acid derivatives

For the *intra*-molecular cyclisation reactions, four *N*-phthalimido carboxylic acid derivatives were prepared. The first of which were **99a** and **99b**, which were synthesised according to Kidd and King¹⁴⁵ by reacting phthalic anhydride with γ -aminobutyric acid and *L*-glutamic acid respectively (**Scheme 6.1**) in DMF at 150 °C. The products were obtained in excellent yields of 98% and 96% respectively (**Table 6.1**). The ¹H-NMR spectrum of **99a** shows a peak at 3.77 ppm that can be assigned to the NCH₂ group, while the peak for the NCH group of **99b** was found at 4.71 ppm.



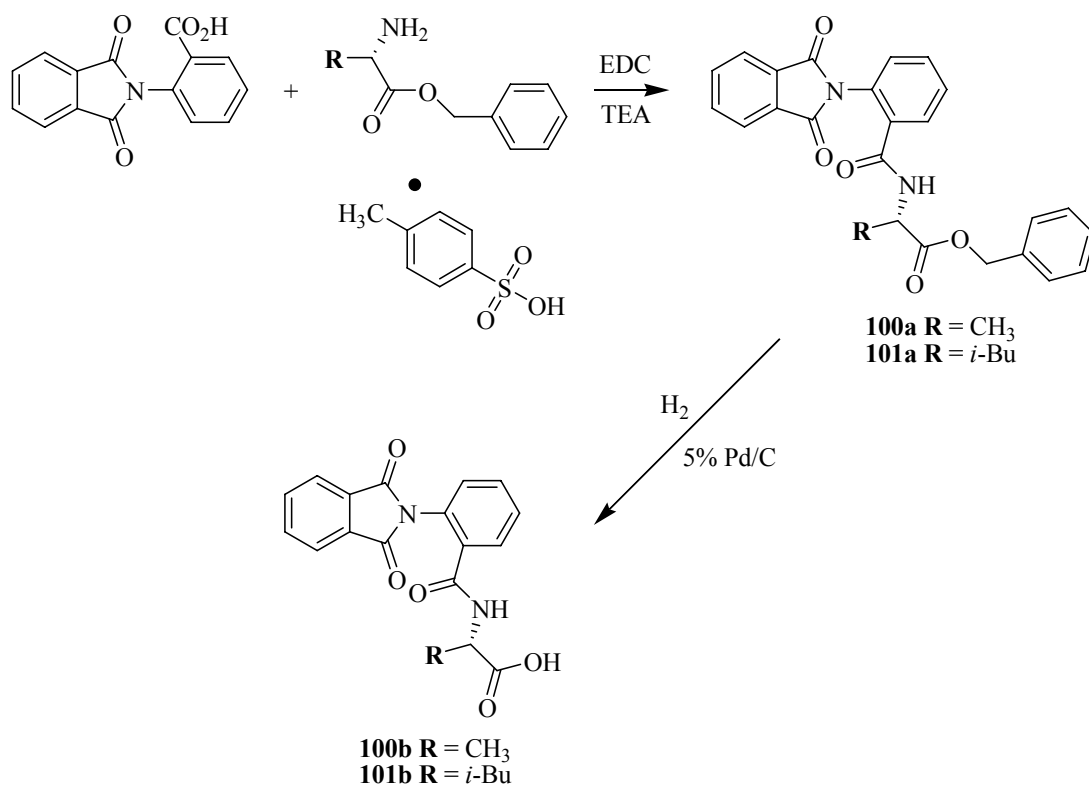
Scheme 6.1 Experiment 118 and 119.

Table 6.1 Synthesis of *N*-phthalimido carboxylic acid derivatives.

compound	R	¹ H-NMR [ppm]	yield [%]
99a	H	3.77 ^a	98
99b	CO ₂ H	4.71 ^b	96

^a NCH₂ peak in CDCl₃, ^b NCH peak in CDCl₃.

Two bulkier *N*-phthalimido carboxylic acid derivatives were also prepared, using a two step procedure (**Scheme 6.2**). The products **100b** and **101b** were made using 2-phthalimido-benzoic acid, EDC, TEA and stirring in DCM at room temperature for 48 hr with *L*-alanine-benzyl ester *p*-toluenesulfonate salt and *L*-leucine-benzyl ester-*p*-toluenesulfonate salt respectively. The intermediates were then hydrogenated giving the desired products in overall yields of 52% and 34% respectively as shown in **Table 6.2**.



Scheme 6.2 Experiments 120 and 121.

Table 6.2 Synthesis of **100b** and **101b**

compound	R	¹ H-NMR [ppm] CHasym	overall yield [%]
100b	CH ₃	4.59	52
101b	<i>i</i> -Bu	4.6	34

In both experiments, the methyl esters of the desired products were also formed during work-up of the final step, due to the fact that methanol was used as the solvent. The crude product had to be further purified to remove the unwanted methyl ester and this, along with the initial two-step procedure contributed to the moderate yields obtained.

During work-up in the final step it was discovered that at high temperatures the methyl ester was formed more readily. For example, upon rotary evaporation of the solvent at 50°C, **101b** was obtained in a low overall yield of <10%. The reactions were subsequently repeated and the solvent evaporated at the lower temperature of 30°C, which gave the product **101b** in an overall yield of 34% shown in **Table 6.2**. To further improve the yield of **100b** ethyl acetate was used in place of methanol in

the final step (experiment 120b) and this eliminated the unwanted esterification side reaction. The overall yield of pure **100a** was 62%.

6.3 Microphotochemical reaction set-up

6.3.1 Experimental set-up

For the irradiation experiments a Luzchem UV panel was selected. The panel was fitted with 5 LZC-UVB lamps ($\lambda = 300\pm 20$ nm) and the microreactor – a *dwell device* manufactured by *Mikroglas Chemtech* - placed underneath it (**Figure 6.1**). The microreactor possesses two separate channels; the reaction channel is 500 μm in depth, 2,000 μm in width and 1.15 m in length, while the second channel was used for cooling during the reactions. The reaction chamber was enclosed with tinfoil sheets to contain the UV light during irradiation.

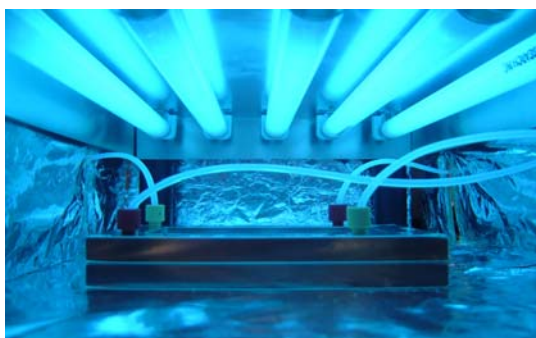


Figure 6.1: Microreactor in irradiation chamber.

Prior to irradiation, the reactant solution was degassed with Argon/Nitrogen while the microreactor was purged by pumping the mobile phase through it. An example of the reactant solution (shown in pink) being pumped through the reaction channel is shown in **Figure 6.2** while the microreactor is kept cool during irradiation by pumping cold water through the second channel.

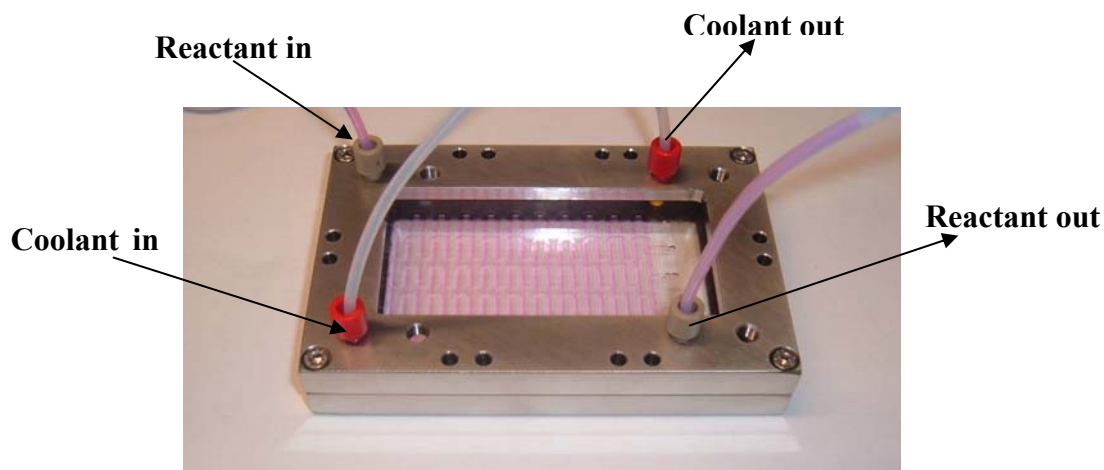


Figure 6.2 Luzchem *dwell device* microreactor.

The complete reaction set-up is shown in **Figure 6.3**. It shows the pre-mixed reactant solution being driven through the microreactor by the syringe pump (**1**), where it is irradiated and subsequently collected on the other side in a round bottom flask (**2**). The coolant is constantly flushed through the second channel by a piston pump (**3**), while the *Luzchem* light panel (**4**) is kept cool by placing a container of ice (**5**) on top during irradiation. Overheating of the lamps was found to be a problem initially, which was thought to be due to the makeshift tinfoil surrounding, however the ice bath proved to be an inexpensive solution to the problem. The UV shield (**6**) is placed around the opening for safety reasons.

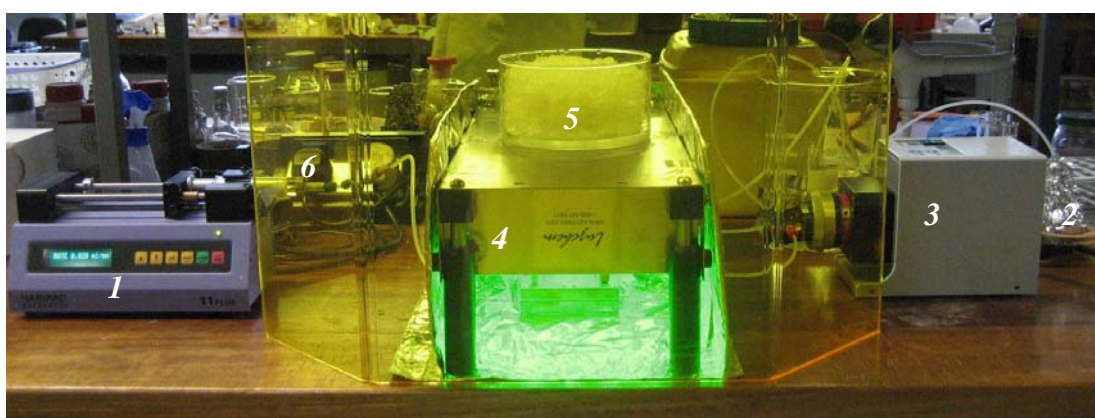


Figure 6.3 Reaction set-up.

Another problem that was encountered occurred during the re-filling of the syringe. Once the 10 ml of reactant solution had been pumped through the system, the syringe pump and the light source had to be turned off simultaneously. When removing the syringe it was necessary to unscrew it from the tubing, which caused air to enter the system and the solution already in the tubing to move forward which in turn affected the residence time. This problem was solved by attaching a valve between the tubing and the syringe (7). The valve was closed before removing the syringe, causing the solution to remain in place while re-filling the syringe with the required solvent. Once the syringe was re-attached, the valve was opened before the syringe pump and the light source were once again turned on in unison.



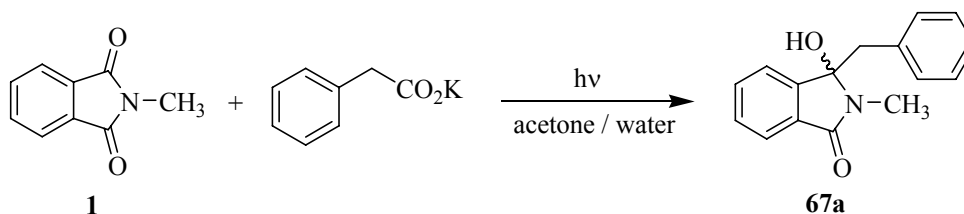
Figure 6.4 Valve (7) introduced to the system.

6.4 Comparison reactions

The following reactions were chosen as model reactions to investigate the effectiveness of microreactors versus standard photoreactors.

6.4.1 Reactions of NMP with phenylacetic acid and 2-iodophenylacetic acid

The first reaction chosen as an optimisation reaction was that of NMP (**1**) with phenylacetic acid (**Scheme 6.3**). As shown in **Table 6.3**, the formation of the desired product increased with slower flow rates. The flow rate is inversely proportional to the residence time so, as the flow rate decreases, the residence time increases which in turn gives the reactants more irradiation time.



Scheme 6.3 Experiments 122-126.

For **67a**, at the lowest attempted flow rate of 0.04 ml/min, the ¹H-NMR showed only the presence of the pure product, a complete conversion of **1** had been achieved after only 42 minutes. No purification of the product was needed. By comparison, in the standard Rayonet set-up, column chromatography had to be performed on the crude product. After 1 hour of irradiation 54% of pure product was obtained. After 42 minutes in the *dwel device*, a yield of 100% was achieved!

Table 6.3 Optimisation of flow rates for reactions of **1** with phenylacetic acid.

flow rate [ml/min]	residence time [min]	composition ^a	
		product	NMP
0.12	14	25	75
0.08	21	40	60
0.06	28	42	58
0.05	33.6	59	41
0.04	42	100	0

^a determined by ¹H-NMR integration.

The graph shown in **Figure 6.5** illustrates the changing composition of **1** and the resulting product (**67a**) with respect to residence time. As the quantity of **1** declines, the amount of product duly increases until there is no more starting material remaining to convert into the corresponding product, meaning the reaction is effectively complete.

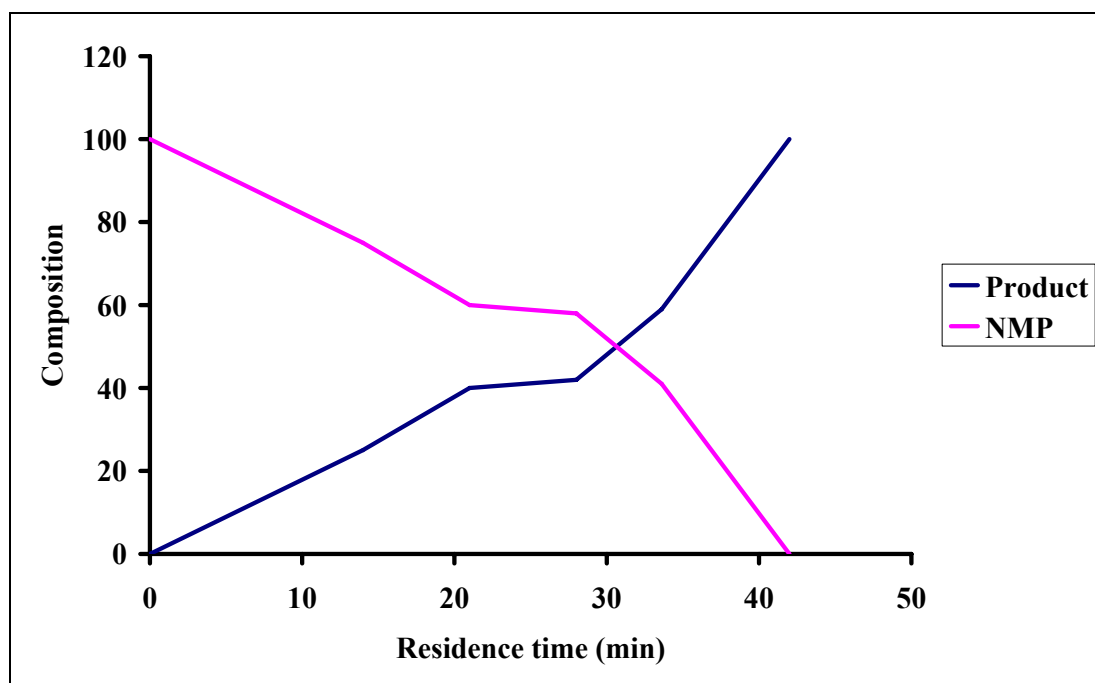
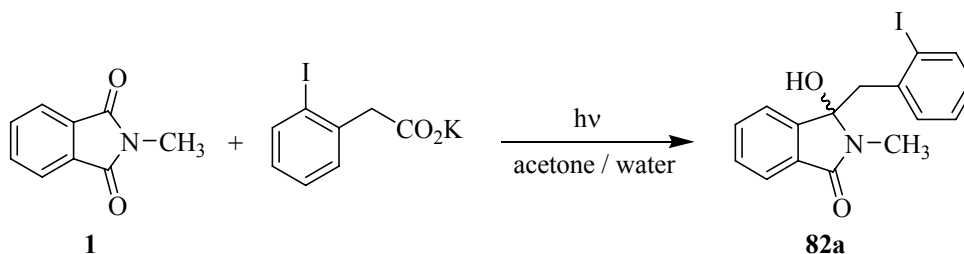


Figure 6.5 Graph representing the changing composition of NMP and product during irradiation in experiments 122-126.

Following the success of the initial reaction, a second model reaction was chosen, one that required a longer irradiation period, that of **1** with 2-iodophenylacetic acid (**Scheme 6.4**).



Scheme 6.4 Experiments 127a-c and 128-130.

Table 6.4 Optimisation of flow rates for reactions of **1** with 2-iodophenylacetic acid.

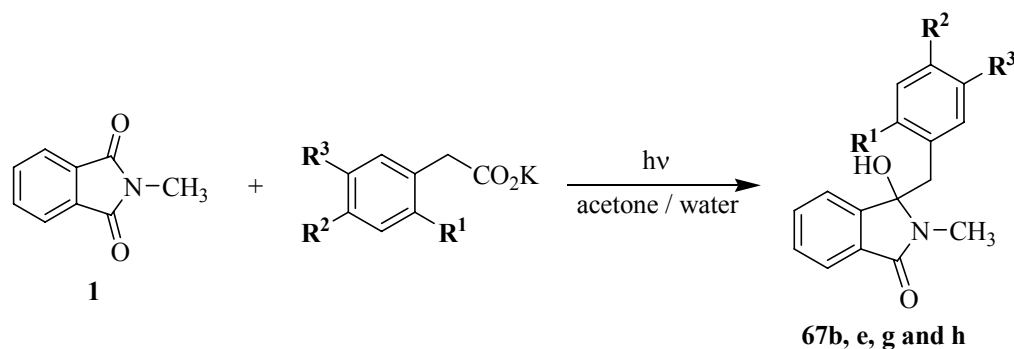
flow rate [ml/min]	residence time [min]	composition ^a	
		product	NMP
0.25	6.7	5	95
0.16	10.4	8	92
0.12	14	10	90
0.08	21	14	86
0.04	42	19	81
0.01	168	23	77

^a determined by ¹H-NMR integration.

In the case of **82a**, at the longest residence time of 168 min, a composition of 23% product to 77% starting material was calculated based on the ¹H-NMR. While full conversion was not achieved during this time, the results were still quite impressive given that, in the Rayonet reactor, an irradiation period of 4 hr was required for a yield of 51% to be achieved.

6.4.2 Reactions of NMP with selected phenylacetates

The merits of using the microreactor were further investigated by attempting various reactions with phenylacetates in the microreactor that were previously carried out in the Rayonet, and comparing the results as shown in **Figure 6.5**.



Scheme 6.5 Experiments 131-134 (R^n groups shown in **Table 6.5**).

Table 6.5 Comparison of results achieved in Rayonet vs Microreactor.

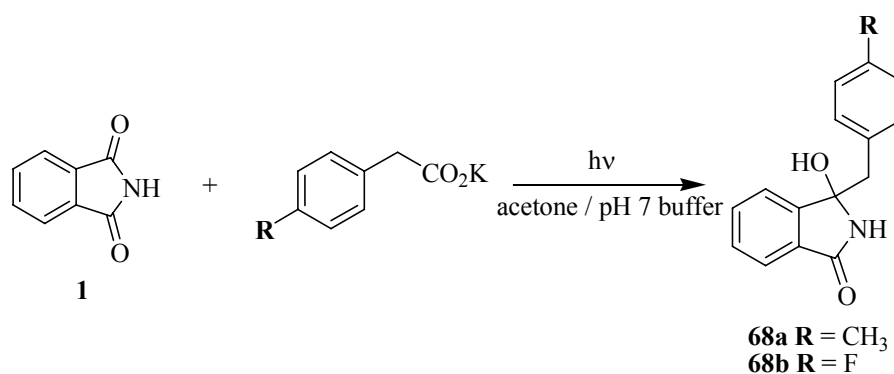
compound	R^1	R^2	R^3	time [hr]	yield [%]	
					rayonet ^a	microreactor
67b	H	CH ₃	H	4	32	93
67e	H	F	H	4	39	53
67 g	H	Cl	Cl	3	53	93
67h	Br	H	H	5	35	60 ^b

^a pure yields, ^b irradiation time 4 hr 40 min

It is apparent that the yields obtained in the microreactor were far superior in all cases despite the irradiation periods being the same for both set-ups. Even in the case of **45**, when the irradiation period was shorter in the microreactor than in the Rayonet reactor, due to limitations of the syringe pump, the result was still an improvement on the conventional method. This indicates that the reaction proceeds more efficiently in the microreactor, and this observation is strengthened by the fact that usually no purification was required with microreactor products compared to the Rayonet.

6.4.3 Reactions of phthalimide with selected phenylacetates

Two examples of reactions using phthalimide as the starting material were then attempted in the microreactor and compared with the conventional results (**Table 6.6**). As in the conventional method, because phthalimide was the chosen starting material, the solvent system used was acetone/pH 7 buffer to prevent deprotonation of the resulting products, which is caused by the increasing pH during irradiation.



Scheme 6.6 Experiments 135 and 136.

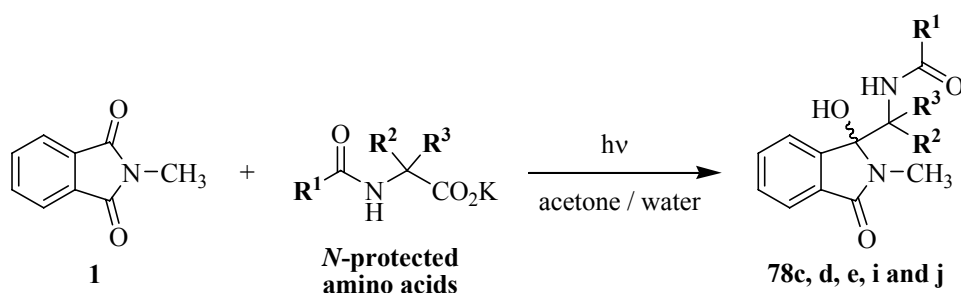
Table 6.6 Comparison results obtained using phthalimide as starting material.

compound	R	yield [%]	
		rayonet [3 hr]	microreactor [2 hr]
68a	CH ₃	92	97
68b	F	85	100

These sample reactions performed in the microreactor both resulted in higher yields of purer photoproducts even with shorter irradiation times. The conventional results obtained were already impressive so it was assumed that the microreactor would make little difference, however remarkably it did in fact improve on the efficiency of both reactions.

6.4.4 Photodecarboxylative addition of *N*-protected amino acids to NMP

As seen in chapter 3, *N*-protected amino acids were successfully reacted with **1** (Scheme 6.7). A selection of these reactions were then scaled down and performed in the microreactor. The results are shown in Table 6.7 below.



Scheme 6.7 Experiments 137-145 (R^n groups shown in Table 6.7 below).

Table 6.7 Results obtained from experiments 137-145.

compound	R^1	R^2	R^3	flow rate [ml/min]	residence time [min]	composition ^a	
						product	NMP
78c	CH ₃	<i>i</i> -Pr	H	0.04	42	4	96
				0.008	210	42	58
78d	CH ₃	<i>i</i> -Bu	H	0.08	21	26	74
				0.04	42	18	82
78e	CH ₃	<i>s</i> -Bu	H	0.08	21	27	73
78i	<i>t</i> -BuCO	CH ₃	H	0.04	42	32	68
				0.01	168	93	7
78j	<i>t</i> -BuCO	PhCH ₂	H	0.04	42	28	72
				0.01	168	53	47

^a determined from ¹H-NMR spectra.

These reactions required longer residence times. However, in all cases, full conversion of **1** was not achieved, even in instances where the irradiation period was the same as in the conventional method such as in the case of **78c**. When irradiated for a period of 3.5 hr, the composition of product vs NMP was calculated to be 42:58. In the conventional set-up, after the same irradiation period, full conversion of **1** was achieved and the product obtained in a yield of 52%. In the case of **78i**, which was irradiated for a length of 2 hr 48 min, a more impressive result was seen with almost full conversion achieved, although in comparison, the conventional reaction

was irradiated for a period of 2 hr resulting in full conversion and the product attained in a yield of 65%.

As the dimensions of the Rayonet reactor and the microreactor differ enormously, space-time yields (STYs), which depend on the reactor geometry, were calculated for the reactions shown in Table 6.7 (in cases of multiple reactions performed the reactions with longest irradiation periods were used for the calculations) and the related comparison reactions performed in the Rayonet reactor (as shown in Chapter 3) using **Equation 2**.

$$STY = n/V_R \times t$$

n = amount of **1** converted

V_R = reactor volume

t = irradiation time

Equation 2 Space-time yield equation.

A more direct comparison can be made between both reactors from these calculated STY values. The results are shown in **Figure 6.6** which depict higher STYs for the microreactor than for the Rayonet reactor.

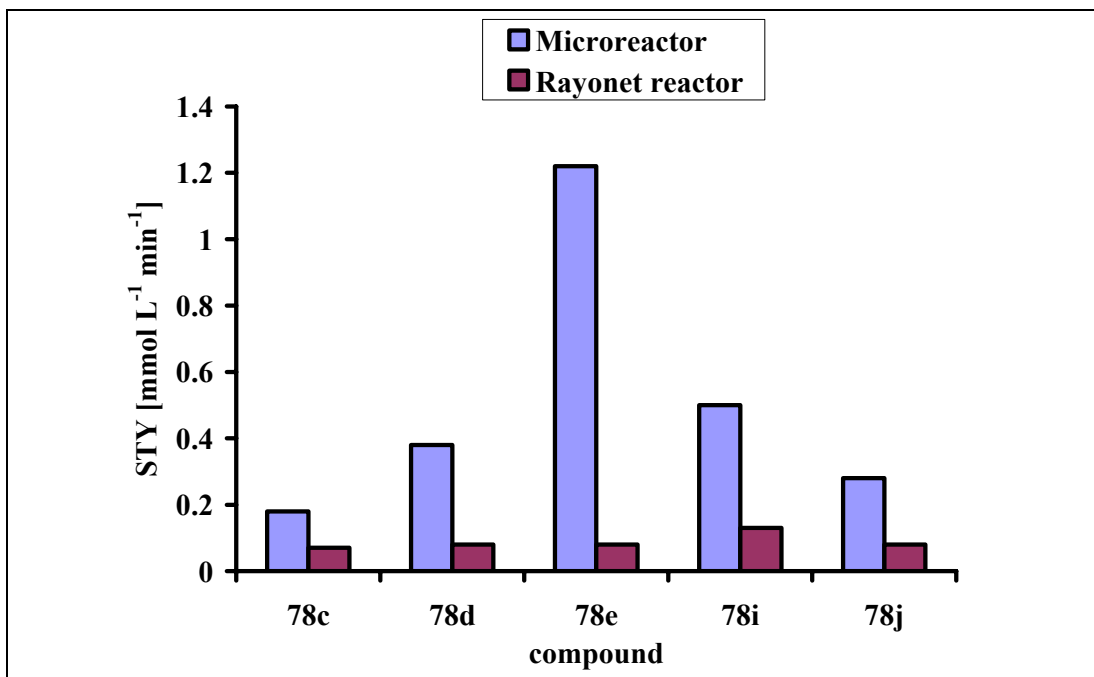
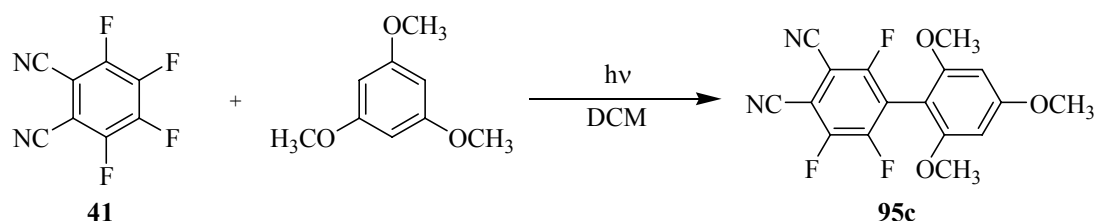


Figure 6.6 STYs for reactions performed in a Rayonet reactor (experiments 42, 44, 46, 50, 52) and comparison reactions performed in a microreactor (experiments 138, 140, 141, 143, 145).

This superiority can be explained by the larger surface to volume ratio of the *dwell device* in combination with the better light penetration within the microreactor. Even though the microreactor results, shown in **Table 6.7**, initially appear less efficient than those obtained in the Rayonet reactor, (as shown in Chapter 3; **Table 3.3**), when the dimensions of both reactors are taken into account the STYs unambiguously show that the microreactor is far superior to the conventional Rayonet reactor.

6.4.5 Reaction of TFPN and trimethoxybenzene

Taking an isolated example from chapter 5, the reaction of TFPN (**41**) and trimethoxybenzene (**Scheme 6.8**) was used to investigate whether the microreactor could improve the production of **95c**. As was found previously with this reaction, the product also absorbs light and hence is in competition with the starting material. It was investigated whether the favourable dimensions of the microreactor would eliminate this competition and therefore result in higher yields of product. The concentration of the reactant solutions were varied, as well as the residence times, in an attempt to achieve a more satisfactory outcome. The results are shown in **Table 6.8**



Scheme 6.8 Experiments 146-149.

Table 6.8 Results obtained from experiments 146-149.

TFPN in 10 ml [mmol]	flow rate [ml/min]	residence time [hr]	composition ^a	
			product ^b	TFPN
0.15	0.007	4	0	100
0.15	0.002	14	18	82
0.03	0.002	14	84	16
0.04	0.001	28	61	39

^a calculated from the ¹⁹F-NMR, ^b **95c**.

Taking the results from the conventional approach into account, the microreactor does appear to increase the performance of the reaction. The concentration of **41** used in the conventional method corresponds to 0.04 mmol, and the reactant solution was irradiated for a total of 70 hr. The composition of product:TFPN was calculated on average to be 58:42 from the ¹⁹F-NMR. Comparing this with the result obtained at a flow rate of 0.001 ml/min, using the same concentration of **41**, it was found that the

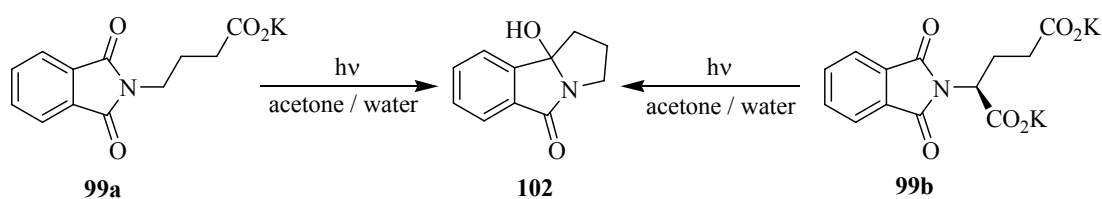
composition ratios were very similar (61:39) even though this reaction was only irradiated for 28 hr. It was initially thought that it would be possible to increase the concentration of the reactants when irradiating in the microreactor, however it seems that this is not the case. In experiment 146, 0.15 mmol of **41** is irradiated for 4 hr and it was found that no reaction took place. Even when the same concentration was used and irradiated for a longer period of time (14 hr) the composition was calculated to be 18:82 with the latter being the product. When a lower concentration (0.03 mmol) of **41** was used and irradiated for the same period of 14 hr, a remarkable improvement in product formation was observed with the composition calculated to be 84:16.

The more dilute the solution, the more the starting material can absorb the light it needs to react and produce the desired product.

6.4.6 *Intra*-molecular cyclisation reactions

All the previous examples featured are examples of *inter*-molecular reactions. In this section a few examples of *intra*-molecular photoreactions were also chosen to investigate how well they would transfer to the microreactor platform.

The reactions shown in **Scheme 6.9** are two examples of these *intra*-molecular reactions which both result in the same final product being formed (**101**).



Scheme 6.9 Experiments 150-155.

Table 6.9 Results for experiments 150 and 151 performed in the Rayonet reactor.

starting material	time [hr]	yield [%]
99a	5.5	82
99b	2	42

In experiments 150 and 151, both **99a** and **99b** were irradiated in the Rayonet photoreactor and the reactions allowed to go to completion, which was 5.5 hr and 2 hr respectively, and yields of 82% and 42% were obtained (**Table 6.9**).

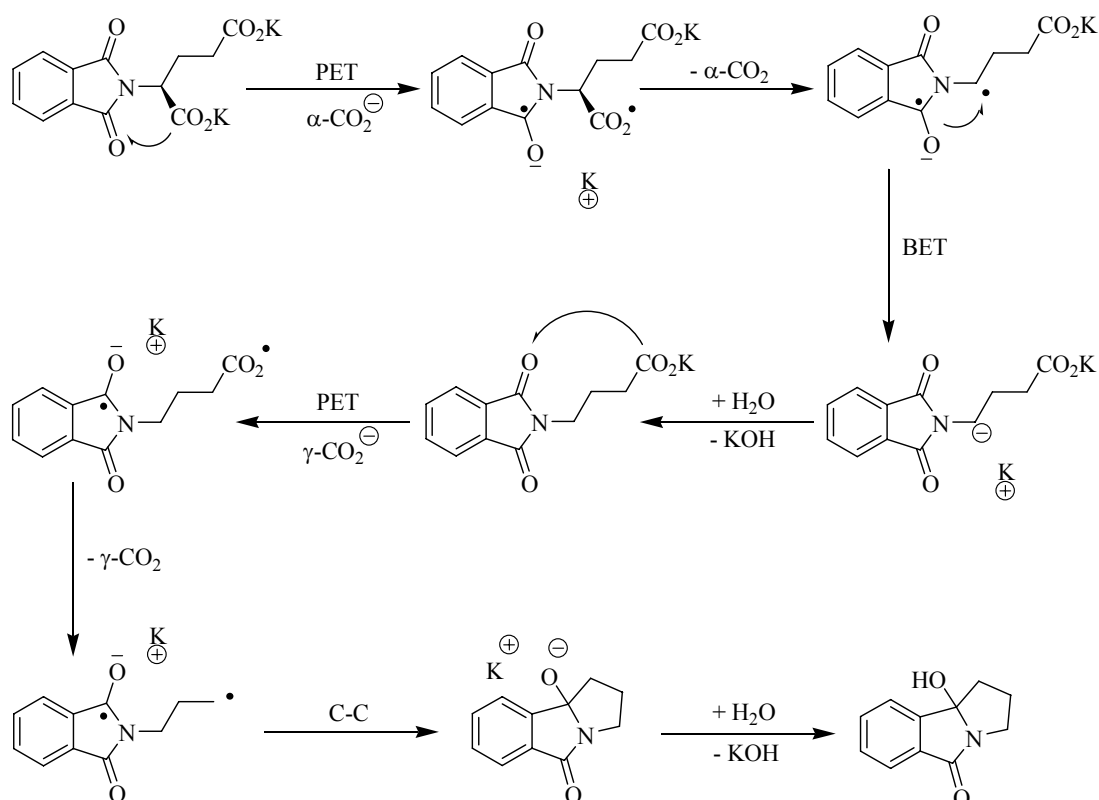
The comparison reactions, experiments 152 and 153 (**Table 6.10**), were carried out in the microreactor at a flow rate of 0.08 ml/min giving a residence time of 21 min for both reactions resulting in yields of 60% and 33% respectively. This result was quite impressive when taking into account the difference in irradiation periods.

As a further comparison, the reactions were again performed using the conventional method, this time only irradiating for 21 min. The corresponding yields for experiments 154 and 155 were found to be 64% and 17% respectively (**Table 6.10**). Similar results were achieved using **99a** as a substrate, while the microreactor produced the product **102** in a more generous yield when **99b** was used as starting material.

Table 6.10 Comparison of cyclisation reactions; conventional vs. micro.

experiment	starting material	time [min]	yield [%]	
			rayonet	microreactor
152 and 154	99a	21	64	60
153 and 155	99b	21	17	33

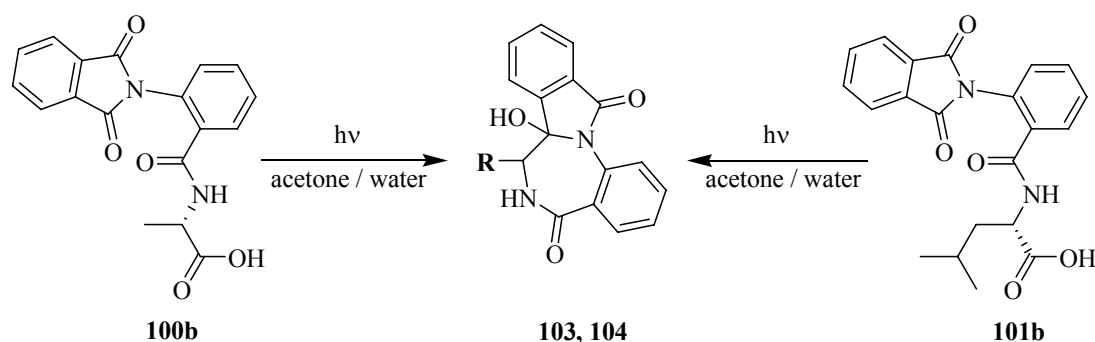
As mentioned previously, in experiment 150, after 5.5 hr irradiation of the substrate **99a**, a high yield of 82% was obtained. However, for experiment 151 a moderate yield of 42% was obtained upon irradiation of the substrate **99b** for 2 hr. The differences in yields obtained can be explained by exploring the mechanisms of these reactions. The starting material **99a** follows the usual photodecarboxylation pathway to obtain the cyclisation product **102**. The reaction mechanism for **99b** is shown in **Scheme 6.10**.



Scheme 6.10 Mechanism for the cyclisation reaction of **99b**.

In the case of **99b**, there are two carboxylates present so it would follow that a longer irradiation time would be needed for this reaction to go to completion. The poor yield can be put down to the fact that the reaction is incomplete, as there are two photochemical reactions taking place here. **99b** undergoes one photodecarboxylation at the α -carboxyl, effectively resulting in the formation of **99a**. This in turn undergoes a second photodecarboxylation at the γ -carboxyl, which leads to the eventual cyclised product.

Two further examples of *intra*-molecular reactions are shown in **Scheme 6.11** using the previously synthesised *N*-phthalimido carboxylic acid derivatives **100b** and **101b**. In experiments 156 and 157, both starting materials were irradiated under conventional conditions for a period of 4 hr and 2.5 hr resulting in yields of 40% and 58% respectively as shown in **Table 6.11**.



Scheme 6.11 Experiment 156-159.

Table 6.11 Results obtained in experiments 156 and 157 using the conventional method.

compound	R	time [hr]	yield [%]
103	CH ₃	4	40
104	<i>i</i> -Bu	2.5	58

In experiments 158 and 159, the same reactions were performed in the microreactor and once again showed more impressive yields than their conventional counterparts with shorter irradiation times (**Table 6.12**).

Table 6.12 Results obtained in experiments 158 and 159 using the microreactor.

compound	R	flow rate [ml/min]	residence time [min]	yield [%]
103	CH ₃	0.01	168	35
104	<i>i</i> -Bu	0.03	56	87

In experiment 158, the product was formed in a yield of 35% after only 2 hr 48 min while the conventional procedure achieved a yield of 40% after a total of 4 hr irradiation. In particular, the result obtained in experiment 159 shows a marked improvement in the efficiency of the reaction with an impressive yield of 87% being achieved after an irradiation period of just 56 min, while the conventional method only achieved a yield of 58% after a longer irradiation period of 2 hr 30 min.

One of the main differences between the two methods was that 16 lamps were used to irradiate the solution in the Rayonet reactor, whereas only 5 lamps were used to irradiate the microreactor under the Luzchem panel. If this is taken into account, all the results obtained in the microreactor are even more impressive.

6.5 Summary

Several model reactions were chosen to perform in a microreactor, including *inter*-molecular decarboxylative additions and *intra*-molecular cyclisation reactions, in an attempt to reproduce or improve the results already obtained by the conventional method. In most cases, the use of a microreactor enabled the decrease of reaction times while also increasing yields. The reaction of NMP with phenylacetic acid was chosen to optimise the reaction conditions in the microreactor as it was known to have a short irradiation time (1-2 hr). It was found that as the flow rate decreased, conversion rates increased until full conversion was achieved after 42 min, which was achieved at a flow rate of 0.04 ml/min. A selection of further reactions including NMP with *N*-protected amino acids, phthalimide with phenylacetates and several cyclisation reactions were also performed. In general all the results obtained were superior to those acquired by the conventional method.

Comparison reactions were carried out in the conventional Rayonet chamber reactor, under similar conditions. Space-time yields (STYs) were calculated for both reactors to give a reasonable comparison. It is apparent from STYs that the microreactor is in fact more efficient than the Rayonet reactor.

Thesis conclusions

One of the main aims of this work was to investigate the feasibility of microreactors in organic synthesis. As a reference for this, a number of *inter*- and *intra*-molecular photodecarboxylative (PDC) additions of carboxylates to phthalimides were first performed in a conventional Rayonet reactor.

Phthalimide chemistry:

Phthalimide chemistry was extensively discussed in Chapters 2 and 3. A number of compounds were successfully synthesised and several of these reactions were used as model reactions to display the advantages of microreactors. The reaction of **1** with phenylacetic acid was used to successfully optimise the microreactor set-up, and it was also the first reaction to show the superiority of the microreactor compared to the conventional method as demonstrated in Chapter 6. A number of comparison addition reactions, using both **1** and **7** with various phenyl acetates, also exhibited better results when performed in the microreactor.

Several reactions of **1** with *N*-acetylated amino acids resulted in incomplete conversions of **1** to the target compounds, even when irradiated for the same irradiation periods as in the conventional reactor. However, upon applying STY calculations to both sets of results, which take reactor geometry into account, the microreactor once again came out on top.

Aristolactam synthesis:

In Chapter 4, it was investigated whether aristolactams could be synthesised from the PDC addition products *via* an efficient photochemical method. Two aristolactams were successfully synthesised by this method, however there were limitations using this approach which were investigated at length. It was thought that solubility problems in addition to electronic effects were the cause of the issues encountered. It was also proved that the final ring closure step occurs *via* dehydrohalogenation and will not occur *via* electrocyclisation.

Phthalonitriles and phthalocyanines:

In Chapter 5, synthetic organic photochemistry was used for the preparation of three phthalonitrile derivatives. Two of these derivatives were successfully selectively sulfonated making them water soluble and thus, suitable compounds for labelling in cell-imaging studies. As water solubility is also a desirable feature of Pcs, it was then attempted to condense the dimethoxy-substituted phthalonitrile derivative to its corresponding phthalonitrile. This method was not successful, however the selectively sulfonated Pc **98b** was thought to be synthesised by performing the sulfonation after the Pc was formed. This valuable achievement has yet to be confirmed, however the work shown in this chapter is certainly an exciting first step in the process of selectively sulfonating a Pc.

The reaction to synthesise the trimethoxy-substituted phthalonitrile derivative was also carried out in the microreactor at various flow rates and concentrations. These reactions also showed an improvement in the conversion of **41** to the target compound **95c**, compared with the results obtained in the Rayonet reactor.

Investigating the feasibility of microreactors in organic photochemistry:

As mentioned in the thesis proposal the ultimate aim of this work was to prove that microphotochemistry is an efficient tool in organic synthesis. By comparing the array of results obtained by the conventional method with those achieved in the microreactor, it was plain to see that the microreactor is a more efficient method of performing reactions. In all cases, the microreactor gave superior results and when it is taken into account that there were 16 lamps in the Rayonet reactor and only 5 lamps in the microreactor set-up, the results are even more impressive. The STY calculations showed the effectiveness of the microreactor was down to its larger surface to volume ratio combined with better light penetration. The fact that the product is removed from the microreactor immediately after being formed is another reason for the improved performance of the microreactor, as this allows the starting materials to absorb the light more efficiently.

In general, the products formed in the microreactor also appeared cleaner which meant that less purification was required, which is another advantage of the microreactor. The only disadvantage with using this method instead of the conventional one is the small amount of product obtained following a lengthy experiment as, for example, at a flow rate of 0.08 ml/min only 1.68 ml of reactant

solution is irradiated during the 21 minute residence time. Consequently, to obtain a sufficient amount of product for analysis becomes quite time-consuming. The solution to this however, if necessary, is to run several microreactors in parallel so a larger amount of product can be synthesised in the same period of time.

Thus far, the investigation into the use of microreactors has been very positive with some remarkable results achieved. Of course there is room for improvement, which could be achieved with new types of microreactors. For example a microreactor could be constructed using a single lamp inserted into a cylindrical glass tube, with clear tubing wrapped around the tube. The reactant solution could be pumped through the tubing, which, depending on the length of tubing, could result in longer residence times for a larger volume of solution. This system would also use less energy due to the single lamp needed, making it a cheaper and more efficient reactor than those commercially available.

From the reactions shown and discussed in this work it has been verified that microreactors are an efficient tool in organic synthesis and that microphotochemistry is a viable alternative to conventional methods.

Chapter 7

7 Experimental

Spectroscopic methods

NMR: NMR spectra were recorded on a *Bruker 400 UltrashieldTM* instrument (400 MHz for ¹H; 100 MHz for ¹³C) using the *Bruker Topspin 2.0* software. Chemical shift values are referred to solvent residual resonances: CDCl₃ (7.26/77.36 ppm), DMSO-d₆ (2.54/40.45 ppm) and acetone-d₆ (2.09/30.60 and 206.3 ppm). Chemical shifts δ are given in ppm, coupling constants *J* in Hz.

UV-Visible spectroscopy: UV-Vis spectra were recorded using a Varian Cary 50 scan UV-Vis spectrophotometer.

Mass spectrometry: Mass spectra (MS) were recorded using a Bruker Daltonics Esquire-LC ion trap MS with an electrospray ionisation interface at atmospheric pressure. 100 μ l of each sample contained in a glass syringe fitted to an automatic syringe pump was injected into the mass spec detector at a rate of 300 μ l/h.

Chromatography methods

Column chromatography: Column chromatography was carried out using Merck silica gel 60 (particle size 0.063-0.200 nm for column chromatography) 70-230 mesh ASTM.

Thin Layer Chromatography (TLC): Analytical thin-layer chromatography was performed on aluminium sheets coated with 0.20 mm of Fluka silica gel ITCL-cards with fluorescent indicator 254 nm, layer thickness: 0.2mm.

Conventional photolysis

Glassware: All photoreactions were performed in *Pyrex*[®] tubes of various volumes.

Conventional reactor: Photochemical reactions were performed in a *RPR-200 Rayonet photochemical chamber reactor* (Southern New England Ultraviolet Company) equipped with *RPR 3000 Å lamps* ($\lambda_{\text{max}} = 300 \pm 25$ nm). All reactions were carried out under an atmosphere of nitrogen.

Micro photolysis

Microreactor: Microreactions were performed in a *dwell-device (Mikroglas)*, made of FOTURAN® glass; total path length of 1.15 m (20 turns) on a 118 mm x 73 mm aperture and consisting of a (bottom) serpentine channel with a second (top), heat-exchanging channel through which cooling water is passed.

Irradiation source: The *dwell-device* was placed under a Luzchem UV-panel equipped with 5 LZC-UVB lamps (300 ± 25 nm).

Pump: A Harvard apparatus *11 plus* syringe pump was used to pump the degassed reactant solution through the *dwell-device*.

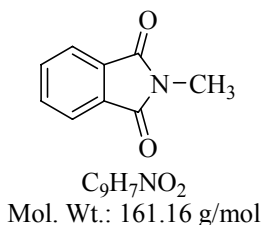
Solvents and reagents

All solvents and starting materials were obtained from commercial suppliers (*Sigma-Aldrich* and *Fluka*) and were used without purification.

7.1 Chapter 2: Photoaddition reactions of NMP and phthalimide

Experiment 1

2-methylisoindoline-1,3-dione (NMP) (1) (SG-3)



N-Methylformamide (80 ml) and phthalic anhydride (10.0 g, 67.52 mmol) were stirred and heated for 8 hr at 150°C. After cooling down to R.T. fine, colourless, needle-like crystals were formed. The mixture was filtered by vacuum filtration, washed with ~10 ml EtOH and then left to dry. This reaction mixture gave 6.5 g (40.40 mmol; 60%) of *N*-methylphthalimide. It was observed that crystals also formed in the filtrate when cooled on ice. These were also vacuum-filtered and washed with ethanol. After drying, the yield of these crystals was found to be 1.3 g (7.75 mmol; 11.5%). ¹H-NMR spectra were obtained for both sets of crystals and as both were found to be very pure, no further purification steps were necessary. The product consisted of fine, colourless, needle-like crystals. The overall yield was 71%.

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 3.11 (s; 3H; NCH₃), 7.70 (dd; ³J = 8.6, ⁴J = 5.6 Hz; 2H; CH_{arom}), 7.84 (dd; ³J = 8.6, ⁴J = 5.6 Hz; 2H; CH_{arom}).

¹³C-NMR: (100 MHz, CDCl₃): δ (ppm) = 24.3 (1C; NCH₃), 123.5 (2C; CH_{arom}), 132.5 (2C; Cq), 134.2 (2C; CH_{arom}), 168.8 (2C; C=O).

Literature reference No.: [123]

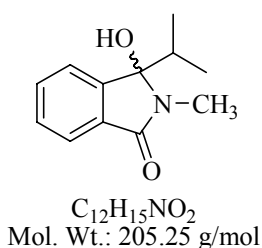
CAS No.: 550-44-7

7.1.1 General Procedure (A):

NMP (1.5 mmol) was dissolved in 10 ml of acetone. The addition partner (4.5 mmol) was added to K_2CO_3 (2.25 mmol) and dissolved in 15 ml of distilled H_2O and 5 ml of acetone. These solutions were mixed together and poured into a 100 ml Pyrex Schlenk flask and sonicated for 5 min. The Schlenk flask containing the solution was placed in the photoreactor and 70 ml of a mixture of acetone/water (50:50) added. The photoreactor was then switched on and the solution irradiated with light ($\lambda = 300 \pm 20$ nm) while purging with a slow stream of N_2 . The progress of the reaction was checked periodically by TLC, using solvent mixture ethyl acetate:hexane (1:1). When the reaction was complete (starting material spot had disappeared and product spot had formed), acetone was removed by rotary evaporation at $\sim 50^\circ C$ and the remaining solution was extracted with DCM (3×50 ml). The two layers were separated (organic \rightarrow bottom layer, aqueous \rightarrow top layer) and the organic layer washed with saturated $NaHCO_3$ (2×30 ml) and then with saturated $NaCl$ (2×30 ml). The organic layer was collected and dried over $MgSO_4$, filtered by gravity filtration and the DCM evaporated from the filtrate by rotary evaporation at $\sim 40^\circ C$. A 1H -NMR was obtained for the crude product. Column chromatography was then carried out using solvent mixture ethyl acetate:hexane (1:1) and the fraction containing the desired product collected. A 1H -NMR was subsequently obtained to confirm this.

Experiment 2

3-hydroxy-3-isopropyl-2-methylisoindolin-1-one (66a) (SG-154b)



General procedure (A) was followed using NMP (0.2 g, 1.51 mmol), *i*-butyric acid (0.4 g, 4.56 mmol) and K_2CO_3 (0.3 g, 2.26 mmol). A bubbler filled with a solution of saturated barium hydroxide was placed on one arm of the Schlenk flask to test for the

presence of CO₂. This test was positive (solution turned from clear to milky) so CO₂ was indeed formed during the reaction. After 7 hr the TLC showed the product was formed. The solution was clear and yellow at this point. The product was found to be a colourless solid and the ¹H-NMR obtained confirmed this was the pure product. The yield was found to be 0.2 g (1.11 mmol, 74%). The product was a yellow solid.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 0.51 (d; ³J = 6.8Hz; 3H; CH₃), 1.21 (d; ³J = 6.8Hz; 3H; CH₃), 2.43 (m; 1H; CH), 2.91 (s; 3H; NCH₃), 5.20 (br.s; 1H; OH), 7.50 (ddd; ³J = 7.2Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.58 (ddd; ³J = 7.2Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.61-7.66 (br.m; 2H; CH_{arom}).

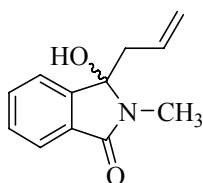
¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 16.8 (1C; CH₃), 17.5 (1C; CH₃), 23.6 (1C; NCH₃), 34.6 (1C; CH), 93.2 (1C; COH), 123.1 (1C; CH_{arom}), 124.1 (1C; CH_{arom}), 129.8 (1C; CH_{arom}), 132.1 (1C; CH_{arom}), 133.6 (1C; Cq), 146.7 (1C; Cq), 167.0 (1C; C=O).

Literature reference No.: [34b]

CAS No.: 32360-86-4

Experiment 3

3-Allyl-3-hydroxy-2-methylisoindolin-1-one (66b) (SG-22)



C₁₂H₁₃NO₂
Mol. Wt.: 203.24 g/mol

General procedure (A) was followed using NMP (0.2 g, 1.53 mmol), vinyl acetic acid (0.38 ml, 4.50 mmol) and K₂CO₃ (0.3 g, 2.27 mmol). After 5 hr the TLC showed a product was formed. The solution changed from colourless to pale yellow. The crude yield was found to be 0.1 g. Following column chromatography it was assumed from the TLC that the desired product was collected in fraction 2, which

was confirmed by $^1\text{H-NMR}$. The yield of the pure product was 0.1 g (0.36 mmol, 24%), which was bright yellow in colour.

$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 2.72 (dd; $^2J = 14.0\text{Hz}$; $^3J = 7.6\text{Hz}$; 1H; CH_2), 2.74 (s; 3H; NCH_3), 2.89 (dd; $^2J = 14.4\text{Hz}$; $^3J = 6.0\text{Hz}$; 1H; CH_2), 4.01 (br.s; 1H; OH), 4.89 (dd; $^2J = 10.0\text{Hz}$; $^3J = 0.8\text{Hz}$; 1H; $\text{CH}_2_{\text{olef}}$), 4.96 (dd; $^2J = 16.8\text{Hz}$; $^3J = 1.2\text{Hz}$; 1H; $\text{CH}_2_{\text{olef}}$), 5.09-5.19 (m; 1H; CH_{olef}) 7.37 (m; 1H; CH_{arom}) 7.48 (d; $^3J = 7.2\text{Hz}$; 1H; CH_{arom}), 7.55 (m; 2H; CH_{arom}).

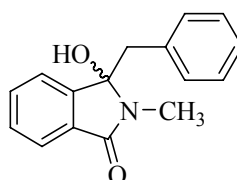
$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 23.4 (1C; NCH_3), 40.3 (1C; CH_2), 90.0 (1C; C-OH), 119.6 (1C; $\text{CH}_{2\text{olef}}$), 122.1 (1C; CH_{olef}), 123.0 (1C; CH_{arom}), 129.5 (1C; CH_{arom}), 130.6 (1C; CH_{arom}), 131.1 (1C; Cq), 132.1 (1C; CH_{arom}), 146.3 (1C; Cq), 167.3 (1C; C=O).

Literature reference No.: [146]

CAS No.: 3103-20-6

Experiment 4

3-Benzyl-3-hydroxy-2-methylisoindolin-1-one (67a) (SG-1)



$\text{C}_{16}\text{H}_{15}\text{NO}_2$
Mol. Wt.: 253.30 g/mol

General procedure (A) was followed using NMP (0.2 g, 1.49 mmol), 2-phenylacetic acid (0.6 g, 4.58 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After 1 hr the TLC showed the product was formed. The solution was clear and a very light yellow in colour. The crude material was found to be 0.5 g. Following column chromatography it was assumed from the TLC, that the desired product was collected in the second fraction. The $^1\text{H-NMR}$ obtained confirmed this and the yield was found to be 0.2 g (0.80 mmol, 54%). The product was colourless and powder-like.

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 2.88 (s; 3H; NCH₃), 3.09 (d; ²J = 14.0Hz; 1H; CH₂), 3.46 (d; ²J = 14.0Hz; 1H; CH₂), 3.67 (br.s; 1H; OH), 6.86 (m; 2H; CH_{arom}), 7.10 (br.m; 3H; CH_{arom}), 7.25 (d; ³J = 7.6Hz; 1H; CH_{arom}), 7.32 (ddd; ³J = 7.2Hz; ⁴J = 0.8Hz; 1H; CH_{arom}), 7.41 (d; ³J = 7.6Hz; 1H; CH_{arom}), 7.45 (ddd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}).

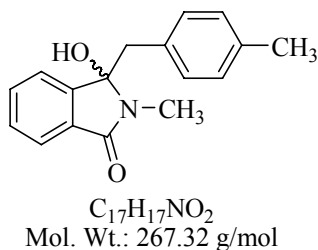
¹³C-NMR: (100 MHz, CDCl₃): δ (ppm) = 23.9 (1C; NCH₃), 42.4 (1C; CH₂), 90.7 (1C; COH), 122.7 (1C; CH_{arom}), 123.0 (1C; CH_{arom}), 127.0 (1C; CH_{arom}), 128.0 (2C; CH_{arom}), 129.5 (1C; CH_{arom}), 130.0 (2C; CH_{arom}), 131.1 (1C; Cq), 131.7 (1C; CH_{arom}), 134.4 (1C; Cq), 146.1 (1C; Cq), 167.1 (C; C=O).

Literature reference No.: [18]

CAS No.: 4770-23-4

Experiment 5

3-(2-iodobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67b) (SG-40)



General procedure (A) was followed using NMP (0.2 g, 1.51 mmol), *p*-tolylacetic acid (0.7 g, 4.51 mmol) and K₂CO₃ (0.3 g, 2.25 mmol). After 2 hr the TLC showed a product was formed. The solution was cloudy and a very pale yellow in colour. The crude yield was found to be 0.4 g. The crude product was washed by adding a small amount of acetone to the round bottom flask, swirling and removing the solvent. This was repeated several times and the product seen to be a colourless powder which was confirmed to be the pure product by ¹H-NMR. The yield of the pure product was 0.2 g (0.80 mmol, 53%).

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 2.19 (s; 3H; CH₃), 3.08 (s; 3H; NCH₃), 3.32 (d; ²J = 13.6Hz; 1H; CH₂), 3.50 (d; ²J = 14.0Hz; 1H; CH₂), 5.38 (br.s; 1H; OH),

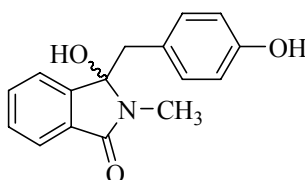
6.82 (dd; $^3J = 8.0\text{Hz}$; 2H; CH_{arom}), 6.90 (dd; $^3J = 8.0\text{Hz}$; 2H; CH_{arom}), 7.42-7.50 (br.m; 2H; CH_{arom}), 7.60 (m; 2H; CH_{arom}).

^{13}C -NMR: (100 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 20.8 (1C; CH_3), 23.9 (1C; NCH_3), 42.4 (1C; CH_2), 90.9 (1C; COH), 122.6 (1C; CH_{arom}), 123.5 (1C; CH_{arom}), 128.8 (2C; CH_{arom}), 129.4 (1C; CH_{arom}), 130.4 (2C; CH_{arom}), 131.8 (1C; CH_{arom}), 132.8 (1C; Cq), 133.0 (1C; Cq), 136.2 (1C; Cq), 148.1 (1C; Cq), 166.6 (1C; $\text{C}=\text{O}$).

CAS No.: 1197385-24-2

Experiment 6

3-(4-hydroxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (67c) (SG-43)



$\text{C}_{16}\text{H}_{15}\text{NO}_3$
Mol. Wt.: 269.3 g/mol

General procedure (A) was followed using NMP (0.2 g, 1.52 mmol), 4-hydroxyphenylacetic acid (0.7 g, 4.50 mmol) and K_2CO_3 (0.3 g, 2.26 mmol). After 5 hr the reaction was worked up and the crude material found to have a yield of 0.20 g. The ^1H -NMR obtained showed the product had been formed, but NMP was also present. The ratio of NMP to product was calculated from the ^1H -NMR to be 79:21. Following column chromatography it was assumed from the TLC, that the desired product was collected in fraction 8. The ^1H -NMR obtained confirmed this and the yield was found to be 0.07 g (0.27 mmol, 18%). The product was a colourless powder.

^1H -NMR: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 3.08 (s; 3H; NCH_3), 3.25 (d; $^2J = 14.0\text{Hz}$; 1H; CH_2), 3.43 (d; $^2J = 14.0\text{Hz}$; 1H; CH_2), 5.35 (br.s; 1H; OH), 6.56 (d; $^3J = 6.4\text{Hz}$; 2H; CH_{arom}), 6.76 (d; $^3J = 6.4\text{Hz}$; 2H; CH_{arom}), 7.43-7.50 (br.m; 2H; CH_{arom}), 7.58 (m; 2H; CH_{arom}), 8.15 (br.s; 1H; OH).

^{13}C -NMR: (100 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 23.9 (1C; NCH_3), 42.2 (1C; CH_2), 91.1 (1C; COH), 115.3 (2C; CH_{arom}), 122.6 (1C; CH_{arom}), 123.6 (1C; CH_{arom}), 126.2 (1C;

CH_{arom}), 129.4 (1C; CH_{arom}), 131.4 (2C; CH_{arom}), 131.8 (1C; Cq), 133.0 (1C; Cq), 148.3 (1C; Cq), 157.0 (1C; Cq), 166.7 (1C; C=O).

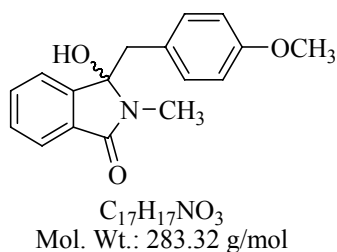
Mass spec: [MS + Na]: 292 m/z; expected 269 m/z

Melting point: 147-150°C

CAS No.: 1197385-25-3

Experiment 7

3-(4-methoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (67d) (SG-47)



General procedure (A) was followed using NMP (0.2 g, 1.53 mmol), 2-(4-methoxyphenyl)acetic acid (0.8 g, 4.53 mmol) and K₂CO₃ (0.3 g, 2.28 mmol). After 4 hr the TLC showed the product was formed. The solution was cloudy and milky at this point. The crude material was found to be 0.5 g. Following column chromatography it was assumed from the TLC, that the desired product was collected in fraction 8. The ¹H-NMR obtained confirmed this and the yield was found to be 0.3 g (1.20 mmol, 78%). The product was a yellow, oily solid.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.08 (s; 3H; NCH₃), 3.29 (d; ²J = 14.0Hz; 1H; CH₂), 3.47 (d; ²J = 13.6Hz; 1H; CH₂), 3.69 (s; 3H; OCH₃), 5.40 (br.s; 1H; OH), 6.65 (d; ³J = 8.8Hz; 2H; CH_{arom}), 6.86 (d; ³J = 8.8Hz; 2H; CH_{arom}), 7.42-7.50 (br.m; 2H; CH_{arom}), 7.59 (m; 2H; CH_{arom}).

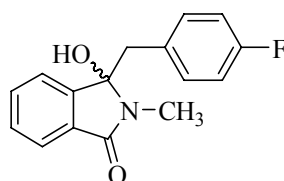
¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 23.7 (1C; NCH₃), 42.1 (1C; CH), 55.2 (1C; OMe), 91.3 (1C; COH), 113.8 (2C; CH_{arom}), 122.9 (1C; CH_{arom}), 123.7 (1C; CH_{arom}), 128.0 (1C; Cq), 129.8 (1C; CH_{arom}), 131.8 (2C; CH_{arom}), 132.1 (1C; CH_{arom}), 133.0 (1C; Cq), 148.0 (1C; Cq), 159.3 (1C; Cq), 166.9 (1C; C=O).

Literature reference No.: [147]

CAS No.: 813460-03-6

Experiment 8

3-(4-fluorobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67e) (SG-41)



$C_{16}H_{14}FNO_2$
Mol. Wt.: 271.29 g/mol

General procedure (A) was followed using NMP (0.2 g, 1.52 mmol), 4-fluorophenylacetic acid (0.7 g, 4.51 mmol) and K_2CO_3 (0.3 g, 2.27 mmol). After 2 hr the TLC showed a product was formed. The solution was cloudy and a very pale yellow in colour. The crude yield was found to be 0.4 g. The crude product was washed by adding a small amount of acetone to the round bottom flask, swirling and removing the solvent. This was repeated several times and the product seen to be a colourless powder which was confirmed to be the pure product by 1H -NMR. The yield of the pure product was 0.1 g (0.55 mmol, 36%).

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.09 (s; 3H; NCH_3), 3.35 (d; $^2J = 13.6$ Hz; 1H; CH_2), 3.53 (d; $^2J = 14.0$ Hz; 1H; CH_2), 5.44 (br.s; 1H; OH), 6.87 (m; 2H; CH_{arom}), 6.99 (m; 2H; CH_{arom}), 7.43-7.51 (br.m; 2H; CH_{arom}), 7.59 (m; 2H; CH_{arom}).

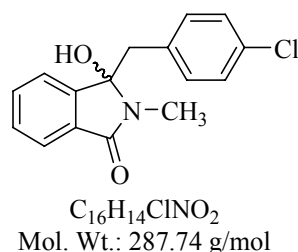
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 23.9 (1C; NCH_3), 41.9 (1C; CH_2), 90.8 (1C; COH), 114.8 (1C; CH_{arom}), 115.0 (1C; CH_{arom}), 122.6 (1C; CH_{arom}), 123.5 (1C; CH_{arom}), 129.5 (1C; CH_{arom}), 131.9 (1C; CH_{arom}), 132.3 (1C; CH_{arom}), 132.4 (1C; CH_{arom}), 132.7 (1C; Cq), 147.9 (1C; Cq), 160.8 (1C; Cq), 163.2 (1C; Cq), 166.6 (1C; C=O).

Melting point: 149-152°C

CAS No.: 1197385-26-4

Experiment 9

3-(4-Chlorobenzyl)-3-hydroxy-2-methylisindolin-1-one (67f) (SG-2)



General procedure (A) was followed using NMP (0.2 g, 1.49 mmol), 2-(4-chlorophenyl) acetic acid (0.8 g, 4.50 mmol) and K₂CO₃ (0.3 g, 2.25 mmol). After 5 hr the TLC showed the product was formed. The solution was cloudy yellow in colour. The crude yield was found to be 0.5 g. Following column chromatography it was assumed from the TLC that the desired product was collected in the second fraction. The NMR obtained confirmed this and the yield was found to be 0.1 g (0.43 mmol, 29%). The product was initially an oily substance but when left overnight a solid, colourless, wax-like product formed. The crude ¹H-NMR revealed that only 52% of the starting material had reacted, and therefore the % yield was calculated based on the conversion factor as 56%.

¹H-NMR: (400 MHz, CDCl₃) : δ (ppm) = 2.71 (s; 3H; NCH₃), 3.30 (br.s; 1H; OH), 3.46 (d; ²J = 14.0Hz; 1H; CH₂), 3.60 (d; ²J = 14.4Hz; 1H; CH₂), 7.01 (d; ³J = 8.4Hz; 2H; CH_{arom}), 7.09 (d; ³J = 8.4Hz; 2H; CH_{arom}), 7.35 (m; 1H; CH_{arom}), 7.39-7.44 (br.m; 2H; CH_{arom}), 7.65 (m; 1H; CH_{arom}).

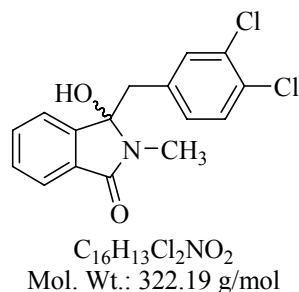
¹³C-NMR: (100 MHz, CDCl₃): δ (ppm) = 23.8 (1C; NCH₃), 41.7 (1C; CH₂), 90.5 (1C; COH), 122.4 (1C; CH_{arom}), 123.3 (1C; CH_{arom}), 129.3 (2C; CH_{arom}), 130.2 (1C; CH_{arom}), 131.9 (1C; Cq), 132.4 (1C; CH_{arom}), 133.2 (2C; CH_{arom}), 133.6 (1C; Cq), 133.8 (1C; Cq), 145.6 (1C; Cq), 167.8 (1C; C=O).

Melting point: 90-94°C

CAS No.: 1197385-27-5

Experiment 10

3-(3,4-Dichlorobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67 g) (SG-5)



General procedure (A) was followed using NMP (0.2 g, 1.50 mmol), 3,4-dichlorophenylacetic acid (0.9 g, 4.50 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After 3 hr the TLC showed a product was formed. Following column chromatography it was assumed from the TLC that the desired product was collected in fraction 4. The 1H -NMR obtained confirmed this and the yield was found to be 0.3 g, (0.80 mmol, 53%). The product formed a colourless, flaky, powder-like substance.

1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) = 2.80 (s; 3H; NCH_3), 2.95 (d; $^2J = 14.0$ Hz; 1H; CH_2), 3.40 (d; $^2J = 13.6$ Hz; 1H; CH_2), 3.98 (br.s; 1H; OH), 6.72 (dd; $^3J = 8.4$ Hz; $^4J = 2.4$ Hz; 1H; CH_{arom}), 7.02 (d; $^4J = 2.0$ Hz; 1H; CH_{arom}), 7.18 (m; 2H; CH_{arom}), 7.34 (ddd; $^3J = 7.2$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}), 7.40 (m; 1H; CH_{arom}), 7.48 (ddd; $^3J = 7.2$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}).

^{13}C -NMR: (100 MHz, $CDCl_3$): δ (ppm) = 23.9 (1C; NCH_3), 41.7 (1C; CH_2), 90.1 (1C; COH), 122.7 (1C; CH_{arom}), 123.2 (1C; CH_{arom}), 129.4 (1C; CH_{arom}), 129.8 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 130.9 (1C; Cq), 131.2 (1C; Cq), 131.9 (1C; CH_{arom}), 132.1 (1C; CH_{arom}), 134.8 (1C; Cq), 145.7 (1C; Cq), 167.0 (1C; C=O).

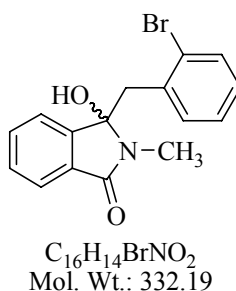
Mass spec: [MS + Na]: 346 m/z; expected 322 m/z

Melting point: 149-151°C

CAS No.: 1197385-28-6

Experiment 11

3-(2-bromobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67h) (SG-42)



General procedure (A) was followed using NMP (0.2 g, 1.52 mmol), 2-bromophenylacetic acid (1.0 g, 4.50 mmol) and K₂CO₃ (0.3 g, 2.26 mmol). After 5 hr the TLC showed a product was formed. The solution was cloudy and milky. The crude yield was found to be 0.4 g. The crude product was washed by adding a small amount of acetone to the round bottom flask, swirling and removing the solvent. This was repeated several times and the product seen to be a pale yellow powder which was confirmed to be the pure product by ¹H-NMR. The yield of the pure product was 0.2 g (0.53 mmol, 35%).

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.05 (s; 3H; NCH₃), 3.39 (d; ²J = 14.0Hz; 1H; CH₂), 3.70 (d; ²J = 14.0Hz; 1H; CH₂), 6.45 (br.s; 1H; OH), 7.15 (ddd; ³J = 7.2Hz; ⁴J = 1.6Hz; 1H; CH_{arom}), 7.24 (ddd; ³J = 8.0Hz; ⁴J = 1.2Hz; 2H; CH_{arom}), 7.30 (ddd; ³J = 8.0Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.45-7.52 (br.m; 3H; CH_{arom}), 7.60 (m; 1H; CH_{arom}).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 24.0 (1C; NCH₃), 42.3 (1C; CH₂), 90.3 (1C; COH), 122.7 (1C; CH_{arom}), 123.7 (1C; CH_{arom}), 126.3 (1C; Cq), 127.7 (1C; CH_{arom}), 129.3 (1C; CH_{arom}), 129.6 (1C; CH_{arom}), 131.8 (1C; CH_{arom}), 132.4 (1C; CH_{arom}), 132.5 (1C; Cq), 133.1 (1C; CH_{arom}), 136.1 (1C; Cq), 147.8 (1C; Cq), 166.6 (1C; C=O).

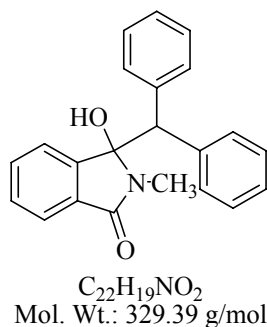
Mass spec: [MS + Na]: 355 m/z; expected 332 m/z

Melting point: 173-177°C

CAS No.: 1197385-29-7

Experiment 12

3-benzhydryl-3-hydroxy-2-methylisindolin-1-one (67i) (SG-207)



General procedure (A) was followed using NMP (0.24 g, 1.50 mmol), diphenylacetic acid (0.96 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.26 mmol). The reaction was monitored for CO_2 formation by bubbling the N_2 supply through the reaction solution and then into a saturated barium hydroxide solution. After 3.5 hr the CO_2 test was negative. A precipitate was visible at the end of the reaction which was filtered before solvent evaporation. The 1H -NMR showed this to be the pure product, which was a colourless powder with a yield of 0.12 g (0.36 mmol; 24%). The filtrate was then worked up as usual and the crude material found to be 0.40 g. The 1H -NMR showed this to be the desired product with some impurities also present. The crude product was purified, in the round bottom flask, by adding a small amount of acetone to dissolve the impurities and then removing the solvent. This was repeated several times and the product found to be a yellow powder with a yield of 0.3 g (0.78 mmol; 52%). The resulting 1H -NMR showed this to be the pure product.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 2.70 (s; 3H; NCH_3), 4.76 (s; 1H; CH), 6.39 (br.s; 1H; OH), 6.56 (dd; $^3J = 7.6Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}), 7.00 (m; 2H; CH_{arom}), 7.18 (m; 3H; CH_{arom}), 7.23-7.31 (br.m; 3H; CH_{arom}), 7.36 (ddd; $^3J = 7.6Hz$; $^4J = 1.2Hz$; 1H; CH_{arom}), 7.50 (m; 3H; CH_{arom}), 7.65 (dd; $^3J = 7.6Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 24.3 (1C; NCH_3), 59.1 (1C; CH), 92.2 (1C; C-OH), 123.2 (1C; CH_{arom}), 125.2 (1C; CH_{arom}), 127.7 (1C; CH_{arom}), 127.8 (1C;

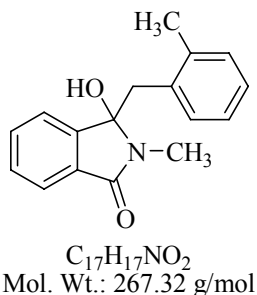
CH_{arom}), 128.4 (2C; CH_{arom}), 129.0 (2C; CH_{arom}), 130.2 (2C; CH_{arom}), 130.2 (1C; CH_{arom}), 131.6 (2C; CH_{arom}), 131.7 (1C; CH_{arom}), 133.9 (1C; Cq), 140.2 (1C; Cq), 140.6 (1C; Cq), 147.2 (1C; Cq), 166.8 (1C; C=O).

Literature reference No.: [148]

CAS No.: 147119-33-3

Experiment 13

3-(2-methylbenzyl)-3-hydroxy-2-methylisoindolin-1-one (67j) (SG-297)



General procedure (A) was followed using NMP (0.24 g, 1.50 mmol), *o*-tolylacetic acid (0.68 g, 4.50 mmol) and K₂CO₃ (0.31 g, 2.25 mmol). After 3 hr the reaction was stopped and the precipitate, which had formed during the reaction, was filtered after evaporating the acetone. This was found to be an off-white powder with a yield of 0.20 g, (0.77 mmol; 51%). The ¹H-NMR showed this to be the desired product. The filtrate was then worked up and the crude material found to have a yield of 0.19 g. The ¹H-NMR showed this to be the desired product with some impurities present. This was purified by adding a small amount of acetone to dissolve the impurities and then removing the solvent. The pure product was found to be an off-white solid with a yield of 0.05 g, (0.18 mmol; 12%). The ¹H-NMR showed this to be the pure product. [Overall yield = 63%].

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 2.04 (s; 3H; CH₃), 3.06 (s; 3H; NCH₃), 3.08 (d; ³J = 15.6Hz; 1H; CH₂), 3.58 (d; ³J = 14.0Hz; 1H; CH₂), 5.40 (br.s; 1H; OH), 6.96 (dd; ³J = 6.8Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.09-7.17 (br.m; 3H; 3 × CH_{arom}), 7.24

(m; 1H; CH_{arom}), 7.42 (ddd; ³J = 7.2Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.46 (ddd; ³J = 7.2Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.61 (dd; ³J = 6.8Hz; ⁴J = 1.2Hz; 1H; CH_{arom}).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 19.8 (1C; CH₃), 23.9 (1C; NCH₃), 39.5 (1C; CH₂), 90.4 (1C; C-OH), 122.6 (1C; CH_{arom}), 123.4 (1C; CH_{arom}), 125.7 (1C; CH_{arom}), 127.1 (1C; CH_{arom}), 129.4 (1C; CH_{arom}), 130.3 (1C; CH_{arom}), 131.1 (1C; CH_{arom}), 131.5 (1C; CH_{arom}), 131.9 (1C; Cq), 134.6 (1C; Cq), 137.4 (1C; Cq), 147.7 (1C; Cq), 166.5 (1C; C=O).

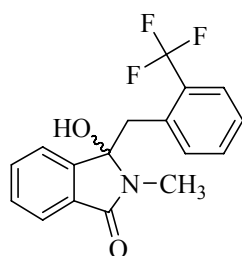
Melting point: 146-148°C

Literature reference No.: [18]

CAS No.: 57445-03-1

Experiment 14

3-(2-(trifluoromethyl)benzyl)-3-hydroxy-2-methylisoindolin-1-one (67k) (SG-308)



C₁₇H₁₄F₃NO₂
Mol. Wt.: 321.29 g/mol

General procedure (A) was followed using NMP (0.24 g, 1.50 mmol), 2-(2-(trifluoromethyl)phenyl)acetic acid (0.92 g, 4.50 mmol) and K₂CO₃ (0.31 g, 2.25 mmol). After 7 hr the reaction was stopped and the precipitate, which had formed during the reaction, was filtered after evaporating the acetone. This was found to be an off-white powder with a yield of 0.22 g, (0.69 mmol; 46%). The ¹H-NMR showed this to be the desired pure product. The filtrate was then worked up and the crude material found to have a yield of 0.05 g. The ¹H-NMR showed this to be the desired product with some impurities present. This was not attempted to be purified.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.02 (s; 3H; NCH₃), 3.32 (d; ²J = 14.4Hz; 1H; CH₂), 3.77 (d; ²J = 14.4Hz; 1H; CH₂), 5.55 (br.s; 1H; OH), 6.84 (d; ³J = 7.6Hz; 1H; CH_{arom}), 7.40 (ddd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.47 (ddd; ³J = 7.2Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.52 (d; ³J = 7.6Hz; 1H; CH_{arom}), 7.64 (m; 2H; CH_{arom}), 7.68 (d; ³J = 8.0Hz; 1H; CH_{arom}), 7.78 (d; ³J = 8.0Hz; 1H; CH_{arom}).

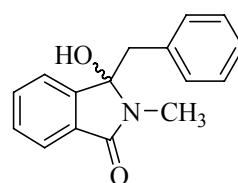
¹⁹F-NMR: (400 MHz, C₂D₆CO / C₆F₆): δ (ppm) = -59.2 (s; 3F; CF₃).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 23.8 (1C; NCH₃), 39.6 (1C; CH₂), 90.2 (1C; C-OH), 123.2 (1C; CH_{arom}), 123.6 (1C; CH_{arom}), 126.6 (1C; Cq), 126.8 (1C; Cq), 128.1 (1C; CH_{arom}), 129.8 (1C; Cq), 130.1 (1C; CH_{arom}), 132.1 (1C; CH_{arom}), 132.5 (1C; CH_{arom}), 132.6 (1C; CH_{arom}), 133.1 (1C; CH_{arom}), 136.0 (1C; Cq), 147.8 (1C; Cq), 168.6 (1C; C=O).

Melting point: 189-190°C

Experiment 15

3-benzyl-3-hydroxy-2-methylisoindolin-1-one (67a) (SG-239)



C₁₆H₁₅NO₂
Mol. Wt.: 253.3 g/mol

General procedure (A) was followed, with the slight variation of halving all amounts used and using a 50 ml reaction flask, using NMP (0.12 g, 0.75 mmol), *L*-3-phenyllactic acid (0.37 g, 2.24 mmol) and K₂CO₃ (0.15 g, 1.11 mmol). After 4 hr the TLC showed the product was formed. The solution had changed from a pale yellow to a bright yellow in colour. The crude material was found to be 0.23 g and the ¹H-NMR showed that this was the desired product with some impurities present including the acetone aldol in quite a substantial amount. Column chromatography was performed using solvent system ethyl acetate:hexane (1:1) and the pure product collected in fractions 9-11. The pure product was seen to be a colourless solid with a yield of 0.04 g (0.16 mmol; 21%).

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.04 (s; 3H; NCH₃), 3.31 (d; ²J = 14.0Hz; 1H; CH₂), 3.50 (d; ²J = 14.0Hz; 1H; CH₂), 5.51 (br.s; 1H; OH), 6.92 (m; 2H; CH_{arom}), 7.06 (m; 3H; CH_{arom}), 7.40 (m; 1H; CH_{arom}), 7.44 (dd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.54 (dd; ³J = 4.4Hz; ⁴J = 1.2Hz; 2H; CH_{arom}).

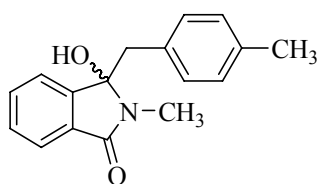
For ¹³C-NMR data see experiment 4.

7.1.2 General Procedure (A1):

As in General Procedure A, substituting distilled water for pH7 buffer. Work-up differs by washing with sat. NHCl₄ instead of sat. NaHCO₃.

Experiment 16

3-(2-iodobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67b) (SG-247)



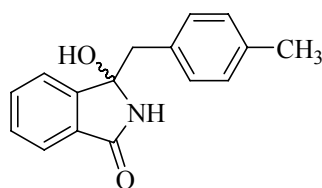
C₁₇H₁₇NO₂
Mol. Wt.: 267.32 g/mol

General procedure (A) was followed using NMP (0.2 g, 1.50 mmol), *p*-tolylacetic acid (0.7 g, 4.50 mmol) and K₂CO₃ (0.3 g, 2.26 mmol). The solution was irradiated for 4 hr and the crude product found to be 0.5 g. Following purification by washing with acetone the pure yield was found to be 0.1 g (0.48 mmol; 32%).

For ¹H-NMR data see experiment 5.

Experiment 17

3-(4-methylbenzyl)-3-hydroxyisoindolin-1-one (68a) (SG-284)



$C_{16}H_{15}NO_2$
Mol. Wt.: 253.3 g/mol

General procedure (A1) was followed using phthalimide (0.22 g, 1.50 mmol), *p*-tolylacetic acid (0.68 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 3 hr the reaction was worked up and the crude material found to have a yield of 0.35 g, (1.38 mmol; 92%). The 1H -NMR showed this to be the desired product.

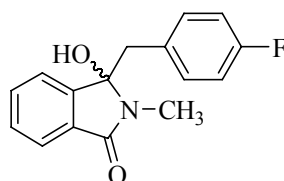
1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 2.22 (s; 3H; CH_3), 3.34 (d; $^3J = 13.2$ Hz; 1H; CH_2), 3.42 (d; $^3J = 13.2$ Hz; 1H; CH_2), 5.41 (br.s; 1H; OH), 6.95 (d; $^3J = 8.0$ Hz; 2H; CH_{arom}), 7.02 (d; $^3J = 8.4$ Hz; 2H; CH_{arom}), 7.45 (m; 1H; CH_{arom}), 7.49 (dd; $^3J = 7.6$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}), 7.62 (dd; $^3J = 4.4$ Hz; $^4J = 1.2$ Hz; 2H; CH_{arom}), 7.90 (br.s; 1H; NH).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 21.0 (1C; CH_3), 45.2 (1C; CH_2), 88.6 (1C; C-OH), 123.3 (1C; CH_{arom}), 123.6 (1C; CH_{arom}), 129.1 (2C; CH_{arom}), 129.7 (1C; CH_{arom}), 131.4 (2C; CH_{arom}), 132.5 (1C; CH_{arom}), 133.0 (1C; Cq), 133.6 (1C; Cq), 136.5 (1C; Cq), 149.6 (1C; Cq), 168.4 (1C; C=O).

CAS No.: 1246376-41-9

Experiment 18

3-(4-fluorobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67e) (SG-248)



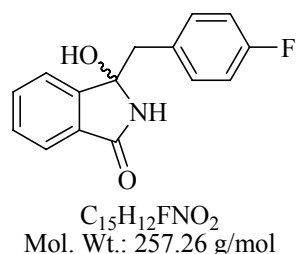
$C_{16}H_{14}FNO_2$
Mol. Wt.: 271.29 g/mol

General procedure (A) was followed using NMP (0.24 g, 1.50 mmol), 4-fluorophenylacetic acid (0.69 g, 4.51 mmol) and K_2CO_3 (0.31 g, 2.26 mmol). The solution was irradiated for 4 hr and following work-up, the crude product was found to be 0.4 g. Following purification by washing with acetone, the pure yield was found to be 0.2 g (0.59 mmol; 39%).

For 1H -NMR data see experiment 8.

Experiment 19

3-(4-fluorobenzyl)-3-hydroxyisoindolin-1-one (68b) (SG-285)



General procedure (A1) was followed using phthalimide (0.22 g, 1.50 mmol), 4-fluorophenylacetic acid (0.69 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.26 mmol). After 3 hr the reaction was worked up and the crude material found to have a yield of 0.33 g, (1.28 mmol; 85%). The 1H -NMR showed this to be the desired product.

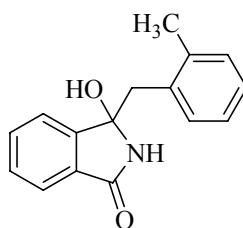
1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.38 (d; $^2J = 13.6$ Hz; 1H; CH_2), 3.45 (d; $^2J = 13.6$ Hz; 1H; CH_2), 5.49 (br.s; 1H; OH), 6.91 (dd; $^3J = 8.8$ Hz; $^4J = 2.0$ Hz; 2H; CH_{arom}), 7.18 (dd; $^3J = 8.8$ Hz; $^4J = 2.0$ Hz; 2H; CH_{arom}), 7.46 (ddd; $^3J = 6.0$ Hz; $^4J = 1.6$ Hz; 1H; CH_{arom}), 7.50 (m; 1H; CH_{arom}), 7.62 (m; 2H; CH_{arom}), 7.95 (br.s; 1H; NH).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 44.8 (1C; CH_2), 88.5 (1C; C-OH), 114.9 (1C; CH_{arom}), 115.1 (1C; CH_{arom}), 123.3 (1C; CH_{arom}), 123.6 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 132.7 (1C; CH_{arom}), 132.8 (1C; Cq), 132.9 (1C; Cq), 133.2 (1C; CH_{arom}), 133.3 (1C; CH_{arom}), 149.3 (1C; Cq), 161.1 (1C; Cq), 168.4 (1C; C=O).

CAS No.: 1246376-43-1

Experiment 20

3-(2-methylbenzyl)-3-hydroxyisoindolin-1-one (68c) (SG-296)



$C_{16}H_{15}NO_2$
Mol. Wt.: 253.3 g/mol

General procedure (A1) was followed using phthalimide (0.22 g, 1.50 mmol), *o*-tolylacetic acid (0.67 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.26 mmol). After 3 hr the reaction was worked up and the crude material found to have a yield of 0.46 g. This was purified by adding a small amount of acetone to dissolve the impurities and then removing the solvent. The pure product was found to be a yellow solid with a yield of 0.21 g, (0.85 mmol; 57%). The 1H -NMR showed this to be the desired product.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 2.25 (s; 3H; CH_3), 3.37 (d; $^3J = 14.0$ Hz; 1H; CH_2), 3.42 (d; $^3J = 14.0$ Hz; 1H; CH_2), 5.35 (br.s; 1H; OH), 7.07 (m; 1H; CH_{arom}), 7.12 (dd; $^3J = 5.2$ Hz; $^4J = 1.2$ Hz; 2H; CH_{arom}), 7.25 (d; $^3J = 7.6$ Hz; 1H; CH_{arom}), 7.43 (m; 1H; CH_{arom}), 7.50 (ddd; $^3J = 7.6$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}), 7.58 (ddd; $^3J = 7.6$ Hz; $^4J = 1.2$ Hz; 2H; CH_{arom}), 7.78 (br.s; 1H; NH).

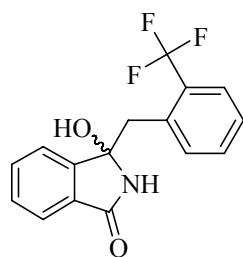
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 20.3 (1C; CH_3), 42.6 (1C; CH_2), 88.7 (1C; C-OH), 123.4 (1C; CH_{arom}), 123.7 (1C; CH_{arom}), 126.0 (1C; CH_{arom}), 127.5 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 130.9 (1C; CH_{arom}), 132.4 (1C; CH_{arom}), 132.5 (1C; CH_{arom}), 132.7 (1C; Cq), 135.3 (1C; Cq), 138.3 (1C; Cq), 150.0 (1C; Cq), 168.1 (1C; C=O).

Melting point: 129-130°C

CAS No.: 1246376-48-6

Experiment 21

3-(2-(trifluoromethyl)benzyl)-3-hydroxyisoindolin-1-one (68d) (SG-311)



$C_{16}H_{12}F_3NO_2$
Mol. Wt.: 307.27 g/mol

General procedure (A1) was followed using phthalimide (0.22 g, 1.51 mmol), 2-(2-(trifluoromethyl)phenyl)acetic acid (0.92 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 6 hr the reaction was stopped and the precipitate, which had formed during the reaction, was filtered after evaporating the acetone. This was found to be an off-white powder with a yield of 0.19 g, (0.61 mmol; 40%). The 1H -NMR showed this to be the desired pure product. The filtrate was then worked up and the crude material found to have a yield of 0.10 g (0.34 mmol; 23%). The 1H -NMR confirmed this to be the desired product. [Overall yield = 63%].

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.56 (d; $^2J = 14.4$ Hz; 1H; CH_2), 3.62 (d; $^2J = 14.4$ Hz; 1H; CH_2), 5.60 (br.s; 1H; OH), 7.31 (d; $^3J = 7.2$ Hz; 1H; CH_{arom}), 7.47 (d; $^3J = 7.6$ Hz; 1H; CH_{arom}), 7.52 (ddd; $^3J = 7.2$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}), 7.57 (m; 1H; CH_{arom}), 7.58 (ddd; $^3J = 7.2$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}), 7.62 (dd; $^3J = 7.2$ Hz; $^4J = 0.8$ Hz; 1H; CH_{arom}), 7.70 (d; $^3J = 7.6$ Hz; 1H; CH_{arom}), 7.78 (d; $^3J = 7.6$ Hz; 1H; CH_{arom}), 7.90 (br.s; 1H; NH).

^{19}F -NMR: (400 MHz, C_2D_6CO/C_6F_6): δ (ppm) = -58.7 (s; 3F; CF_3).

^{13}C -NMR: (100 MHz, C_2D_6CO / C_6F_6): δ (ppm) = 41.7 (1C; CH_2), 88.0 (1C; C-OH), 123.4 (1C; CH_{arom}), 123.5 (1C; CH_{arom}), 126.5 (1C; Cq), 126.8 (1C; Cq), 128.0 (1C; CH_{arom}), 129.8 (1C; Cq), 130.0 (1C; CH_{arom}), 132.3 (1C; CH_{arom}), 132.4 (1C; CH_{arom}), 132.7 (1C; CH_{arom}), 133.6 (1C; CH_{arom}), 135.7 (1C; Cq), 149.7 (1C; Cq), 168.2 (1C; C=O).

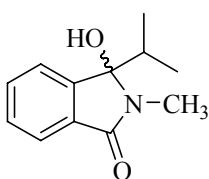
Melting point: 136-138°C

7.1.3 General Procedure (B):

For these experiments a variation of general procedure (A) was used. In these cases the addition partners were sodium salts so, as there was no need for deprotonation by K_2CO_3 , this was not used. The NMP was dissolved in 10 ml of acetone as usual and the addition partner dissolved in 10 ml of distilled H_2O . These were then mixed together and general procedure (A) followed as usual.

Experiment 22

(R) and (S)-3-hydroxy-3-isopropyl-2-methylisindolin-1-one (69a/66a) (SG-34)



$C_{12}H_{15}NO_2$
Mol. Wt.: 205.25 g/mol

General procedure (B) was followed using NMP (0.2 g, 1.50 mmol) and sodium 3-methyl-2-oxobutanoate (0.6 g, 4.51 mmol). After 3 hr the TLC showed the product had been formed. The solution was clear and a luminous yellow in colour. The crude material was found to be 0.2 g. Following column chromatography it was assumed from the TLC, that the desired product was collected in fraction 4. The 1H -NMR obtained confirmed this and the yield was found to be 0.1 g (0.44 mmol, 29%). The product was a colourless powder.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 0.55 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 1.25 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 2.47 (m; 1H; CH), 2.95 (s; 3H; NCH_3), 5.23 (br.s; 1H; OH), 7.54 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.62 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.65-7.70 (br.m; 2H; CH_{arom}).

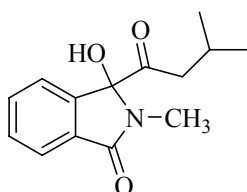
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 16.8 (1C; CH_3), 17.5 (1C; CH_3), 23.6 (1C; NCH_3), 34.7 (1C; CH), 93.2 (1C; COH), 123.1 (1C; CH_{arom}), 124.2 (1C; CH_{arom}), 129.8 (1C; CH_{arom}), 132.0 (1C; CH_{arom}), 133.7 (1C; Cq), 146.7 (1C; Cq), 166.9 (1C; C=O).

Literature reference No.: [132]

CAS No.: 32360-86-4

Experiment 23

3-(3-methylbutanoyl)-3-hydroxy-2-methylisoindolin-1-one (70b) (SG-37)



$C_{14}H_{17}NO_3$
Mol. Wt.: 247.29 g/mol

General procedure (B) was followed using NMP (0.2 g, 1.55 mmol) and sodium 4-methyl-2-oxopentanoate (0.7 g, 4.51 mmol). After 4.5 hr the TLC showed the product was formed. The solution was clear and yellow-orange in colour. The crude material was found to be 0.4 g. Following column chromatography it was assumed from the TLC, that the desired product was collected in fraction 4. The 1H -NMR obtained confirmed this and the yield was found to be 0.1 g (0.41 mmol, 26%). The product was a yellow, slightly oily powder.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 0.80 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 0.86 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 2.13 (m; 1H; CH), 2.32 (dd; $^2J = 18.0\text{Hz}$; $^3J = 6.8\text{Hz}$ 1H; CH_2), 2.48 (dd; $^2J = 18.0\text{Hz}$; $^3J = 6.8\text{Hz}$ 1H; CH_2), 2.89 (s; 3H; NCH_3), 6.16 (br.s; 1H; OH), 7.59 (m; 1H; CH_{arom}), 7.64-7.72 (br.m; 2H; CH_{arom}), 7.80 (m; 1H; CH_{arom}).

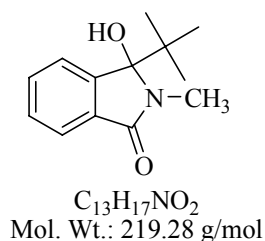
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 23.2 (1C; CH_3), 23.2 (1C; CH_3), 25.1 (1C; CH), 25.4 (1C; NCH_3), 46.3 (1C; CH_2), 93.7 (1C; C-OH), 124.1 (1C; CH_{arom}), 124.7 (1C; CH_{arom}), 131.9 (1C; CH_{arom}), 133.2 (1C; Cq), 133.9 (1C; CH_{arom}), 145.3 (1C; Cq), 168.6 (1C; C=O), 195.5 (1C; C=O).

Literature reference No.: [132]

CAS No.: 556067-40-4

Experiment 24

3-tert-butyl-3-hydroxy-2-methylisoindolin-1-one (69c) (SG-33)



General procedure (B) was followed using NMP (0.2 g, 1.53 mmol) and sodium 3,3-dimethyl-2-oxobutanoate (0.7 g, 4.51 mmol). After 2.5 hr the TLC showed the product was formed. The solution was clear and a luminous yellow in colour. The crude material was found to be 0.4 g. Following column chromatography it was assumed from the TLC, that the desired product was collected in the second fraction. The ¹H-NMR obtained confirmed this and the yield was found to be 0.2 g (1.04 mmol, 69%). The product was a colourless powder.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 1.08 (s; 9H; 3×CH₃), 3.06 (s; 3H; NCH₃) 5.26 (br.s; 1H; OH), 7.52 (ddd; ³J = 7.2Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.59 (ddd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.68 (t; ³J = 8.0Hz; 2H; CH_{arom}).

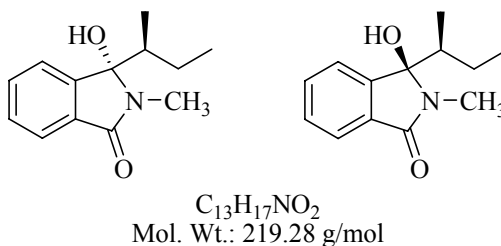
¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 26.6 (3C; 3 × CH₃), 27.7 (1C; NCH₃) 40.4 (1C; C_q), 95.0 (1C; COH), 122.9 (1C; CH_{arom}), 125.1 (1C; CH_{arom}), 129.7 (1C; CH_{arom}), 131.6 (1C; CH_{arom}), 133.8 (1C; C_qarom), 148.8 (1C; C_qarom), 168.0 (1C; C=O).

Literature reference No.: [132]

CAS No.: 39563-77-4

Experiment 25

Like and Unlike-3-sec-butyl-3-hydroxy-2-methylisoindolin-1-one (69d) (SG-35)



General procedure (B) was followed using NMP (0.2 g, 1.53 mmol) and sodium 3-methyl-2-oxopentanoate (0.7 g, 4.52 mmol). After 3 hr the TLC showed both isomers of the product had been formed. The solution was clear and a luminous yellow in colour. The crude material was found to be 0.3 g. Following column chromatography it was assumed from the TLC, that the desired product was collected in fraction 3. The 1H -NMR obtained confirmed this; however both isomers were present in a ratio of 53:47. The yield was found to be 0.1 g (0.60 mmol, 39%). The product was a colourless powder.

Major Isomer:

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 0.53 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 1.02 (t; $^3J = 7.6\text{Hz}$; 3H; CH_3), 1.30 (m; 1H; CH), 2.19 (m; 2H; CH_2), 2.94 (s; 3H; NCH_3) 5.24 (br.s; 1H; OH), 7.53 (m; 1H; CH_{arom}), 7.62 (m; 2H; CH_{arom}), 7.68 (m; 1H; CH_{arom}).

Minor Isomer:

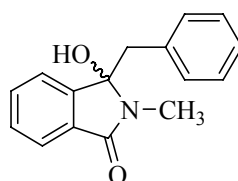
1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 0.46 (m; 1H; CH), 0.85 (t; $^3J = 7.6\text{Hz}$; 3H; CH_3), 1.23 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 2.19 (m; 2H; CH_2), 2.94 (s; 3H; NCH_3) 5.22 (br.s; 1H; OH), 7.53 (m; 1H; CH_{arom}), 7.62 (m; 2H; CH_{arom}), 7.68 (m; 1H; CH_{arom}).

Literature reference No.: [132]

CAS No.: 312909-75-4

Experiment 26

3-benzyl-3-hydroxy-2-methylisoindolin-1-one (69e/67a) (SG-36)



$C_{16}H_{15}NO_2$
Mol. Wt.: 253.3 g/mol

General procedure (B) was followed using NMP (0.2 g, 1.52 mmol) and sodium 2-oxo-3-phenylpropanoate (0.8 g, 4.50 mmol). After 6.5 hr the TLC showed the product was formed. The solution was clear and yellow at this point. The crude material was found to be 0.4 g. The crude product was then recrystallised from acetone and the pure product found to be an off-white powder. The 1H -NMR obtained confirmed this was the pure product, and the yield was found to be 0.2 g (0.79 mmol, 52%).

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.09 (s; 3H; NCH_3), 3.36 (d; $^2J = 14.0$ Hz; 1H; CH_2), 3.54 (d; $^2J = 13.6$ Hz; 1H; CH_2), 5.43 (br.s; 1H; OH), 6.96 (m; 2H; CH_{arom}), 7.10 (m; 3H; CH_{arom}), 7.42-7.49 (br.m; 2H; CH_{arom}), 7.59 (m; 2H; CH_{arom}).

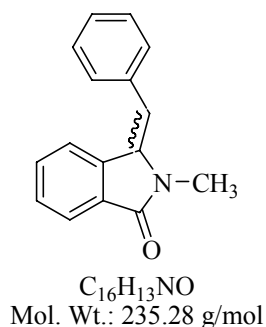
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 24.7 (1C; NCH_3), 43.7 (1C; CH_2), 91.9 (1C; C-OH), 123.7 (1C; CH_{arom}), 124.5 (1C; CH_{arom}), 128.1 (1C; CH_{arom}), 129.3 (2C; CH_{arom}), 130.6 (1C; CH_{arom}), 131.6 (2C; CH_{arom}), 132.9 (1C; CH_{arom}), 133.8 (1C; Cq), 137.0 (1C; Cq), 148.6 (1C; Cq), 167.5 (1C; C=O).

7.1.4 General Procedure (C):

The photoproduct was dissolved in DCM, then concentrated HCl was added and the mixture stirred overnight. Distilled water (~25 ml) was added and the organic layer extracted with DCM (3 \times 25 ml), washed with saturated $NaHCO_3$ (2 \times 10 ml) and saturated NaCl, dried over $MgSO_4$, gravity filtered and the solvent evaporated to afford the dehydrated photoproduct.

Experiment 27

(E) and (Z)-3-benzylidene-2-methylisoindolin-1-one (71a) (SG-57)



Following general procedure (C), **67a** (0.1 g; 0.47 mmol) was dissolved in ~12 ml of DCM. Concentrated HCl (~4 ml) was added and the mixture stirred overnight. The 1H -NMR of the crude product confirmed the presence of both isomers of the desired product, with the ratio calculated to be 90:10. The crude product was then purified by column chromatography, using solvent system ethyl acetate:hexane 1:1, and the product collected in fraction 1. The product appeared as a brown solid and had a yield of 0.1 g; (0.32 mmol; 68%). The 1H -NMR showed this to be an isolated isomer of the desired product.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.36 (s; 3H; NCH_3), 6.69 (s; 1H; CH_{olef}), 7.35 (d; $^3J = 7.6$ Hz; 1H; CH_{arom}), 7.41 (m; 2H; CH_{arom}), 7.48 (m; 5H; CH_{arom}), 7.75 (d; $^3J = 7.6$ Hz; 1H; CH_{arom}).

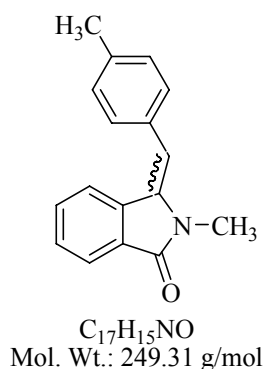
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 26.1 (1C; NCH_3), 111.0 (1C; CH_{olef}), 123.5 (1C; CH_{arom}), 123.7 (1C; CH_{arom}), 128.6 (1C; CH_{arom}), 129.5 (2C; CH_{arom}), 130.2 (1C; CH_{arom}), 130.4 (2C; CH_{arom}), 131.6 (1C; Cq), 132.3 (1C; CH_{arom}), 135.8 (1C; Cq), 136.2 (1C; Cq), 138.1 (1C; Cq), 166.3 (1C; $C=O$).

Literature reference No.: [149]

CAS No.: 4770-24-5

Experiment 28

(E) and (Z)-3-(4-methylbenzylidene)-2-methylisoindolin-1-one (71b) (SG-61)



Following general procedure (C), **67b** (0.13 g; 0.47 mmol) was dissolved in 12 ml of DCM. Concentrated HCl (4 ml) was added and the mixture stirred overnight. The 1H -NMR of the crude product confirmed the presence of both isomers of the desired product, with the ratio calculated to be 91:9. The crude product was then purified by column chromatography, using solvent system ethyl acetate:hexane 1:1, and the product collected in fraction 1. The product appeared as a brown solid and had a yield of 0.1 g; (0.29 mmol; 62%). The 1H -NMR showed this to also contain both isomers of the desired product which meant full spectral data could not be determined. However, some selected peaks are shown.

1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) =

Selected peaks for CH_3 :

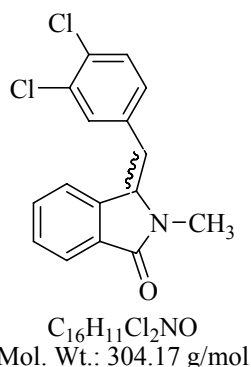
Major isomer: 3.38 (s; 3H; CH_3); Minor isomer: 3.05 (s; 3H; CH_3).

Selected peaks for CH_{olef} :

Major isomer: 6.49 (s; 1H; CH_{olef}); Minor isomer: 6.75 (s; 1H; CH_{olef}).

Experiment 29

(E) and (Z)-3-(3,4-dichlorobenzylidene)-2-methylisoindolin-1-one (71c) (SG-59)



Following general procedure (C), **67 g** (0.11 g; 0.35 mmol) was dissolved in 12 ml of DCM. Concentrated HCl (4 ml) was added and the mixture stirred overnight. The 1H -NMR of the crude product confirmed the presence of both isomers of the desired product, with the ratio calculated to be 82:18. The crude product was then purified by washing with a small amount of acetone. The product appeared as a pale yellow, oily solid and had a yield of 0.1 g; (0.26 mmol; 64%). The 1H -NMR showed this to also contain both isomers of the desired product which meant full spectral data could not be determined. However, some selected peaks are shown.

1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) =

Selected peaks for CH_3 :

Major isomer: 3.17 (s; 3H; CH_3); Minor isomer: 2.85 (s; 3H; CH_3).

Selected peaks for CH_{olef} :

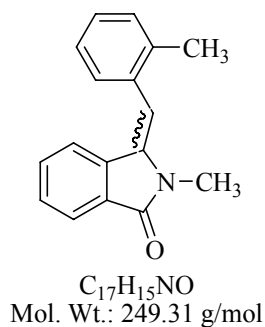
Major isomer: 6.46 (s; 1H; CH_{olef}); Minor isomer: 6.18 (s; 1H; CH_{olef}).

Mass spec: [MS]: 304 m/z; expected 304 m/z

Melting point: 129-132°C

Experiment 30

(E) and (Z)-3-(2-methylbenzylidene)isoindolin-1-one (71d) (SG-304)



Following general procedure (C) **67j** (0.21 g; 0.78 mmol) was dissolved in ~15 ml of DCM. Concentrated HCl (~4 ml) was added and the mixture stirred overnight. The crude product had a yield of 0.19 g. The 1H -NMR showed the desired product had been formed, however both isomers had been formed in a ratio of 85:15. Upon purifying the product, by washing with a small amount of acetone then removing the solvent, only one isomer remained. The pure product appeared as off-white, clear crystals. The yield was found to be 0.11 g; (0.45 mmol; 58%).

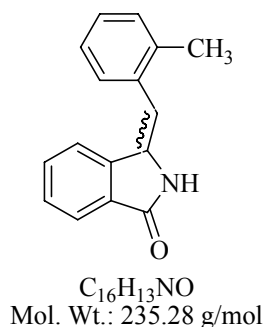
1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 2.35 (s; 3H; CH_3), 3.43 (s; 3H; NCH_3), 6.67 (s; 1H; H_{olef}), 7.02 (dd; $^3J = 8.0Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}), 7.31 (m; 1H; CH_{arom}), 7.36-7.42 (br.m; 3H; $3 \times CH_{arom}$), 7.43 (d; $^3J = 7.6Hz$; 1H; CH_{arom}), 7.52 (ddd; $^3J = 7.2Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}), 7.79 (dd; $^3J = 7.6Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 20.2 (1C; CH_3), 26.1 (1C; NCH_3), 109.8 (1C; CH_{olef}), 123.4 (1C; CH_{arom}), 123.6 (1C; CH_{arom}), 126.8 (1C; CH_{arom}), 129.0 (1C; CH_{arom}), 130.1 (1C; CH_{arom}), 130.8 (1C; CH_{arom}), 131.0 (1C; CH_{arom}), 131.5 (1C; Cq), 132.4 (1C; CH_{arom}), 135.6 (1C; Cq), 136.1 (1C; Cq), 137.9 (1C; Cq), 138.0 (1C; Cq), 166.4 (1C; C=O).

Melting point: 140-142°C

Experiment 31

(E) and (Z)-3-(2-methylbenzylidene)isoindolin-1-one (71e) (SG-303)



Following general procedure (C) **68c** (0.21 g; 0.83 mmol) was dissolved in ~15 ml of DCM. Concentrated HCl (~4 ml) was added and the mixture stirred overnight. The crude product had a yield of 0.18 g. The 1H -NMR showed the desired product was present, however both isomers were formed in a ratio of 76:24. Upon purifying the product, by washing with a small amount of acetone then removing the solvent, it was found that only one isomer remained. The yield was found to be 0.13 g; (0.56 mmol; 67%).

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 2.45 (s; 3H; CH_3), 6.83 (s; 1H; H_{olef}), 7.22-7.31 (br.m; 3H; $3 \times CH_{arom}$), 7.62 (ddd; $^3J = 7.6Hz$; $^4J = 0.8Hz$; 2H; CH_{arom}), 7.75 (ddd; $^3J = 7.6Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}), 7.83 (dd; $^3J = 7.6Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}), 8.11 (d; $^3J = 8.0Hz$; 1H; CH_{arom}), 9.46 (br.s; 1H; NH).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 20.1 (1C; CH_3), 104.3 (1C; CH_{olef}), 121.0 (1C; CH_{arom}), 123.4 (1C; CH_{arom}), 127.0 (1C; CH_{arom}), 128.0 (1C; CH_{arom}), 129.7 (1C; CH_{arom}), 130.0 (1C; Cq), 130.1 (1C; CH_{arom}), 130.8 (1C; CH_{arom}), 132.7 (1C; CH_{arom}), 134.5 (1C; Cq), 134.6 (1C; Cq), 137.4 (1C; Cq), 139.4 (1C; Cq), 169.3 (1C; C=O).

Melting point: 188-190°C

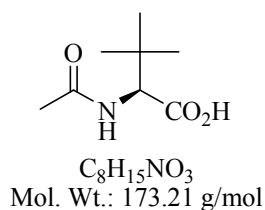
7.2 Chapter 3: Photoaddition reactions of phthalimides with heteroatom-containing addition partners

7.2.1 General Procedure (D):

The amino acid (5.0 mmol), glacial acetic acid (~30 ml) and acetic anhydride (1 ml) were placed in a 50 ml round bottom flask. The solution was refluxed for 3 nights and stirred at room temperature for a further 3 nights. The solvent was then distilled off, the product dried under vacuum overnight, and a $^1\text{H-NMR}$ obtained. The crude product was washed several times with diethyl ether by adding ~3 ml, sonicating and then removing the solvent. The pure product was then dried under vacuum and a second $^1\text{H-NMR}$ obtained.

Experiment 32

(S)-2-acetamido-3,3-dimethylbutanoic acid (72a) (SG-120)



General procedure (D) was followed using *L-t*-Leucine (0.7 g, 5.03 mmol). Following purification, the $^1\text{H-NMR}$ showed this to be pure product. The yield was found to be 0.3 g (2.00 mmol; 40%). The product was an orange-brown solid.

$^1\text{H-NMR}$: (400 MHz, $\text{CDCl}_3/5\%$ TFA): δ (ppm) = 1.00 (s; 9H; $3 \times \text{CH}_3$), 2.18 (s; 3H; CH_3), 4.48 (d; $^3J = 9.0\text{Hz}$; 1H; CH), 7.42 (d; $^3J = 9.0\text{Hz}$; 1H; NH).

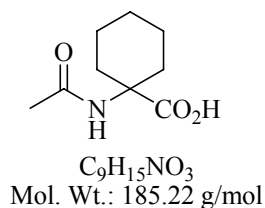
$^{13}\text{C-NMR}$: (100 MHz, $\text{CDCl}_3/5\%$ TFA): δ (ppm) = 21.4 (1C; CH_3), 26.1 (3C; $3 \times \text{CH}_3$), 34.6 (1C; Cq), 61.5 (1C; CH), 175.1 (1C; C=O), 175.5 (1C; C=O).

Literature reference No.: [150]

CAS No.: 22146-59-4

Experiment 33

1-acetamidocyclohexanecarboxylic acid (72b) (SG-136)



General procedure (D) was followed using 1-aminocyclohexane carboxylic acid (0.7 g, 5.0 mmol). No purification was necessary as the 1H -NMR showed this to be pure product. The yield was found to be 0.9 g (4.77 mmol; 95%). The product was a yellow-brown powder.

1H -NMR: (400 MHz, $CDCl_3$ /5% TFA): δ (ppm) = 1.42 (m; 3H; $2 \times CH_2$), 1.72 (m; 3H; $2 \times CH_2$), 1.94 (m; 2H; CH_2), 2.09 (m; 2H; CH_2), 2.22 (s; 3H; CH_3), 6.60 (br.s; 1H; NH).

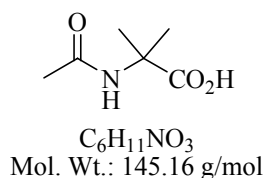
^{13}C -NMR: (100 MHz, $CDCl_3$ /5% TFA): δ (ppm) = 21.2 (2C; $2 \times CH_2$), 21.8 (1C; CH_3), 24.7 (1C; CH_2), 32.0 (2C; $2 \times CH_2$), 60.7 (1C; Cq), 175.4 (1C; C=O), 180.3 (1C; C=O).

Literature reference No.: [151]

CAS No.: 4854-47-1

Experiment 34

2-acetamido-2-methylpropanoic acid (72c) (SG-134)



General procedure (D) was followed using 2-amino-2-methylpropanoic acid (0.5 g, 5.01 mmol). No purification was necessary as the 1H -NMR showed this to be pure

product. The yield was found to be 0.7 g (4.5 mmol; 89%). The product was a pale yellow powder.

¹H-NMR: (400 MHz, CDCl₃/5% TFA): δ (ppm) = 1.63 (s; 6H; 2 × CH₃), 2.19 (s; 3H; CH₃), 6.86 (br.s; 1H; NH).

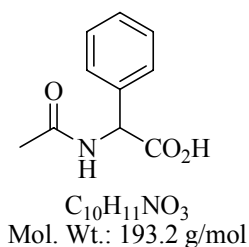
¹³C-NMR: (100 MHz, CDCl₃/5% TFA): δ (ppm) = 21.8 (1C; CH₃), 24.2 (2C; 2 × CH₃), 57.9 (1C; Cq), 175.0 (1C; C=O), 180.3 (1C; C=O).

Literature reference No.: [152]

CAS No.: 5362-00-5

Experiment 35

2-acetamido-2-phenylacetic acid (72d) (SG-148)



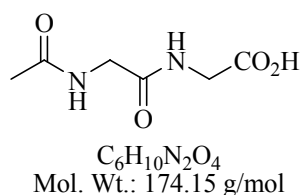
General procedure (D) was followed using 2-amino-2-phenylacetic acid (0.8 g, 5.01 mmol). Following purification, the ¹H-NMR showed this to be pure product. The yield was found to be 0.5 g (2.6 mmol; 51%). The product was a pale yellow powder.

¹H-NMR: (400 MHz, CDCl₃/5% TFA): δ (ppm) = 2.26 (s; 3H; CH₃), 5.63 (d; ²J = 6.0Hz; 1H; CH), 7.28 (br.s; 1H; NH), 7.40 (m; 2H; CH_{arom}), 7.44 (m; 3H; CH_{arom}).

¹³C-NMR: (100 MHz, CDCl₃/5% TFA): δ (ppm) = 21.7 (1C; CH₃), 57.9 (1C; CH), 127.6 (2C; 2 × CH_{arom}), 129.9 (2C; 2 × CH_{arom}), 130.3 (1C; CH_{arom}), 133.2 (1C; Cq), 170.3 (1C; C=O), 176.4 (1C; C=O).

Experiment 36

Acetyl Glycyl-Glycine (72e) (SG-153)



General procedure (D) was followed, with slight variation, using 1-aminocyclohexane carboxylic acid (0.7 g, 5.0 mmol). The solution was not refluxed, instead it was heated gently to 120°C until all the acid had dissolved and was then stirred at room temperature for 3 nights. Following distillation, no purification was necessary as the 1H -NMR showed this to be pure product. The yield was found to be 0.8 g (4.81 mmol; 96%). The product was a pale yellow powder.

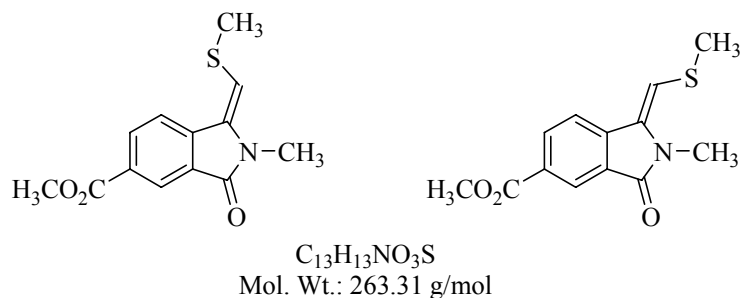
1H -NMR: (400 MHz, $CDCl_3$ /5% TFA): δ (ppm) = 2.24 (s; 3H; CH_3), 4.21 (t; $^3J = 5.0$ Hz; 4H; $2 \times CH_2$), 7.47 (br.s; 1H; NH), 7.78 (br.s; 1H; NH).

^{13}C -NMR: (100 MHz, $CDCl_3$ /5% TFA): δ (ppm) = 21.4 (1C; CH_3), 41.6 (1C; CH_2), 43.5 (1C; CH_2), 171.6 (1C; C=O), 175.2 (2C; $2 \times C=O$).

CAS No.: 5687-48-9

Experiment 37

E- and *Z*-2-methyl-1-methylsulfanylmethylene-3-oxo-2,3-dihydro-1H-indole-5-carboxylic acid methyl ester (*E*-, *Z*-74) (SG-20)



General procedure (A) was followed with a few modifications, using 0.2 g (1.1 mmol) of *N*-methyl trimellitic acid imide methyl ester (instead of NMP). The solution was then degassed by N₂ and 1 ml of dimethylsulfide added. Due to the volatility of the reagent another 1 ml of dimethylsulfide was added after 4.5 hr. After 24 hr the TLC showed the product was formed. The solution gradually turned pale yellow in colour. The crude yield was found to be 0.4 g. Following column chromatography it was assumed from the TLC that the desired product was collected in fraction 2. The yield of the pure product was found to be 0.1 g (0.52 mmol, 47%). The product was bright yellow in colour with a strong odour. Solely the dehydrated olefinic products were found in the ¹H-NMR and dehydration most likely occurred in the slightly acidic NMR solution upon standing.

Major isomer (*E*-8):

¹H-NMR: (400 MHz, CDCl₃) δ (ppm) = 2.57 (s; 3H; SCH₃), 3.31 (s; 3H; NCH₃), 3.96 (s; 3H; OCH₃), 6.09 (s; 1H; CH_{olef}), 8.20 (d; ³*J* = 8.0Hz; 1H; CH_{arom}), 8.29 (d; ³*J* = 8.4Hz; 1H; CH_{arom}), 8.52 (s; 1H; CH_{arom}).

Minor isomer (*Z*-8):

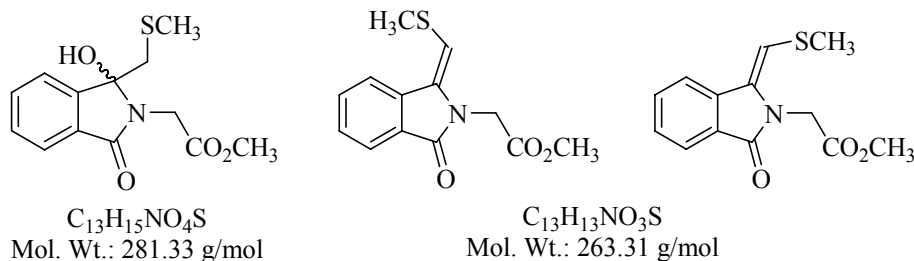
¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 2.53 (s; 3H; SCH₃), 3.62 (s; 3H; NCH₃), 3.94 (s; 3H; OCH₃), 6.26 (s; 1H; CH_{olef}), 8.20 (d; ³*J* = 8.4Hz; 1H; CH_{arom}), 8.28 (d; ³*J* = 8.4Hz; 1H; CH_{arom}), 8.49 (s; 1H; CH_{arom}).

Mass spec: [MS + H]: 289 m/z; expected 288 m/z

Melting point: 156-159°C

Experiment 38

Methyl 2-(1-hydroxy-1-((methylthio)methyl)-3-oxoisindolin-2-yl)acetate (75) and *E*- and *Z*-(1-methylsulfanylmethylene-3-oxo-1,3-dihydroisindol-2-yl) acetic acid methyl ester (*E*-, *Z*-76) (SG-27)



General procedure (A) was followed with a few modifications, using 0.2 g (1.1 mmol) of phthaloyl glycine methyl ester (instead of NMP). The solution was then degassed by N_2 and 1 ml of dimethylsulfide added. After 4.5 hr the TLC showed the product was formed. The solution remained colourless. The crude yield was 0.3 g (1.21 mmol). Following column chromatography it was assumed from the TLC that the desired product was collected in fractions 2 and 3. The yield was found to be 0.2 g (0.81 mmol, 74%). The product was a light beige viscous oil with a strong odour. The desired photoproduct and its corresponding dehydrated olefinics were found in the 1H -NMR. Dehydration most likely occurred in the slightly acidic NMR solution upon standing.

Main product (75):

1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) = 1.86 (s; 3H; SCH_3), 3.02 (d; $^2J = 15.7$ Hz; 1H; CH_2S), 3.05 (d; $^2J = 15.7$ Hz; 1H; CH_2S), 3.67 (s; 3H; OCH_3), 3.93 (d; $^2J = 17.7$ Hz; 1H; NCH_2), 4.17 (br.s; 1H; OH), 4.46 (d; $^2J = 17.7$ Hz; 1H; NCH_2), 7.43 (ddd; $^3J = 7.3 + 7.6$ Hz; $^4J = 1.0$ Hz; 1H; CH_{arom}), 7.52 (ddd; $^3J = 7.3 + 7.6$ Hz; $^4J = 1.0$ Hz; 1H; CH_{arom}), 7.60 (dd; $^3J = 7.6$ Hz; $^4J = 1.0$ Hz; 1H; CH_{arom}), 7.69 (dd; $^3J = 7.3$ Hz; $^4J = 1.0$ Hz; 1H; CH_{arom}).

Major isomer (*Z*-76):

1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) = 2.43 (s; 3H; SCH_3), 3.67 (s; 3H; OCH_3), 4.49 (s; 2H; NCH_2), 5.78 (s; 1H; CH_{olef}), 7.41 (ddd; $^3J = 7.6 + 7.8$ Hz; $^4J = 1.0$ Hz;

1H; CH_{arom}), 7.56 (ddd; ³J = 7.6 + 7.8Hz; ⁴J = 1.0Hz; 1H; CH_{arom}), 7.79 (dd; ³J = 7.6Hz; ⁴J = 1.0Hz; 1H; CH_{arom}), 8.11 (dd; ³J = 7.8Hz; ⁴J = 1.0Hz; 1H; CH_{arom}).

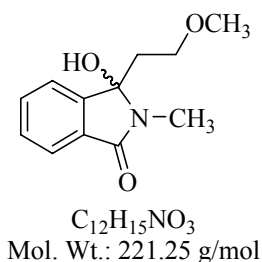
Minor isomer (E-76):

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 2.38 (s; 3H; SCH₃), 3.70 (s; 3H; OCH₃) 4.83 (s; 2H; NCH₂), 6.10 (s; 1H; CH_{olef}), 7.36 (ddd; ³J = 7.6Hz; ⁴J = 1.0Hz; 1H; CH_{arom}), 7.48 (ddd; ³J = 7.6Hz; ⁴J = 1.0Hz; 1H; CH_{arom}), 7.51 (dd; ³J = 7.6Hz; ⁴J = 1.0Hz; 1H; CH_{arom}), 7.74 (dd; ³J = 7.6Hz; ⁴J = 1.0Hz; 1H; CH_{arom}).

Mass spec: [MS + H]: 264 m/z; expected 263 m/z

Experiment 39

3-Hydroxy-3-(methoxyethyl)-2-methylisoindolin-1-one (77) (SG-7)



General procedure (A) was followed using NMP (0.2 g, 1.50 mmol), 3-methoxypropionic acid (0.5 g, 4.50 mmol) and K₂CO₃ (0.3 g, 2.26 mmol). After 16 hr the TLC showed a product was formed. The solution was clear and a yellow-green in colour. The crude yield was found to be 0.2 g (0.76 mmol). Following column chromatography it was assumed from the TLC that the desired product was collected in fractions 4 and 5. The ¹H-NMR obtained confirmed this and the yield was found to be 0.03 g (0.12 mmol, 8%). The product was colourless and crystalline. From the crude ¹H-NMR a conversion of just 33% was calculated. Thus, the % yield based on conversion was determined as 24%.

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 2.25 (m; 1H; CH₂), 2.44 (m; 1H; CH₂), 2.84 (s; 3H; NCH₃), 3.10 (t; ³J = 6.4Hz; 2H; CH₂), 3.16 (s; 3H; OCH₃) 4.14 (br.s;

1H; OH), 7.41 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 2.0\text{Hz}$; 1H; CH_{arom}), 7.54 (ddd; $^3J = 6.0\text{Hz}$; $^4J = 0.8\text{Hz}$; 2H; CH_{arom}), 7.58 (dd; $^3J = 7.2\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}).

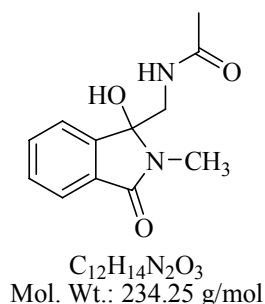
¹³C-NMR: (100 MHz, CDCl₃): δ (ppm) = 23.9 (1C; NCH₃), 36.0 (1C; CH₂), 59.2 (1C; CH₂O), 68.3 (1C; OCH₃), 89.8 (1C; C-OH), 122.3 (1C; CH_{arom}), 123.5 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 131.3 (1C; Cq), 132.5 (1C; CH_{arom}), 146.9 (1C; Cq), 167.3 (1C; C=O).

Literature reference No.: [38a]

CAS No.: 261730-87-4

Experiment 40

N-((1-hydroxy-2-methyl-3-oxoisindolin-1-yl)methyl)acetamide (78a) (SG-107)



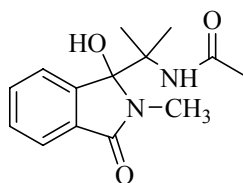
General procedure (A) was followed using NMP (0.2 g, 1.51 mmol), *N*-acetyl-glycine (0.5 g, 4.51 mmol) and K₂CO₃ (0.3 g, 2.24 mmol). After 3.5 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.02 g. The aqueous layer from the extraction was then extracted with DCM (3 × 50 ml). The solvent was evaporated and a brown oily solid visible. This was proved to be the desired product by ¹H-NMR and the yield was found to be 0.1 g (0.29 mmol, 19%) although this was not entirely pure. There was not enough product available to obtain a ¹³C NMR.

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 1.76 (s; 3H; CH₃), 2.79 (s; 3H; NCH₃), 3.65 (dd; $^2J = 14.4\text{Hz}$; $^3J = 6.4\text{Hz}$; 1H; CH₂), 3.80 (dd; $^2J = 14.4\text{Hz}$; $^3J = 6.4\text{Hz}$; 1H; CH₂), 5.60 (br.s; 1H; OH), 6.11 (br.t; $^3J = 6.0\text{Hz}$; 1H; NH), 7.35 (ddd; $^3J = 8.0\text{Hz}$; $^4J = 1.6\text{Hz}$; 1H; CH_{arom}), 7.42 (d; $^3J = 7.6\text{Hz}$; 1H; CH_{arom}), 7.49 (m; 2H; CH_{arom}).

CAS No.: 1238840-19-1

Experiment 41

***N*-(2-(1-hydroxy-2-methyl-3-oxoisindolin-1-yl)propan-2-yl)acetamide (78b)**
(SG-139)



$C_{14}H_{18}N_2O_3$
Mol. Wt.: 262.3 g/mol

General procedure (A) was followed, with the slight variation of halving all amounts used and performing the irradiation in a 50 ml Schlenk flask, using NMP (0.1 g, 0.76 mmol), **72c** (0.3 g, 2.26 mmol) and K_2CO_3 (0.2 g, 1.15 mmol). After 4.5 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The product was found to be pale yellow, oily crystals and the 1H -NMR showed this was the pure product. The yield was found to be 0.2 g (0.63 mmol, 83%).

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 1.00 (s; 3H; CH_3), 1.53 (s; 3H; CH_3), 2.09 (s; 3H; CH_3), 3.00 (s; 3H; NCH_3), 7.50 (ddd; $^3J = 7.2Hz$; $^4J = 1.2Hz$; 1H; CH_{arom}), 7.58 (ddd; $^3J = 7.6Hz$; $^4J = 1.2Hz$; 1H; CH_{arom}), 7.61 (d; $^3J = 7.2Hz$; 1H; CH_{arom}), 7.65 (dd; $^3J = 7.2Hz$; $^4J = 0.8Hz$; 1H; CH_{arom}), 7.74 (br.s; 1H; OH).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 23.3 (1C; CH_3), 23.8 (1C; CH_3), 25.0 (1C; CH_3), 26.1 (1C; NCH_3), 62.8 (1C; Cq), 95.9 (1C; COH), 123.1 (1C; CH_{arom}), 124.3 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 132.2 (1C; CH_{arom}), 133.3 (1C; Cq_{arom}), 148.4 (1C; Cq_{arom}), 168.2 (1C; C=O), 174.9 (1C; C=O).

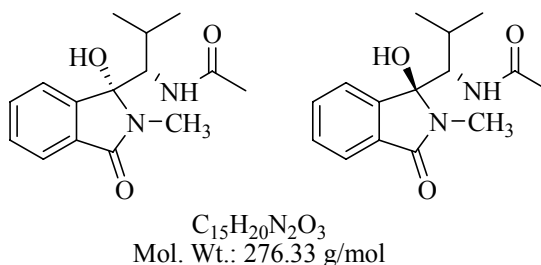
Mass spec: [MS + Na]: 285 m/z; expected 262 m/z

Melting point: 135-138°C

CAS No.: 1238840-34-0

Experiment 42

***N*-((*S*)-1-(*Like* and *Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-methylpropyl)acetamide (**78c**) (SG-68)**



General procedure (A) was followed using NMP (0.2 g, 1.51 mmol), acetyl-valine (0.7 g, 4.51 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After 3.5 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.2 g. This was washed several times with hexane and the solvent removed. The 1H -NMR obtained confirmed that both isomers were present in a ratio of 75:25 and the yield was found to be 0.2 g (0.79 mmol, 52%). The product was an off-white powdery solid. These isomers were not isolated.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 0.30 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 0.91 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 1.72 (m; 1H; CH), 2.11 (s; 3H; $C(O)CH_3$), 3.00 (s; 3H; NCH_3), 4.53 (dd; $^3J = 8.8\text{Hz}$; $^4J = 3.2\text{Hz}$; 1H; CH_{asym}), 6.09 (s; 1H; OH), 7.23 (br.d; $^3J = 8.0\text{Hz}$; 1H; NH), 7.51 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.56 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.66 (m; 1H; CH_{arom}), 7.74 (m; 1H; CH_{arom}).

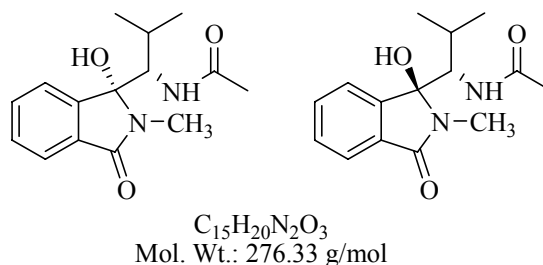
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 17.45 (1C; CH_3), 22.30 (1C; CH_3), 22.72 (1C; CH), 24.27 (1C; $C(O)CH_3$), 28.30 (1C; NCH_3), 58.57 (1C; CH_{asym}), 91.93 (1C; COH), 122.81 (1C; CH_{arom}), 124.49 (1C; CH_{arom}), 129.78 (1C; CH_{arom}), 132.00 (1C; CH_{arom}), 134.74 (1C; Cq), 147.37 (1C; Cq), 167.09 (1C; $C=O$), 172.02 (1C; $C=O$).

Mass spec: [MS + Na]: 299 m/z; expected 276 m/z

Melting point: 110-114°C

Experiment 43

***N*-((*S*)-1-(*Like* and *Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-methylpropyl)acetamide (78c) (SG-181)**

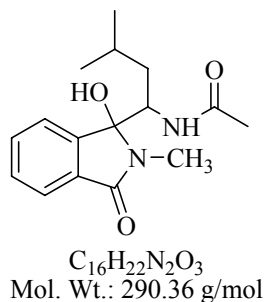


General procedure (A1) was followed using NMP (0.24 g, 1.50 mmol), acetyl-valine (0.72 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 3.5 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.30 g. The 1H -NMR obtained confirmed that both isomers were present in a ratio of 62:38. Column chromatography was performed and one isomer isolated in fractions 13-35 which had a combined yield of 0.13 g (0.48 mmol, 32%). The product was an off-white powdery solid.

For 1H -NMR data see experiment 42.

Experiment 44

***N*-(1-(1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-3-methylbutyl)acetamide (78d) (SG-60)**



General procedure (A) was followed using NMP (0.24 g, 1.50 mmol), acetyl-leucine (0.78 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 3 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.42 g and the 1H -NMR showed that both isomers had been formed in a ratio of 38:62. Following column chromatography it was assumed from the TLC, that the desired product was collected in fraction 9. The 1H -NMR obtained confirmed this to be a single isomer which had a yield of 0.11 g (0.39 mmol, 26%). The product was a colourless foam.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 0.95 (q; $^3J = 6.4\text{Hz}$; $^4J = 2.0\text{Hz}$; 6H; $2 \times CH_3$), 1.59-1.76 (m; 3H; $CH_2 + CH$), 1.78 (s; 3H; CH_3), 3.03 (s; 3H; NCH_3), 4.70 (ddd; $^3J = 11.6\text{Hz}$; $^4J = 2.0\text{Hz}$; 1H; CH), 5.73 (s; 1H; OH), 6.59 (br.d; $^3J = 8.8\text{Hz}$; 1H; NH), 7.54 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.62 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.68 (m; 2H; CH_{arom}).

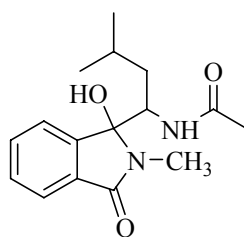
^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 21.7 (1C; CH), 22.7 (1C; NCH_3), 24.1 (1C; CH_3), 24.2 (1C; CH_3), 25.9 (1C; CH_3), 39.8 (1C; CH_2), 52.1 (1C; CH), 92.4 (1C; COH), 123.1 (1C; CH_{arom}), 124.2 (1C; CH_{arom}), 130.1 (1C; CH_{arom}), 132.0 (1C; CH_{arom}), 134.2 (1C; Cq), 146.3 (1C; Cq), 166.9 (1C; C=O), 171.0 (1C; C=O).

Mass spec: [MS + Na]: 313 m/z; expected 290 m/z

Melting point: 105-108°C

Experiment 45

N-(1-(1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-3-methylbutyl)acetamide (78d)
(SG-177)



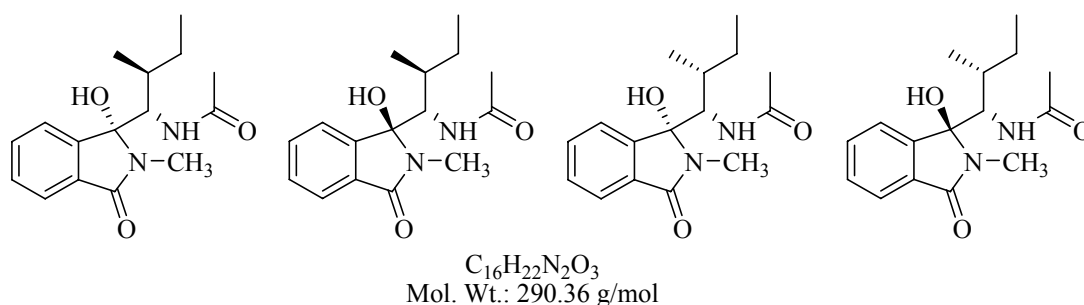
$C_{16}H_{22}N_2O_3$
Mol. Wt.: 290.36 g/mol

General procedure (A1) was followed using NMP (0.24 g, 1.51 mmol), acetyl-leucine (0.78 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.26 mmol). After 4 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.32 g. The 1H -NMR showed that both isomers of the product had formed in a ratio of 39:61. Following column chromatography, one isomer was isolated in fraction 25. The 1H -NMR obtained confirmed this and the yield was found to be 0.16 g (0.54 mmol, 36%). The product was a colourless foam.

For 1H -NMR data see experiment 44.

Experiment 46

***N*-((1*S*,2*S*) and (1*S*,2*R*)-1-((*R*) and (*S*)-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-methylbutyl)acetamide (78e) (SG-69)**



General procedure (A) was followed using NMP (0.2 g, 1.50 mmol), acetyl-iso-leucine (0.8 g, 4.51 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After 3 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.4 g. This was washed several times with hexane and the solvent removed. The 1H -NMR obtained confirmed that four diastereoisomers were formed in a ratio of 32:15:34:19. The yield was found to be 0.3 g (1.17 mmol, 78%). The product was an off-white powder with some yellow oily spots. These isomers were not isolated, however data for some selected peaks is listed.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) =

Selected peaks for NH:

6.43 (d; ³J = 6.8Hz; 1H; NH), 6.49 (d; ³J = 4.8Hz; 1H; NH), 6.82 (d; ³J = 10.4Hz; 1H; NH), 6.92 (d; ³J = 10.4Hz; 1H; NH).

Selected peaks for CH(NH):

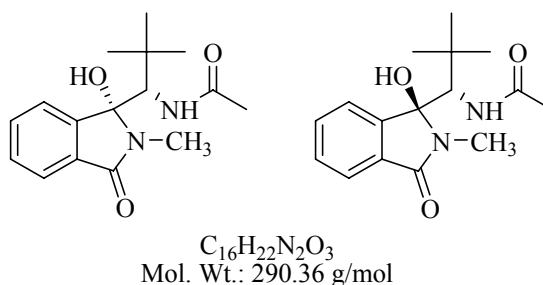
4.39 (dd; ³J = 10.4Hz; ³J = 4.0Hz; 1H; CH), 4.48 (dd; ³J = 9.6Hz; ³J = 4.0Hz; 1H; CH), 4.57 (dd; ³J = 10.4Hz; ³J = 4.0Hz; 1H; CH), 4.65 (dd; ³J = 10.0Hz; ³J = 2.4Hz; 1H; CH).

Mass spec: [MS + Na]: 313 m/z; expected 290 m/z

Melting point: 115-117°C

Experiment 47

***N*-((*S*)-1-(*Like* and *Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2,2-dimethylpropyl)acetamide (78f) (SG-127)**



General procedure (A) was followed, with slight variation of amounts used but not the ratio, using NMP (0.1 g, 0.66 mmol), **72a** (0.3 g, 1.95 mmol) and K₂CO₃ (0.1 g, 0.98 mmol). After 8.5 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.1 g. The ¹H-NMR showed both isomers had been formed in a ratio of 74:26. There were also a few impurities present so the product was washed with acetone several times. A colourless powder was obtained and a second ¹H-NMR showed this to be only one isomer of the pure product. The yield was found to be 0.01 g (0.04 mmol, 6%).

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 0.67 (s; 9H; 3 × CH₃), 2.14 (s; 3H; CH₃), 3.00 (s; 3H; NCH₃), 4.55 (d; ³J = 9.2Hz; 1H; CH), 5.91 (br.s; 1H; OH), 7.45 (br.d; ³J = 8.8Hz; 1H; NH), 7.50-7.57 (br.m; 2H; CH_{arom}), 7.67 (m; 1H; CH_{arom}), 7.86 (m; 1H; CH_{arom}).

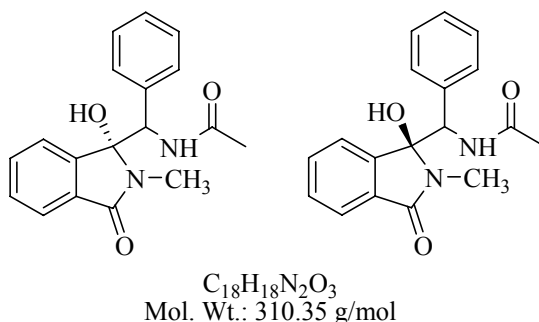
¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 24.8 (1C; NCH₃), 28.3 (3C; 3 × CH₃), 35.0 (1C; C_q), 38.3 (1C; CH₃), 60.4 (1C; CH), 91.7 (1C; COH), 123.4 (1C; CH_{arom}), 125.0 (1C; CH_{arom}), 130.3 (1C; CH_{arom}), 132.3 (1C; CH_{arom}), 134.0 (1C; C_{qarom}), 148.8 (1C; C_{qarom}), 167.8 (1C; C=O), 170.9 (1C; C=O).

Mass spec: [MS + Na]: 313 m/z; expected 290 m/z

Melting point: 143-147°C

Experiment 48

N-(*Like and Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)(phenyl)methyl)acetamide (**78g**) (SG-152)

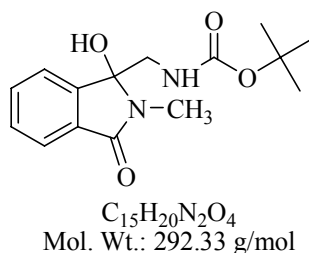


General procedure (A) was followed, with the slight variation of halving all amounts used and using a 50 ml reaction flask, using NMP (0.1 g, 0.75 mmol), **72d** (0.4 g, 2.18 mmol) and K₂CO₃ (0.2 g, 1.12 mmol). After 2 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The product was found to be a colourless/yellow solid and the ¹H-NMR showed that both isomers had been formed. The ratio was determined to be 54:46 so almost no preference was shown for either isomer. The yield was found to be 0.2 g (0.78 mmol, 104%), but this obviously includes a few impurities. The isomers were not isolated and the peaks could not be assigned from the ¹H-NMR.

Melting point: 189-191°C

Experiment 49

***tert*-butyl (1-hydroxy-2-methyl-3-oxoisindolin-1-yl)methylcarbamate (78h)**
(SG-73)



General procedure (A) was followed using NMP (0.2 g, 1.52 mmol), *N*-(*tert*-butoxycarbonyl)-glycine (0.8 g, 4.51 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After 1 hr the TLC showed the product was formed. The solution remained clear and colourless. During work-up, a precipitate was formed. This was filtered and found to be a colourless powder. The 1H -NMR showed that this was the pure product with a yield of 0.3 g (0.90 mmol; 59%). Work-up was continued as usual and the crude material was found to be 0.2 g. This was washed several times with acetone and the solvent removed. The 1H -NMR obtained confirmed that this was the pure product and the yield was found to be 0.1 g (0.22 mmol, 15%). The product was a colourless powder. Collective yield = 74%.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 1.21 (s; 9H; 3 \times CH_3), 2.97 (s; 3H; NCH_3), 3.66 (dd; $^2J = 14.4Hz$; $^3J = 6.4Hz$; 1H; CH_2), 3.84 (dd; $^2J = 14.4Hz$; $^3J = 6.8Hz$; 1H; CH_2), 5.46 (br.s; 1H; OH), 5.87 (br.s; 1H; NH), 7.47 (t; $^3J = 7.2Hz$; 1H; CH_{arom}), 7.55 (t; $^3J = 7.6Hz$; 1H; CH_{arom}), 7.62 (t; $^3J = 8.4Hz$; 2H; CH_{arom}).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 23.5 (1C; NCH_3), 28.2 (3C; 3 \times CH_3), 44.1 (1C; CH_2), 78.4 (1C; Cq), 90.2 (1C; COH), 122.3 (1C; CH_{arom}), 123.9 (1C; CH_{arom}), 129.6 (1C; CH_{arom}), 131.8 (1C; CH_{arom}), 147.0 (1C; Cq_{arom}), 156.2 (1C; Cq_{arom}), 167.2 (1C; C=O), 170.1 (1C; C=O).

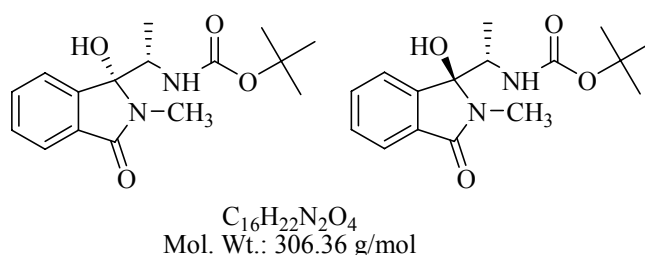
Mass spec: [MS + Na]: 315 m/z; expected 292 m/z

Melting point: 108-112°C

CAS No.: 1238840-25-9

Experiment 50

***tert*-butyl (*S*)-1-(*Like and Unlike*- 1-hydroxy-2-methyl-3-oxoisindolin-1-yl)ethylcarbamate (**78i**) (SG-63)**



General procedure (A) was followed using NMP (0.2 g, 1.50 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-alanine (0.9 g, 4.50 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After 2 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.5 g. The 1H -NMR showed both isomers of the product had been formed in a ratio of 69:31, however an assignment could not be made. Following column chromatography, it was found that the isomers could not be separated and were both collected in fractions 3-7. The 1H -NMR obtained showed this and the yield was found to be 0.30 g (0.97 mmol, 65%). The product was an off-white solid.

Major Isomer:

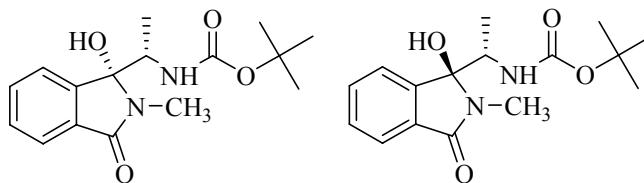
1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 1.37 (s; 6H; $2 \times CH_3$), 1.41 (s; 3H; CH_3), 1.44 (d; $^3J = 6.8\text{Hz}$; 3H; CH_3), 3.03 (s; 3H; NCH_3), 4.40 (m; 1H; CH), 5.52 (br.d; $^3J = 8.0\text{Hz}$; 1H; NH), 5.67 (br.s; 1H; OH), 7.54 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.60 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.68 (m; 2H; CH_{arom}).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 16.67 (1C; CH_3), 24.14 (1C; NCH_3), 28.45 (3C; $3 \times CH_3$), 50.65 (1C; CH), 79.13 (1C; Cq), 92.47 (1C; C-OH), 123.13

(1C; CH_{arom}), 124.33 (1C; CH_{arom}), 130.09 (1C; CH_{arom}), 132.03 (1C; CH_{arom}), 134.03 (1C; C_{qarom}), 145.79 (1C; C_{qarom}), 156.53 (1C; C=O), 167.09 (1C; C=O).

Experiment 51

***tert*-butyl (*S*)-1-(*Like and Unlike*- 1-hydroxy-2-methyl-3-oxoisindolin-1-yl)ethylcarbamate (78i) (SG-184)**



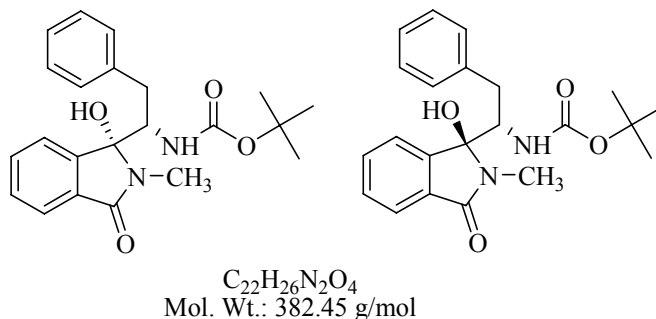
C₁₆H₂₂N₂O₄
Mol. Wt.: 306.36 g/mol

General procedure (A1) was followed using NMP (0.24 g, 1.50 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-alanine (0.85 g, 4.51 mmol) and K₂CO₃ (0.31 g, 2.26 mmol). After 4 hr the TLC showed the product was formed. The crude material was found to be 0.53 g. The ¹H-NMR showed both isomers of the product had been formed, however the ratio could not be determined and an assignment could not be made. Following column chromatography, it was found that the isomers could not be separated and were both collected in fractions 2-3. The ¹H-NMR obtained showed this and the yield was found to be 0.37 g (1.21 mmol; 81%). The product was an off-white solid.

For ¹H-NMR data see experiment 50.

Experiment 52

tert-butyl (*S*)-1-(*Like* and *Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-phenylethylcarbamate (**78j**) (SG-64)



General procedure (A) was followed using NMP (0.2 g, 1.50 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-phenylalanine (1.2 g, 4.50 mmol) and K_2CO_3 (0.3 g, 2.26 mmol). After 3 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.6 g. From the 1H -NMR it was evident that both isomers of the product had been formed. The ratio was calculated from the crude 1H -NMR to be 32:68, although it was not possible to distinguish between the two. Following column chromatography it was assumed from the TLC, that one isomer, a colourless solid, was collected in fraction 4 (minor isomer) and the other, an off-white solid, in fraction 8 (major isomer). The 1H -NMRs obtained confirmed this and the yields were found to be 0.04 g (0.10 mmol, 7%) and 0.1 g (0.29 mmol, 19%) respectively.

Major Isomer:

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 1.20 (s; 9H; $3 \times CH_3$), 2.98 (dd; $^2J = 11.2$ Hz; $^3J = 1.6$ Hz; 1H; CH_2), 3.06 (s; 3H; NCH_3), 3.63 (dd; $^2J = 14.0$ Hz; $^3J = 2.0$ Hz; 1H; CH_2), 4.47 (ddd; $^3J = 10.0$ Hz; $^4J = 2.4$ Hz; 1H; CH), 5.61 (br.d; $^3J = 8.4$ Hz; 1H; NH), 5.73 (br.s; 1H; OH), 7.20-7.38 (m; 5H; CH_{arom}), 7.57 (ddd; $^3J = 7.2$ Hz; $^4J = 0.8$ Hz; 1H; CH_{arom}), 7.64 (ddd; $^3J = 7.6$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}), 7.70 (d; $^3J = 7.2$ Hz; 1H; CH_{arom}), 7.81 (d; $^3J = 7.6$ Hz; 1H; CH_{arom}).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 23.9 (1C; NCH_3), 28.3 (3C; $3 \times CH_3$), 36.6 (1C; CH_2), 56.8 (1C; CH), 78.3 (1C; Cq), 92.0 (1C; C-OH), 122.6 (1C; CH_{arom}), 124.7 (1C; CH_{arom}), 126.4 (1C; CH_{arom}), 128.5 (2C; CH_{arom}), 129.7 (1C; CH_{arom}),

129.8 (2C; CH_{arom}), 131.7 (1C; CH_{arom}), 134.2 (1C; C_{qarom}), 140.4 (1C; C_{qarom}), 145.9 (1C; C_{qarom}), 156.2 (1C; C=O), 166.7 (1C; C=O).

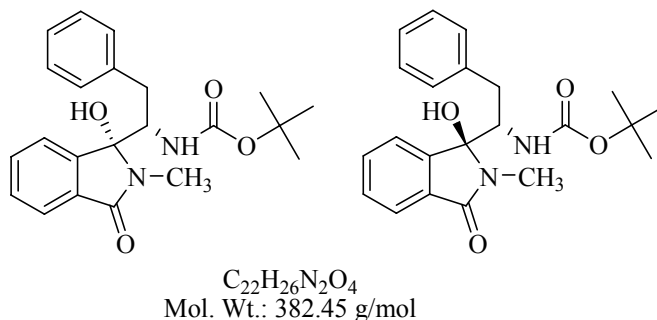
Minor Isomer:

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 1.21 (s; 9H; 3 × CH₃), 2.50 (dd; ²J = 11.2Hz; ³J = 5.6Hz; 1H; CH₂) 3.07 (dd; ²J = 11.2Hz; ³J = 5.6Hz; 1H; CH₂), 3.15 (s; 3H; NCH₃), 4.58 (t; ³J = 9.6Hz; 1H; CH), 5.79 (br.s; 1H; OH), 6.36 (br.d; ³J = 8.4Hz; 1H; NH), 7.21 (m; 1H; CH_{arom}), 7.30 (m; 4H; CH_{arom}), 7.53 (ddd; ³J = 7.2Hz; ⁴J = 0.8Hz; 1H; CH_{arom}), 7.60 (t; ³J = 7.2Hz; 1H; CH_{arom}), 7.68 (d; ³J = 7.2Hz; 1H; CH_{arom}), 7.75 (d; ³J = 7.2Hz; 1H; CH_{arom}).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 24.9 (1C; NCH₃), 28.3 (3C; 3 × CH₃), 36.2 (1C; CH₂), 58.2 (1C; CH), 79.2 (1C; C_q), 92.5 (1C; C-OH), 122.8 (1C; CH_{arom}), 124.4 (1C; CH_{arom}), 126.9 (1C; CH_{arom}), 129.0 (2C; CH_{arom}), 129.9 (1C; CH_{arom}), 130.0 (2C; CH_{arom}), 132.2 (1C; CH_{arom}), 133.2 (1C; C_{qarom}), 139.8 (1C; C_{qarom}), 143.8 (1C; C_{qarom}), 157.2 (1C; C=O), 169.9 (1C; C=O).

Experiment 53

***tert*-butyl (*S*)-1-(*Like* and *Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-phenylethylcarbamate (**78j**) (SG-185)**



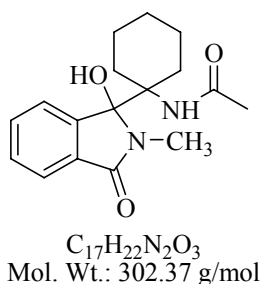
General procedure (A1) was followed using NMP (0.24 g, 1.51 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-phenylalanine (1.19 g, 4.50 mmol) and K₂CO₃ (0.31 g, 2.25 mmol). After 4 hr the TLC showed the product was formed. The crude material was found to be 0.72 g. From the ¹H-NMR it was evident that both isomers of the product had been formed. The ratio was calculated from the crude ¹H-NMR to be 35:65, although it was not possible to distinguish between the two. Following column

chromatography, the isomers could not be separated and the resulting $^1\text{H-NMR}$ was almost identical to the crude.

For $^1\text{H-NMR}$ data see experiment 52.

Experiment 54

***N*-(1-(1-hydroxy-2-methyl-3-oxoisindolin-1-yl)cyclohexyl)acetamide (78k)** (SG-140)



General procedure (A) was followed, with the slight variation of halving all amounts used and using a 50 ml Schlenk flask, using NMP (0.1 g, 0.75 mmol), **72b** (0.4 g, 2.27 mmol) and K_2CO_3 (0.2 g, 1.12 mmol). After 4 hr the TLC showed the product was formed. The solution was clear and a pale yellow in colour at this point. The crude material was found to be 0.2 g. The $^1\text{H-NMR}$ showed a few impurities were present so the product was washed with acetone several times. The impurities did not dissolve in the acetone so the product was removed with the solvent and the yield found to be 0.2 g (0.65 mmol; 87%) when the solvent had evaporated. A second $^1\text{H-NMR}$ confirmed this to be the product.

$^1\text{H-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 0.74-1.81 (br.m; 10H; $5 \times \text{CH}_2$), 2.19 (s; 3H; CH_3), 3.01 (s; 3H; NCH_3), 7.36 (br.s; 1H; NH), 7.50 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.58 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.64 (m; 2H; CH_{arom}), 8.43 (br.s; 1H; OH).

$^{13}\text{C-NMR}$: (100 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 21.6 (2C; $2 \times \text{CH}_2$), 23.2 (1C; CH_2), 25.7 (2C; $2 \times \text{CH}_2$), 26.3 (1C; NCH_3), 26.6 (1C; CH_3), 48.7 (1C; Cq), 97.2 (1C; COH), 123.0 (1C; CH_{arom}), 124.7 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 132.1 (1C; CH_{arom}), 133.5 (1C; Cq_{arom}), 148.4 (1C; Cq_{arom}), 168.3 (1C; C=O), 175.4 (1C; C=O).

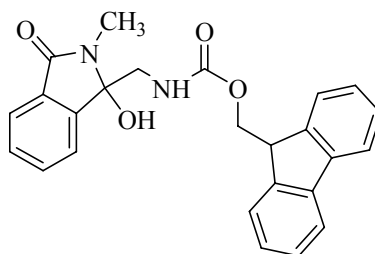
Mass spec: [MS + Na]: 325 m/z; expected 302 m/z

Melting point: 160-164°C

CAS No.: 1238840-37-3

Experiment 55

(9H-fluoren-9-yl)methyl (1-hydroxy-2-methyl-3-oxoisindolin-1-yl)methylcarbamate (78l) (SG-67)



$C_{25}H_{22}N_2O_4$
Mol. Wt.: 414.45 g/mol

General procedure (A) was followed using NMP (0.2 g, 1.50 mmol), *N*-(9-fluorenylmethoxycarbonyl)glycine (1.3 g, 4.50 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After 1.5 hr the TLC showed the product was formed. The solution had changed from clear and a pale yellow in colour to a cloudy, milky solution. When attempting to extract the solution with DCM, a precipitate was formed. This was filtered and found to be a colourless powder with a yield of 1.4 g. The filtrate was then worked up as usual and the crude material found to be 0.3 g. From the 1H -NMR it was evident that the product had been formed, however an analogue of the acid starting material was also present. The crude product was washed, in the round bottom flask, with hexane several times, however the 1H -NMR showed little change. Following column chromatography it was clear that the product had not been isolated in any of the fractions collected.

The precipitate was then purified by dissolving it in ethyl acetate (~30 ml) and then washing the organic layer with saturated $NaHCO_3$ (3 × 30 ml). The aqueous layer was then extracted with ethyl acetate (3 × 30 ml) and the organic layer washed with

NaCl (2 × 20 ml). A precipitate visible throughout the procedure was filtered at this point. It appeared as a colourless powder and ¹H-NMR showed it to be the desired product with a yield of 0.02 g (0.04 mmol; 3%). Continuing with the purification, the organic layer was dried over MgSO₄ and the solvent evaporated. The product was seen to be an off-white powder and ¹H-NMR confirmed that this was the pure product, with a yield of 0.1 g (0.24 mmol; 16%).

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 2.94 (s; 3H; NCH₃), 3.59 (dd; ²J = 14.4Hz; ³J = 6.0Hz; 1H; CH₂), 3.79 (dd; ²J = 14.4Hz; ³J = 6.8Hz; 1H; CH₂), 4.00-4.14 (br.m; 3H; OCH₂ + CH), 6.54 (br.s; 1H; OH), 7.18 (t; ³J = 6.4Hz; 1H; NH), 7.28 (m; 2H; CH_{arom}), 7.39 (t; ³J = 7.2Hz; 2H; CH_{arom}), 7.46 (ddd; ³J = 7.6Hz; ⁴J = 1.2Hz; 2H; CH_{arom}), 7.53 (d; ³J = 7.6Hz; 1H; CH_{arom}), 7.57 (t; ³J = 7.2Hz; 1H; CH_{arom}), 7.62 (d; ³J = 8.0Hz; 2H; CH_{arom}), 7.84 (d; ³J = 7.6Hz; 2H; CH_{arom}).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 23.3 (1C; NCH₃), 43.9 (1C; CH), 46.8 (1C; CH₂), 66.0 (1C; OCH₂), 89.5 (1C; COH), 120.2 (1C; CH_{arom}), 120.2 (1C; CH_{arom}), 122.0 (1C; CH_{arom}), 123.3 (1C; CH_{arom}), 125.4 (1C; CH_{arom}), 125.5 (1C; CH_{arom}), 127.3 (1C; CH_{arom}), 127.8 (1C; CH_{arom}), 129.3 (1C; CH_{arom}), 131.6 (1C; CH_{arom}), 132.6 (1C; CH_{arom}), 140.9 (1C; CH_{arom}), 141.0 (1C; Cq), 144.0 (1C; Cq), 144.1 (1C; Cq), 146.3 (1C; Cq), 147.8 (1C; Cq), 156.4 (1C; Cq), 166.7 (1C; C=O), 169.9 (1C; C=O).

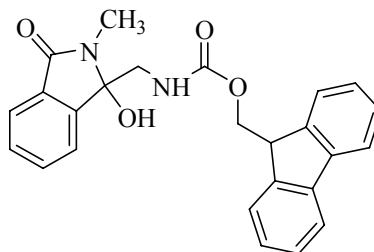
Mass spec: [MS + Na]: 437 m/z; expected 414m/z

Melting point: 185-187°C

CAS No.: 1238840-31-7

Experiment 56

(9H-fluoren-9-yl)methyl (1-hydroxy-2-methyl-3-oxoisindolin-1-yl)methylcarbamate (78l) (SG-187)



$C_{25}H_{22}N_2O_4$
Mol. Wt.: 414.45 g/mol

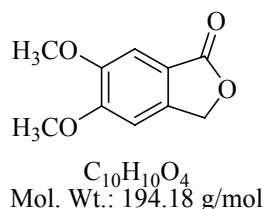
General procedure (A1) was followed, with slight variation, using NMP (0.24 g, 1.51 mmol), *N*-(9-fluorenylmethoxycarbonyl)glycine (0.85 g, 2.88 mmol) and K_2CO_3 (0.31 g, 2.24 mmol). There was not enough acid available to add the usual 4.50 mmol although it was still used in excess. After 3 hr the TLC showed the product was formed and the crude material found to be 0.52 g. From the 1H -NMR it was evident that the product had been formed, however impurities were also present. The crude product was washed, in the round bottom flask, by adding a small amount of acetone to dissolve the impurities and then removing the solvent. This was repeated several times, and the product found to be an off-white powder with a yield of 0.12 g (0.30 mmol; 20%). The resulting 1H -NMR showed this to be the pure product.

For 1H -NMR data see experiment 55.

7.3 Chapter 4: Synthesis of aristolactams using phthalimide derivatives as precursors

Experiment 57

5,6-dimethoxyisobenzofuran-1(3H)-one (m-meconine) (79a) (SG-236)



3,4-dimethoxybenzoic acid (veratric acid) (7.5 g; 41.1 mmol) and paraformaldehyde (10.0 g) were refluxed in concentrated HCl (250 ml) at 80°C for ~6 hr. The solution was cooled to R.T and then a solution of NH₄OH poured over ice (250 ml) was added slowly until the pH changed from 1 to 7. A beige precipitate was visible which was filtered and washed with H₂O. The yield was found to be 3.7 g; (19.1 mmol; 46%). The ¹H-NMR confirmed this to be the desired product in its pure state.

SG-243:

The procedure was repeated using 3,4-dimethoxybenzoic acid (veratric acid) (7.51 g; 41.21 mmol) and paraformaldehyde (10.01 g). The product was found to have a yield of 6.29 g; (32.37 mmol; 79%). The ¹H-NMR showed this to be the desired pure product.

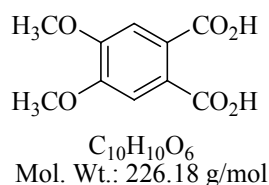
¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 3.93 (s; 3H; OCH₃), 3.97 (s; 3H; OCH₃), 5.21 (s; 2H; CH₂), 6.90 (s; 1H; CH_{arom}), 7.29 (s; 1H; CH_{arom}).

¹³C-NMR: (100 MHz, CDCl₃): δ (ppm) = 56.4 (1C; OCH₃), 56.5 (1C; OCH₃), 69.3 (1C; CH₂), 103.5 (1C; CH_{arom}), 106.2 (1C; CH_{arom}), 117.8 (1C; C_q), 141.2 (1C; C_q), 150.5 (1C; C_q), 155.0 (1C; C_q), 171.6 (1C; C=O).

CAS No.: 531-88-4

Experiment 58

4,5-dimethoxybenzene-1,2-dioic acid (79b) (SG-62)



m-Meconine (4.5 g; 23.5 mmol), 1.1 equivalents of $KMnO_4$ and 2.2 equivalents of a 10% Na_2CO_3 solution were dissolved by heating, and then stirred at R.T for 1 week. Ethanol (30 ml) was then added dropwise and the reaction solution allowed to stir for a further 3 hr. The precipitate formed was discarded after filtering and rinsing with distilled H_2O . The filtrate was then acidified to pH 1 using conc. HCl and left in the fridge overnight. The colourless precipitate that had formed was filtered and found to have a yield of 2.4 g (10.7 mmol; 46%). The 1H -NMR showed this was the desired product. The filtrate was extracted with ethyl acetate (2×100 ml), the organic layer dried over $MgSO_4$, gravity filtered and the solvent evaporated by rotary evaporation. The crude product was purified by dissolving it in ethyl acetate and washing it with sat. $NaHCO_3$ in a separating funnel. The bottom aqueous layer was then dropped onto acidified ice and, when left overnight, a colourless precipitate had formed. When filtered, this was found to have a yield of 0.94 g (4.16 mmol; 18%). The 1H -NMR showed this to be the pure product. The second aqueous layer was then extracted, same as the previous one, and the yield found to be 0.64 g (2.84 mmol; 12%). The product was a colourless powder. [Overall yield = 76%].

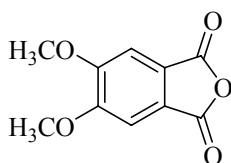
1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) = 3.93 (s; 6H; $2 \times OCH_3$), 7.26 (s; 2H; CH_{arom}), 7.78 (br.s; 2H; OH).

^{13}C -NMR: (100 MHz, $CDCl_3$): δ (ppm) = 55.8 (2C; $2 \times OCH_3$), 111.6 (2C; CH_{arom}), 126.1 (2C; Cq), 149.9 (2C; Cq), 168.4 (2C; $2 \times C=O$).

CAS No.: 577-68-4

Experiment 59

5,6-dimethoxyisobenzofuran-1,3-dione (79c) (SG-65)



$C_{10}H_8O_5$
Mol. Wt.: 208.17 g/mol

79b (2.0 g; 8.89 mmol) was heated at 140°C for 1 hr while stirring in acetic anhydride (25 ml). The acetic anhydride was then distilled off and a yellow solid was formed. The yield was 1.6 g (7.82 mmol; 88%) and the 1H -NMR confirmed this was the pure product.

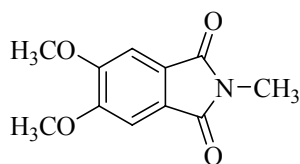
1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) = 4.03 (s; 6H; 2 \times OCH_3), 7.36 (s; 2H; CH_{arom}).

^{13}C -NMR: (100 MHz, $CDCl_3$): δ (ppm) = 56.9 (2C; 2 \times OCH_3), 106.1 (2C; CH_{arom}), 124.9 (2C; Cq), 155.8 (2C; Cq), 163.1 (2C; 2 \times C=O).

CAS No.: 4821-94-7

Experiment 60

5,6-dimethoxy-2-methylisobenzofuran-1,3-dione (79d) (SG-66)



$C_{11}H_{11}NO_4$
Mol. Wt.: 221.21 g/mol

79c (2.0 g; 9.04 mmol) was refluxed at 190°C for 2 hr while stirring in *N*-methylformamide (25 ml). This was left overnight to cool and the next day, pale yellow, fine needles were seen to have formed. These were filtered and washed with

a small amount of ethanol. The yield was 1.7 g (7.59 mmol; 84%) and the $^1\text{H-NMR}$ confirmed this was the pure product.

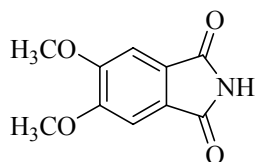
$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 3.14 (s; 3H; NCH_3), 3.99 (s; 6H; $2 \times \text{OCH}_3$), 7.30 (s; 2H; CH_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 24.1 (1C; NCH_3), 56.8 (2C; $2 \times \text{OCH}_3$), 105.4 (2C; CH_{arom}), 125.8 (2C; Cq), 153.8 (2C; Cq), 168.8 (2C; $2 \times \text{C=O}$).

CAS No.: 92288-92-1

Experiment 61

5,6-dimethoxyisoindoline-1,3-dione (79e) (SG-289)



$\text{C}_{10}\text{H}_9\text{NO}_4$
Mol. Wt.: 207.18 g/mol

79c (0.27 g; 1.30 mmol) was refluxed at 190°C for 3 hr while stirring in formamide (20 ml). This was left overnight to cool and the next day, pale yellow, fine needles were seen to have formed. These were filtered and washed with a small amount of ethanol. The yield was 0.20 g (0.94 mmol; 72%) and the $^1\text{H-NMR}$ confirmed this was the pure product.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ (ppm) = 3.97 (s; 6H; $2 \times \text{OCH}_3$), 7.62 (s; 2H; CH_{arom}), 10.58 (br.s; 1H; NH).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ (ppm) = 55.8 (2C; $2 \times \text{OCH}_3$), 104.3 (2C; CH_{arom}), 125.7 (2C; Cq), 153.0 (2C; Cq), 168.8 (2C; C=O).

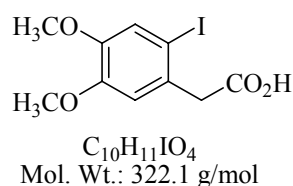
CAS No.: 4764-20-9

7.3.1 General Procedure (E)

Silver trifluoroacetate (20.00 mmol) and the methoxylated phenylacetic acid (20.00 mmol) were stirred while a solution of iodine (20.00 mmol) dissolved in CHCl_3 (~60 ml) was added dropwise over a period of ~30 min. After stirring for 2 nights, the precipitated silver iodide was filtered and washed with CHCl_3 . The solvent was then removed by rotary evaporation and the crude product recrystallised from ethanol.

Experiment 62

2-(2-iodo-4,5-dimethoxyphenyl)acetic acid (81a) (SG-203)



General procedure (E) was followed using silver trifluoroacetate (4.42 g; 20.01 mmol), 3,4-dimethoxyphenylacetic acid (3.93 g; 20.01 mmol) and iodine (5.08 g; 20.00 mmol). The product was found to be a grey/purple crystalline solid with a yield of 4.89 g (15.18 mmol; 76%). The $^1\text{H-NMR}$ showed this to be the pure product.

SG-258:

General procedure (E) was followed using silver trifluoroacetate (2.21 g; 10.00 mmol), 3,4-dimethoxyphenylacetic acid (1.96 g; 10.01 mmol) and iodine (2.54 g; 10.00 mmol). The product was found to be a brown powdery solid with a yield of 3.12 g (9.67 mmol; 97%). This product was not recrystallised as the $^1\text{H-NMR}$ showed this to be the pure product.

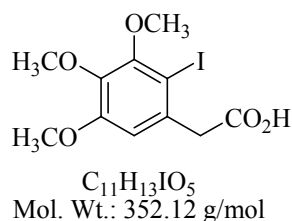
$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 3.78 (s; 2H; CH_2), 3.85 (s; 6H; $2 \times \text{OCH}_3$), 6.80 (s; 1H; CH_{arom}), 7.23 (s; 1H; CH_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 45.49 (1C; CH_2), 56.03 (1C; OCH_3), 56.21 (1C; OCH_3), 88.99 (1C; CI), 113.32 (1C; CH_{arom}), 121.66 (1C; CH_{arom}), 129.30 (1C; Cq), 148.87 (1C; Cq), 149.42 (1C; Cq), 176.83 (1C; C=O).

CAS No.: 35323-09-2

Experiment 63

2-(2-iodo-3,4,5-trimethoxyphenyl)acetic acid (81b) (SG-232)



General procedure (E) was followed using silver trifluoroacetate (4.42 g; 20.00 mmol), 3,4,5-trimethoxyphenylacetic acid (4.53 g; 20.00 mmol) and iodine (5.08 g; 20.00 mmol). This reaction was only stirred for 1 night. The product was found to be an off-white powder with a yield of 3.22 g (9.14 mmol; 46%). The 1H -NMR showed this to be the pure product.

SG-261:

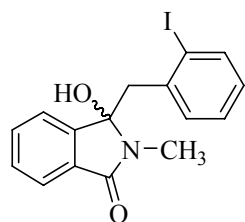
General procedure (E) was followed using silver trifluoroacetate (4.42 g; 20.00 mmol), 3,4,5-trimethoxyphenylacetic acid (4.52 g; 20.00 mmol) and iodine (5.08 g; 20.00 mmol). This reaction was only stirred for 1 night. The product was found to be an off-white powder with a yield of 4.40 g (12.50 mmol; 63%). The 1H -NMR showed this to be the pure product.

1H -NMR: (400 MHz, $CDCl_3$): δ (ppm) = 3.85 (s; 3H; OCH_3), 3.86 (s; 2H; CH_2), 3.86 (s; 3H; OCH_3), 3.87 (s; 3H; OCH_3), 6.71 (s; 1H; CH_{arom}).

^{13}C -NMR: (100 MHz, $CDCl_3$): δ (ppm) = 46.2 (1C; CH_2), 56.2 (1C; OCH_3), 60.9 (1C; OCH_3), 61.1 (1C; OCH_3), 89.2 (1C; CI), 110.2 (1C; CH_{arom}), 132.5 (1C; Cq), 141.4 (1C; Cq), 153.4 (1C; Cq), 153.7 (1C; Cq), 176.6 (1C; $C=O$).

Experiment 64

3-(2-iodobenzyl)-3-hydroxy-2-methylisoindolin-1-one (82a) (SG-71)



$C_{16}H_{14}INO_2$
Mol. Wt.: 379.19 g/mol

General procedure (A) was followed, with slight modification of halving the amounts used and thus using a 50 ml Schlenk flask, using NMP (0.1 g, 0.76 mmol), 2-iodophenylacetic acid (0.6 g, 2.26 mmol) and K_2CO_3 (0.2 g, 1.12 mmol). After 4 hr the TLC showed a product was formed. The solution was colourless, however a precipitate was visible at this point, which was filtered and found to have a yield of 0.1 g and was shown by 1H -NMR to be the desired product. Following work-up of the filtrate, the crude yield was found to be 0.4 g. The precipitate was combined with the crude product and column chromatography performed. The product was collected in fractions 5-15 and seen to be a colourless powder which was confirmed to be the pure product by 1H -NMR. The yield of the pure product was 0.1 g (0.39 mmol, 51%).

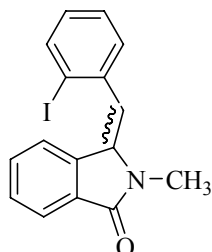
1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.00 (s; 3H; NCH_3), 3.26 (d; $^2J = 14.0$ Hz; 1H; CH_2), 3.68 (d; $^2J = 14.4$ Hz; 1H; CH_2), 6.42 (br.s; 1H; OH), 6.95 (ddd; $^3J = 7.6$ Hz; $^4J = 1.6$ Hz; 1H; CH_{arom}), 7.04 (m; 1H; CH_{arom}), 7.29 (ddd; $^3J = 7.6$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}), 7.35 (dd; $^3J = 7.6$ Hz; $^4J = 1.6$ Hz; 1H; CH_{arom}), 7.41-7.47 (br.m; 2H; CH_{arom}), 7.58-7.62 (m; 1H; CH_{arom}), 7.76 (dd; $^3J = 8.0$ Hz; $^4J = 1.2$ Hz; 1H; CH_{arom}).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 24.0 (1C; NCH_3), 47.7 (1C; CH_2), 90.2 (1C; COH), 104.0 (1C; CI), 122.8 (1C; CH_{arom}), 123.9 (1C; CH_{arom}), 128.5 (1C; CH_{arom}), 129.3 (1C; CH_{arom}), 129.6 (1C; CH_{arom}), 131.4 (1C; CH_{arom}), 131.8 (1C; CH_{arom}), 132.5 (1C; Cq), 139.6 (1C; Cq), 139.9 (1C; CH_{arom}), 147.7 (1C; Cq), 166.5 (1C; C=O).

CAS No.: 1197385-30-0

Experiment 65

(Z)-3-(2-iodobenzylidene)-2-methylisindolin-1-one (82b) (SG-76)



C₁₆H₁₂INO
Mol. Wt.: 361.18 g/mol

Following general procedure (C), **82a** (0.1 g; 0.38 mmol) was stirred in of DCM (12 ml) and conc. HCl (4 ml) overnight. The product appeared as a yellow oily crystalline solid and had a yield of 0.1 g; (0.34 mmol; 90%). The ¹H-NMR confirmed the desired product was formed. There was not enough product available to obtain a ¹³C NMR.

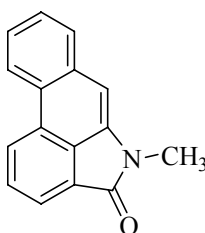
¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.44 (s; 3H; NCH₃), 6.50 (s; 1H; CH_{olef}), 7.02 (d; ³J = 7.6Hz; 1H; CH_{arom}), 7.26 (m; 1H; CH_{arom}), 7.43 (ddd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.53-7.58 (br.m; 2H; CH_{arom}), 7.64 (dd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.81 (d; ³J = 7.6Hz; 1H; CH_{arom}), 8.10 (dd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}).

Literature reference No.: [153]

CAS No.: 202122-80-3

Experiment 66

5-methyl-5H-dibenz[*cd,f*]indol-4-one (82c) (SG-78)



C₁₆H₁₁NO
Mol. Wt.: 233.26 g/mol

82b (0.1 g; 0.34 mmol) was dissolved in 50 ml of benzene and placed in a 50 ml Schlenk flask. This was placed in the photoreactor and the solution degassed with a stream of N₂ for a few minutes. The tube was then removed, and the reaction vessel sealed and irradiated for 25 hr. The TLC showed a fluorescent spot so it was assumed the product was formed. The solution was a dark pink in colour at this point. The benzene was evaporated by rotary evaporation, water and DCM added and the organic layer extracted, washed and dried as usual. The crude product had a yield of 0.1 g and the ¹H-NMR showed the product had been formed but was impure. Column chromatography was performed using solvent system ethylacetate:hexane (1:1). The product was seen to be collected in the second fraction with a yield of 0.02 g (0.08 mmol; 24%), and was a yellow, oily solid. The ¹H-NMR obtained confirmed this was the product, however it was still not entirely pure. There was not enough product available to obtain a ¹³C NMR.

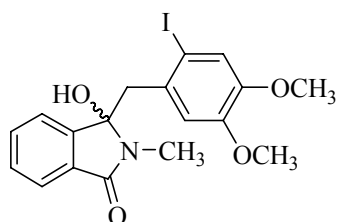
¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.47 (s; 3H; NCH₃), 7.39 (s; 1H; CH_{arom}), 7.62 (m; 2H; CH_{arom}), 7.92 (t; ³J = 7.2Hz; 1H; CH_{arom}), 7.99 (d; ³J = 7.6Hz; 1H; CH_{arom}), 8.06 (d; ³J = 7.2Hz; 1H; CH_{arom}), 8.70 (d; ³J = 8.0Hz; 1H; CH_{arom}), 8.82 (d; ³J = 8.0Hz; 1H; CH_{arom}).

Literature reference No.: [153]

CAS No.: 202122-84-7

Experiment 67

3-(2-iodo-4,5-dimethoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (83) (SG-197)



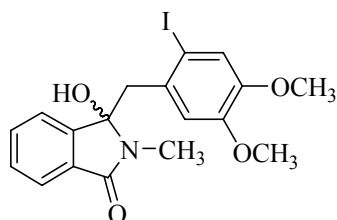
$C_{18}H_{18}INO_4$
Mol. Wt.: 439.24 g/mol

General procedure (A) was followed, with slight variation, using NMP (0.24 g, 1.50 mmol), **81a** (1.23 g, 3.82 mmol) and K_2CO_3 (0.31 g, 2.26 mmol). There was not enough acid available to add the usual 4.50 mmol although it was still used in excess. After 8 hr the TLC showed the product was formed and the crude material found to be 0.41 g. From the NMR it was evident that the product had been formed, however NMP still remained and impurities were also present. The crude product was purified, in the round bottom flask, by dissolving in a small amount of acetone and adding hexane. This was then sonicated and the product seen to precipitate. This was filtered and found to be a brown powder with a yield of 0.05 g (0.12 mmol; 8%). The resulting 1H -NMR showed this to be the pure product.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.05 (s; 3H; NCH_3), 3.32 (d; $^2J = 14.4$ Hz; 1H; CH_2), 3.60 (s; 3H; OCH_3), 3.65 (d; $^2J = 14.4$ Hz; 1H; CH_2), 3.75 (s; 3H; OCH_3), 5.44 (br.s; 1H; OH), 6.70 (s; 1H; CH_{arom}), 7.16 (s; 1H; CH_{arom}), 7.31 (dd; $^3J = 7.6$ Hz; 1H; CH_{arom}), 7.43-7.52 (br.m; 2H; CH_{arom}), 7.57 (dd; $^3J = 6.8$ Hz; 1H; CH_{arom}).

Experiment 68

3-(2-iodo-4,5-dimethoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (83) (SG-241)



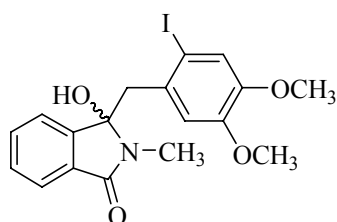
$C_{18}H_{18}INO_4$
Mol. Wt.: 439.24 g/mol

General procedure (A) was followed using NMP (0.24 g, 1.51 mmol), **81a** (1.45 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 16.5 hr the reaction was worked up and the crude material found to have a yield of 0.85 g. The 1H -NMR showed the product was formed but NMP still dominated. Purification was carried out by washing with a small amount of acetone and the product isolated in a yield of 0.06 g (0.14 mmol; 9%).

For 1H -NMR data see experiment 67.

Experiment 69

3-(2-iodo-4,5-dimethoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (83) (SG-244)



$C_{18}H_{18}INO_4$
Mol. Wt.: 439.24 g/mol

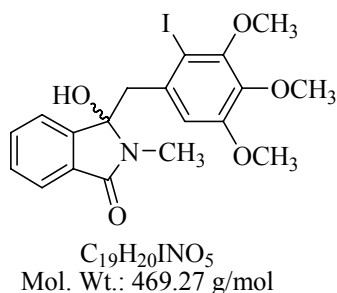
General procedure (A) was followed, with the slight variation of halving the amounts used and therefore performing the reaction in a 50 ml Schlenk flask, using NMP (0.12 g, 0.75 mmol), **81a** (0.73 g, 2.25 mmol) and K_2CO_3 (0.16 g, 1.13 mmol). After

31 hr the reaction was stopped and the precipitate, which was visible throughout the reaction, was filtered after the acetone had been evaporated. The $^1\text{H-NMR}$ showed this to be mainly **81a** however a small amount of NMP was also present. The filtrate was then worked up as usual and the crude material found to have a yield of 0.30 g. The $^1\text{H-NMR}$ showed NMP to be the major component however purification was carried out by washing with a small amount of acetone and the product isolated in a yield of 0.03 g (0.08 mmol; 11%).

For $^1\text{H-NMR}$ data see experiment 67.

Experiment 70

3-(2-iodo-3,4,5-trimethoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (**84**) (SG-201)



General procedure (A) was followed using NMP (0.24 g, 1.50 mmol), **81b** (1.58 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 13 hr the TLC showed the product was formed and the crude material found to be 0.85 g. From the $^1\text{H-NMR}$ it was evident that the product had been formed, however NMP still remained and impurities were also present. The crude product was purified, in the round bottom flask, by dissolving in a small amount of acetone and adding hexane. This was then sonicated and the product seen to precipitate. This was filtered and found to be a yellow powder with a yield of 0.24 g (0.50 mmol; 33%). The resulting $^1\text{H-NMR}$ showed this to be the pure product.

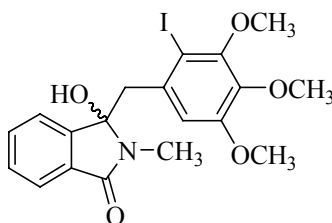
$^1\text{H-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 3.04 (s; 3H; NCH_3), 3.32 (d; $^2J = 14.4\text{Hz}$; 1H; CH_2), 3.68 (s; 3H; OCH_3), 3.71 (s; 3H; OCH_3), 3.75 (d; $^2J = 14.0\text{Hz}$; 1H; CH_2), 3.76 (s; 3H; OCH_3), 5.43 (br.s; 1H; OH), 6.70 (s; 1H; CH_{arom}), 7.21 (dd; 3J

= 6.0Hz; 1H; CH_{arom}), 7.42-7.49 (br.m; 2H; CH_{arom}), 7.57 (dd; ³J = 6.0Hz; 1H; CH_{arom}).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 24.1 (1C; NCH₃), 47.4 (1C; CH₂), 56.1 (1C; OCH₃), 60.7 (1C; OCH₃), 60.9 (1C; OCH₃), 90.6 (1C; C-OH), 92.0 (1C; CI), 110.6 (1C; CH_{arom}), 122.8 (1C; CH_{arom}), 124.1 (1C; CH_{arom}), 129.7 (1C; CH_{arom}), 131.9 (1C; CH_{arom}), 132.9 (1C; Cq), 135.1 (1C; Cq), 141.8 (1C; Cq), 147.8 (1C; Cq), 153.4 (1C; Cq), 153.8 (1C; Cq), 166.6 (1C; C=O).

Experiment 71

3-(2-iodo-3,4,5-trimethoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (84) (SG-242)



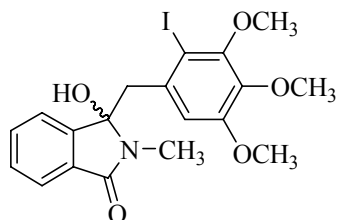
C₁₉H₂₀INO₅
Mol. Wt.: 469.27 g/mol

General procedure (A) was followed using NMP (0.24 g, 1.50 mmol), **81b** (1.58 g, 4.49 mmol) and K₂CO₃ (0.31 g, 2.25 mmol). After 16.5 hr the reaction was worked up and the crude material found to have a yield of 0.85 g. Purification was carried out by washing with a small amount of acetone and the product isolated in a yield of 0.25 g (0.53 mmol; 35%).

For ¹H-NMR data see experiment 201.

Experiment 72

3-(2-iodo-3,4,5-trimethoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one (84) (SG-245)



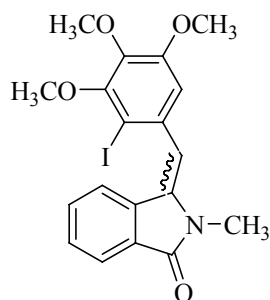
C₁₉H₂₀INO₅
Mol. Wt.: 469.27 g/mol

General procedure (A) was followed, with the slight variation of halving the amounts used and therefore performing the reaction in a 50 ml Schlenk flask, using NMP (0.12 g, 0.76 mmol), **81b** (0.79 g, 2.25 mmol) and K₂CO₃ (0.16 g, 1.13 mmol). After 31 hr the reaction was worked up and the crude material found to have a yield of 0.60 g. Purification was carried out by washing with a small amount of acetone and the product isolated in a yield of 0.26 g (0.53 mmol; 35%).

For ¹H-NMR data see experiment 201.

Experiment 73

(E) and (Z)-3-(2-iodo-3,4,5-trimethoxybenzylidene)-2-methylisoindolin-1-one (85) (SG-208)



C₁₉H₁₈INO₄
Mol. Wt.: 451.25 g/mol

Following general procedure (C) **84** (0.23 g; 0.50 mmol) was stirred in of DCM (12 ml) and conc. HCl (4 drops) and the mixture stirred overnight. The product appeared

as a yellow oily solid and had a yield of 0.21 g; (0.47 mmol; 94%). The $^1\text{H-NMR}$ confirmed the desired product was formed, however both isomers were present in a ratio of 83:17.

Major Isomer:

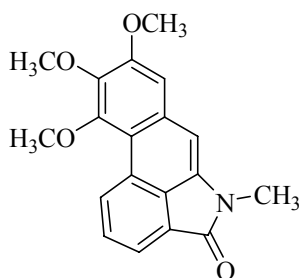
$^1\text{H-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 3.39 (s; 3H; NCH_3), 3.83 (s; 3H; OCH_3), 3.89 (s; 3H; OCH_3), 3.91 (s; 3H; OCH_3), 6.41 (s; 1H; CH_{olef}), 7.12 (s; 1H; CH_{arom}), 7.19 (dd; $^3J = 7.6\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}), 7.44 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.51 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.76 (dd; $^3J = 7.6\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}).

Minor Isomer:

$^1\text{H-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 3.39 (s; 3H; NCH_3), 3.87 (s; 3H; OCH_3), 3.88 (s; 3H; OCH_3), 3.92 (s; 3H; OCH_3), 6.68 (s; 1H; CH_{olef}), 7.03 (s; 1H; CH_{arom}), 7.24 (dd; $^3J = 7.2\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}), 7.59 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.71 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 8.02 (dd; $^3J = 7.6\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}).

Experiment 74

Trimethoxy-substituted aristolactam (86) (SG-213)



$\text{C}_{19}\text{H}_{17}\text{NO}_4$
Mol. Wt.: 323.34 g/mol

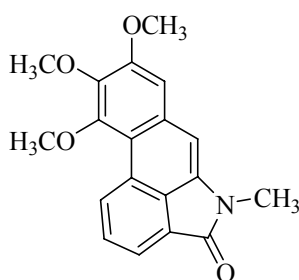
85 (0.02 g; 0.04 mmol) was placed in an NMR tube, dissolved in benzene- d_6 (0.75 ml) degassed briefly with nitrogen and irradiated in the Rayonet photoreactor. An NMR study was performed on this reaction by obtaining a $^1\text{H-NMR}$ periodically. $^1\text{H-NMR}$'s were obtained for this reaction at 0 hr, 0.25 hr, 0.50 hr, 0.75 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 9 hr, 10 hr, 11 hr, 12 hr, 13 hr, 14 hr, 15 hr, 16 hr, 17 hr, 18 hr, 19 hr and 36 hr. This enabled us to see the *E-Z* isomerisation occurring

initially, and then the eventual formation of the aristolactam. The product was seen to be present in a minor quantity after 4 hr and formation increased gradually until it was clearly visible at 36 hr even though both isomers of the starting material were still present.

For $^1\text{H-NMR}$ data see experiment 218.

Experiment 75

Trimethoxy-substituted aristolactam (**86**) (SG-218)



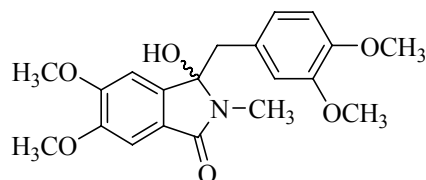
$\text{C}_{19}\text{H}_{17}\text{NO}_4$
Mol. Wt.: 323.34 g/mol

85 (0.01 g; 0.03 mmol) and DDQ (0.04 g; 0.16 mmol) were placed in an NMR tube, dissolved in benzene- d_6 (0.75 ml) degassed briefly with nitrogen and irradiated in the Rayonet photoreactor. An NMR study was performed on this reaction by obtaining a $^1\text{H-NMR}$ periodically. $^1\text{H-NMR}$'s were obtained for this reaction at 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 14 hr, 16 hr, 18 hr, 20 hr, 22 hr and 25 hr. This enabled us to see the *E-Z* isomerisation occurring initially, and then the eventual formation of the aristolactam. The product was seen to be present in a minor quantity after 2 hr and formation increased gradually until it was clearly visible at 36 hr. A significant decrease in the presence of the isomers of the starting material resulted in quite a clear $^1\text{H-NMR}$ spectrum.

$^1\text{H-NMR}$: (400 MHz, C_6D_6): δ (ppm) = 3.11 (s; 3H; NCH_3), 3.61 (s; 3H; OCH_3), 3.82 (s; 3H; OCH_3), 3.93 (s; 3H; OCH_3), 6.28 (s; 1H; CH_{arom}), 6.65 (s; 1H; CH_{arom}), 7.42 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}), 7.95 (d; $^3J = 7.2\text{Hz}$; 1H; CH_{arom}), 9.00 (d; $^3J = 8.0\text{Hz}$; 1H; CH_{arom}).

Experiment 76

3-(3,4-dimethoxybenzyl)-3-hydroxy-5,6-dimethoxy-2-methylisoindolin-1-one
(88) (SG-220)



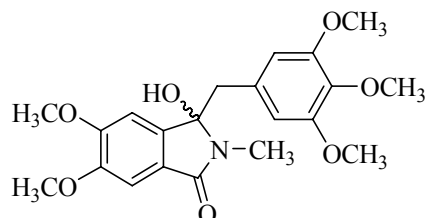
$C_{20}H_{23}NO_6$
Mol. Wt.: 373.4 g/mol

General procedure (A) was followed using **79d** (0.33 g, 1.50 mmol), 3,4-dimethoxyphenylacetic acid (0.88 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 8 hr the reaction was stopped and a precipitate which was visible throughout the reaction filtered and found to be a colourless powder with a yield of 0.24 g. The 1H -NMR showed this to be a mixture of **79d** and the acid starting material. The filtrate was worked up as usual and the crude material found to have a yield of 0.36 g. From the 1H -NMR it was evident that the product had been formed, however was not pure. The crude product was purified by dissolving it in a small amount of acetone, adding hexane and sonicating. The precipitate formed was filtered and found to be a colourless powder with a yield of 0.12 g (0.32 mmol; 21%). The resulting 1H -NMR showed this to be the desired product.

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 3.01 (s; 3H; NCH_3), 3.18 (d; $^3J = 14.0Hz$; 1H; CH_2), 3.41 (d; $^3J = 14.0Hz$; 1H; CH_2), 3.54 (s; 3H; OCH_3), 3.68 (s; 3H; OCH_3), 3.82 (s; 3H; OCH_3), 3.89 (s; 3H; OCH_3), 5.15 (br.s; 1H; OH), 6.45 (d; $^4J = 2.0Hz$; 1H; CH_{arom}), 6.52 (dd; $^3J = 8.4Hz$; $^4J = 2.0Hz$; 1H; CH_{arom}), 6.67 (d; $^3J = 8.0Hz$; 1H; CH_{arom}), 6.94 (s; 1H; CH_{arom}), 7.12 (s; 1H; CH_{arom}).

Experiment 77

3-(3,4,5-trimethoxybenzyl)-3-hydroxy-5,6-dimethoxy-2-methylisoindolin-1-one (89) (SG-219)



C₂₁H₂₅NO₇
Mol. Wt.: 403.43 g/mol

General procedure (A) was followed using **79d** (0.33 g, 1.50 mmol), 3,4,5-trimethoxyphenylacetic acid (1.02 g, 4.50 mmol) and K₂CO₃ (0.31 g, 2.26 mmol). After 8 hr the reaction was stopped and the precipitate formed during the reaction filtered and found to be a colourless powder with a yield of 0.54 g (1.33; 89%). The ¹H-NMR showed this to be the desired product. The filtrate was worked up as usual and the crude material found to be 0.17 g. From the ¹H-NMR it was evident that the product had been formed, however was not pure. The crude product was purified by dissolving the impurities in a small amount of acetone and the removing the solvent. This was repeated several times and the product found to be a colourless powder with a yield of 0.05 g (0.12 mmol; 8%). The resulting ¹H-NMR showed this to also be the pure product. [Overall yield = 97%].

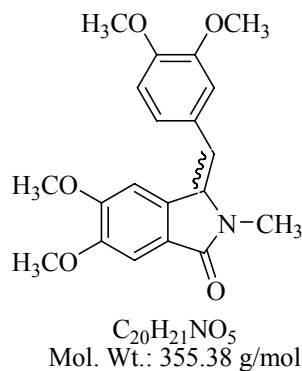
¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.00 (s; 3H; NCH₃), 3.14 (d; ³J = 13.6Hz; 1H; CH₂), 3.38 (d; ³J = 14.0Hz; 1H; CH₂), 3.57 (s; 3H; OCH₃), 3.58 (s; 6H; 2 × OCH₃), 3.81 (s; 3H; OCH₃), 3.89 (s; 3H; OCH₃), 6.19 (br.s; 1H; OH), 6.20 (s; 2H; CH_{arom}), 6.99 (s; 1H; CH_{arom}), 7.16 (s; 1H; CH_{arom}).

Literature reference No.: [65]

CAS No.: 813460-05-8

Experiment 78

(E) and (Z)-3-(3,4-dimethoxybenzylidene)-5,6-dimethoxy-2-methylisoindolin-1-one (90) (SG-225)



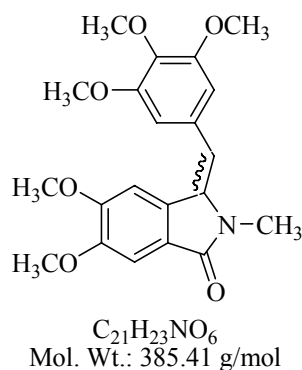
Following general procedure (C) **88** (0.12 g; 0.32 mmol) was stirred in DCM (15 ml) and conc. HCl (2 ml) overnight. The crude product had a yield of 0.11 g, (0.31 mmol; 97%) and the 1H -NMR confirmed the desired product was present, however both isomers were formed in a ratio of 74:26.

Major Isomer:

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 2.84 (s; 3H; NCH_3), 3.28 (s; 3H; OCH_3), 3.57 (s; 3H; OCH_3), 3.84 (s; 3H; OCH_3), 3.90 (s; 3H; OCH_3), 6.50 (s; 1H; CH_{olef}), 7.00 (s; 1H; CH_{arom}), 7.07 (dd; $^3J = 2.0Hz$; 1H; CH_{arom}), 7.18 (dd; $^3J = 1.2Hz$; 1H; CH_{arom}), 7.51 (s; 1H; CH_{arom}).

Experiment 79

(E) and (Z)-3-(3,4,5-trimethoxybenzylidene)-5,6-dimethoxy-2-methylisoindolin-1-one (91) (SG-222)



Following general procedure (C) **89** (0.53 g; 1.30 mmol) was stirred in DCM (15 ml) and conc. HCl (2 ml) overnight. The crude product had a yield of 0.49 g, (1.28 mmol; 98%) and the $^1\text{H-NMR}$ confirmed the desired product was present; however both isomers were formed in a ratio of 78:22.

Major Isomer:

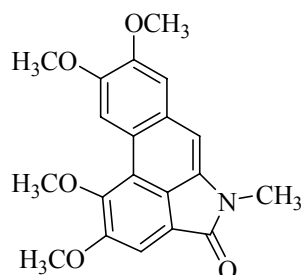
$^1\text{H-NMR}$: (400 MHz, C_2D_6CO): δ (ppm) = 3.28 (s; 3H; NCH_3), 3.58 (s; 3H; OCH_3), 3.77 (s; 3H; OCH_3), 3.85 (s; 6H; $2 \times OCH_3$), 3.90 (s; 3H; OCH_3), 6.51 (s; 1H; CH_{olef}), 6.80 (dd; $^4J = 0.4\text{Hz}$; 2H; CH_{arom}), 6.90 (s; 1H; CH_{arom}), 7.19 (s; 1H; CH_{arom}).

Minor Isomer:

$^1\text{H-NMR}$: (400 MHz, C_2D_6CO): δ (ppm) = 3.03 (s; 3H; NCH_3), 3.68 (s; 3H; OCH_3), 3.87 (s; 6H; $2 \times OCH_3$), 3.93 (s; 3H; OCH_3), 3.96 (s; 3H; OCH_3), 6.51 (s; 1H; CH_{olef}), 6.69 (dd; $^4J = 0.4\text{Hz}$; 2H; CH_{arom}), 7.19 (s; 1H; CH_{arom}), 7.51 (s; 1H; CH_{arom}).

Experiment 80

SG-230

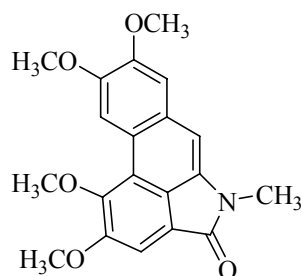


$C_{20}H_{19}NO_5$
Mol. Wt.: 353.37 g/mol

90 (0.01 g; 0.02 mmol) and DDQ (0.01 g; 0.02 mmol) were placed in an NMR tube, dissolved in benzene-d₆ (0.75 ml) and irradiated in the Rayonet photoreactor. ¹H-NMR's were obtained after 23 hr and 35 hr. There was no aristolactam formed during this reaction.

Experiment 81

SG-231

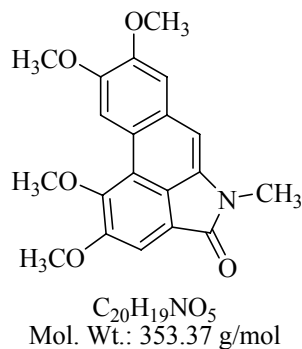


$C_{20}H_{19}NO_5$
Mol. Wt.: 353.37 g/mol

90 (0.01 g; 0.02 mmol) was placed in an NMR tube, dissolved in benzene-d₆ (0.75 ml) and irradiated in the Rayonet photoreactor. ¹H-NMR's were obtained after 23 hr and 35 hr. There was no evidence of the aristolactam being formed during this reaction.

Experiment 82

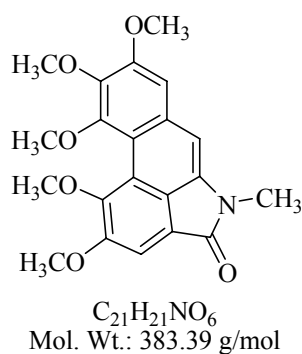
SG-230a



90 (0.20 g; 0.55 mmol) and DDQ (0.12 g; 0.55 mmol) were stirred in benzene (30 ml) at R.T for 48 hr. The solvent was then evaporated by rotary evaporation and the product found to have a yield of 0.20 g. The 1H -NMR showed this to be **90** and it was evident that no aristolactam was formed during this reaction.

Experiment 83

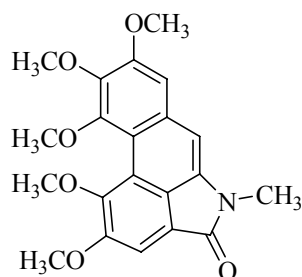
SG-228



91 (0.01 g; 0.02 mmol) and DDQ (0.01 g; 0.02 mmol) were placed in an NMR tube, dissolved in benzene- d_6 (0.75 ml) and irradiated in the Rayonet photoreactor. 1H -NMR's were obtained after 25 hr and 35 hr. There was no aristolactam formed during this reaction.

Experiment 84

SG-229

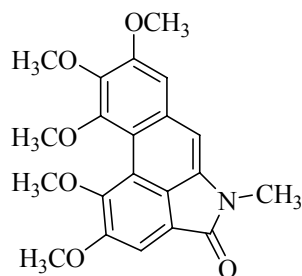


$C_{21}H_{21}NO_6$
Mol. Wt.: 383.39 g/mol

91 (0.01 g; 0.02 mmol) was placed in an NMR tube, dissolved in benzene-d₆ (0.75 ml) and irradiated in the Rayonet photoreactor. ¹H-NMR's were obtained after 25 hr and 35 hr. There was no aristolactam formed during this reaction.

Experiment 85

SG-234

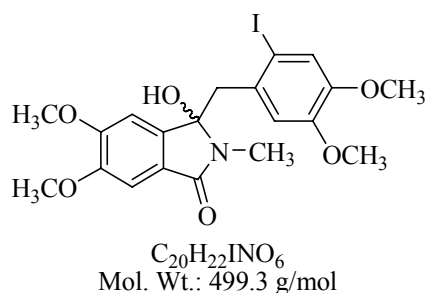


$C_{21}H_{21}NO_6$
Mol. Wt.: 383.39 g/mol

91 (0.21 g; 0.55 mmol) and DDQ (0.12 g; 0.55 mmol) were stirred in benzene (30 ml) at R.T for 48 hr. The solvent was then evaporated by rotary evaporation and the product found to have a yield of 0.21 g. The ¹H-NMR showed this to be **91** and it was evident that no aristolactam was formed during this reaction.

Experiment 86

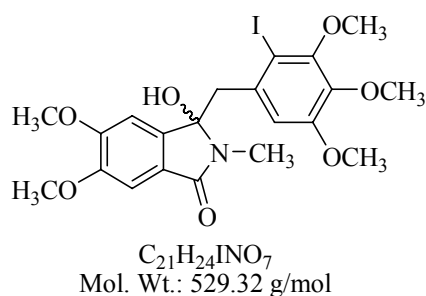
SG-233



General procedure (A) was followed, with slight variation, using **79d** (0.17 g, 0.77 mmol), **81a** (0.73 g, 2.25 mmol) and K₂CO₃ (0.16 g, 1.14 mmol). As the quantities were halved for this reaction, the irradiation was performed in a 50 ml Schlenk flask. After 32 hr the reaction was stopped and the precipitate which was visible throughout the reaction was filtered, after evaporating the acetone, and found to have a yield of 0.09 g. The ¹H-NMR showed this to be **79d**. The filtrate was worked up as usual and the crude material found to have a yield of 0.22 g. The ¹H-NMR showed that the product had not been formed and unreacted **79d** was also visible.

Experiment 87

SG-263

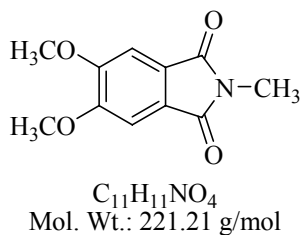


General procedure (A) was followed, with slight variation, using **79d** (0.33 g, 1.50 mmol), **81b** (1.58 g, 4.50 mmol) and K₂CO₃ (0.31 g, 2.27 mmol). This reaction was not cooled as usual, to encourage the starting materials to dissolve. After 53 hr the reaction was stopped and the precipitate which was visible throughout the reaction was filtered, after evaporating the acetone, and found to have a yield of 0.35 g. The

¹H-NMR showed this to be **79d**. The filtrate was worked up as usual and the crude material found to have a yield of 0.69 g. The ¹H-NMR showed that the product had not been formed and unreacted **79d** was also visible.

Experiment 88

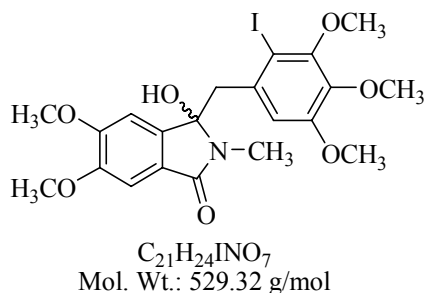
Stability test of **79d** (SG-282)



A stability test was performed on SG-256 (0.10 g; 0.46 mmol) by dissolving in DMF (50 ml) and irradiating it at 300nm overnight. The DMF was distilled, the product dried under vacuum and the yield found to be 0.08 g, (0.36 mmol; 78%). The ¹H-NMR obtained showed no change in the starting material.

Experiment 89

SG-263a

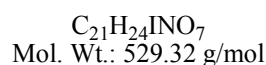
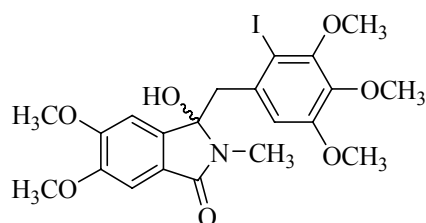


General procedure (A) was followed, with the variation of reducing the amounts and performing the reaction in a 20 ml pyrex tube, using **79d** (0.06 g; 0.30 mmol), **81b** (0.32 g; 0.90 mmol) and K_2CO_3 (0.06 g; 0.45 mmol). A solvent system of acetone:water (2:1) was made up and used to dissolve the reagents. There wasn't much improvement in dissolving the reagents and following irradiation for 24 hr, the ¹H-NMR showed the presence of **79d** and no evidence of product formation.

following work-up the $^1\text{H-NMR}$ showed the presence of **79d** and no evidence of product formation.

Experiment 92

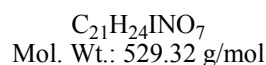
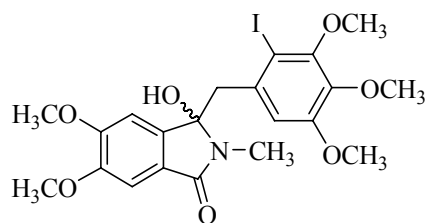
SG-264



General procedure (A) was followed, with the slight variation of using acetone:DCM 1:1 as the solvent and halving all amounts, using **79d** (0.17 g, 0.75 mmol), **81b** (0.79 g, 2.25 mmol) and K_2CO_3 (0.16 g, 1.12 mmol). This reaction was not cooled as usual, to encourage the starting materials to dissolve. (After 9.5 hr ~10 ml of H_2O was added to encourage solvation of the reagents, while the N_2 was bubbled through quite vigorously to homogenise the solution.) After 31 hr the reaction was stopped, the DCM evaporated, H_2O added and then worked up as usual. The crude material was found to have a yield of 0.54 g. The $^1\text{H-NMR}$ showed that the product had not been formed, and a substantial amount of unreacted **79d** was also visible.

Experiment 93

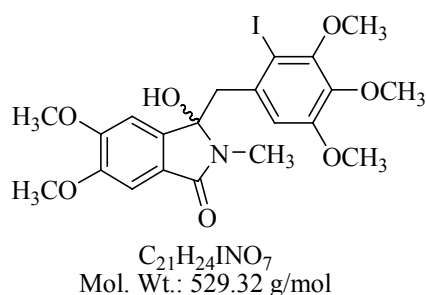
SG-283



General procedure (A) was followed, with variations, using **79d** (0.17 g; 0.75 mmol), **81b** (0.79 g; 2.25 mmol) and K₂CO₃ (0.15 g; 1.12 mmol). A solvent system of (acetone:water):DMF (4:1) was made up and used to dissolve the reagents. DMF encouraged the starting materials to go into solution initially; however **79d** did precipitate during irradiation. The reaction was stopped after 25 hr and following work-up, the ¹H-NMR showed no evidence of product formation.

Experiment 94

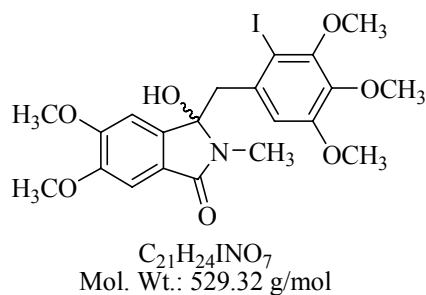
SG-283a



General procedure (A) was followed, with variations, using **79d** (0.16 g; 0.76 mmol), **81b** (0.79 g; 2.25 mmol) and K₂CO₃ (0.15 g; 1.12 mmol). A solvent system of (acetone:water):DMF (1:1) was made up and used to dissolve the reagents. This solvent system proved effective at dissolving the reagents; however following irradiation for 24 hr, the crude ¹H-NMR showed no evidence of the desired product. Following purification by washing with a small amount of acetone, **79d** was recovered in a yield of 0.10 g.

Experiment 95

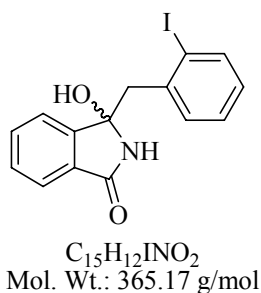
SG-329



General procedure (A) was followed, with the variation of substituting H₂O for an ethanolic emulsion, quartering the amounts used and performing the reaction in a 50 ml Schlenk flask, using **79d** (0.08 g, 0.38 mmol), **81b** (0.40 g, 1.12 mmol) and K₂CO₃ (0.08 g, 0.56 mmol). The reaction was performed at a low concentration to encourage the starting materials to dissolve. The reaction was irradiated for 25 hr and the precipitate, which was visible throughout the reaction, was filtered and found to have a yield of 0.05 g. The ¹H-NMR showed this to be **79d** and there was no evidence of the desired product.

Experiment 96

3-(2-iodobenzyl)-3-hydroxyisoindolin-1-one (**92**) (SG-341)



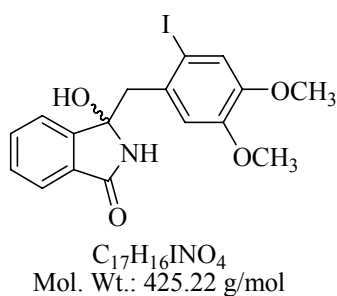
The general procedure (A1) was followed, with slight variation, using phthalimide (0.22 g; 1.50 mmol), 2-iodophenylacetic acid (1.18 g, 4.50 mmol) and K₂CO₃ (0.31 g, 2.26 mmol). After 6 hr irradiation, the reaction was stopped and following work-up, the product was found to be a yellow oily solid with a yield of 0.58 g. Purification was carried out by washing with a small amount of acetone and the yield found to be 0.43 g (1.17 mmol; 78%). The ¹H-NMR obtained showed this to be the desired product.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.55 (d; ²J = 14.0Hz; 1H; CH₂), 3.60 (d; ²J = 14.0Hz; 1H; CH₂), 5.50 (br.s; 1H; OH), 6.94 (ddd; ³J = 7.6Hz; ⁴J = 1.6Hz; 1H; CH_{arom}), 7.26 (ddd; ³J = 7.6Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.36 (ddd; ³J = 7.2Hz; ⁴J = 0.8Hz; 1H; CH_{arom}), 7.46 (ddd; ³J = 7.2Hz; ⁴J = 0.8Hz; 2H; CH_{arom}), 7.54 (m; 2H; CH_{arom}), 7.79 (dd; ³J = 8.0Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.87 (dd; ³J = 8.0Hz; ⁴J = 1.2Hz; 1H; CH_{arom}), 7.93 (br.s; 1H; NH).

CAS No.: 1246376-50-0

Experiment 97

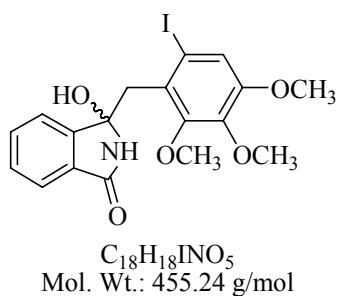
SG-344



General procedure (A1) was followed, with the slight variation of reducing amounts and performing the reaction in a 20 ml pyrex flask, using phthalimide (0.04 g, 0.30 mmol) instead of the usual NMP, **81a** (0.29 g, 0.90 mmol) and K₂CO₃ (0.06 g, 0.45 mmol). After 23 hr the reaction was stopped and following work-up, the product was found to be a yellow oily solid with a yield of 0.16 g. The ¹H-NMR showed this to be a mix of starting materials. The crude product was purified by washing with a small amount of acetone and **81a** was recovered. The desired product was not obtained.

Experiment 98

SG-343

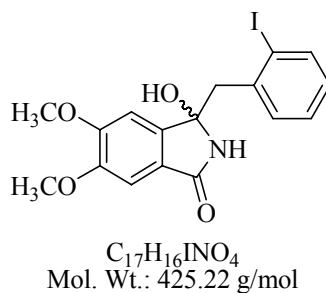


General procedure (A1) was followed, with the slight variation of reducing amounts and performing the reaction in a 20 ml pyrex flask, using phthalimide (0.05 g, 0.31 mmol), **81a** (0.32 g, 0.90 mmol) and K₂CO₃ (0.06 g, 0.45 mmol). After 23 hr the

reaction was stopped and following work-up, the product was found to be a brown oily solid with a yield of 0.14 g. The $^1\text{H-NMR}$ showed this to be a mix of starting materials. There was no evidence of the desired product.

Experiment 99

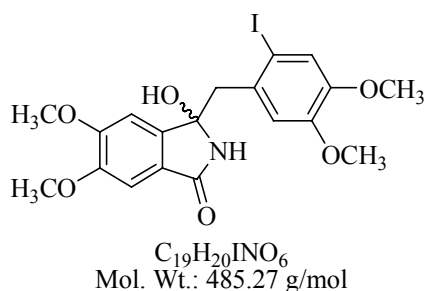
SG-346



General procedure (A1) was followed, with the slight variation of reducing the amounts (the reaction was still performed in a 100 ml Schlenk flask), using **79e** (0.03 g, 0.15 mmol), 2-iodophenylacetic acid (0.12 g, 0.45 mmol) and K_2CO_3 (0.03 g, 0.23 mmol). The solvent used was (acetone:pH 7 buffer):formamide 7:3. After 21 hr of irradiation the reaction was stopped and following work-up, the $^1\text{H-NMR}$ showed the desired product was not obtained.

Experiment 100

SG-345

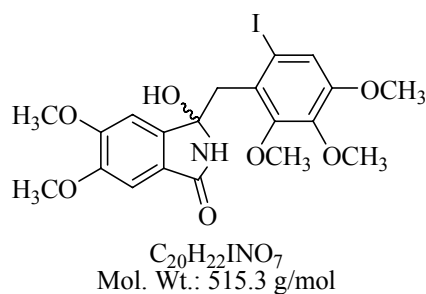


General procedure (A1) was followed, with the slight variation of reducing the amounts (the reaction was still performed in a 100 ml Schlenk flask), using **79e** (0.03 g, 0.15 mmol), **81a** (0.14 g, 0.45 mmol) and K_2CO_3 (0.03 g, 0.23 mmol). The solvent

used was (acetone:pH 7 buffer):DMF 7:3. After 21 hr of irradiation the reaction was stopped and following work-up, the $^1\text{H-NMR}$ showed the desired product was not obtained.

Experiment 101

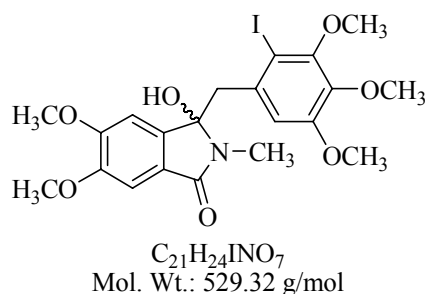
SG-342



General procedure (A1) was followed, with the slight variation of reducing the amounts and performing the reaction in a 20 ml pyrex tube, using **79e** (0.03 g, 0.15 mmol), **81b** (0.16 g, 0.45 mmol) and K_2CO_3 (0.03 g, 0.23 mmol). The solvent used was (acetone:pH 7 buffer):DMF 3:1. After 45.5 hr of irradiation the reaction was stopped, the precipitate formed was isolated and found to be the starting material **79e** in a yield of 0.02 g. Following work-up, the $^1\text{H-NMR}$ of the crude product showed the desired product was not obtained.

Experiment 102

SG-270

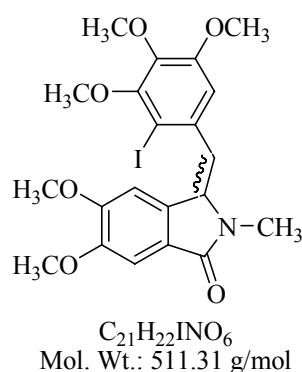


The general procedure (E) was followed using silver trifluoroacetate (0.04 g; 0.20 mmol), **89** (0.09 g; 0.19 mmol) and iodine (0.05 g; 0.22 mmol), (DCM 15 ml). The

crude yield was found to be 0.06 g. The $^1\text{H-NMR}$ showed a lot of impurities so column chromatography was performed using solvent system ethyl acetate:hexane 1:1. The product was thought to be collected in fractions 2-3, however the $^1\text{H-NMR}$ showed this to be **79d**. This reaction was not successful.

Experiment 103

SG-271

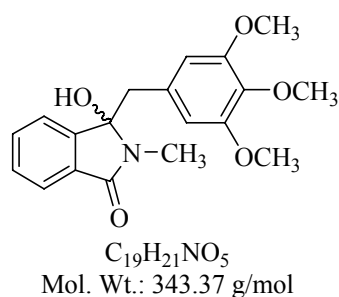


The general procedure (E) was followed using silver trifluoroacetate (0.04 g; 0.17 mmol), **91** (0.07 g; 0.17 mmol) and iodine (0.04 g; 0.17 mmol), (DCM 20 ml). The crude yield was found to be 0.10 g. The $^1\text{H-NMR}$ showed no evidence of the desired product being formed.

Additional reactions:

3-(3,4,5-trimethoxybenzyl)-3-hydroxy-2-methylisoindolin-1-one

SG-4



General procedure (A) was followed using NMP (0.2 g, 1.51 mmol), 3,4,5-trimethoxyphenylacetic acid (1.0 g, 4.50 mmol) and K_2CO_3 (0.3 g, 2.25 mmol). After

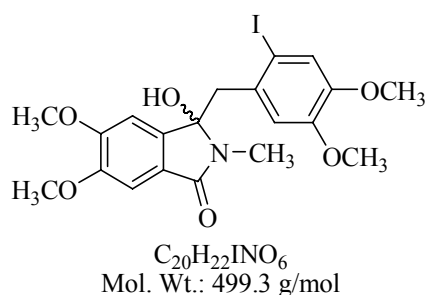
1.5 hr the TLC showed a product was formed. The solution was clear and colourless. The crude yield was found to be 1.1 g (3.29 mmol). Following column chromatography it was assumed from the TLC that the desired product was collected in fractions 2-5. The $^1\text{H-NMR}$ obtained confirmed this and the overall weight of the fractions was found to be 0.3 g, (0.75 mmol, 50%). The product was then further recrystallised from acetone using hexane and formed a colourless, fine, powder-like substance. The yield of the purified product was 0.1 g (0.30 mmol, 20%).

$^1\text{H-NMR}$: (400 MHz, CDCl_3) : δ (ppm) = 2.50 (br.s; 1H; OH), 3.06 (s; 3H; NCH_3), 3.06 (d; $^2J = 14.0\text{Hz}$; 1H; CH_2), 3.46 (d; $^2J = 14.0\text{Hz}$; 1H; CH_2), 3.62 (s; 6H; *o*- OCH_3) 3.76 (s; 3H; *p*- OCH_3) 6.07 (s; 2H; CH_{arom}), 7.33 (d; $^3J = 7.6\text{Hz}$; 1H; CH_{arom}), 7.44 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.51 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.67 (d; $^3J = 7.6\text{Hz}$; 1H; CH_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 23.9 (1C; NCH_3), 42.7 (1C; CH_2), 55.9 (2C; *o*- OCH_3), 60.9 (1C; *p*- OCH_3), 90.6 (1C; COH), 107.0 (2C; CH_{arom}), 122.8 (1C; CH_{arom}), 123.2 (1C; CH_{arom}), 129.7 (1C; CH_{arom}), 129.9 (1C; C_{qarom}), 131.4 (1C; C_{qarom}), 131.6 (1C; CH_{arom}), 136.9 (1C; C_{qarom}), 146.2 (1C; *p*- C-OCH_3), 152.6 (2C; *o*- COCH_3), 166.9 (1C; C=O).

CAS No.: 881376-83-6

SG-259



General procedure (A) was followed using **79d** (0.31 g, 1.41 mmol), **81a** (1.45 g, 4.50 mmol) and K_2CO_3 (0.31 g, 2.25 mmol). After 32 hr the reaction was stopped and the precipitate, which was visible throughout the reaction, was filtered and found to have a yield of 0.43 g. The $^1\text{H-NMR}$ showed this to be **79d**. The filtrate was

worked up as usual and the crude material found to have a yield of 0.38 g. The $^1\text{H-NMR}$ showed that the product had not been formed and unreacted **79d** was also visible.

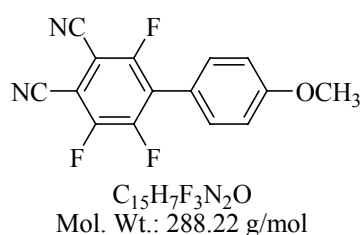
7.4 Chapter 5: Synthesis of phthalocyanines from photochemically derived fluorinated phthalonitriles

7.4.1 General Procedure (F):

TFPN (1.50 mmol) and methoxy-substituted benzene partner (3.00 mmol) were dissolved in DCM (10 ml) and transferred to a 350 ml Schlenk flask which was then filled up to the neck with DCM. This was placed in the Rayonet reactor, the cold finger inserted and both neck openings sealed. The solution was irradiated at 300nm, while being cooled, and the progress monitored by TLC. Upon completion of the reaction, the DCM was removed by rotary evaporation and a $^1\text{H-NMR}$ of the crude product obtained. Column chromatography was carried out using solvent system ethyl acetate:hexane (1:6). A $^1\text{H-NMR}$ of the pure product was then obtained.

Experiment 104

Methoxy-substituted phthalonitrile derivative (95a) (SG-294)



Following general procedure (F), TFPN (0.30 g; 1.51 mmol) and anisole (325 μl ; 2.98 mmol) were irradiated in DCM for 70 hr. The crude yield was found to be 0.53 g and the $^1\text{H-NMR}$ showed this to be a mixture of TFPN and the desired product. Following purification, the product appeared as an off-white powder and was collected in fractions 4-11 with a yield of 0.17 g, (0.59 mmol; 39%).

SG-295:

General procedure (F) was followed using TFPN (0.30 g; 1.50 mmol) and anisole (325 μ l; 2.98 mmol). The solution was irradiated for 70 hr and the crude yield found to be 0.59 g. The $^1\text{H-NMR}$ showed this to be a mixture of TFPN and the desired product. Following column chromatography, the pure product was collected in fractions 5-25, and was seen to be an off-white powder with a yield of 0.19 g, (0.66 mmol; 44%).

[Average yield = 42%]

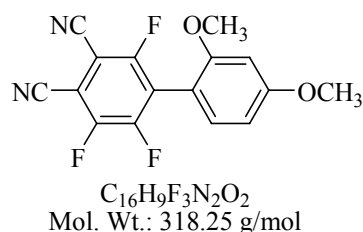
$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 3.89 (s; 3H; OCH_3), 7.06 (dd; $^3J = 8.8\text{Hz}$; $^4J = 2.0\text{Hz}$; 2H; CH_{arom}), 7.42 (dd; $^3J = 8.8\text{Hz}$; $^4J = 1.6\text{Hz}$; 2H; CH_{arom}).

$^{19}\text{F-NMR}$: (400 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$): δ (ppm) = -131.8 (q; $J = 12\text{Hz}$; 1F; CF_{arom}), -126.4 (q; $J = 12\text{Hz}$; 1F; CF_{arom}), -109.2 (t; $J = 12\text{Hz}$; 1F; CF_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 55.6 (1C; OCH_3), 114.8 (2C; CH_{arom}), 131.6 (2C; CH_{arom}), 161.7 (1C; Cq).

Literature reference No.: [142]

CAS No.: 75860-37-6

*Experiment 105***Trimethoxy-substituted phthalonitrile derivative (95b) (SG-318/319)**

General procedure (F) was followed for both reactions and the crude products combined before performing column chromatography, using TFPN (0.30 g; 1.50 mmol/0.30 g; 1.50 mmol) and 1,3-dimethoxybenzene (393 μ l; 3.00 mmol/393 μ l; 3.00 mmol). The solution was irradiated for 96 hr and following column

chromatography, the pure product was collected in fractions 3-5, and was seen to be an off-white powder with a yield of 0.47 g, (1.49 mmol; 50%).

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 3.80 (s; 3H; OCH₃), 3.88 (s; 3H; OCH₃), 6.59 (d; ⁴J = 2.4Hz; 1H; CH_{arom}), 6.63 (dd; ³J = 8.4Hz; ⁴J = 2.4Hz; 1H; CH_{arom}), 7.14 (d; ³J = 8.4Hz; 1H; CH_{arom}).

¹⁹F-NMR: (400 MHz, CDCl₃/C₆F₆): δ (ppm) = -133.5 (q; J = 12Hz; 1F; CF_{arom}), -120.2 (q; J = 12Hz; 1F; CF_{arom}), -104.2 (t; J = 12Hz; 1F; CF_{arom}).

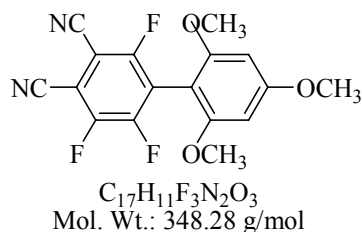
¹³C-NMR: (100 MHz, CDCl₃): δ (ppm) = 55.7 (1C; OCH₃), 55.9 (1C; OCH₃), 99.1 (1C; CH_{arom}), 105.5 (1C; CH_{arom}), 131.9 (1C; CH_{arom}), 158.2 (1C; Cq), 163.4 (1C; Cq).

Literature reference No.: [142]

CAS No.: 75860-38-7

Experiment 106

Trimethoxy-substituted phthalonitrile derivative (95c) (SG-298/299)



General procedure (F) was followed for both reactions and the crude products combined before performing column chromatography, using TFPN (0.30 g; 1.51 mmol/0.30 g; 1.50 mmol) and 1,3,5-trimethoxybenzene (0.51 g; 3.00 mmol/0.51 g; 3.01 mmol). The solution was irradiated for 70 hr and the crude yield found to be 0.94 g/0.89 g. [Total yield = 1.84 g]. The ¹H-NMR showed this to be a mixture of TFPN and the desired product. Following column chromatography, the pure product was collected in fractions 5-13, and was seen to be a yellow crystalline solid with a yield of 0.49 g, (1.41 mmol; 47%).

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 3.77 (s; 6H; 2 × OCH₃), 3.88 (s; 3H; OCH₃), 6.21 (s; 2H; CH_{arom}).

¹⁹F-NMR: (400 MHz, CDCl₃/C₆F₆): δ (ppm) = -132.7 (q; *J* = 12Hz; 1F; CF_{arom}), -122.3 (q; *J* = 12Hz; 1F; CF_{arom}), -106.9 (t; *J* = 12Hz; 1F; CF_{arom}).

¹³C-NMR: (100 MHz, CDCl₃): δ (ppm) = 55.7 (1C; OCH₃), 56.0 (2C; 2 × OCH₃), 90.8 (2C; CH_{arom}), 158.8 (2C; Cq), 164.2 (1C; Cq).

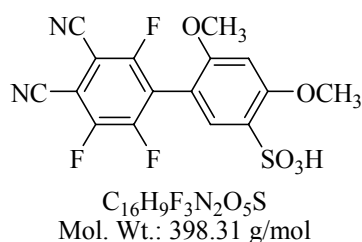
Mass spec: [MS]: 348 m/z; expected 348 m/z

7.4.2 General procedure (G):

The desired methoxy-substituted phthalonitrile derivative were stirred at R.T in TFA:H₂SO₄ (4:1) for 48 hr. The reaction was quenched by pouring onto ice-water. This was extracted with ethyl acetate (×3), the organic layers combined, dried over MgSO₄ and the solvent evaporated. A crude ¹H-NMR was obtained. Purification was performed by recrystallisation from ethanol and a second ¹H-NMR obtained.

Experiment 107

Sulfonated dimethoxy-substituted phthalonitrile derivative (96b) (SG-301)



Following general procedure (G) **95b** (0.08 g; 0.26 mmol) was stirred at R.T in TFA:H₂SO₄ (4:1) (8 ml) for 48 hr. The crude yield was found to be 0.12 g. The ¹H-NMR showed this to be a mixture of starting material and product. This was recrystallised from ethanol, the precipitate formed was filtered, and the ¹H-NMR showed this not to be the product. The filtrate was then evaporated and the yield found to be 0.09 g, (0.23 mmol; 88%). The ¹H-NMR showed this to be the desired product.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.99 (s; 3H; OCH₃), 4.07 (s; 3H; OCH₃), 7.03 (s; 1H; CH_{arom}), 7.84 (s; 1H; CH_{arom}).

¹⁹F-NMR: (400 MHz, C₂D₆CO/C₆F₆): δ (ppm) = -133.0 (q; *J* = 12Hz; 1F; CF_{arom}), -122.5 (q; *J* = 12Hz; 1F; CF_{arom}), -106.6 (t; *J* = 12Hz; 1F; CF_{arom}).

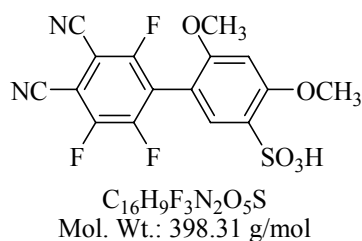
¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 56.9, 57.1, 97.7, 105.3, 123.3, 132.8, 154.4, 161.6, 162.2, 198.3.

Mass spec: [MS - H]: 397 m/z, expected: 398 m/z

Melting point: 112-115°C

Experiment 108

Sulfonated dimethoxy-substituted phthalonitrile derivative (96b) (SG-340)

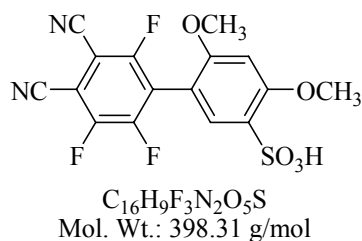


General procedure (G) was followed, with the variation of using H₂SO₄ (4 ml) as the sole solvent, using **95b** (0.05 g; 0.16 mmol). The solution was stirred at R.T for 43 hr, then worked up. The ¹H-NMR showed this to be the desired product which was obtained in a yield of 0.02 g, (0.06 mmol; 38%). No purification was carried out.

For ¹H-NMR data see experiment 107.

Experiment 109

Sulfonated dimethoxy-substituted phthalonitrile derivative (**96b**) (SG-347)

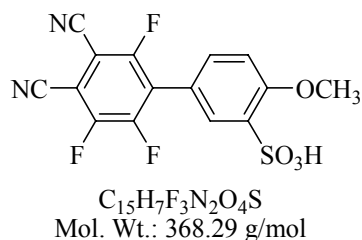


General procedure (G) was followed, with slight variation, using **95b** (0.20 g; 0.63 mmol) and TFA:H₂SO₄ (1:1) (10 ml). The solution was stirred at R.T for 96 hr, then worked up. The ¹H-NMR showed this to be the desired product and was obtained in a yield of 0.07 g, (0.18 mmol; 29%). No purification was carried out.

For ¹H-NMR data see experiment 107.

Experiment 110

Sulfonated methoxy-substituted phthalonitrile derivative (**96a**) (SG-316)



Following general procedure (G) **95a** (0.07 g; 0.26 mmol) was stirred in TFA:H₂SO₄ (4:1) (8 ml) overnight. The TLC showed the starting material spot had disappeared so the reaction was quenched by pouring onto ice-water. A precipitate was formed which was found to be a colourless powder with a yield of 0.03 g. The ¹H-NMR was very similar to the starting material, however a mass spectrum was also obtained which implied that this was the anhydride of the starting material as there was a peak at 308 m/z. However, the filtrate was also extracted with ethyl acetate (×3), the organic layers combined and dried over MgSO₄ and the solvent evaporated. The crude yield was found to be 0.05 g and the ¹H-NMR showed the presence of the

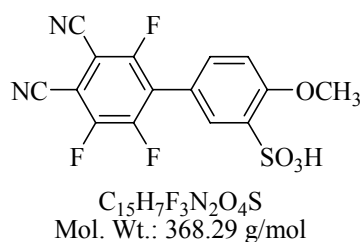
sulfonated product with the starting material **95a** also present. Recrystallisation from ethanol afforded **96a** in a yield of 26%.

For $^1\text{H-NMR}$ data see experiment 111.

Mass spec: [MS]: 308 m/z; expected 308 m/z [anhydride]

Experiment 111

Sulfonated methoxy-substituted phthalonitrile derivative (**96a**) (SG-339)

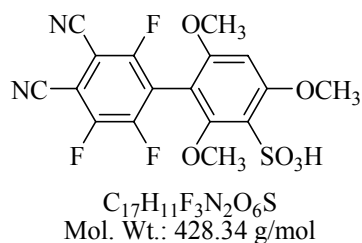


Following general procedure (G) **95a** (0.07 g; 0.26 mmol) was stirred in TFA: H_2SO_4 (1:1) (8 ml) for 96 hr. Following work-up the crude yield was found to be 0.07 g (0.19 mmol; 73%). The $^1\text{H-NMR}$ showed this to be the sulfonated product.

$^1\text{H-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 4.02 (s; 3H; OCH_3), 7.37 (dd; $^3J = 8.8\text{Hz}$; 1H; CH_{arom}), 7.76 (dd; $^3J = 8.8\text{Hz}$; 1H; CH_{arom}), 8.04 (s; 1H; CH_{arom}).

Experiment 112

SG-317



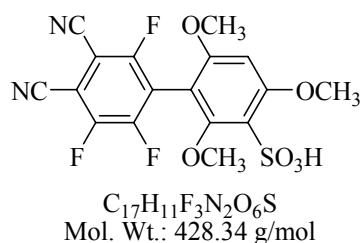
Following general procedure (G) **95c** (0.09 g; 0.26 mmol) was stirred in TFA: H_2SO_4 (4:1) (8 ml) overnight. The TLC showed the starting material spot had disappeared

so the reaction was quenched by pouring onto ice-water. A precipitate was formed which was found to be an orange powder with a yield of 0.08 g. The $^1\text{H-NMR}$ was very similar to the starting material; however a mass spectrum was also obtained which implied that this was the anhydride of the starting material as there was a peak at 368 m/z. However, the filtrate was also extracted with ethyl acetate ($\times 3$), the organic layers combined and dried over MgSO_4 and the solvent evaporated. The crude yield was found to be 0.02 g and the $^1\text{H-NMR}$ showed no evidence of the sulfonated product.

Mass spec: [MS]: 368 m/z; expected 368 m/z [anhydride]

Experiment 113

SG-348



Following general procedure (G) **95c** (0.21 g; 0.59 mmol) was stirred in $\text{TFA}:\text{H}_2\text{SO}_4$ (4:1) (8 ml) for 96 hr. The reaction was worked up as usual and the $^1\text{H-NMR}$ of the crude product showed no evidence of the sulfonated product.

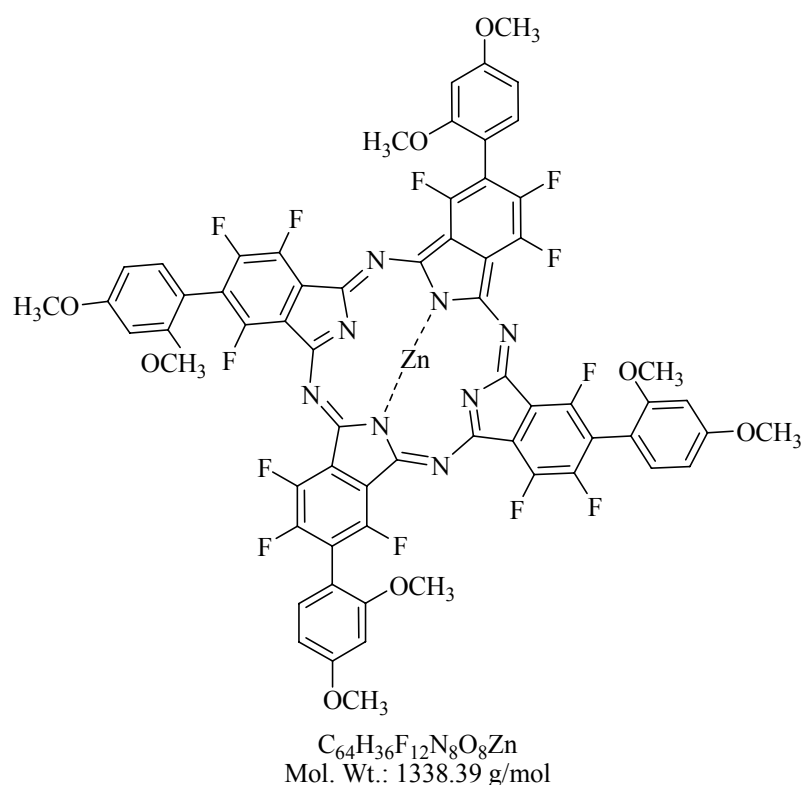
7.4.3 General procedure (H):

The desired methoxy-substituted phthalonitrile derivative (2 equiv.) and zinc acetate dihydrate (1 equiv.) were crushed together using a pestle and mortar and transferred to a pyrex test tube. This was inserted into a steel carousel which was placed on top of a hotplate. The cap was screwed on to the test tube and the N_2 tubing hooked up to the carousel. The test tube was flushed with N_2 for several minutes and then a balloon filled to keep the reaction under N_2 , after which the tap was closed. The reaction mixture was then heated to 190°C for 1.5 hr. The melt that formed was a dark green in colour. The reaction was then allowed to cool down, acetone added and

the solution centrifuged. The resulting dark green solvent was then evaporated and the product obtained.

Experiment 114

Dimethoxy-substituted phthalocyanine (97b) (SG-335)



General procedure (H) was followed using **95b** (0.16 g; 0.50 mmol) and zinc acetate dihydrate (0.06 g; 0.26 mmol). The reaction mixture was heated to 190°C for 1.5 hr. The melt that formed was a dark green in colour. The reaction was then allowed to cool down, acetone added and the solution centrifuged. The resulting dark green solvent was then evaporated and the product found to be a dark green solid with a yield of 0.15 g (0.45 mmol; 90%). The ¹H-NMR showed this to be identical to the starting material, however the green colour is proof that the desired phthalocyanine was formed.

SG-336:

General procedure (H) was followed using, **95b** (0.14 g; 0.44 mmol) and zinc acetate dihydrate (0.05 g; 0.22 mmol). The crude yield was found to be 0.16 g (0.48 mmol;

109%). Again the $^1\text{H-NMR}$ showed this to be identical to the starting material, however the green colour is proof that the desired phthalocyanine was formed.

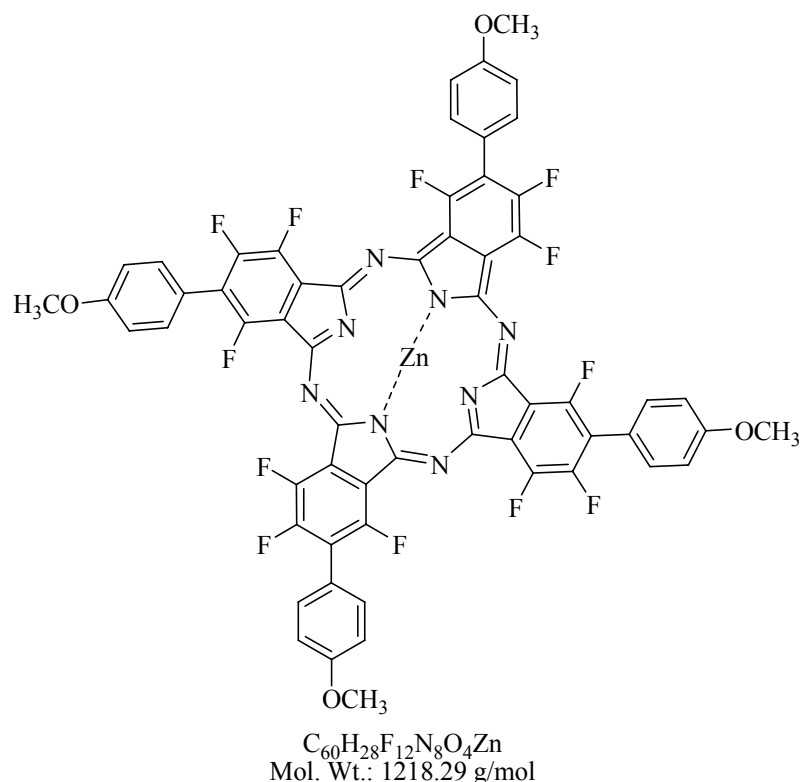
$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 3.81 (s; 3H; OCH_3), 3.88 (s; 3H; OCH_3), 6.58 (d; $^4J = 2.0\text{Hz}$; 1H; CH_{arom}), 6.62 (dd; $^3J = 8.4\text{Hz}$; $^4J = 2.0\text{Hz}$; 1H; CH_{arom}), 7.15 (d; $^3J = 8.4\text{Hz}$; 1H; CH_{arom}).

$^{19}\text{F-NMR}$: (400 MHz, $\text{CDCl}_3/\text{C}_6\text{F}_6$): δ (ppm) = -132.8 (q; $J = 12\text{Hz}$; 1F; CF_{arom}), -122.4 (q; $J = 12\text{Hz}$; 1F; CF_{arom}), -106.0 (t; $J = 12\text{Hz}$; 1F; CF_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 55.7 (1C; OCH_3), 55.9 (1C; OCH_3), 99.1 (1C; CH_{arom}), 105.4 (1C; CH_{arom}), 132.0 (1C; CH_{arom}), 158.2 (1C; Cq), 163.5 (1C; Cq).

Experiment 115

Dimethoxy-substituted phthalocyanine (**97a**) (SG-349)



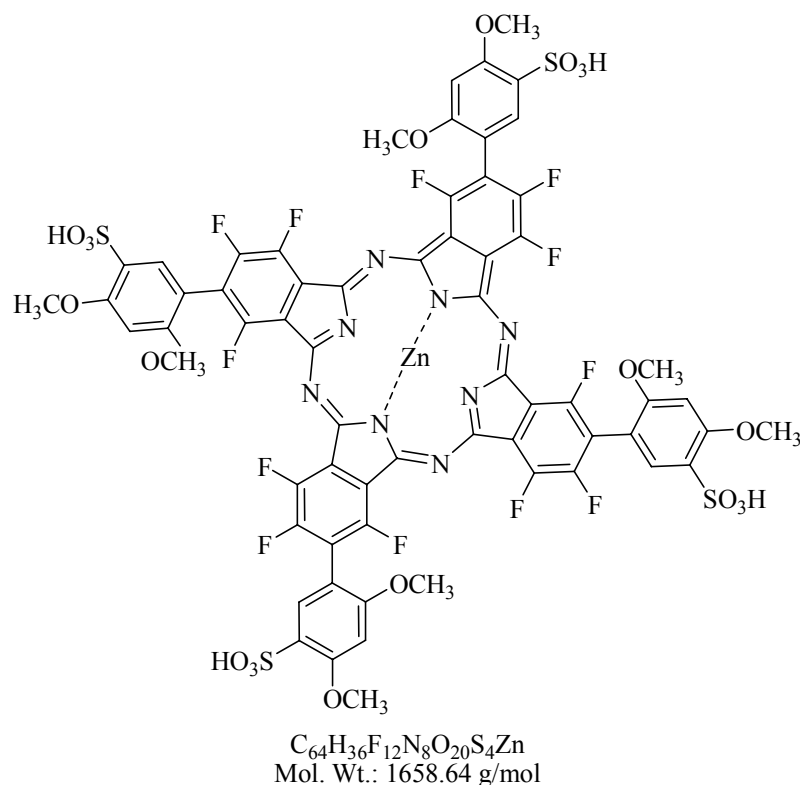
General procedure (H) was followed using **95a** (0.04 g; 0.15 mmol) and zinc acetate dihydrate (0.02 g; 0.08 mmol). The reaction mixture was heated to 190°C for 2 hr. The melt that formed was a dark green in colour. The reaction was then allowed to

cool down, acetone added and the solution centrifuged. The resulting dark green solvent was then evaporated and the product found to be a dark green solid with a yield of 0.03 g (0.10 mmol; 67%). The $^1\text{H-NMR}$ showed this to be similar to the starting material, however the green colour is proof that the desired phthalocyanine was formed.

$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 3.89 (s; 3H; OCH_3), 7.06 (dd; $^3J = 6.8\text{Hz}$; $^4J = 2.4\text{Hz}$; 2H; CH_{arom}), 7.42 (dd; $^3J = 6.8\text{Hz}$; $^4J = 2.0\text{Hz}$; 2H; CH_{arom}).

Experiment 116

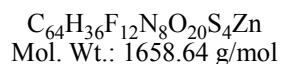
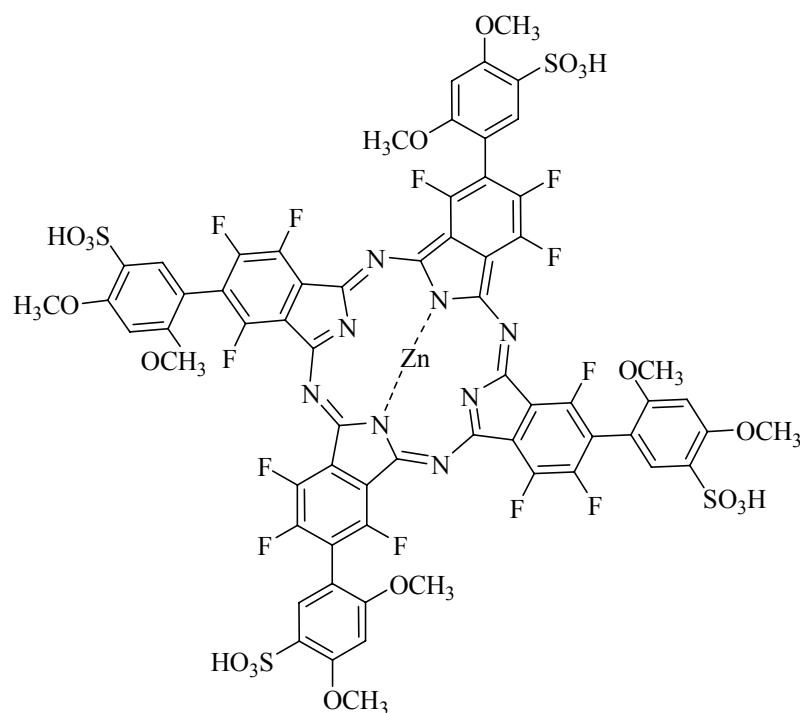
SG-337



General procedure (H) was followed using **96b** (0.04 g; 0.11 mmol) and zinc acetate dihydrate (0.01 g; 0.06 mmol). The reaction was heated for 2 hr and the crude yield was found to be 0.01 g. The $^1\text{H-NMR}$ showed this to be similar to **96b**, which means the sulfonate group may have been lost, however the green colour is proof that a phthalocyanine was formed. The sulfonated Pc was not formed.

Experiment 117

Sulfonated dimethoxy-substituted phthalocyanine (**98b**) (SG-338)



General procedure (G) was followed, using **97b** (0.14 g; 0.11 mmol) and TFA:H₂SO₄ (4:1) (5 ml). The solution was stirred at R.T for 48 hr, when checked by TLC starting material was still present so H₂SO₄ (~1 ml) was added and the solution allowed to stir overnight. Following work-up the yield was found to be 0.10 g. The ¹H-NMR showed the desired product had been formed, however was not pure. The product was still green in colour.

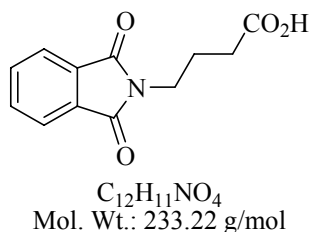
¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 3.92 (s; 3H; OCH₃), 3.93 (s; 3H; OCH₃), 6.95 (s; 1H; CH_{arom}), 7.86 (s; 1H; CH_{arom}).

¹⁹F-NMR: (400 MHz, C₂D₆CO/C₆F₆): δ (ppm) = -133.2 (q; *J* = 12Hz; 1F; CF_{arom}), -122.5 (q; *J* = 12Hz; 1F; CF_{arom}), -106.6 (t; *J* = 12Hz; 1F; CF_{arom}).

7.5 Chapter 6: Microphotochemistry performed with selected reactions

Experiment 118

4-(1,3-dioxisoindolin-2-yl)butanoic acid (**99a**) (SG-16)



Phthalic anhydride (7.7 g, 52.0 mmol) and 4-aminobutanoic acid (5.4 g, 52.0 mmol) were heated in DMF to 150°C for 1.5 hr. Once the solution had cooled to ~50°C, acetone (10 ml) was added and the resulting solution poured onto ice. A precipitate was observed, which was filtered by vacuum filtration and washed with distilled H₂O. The product was obtained as a light yellow solid with a yield of 11.9 g (52.0 mmol; 98 %).

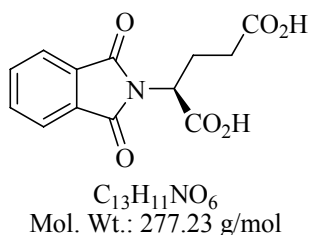
¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 2.01 (m; 2H; CH₂), 2.44 (t; ³J = 7.0 Hz; 2H; CH₂), 3.77 (t; ³J = 7.0 Hz; 2H; CH₂), 7.88 (m; 4H; CH_{arom}).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 24.6 (1C; CH₂), 32.5 (1C; CH₂), 38.3 (1C; CH₂), 123.7 (2C; CH_{arom}), 133.2 (2C; C_q), 134.9 (2C; CH_{arom}), 168.9 (2C, C=O).

CAS No.: 3130-75-4

Experiment 119

(S)-2-(1,3-dioxoisindolin-2-yl)pentanedioic acid (99b) (SG-141)



Phthalic anhydride (5.0 g; 34.0 mmol) and *L*-glutamic acid (5.0 g, 34.0 mmol) were heated in DMF to 150°C for 1.5 hr. Following addition of acetone (10 ml), the product did not precipitate as expected when poured over ice, so the water was evaporated and a brown oil obtained. A $^1\text{H-NMR}$ showed this was the desired product; however some phthalic anhydride was also present. To purify, the oil was dissolved in CDCl_3 and hexane added. After sonication, a colourless solid was observed to precipitate which was filtered and dried. The yield was found to be 12.4 g (43.8 mmol; 129%). This high yield can be explained by the presence of the starting material. This was nevertheless used in the photoreactions. To remove the phthalic anhydride, a portion of this (0.05 g) was then recrystallised from distilled H_2O and the NMR showed this was solely the pure product. The yield was found to be 0.04 g (80%). [Overall yield: (0.15 mmol; 0.4%)]. The product was a colourless powder.

$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 2.16 (t; $^3J = 7.6\text{Hz}$; 2H; CH_2), 2.28 (m; 1H; CH_2), 2.41 (m; 1H; CH_2), 4.71 (m; 1H; CH_{asym}), 7.57 (m; 2H; CH_{arom}), 7.67 (m; 2H; CH_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 23.8 (1C; CH_2), 30.5 (1C; CH_2), 51.1 (1C; CH_{asym}), 123.1 (2C; CH_{arom}), 131.5 (2C; CH_{arom}), 133.9 (2C; Cq), 167.3 (2C; $2 \times \text{C}=\text{O}$), 170.5 (1C; $\text{C}=\text{O}$), 173.9 (1C; $\text{C}=\text{O}$).

CAS No.: 340-90-9

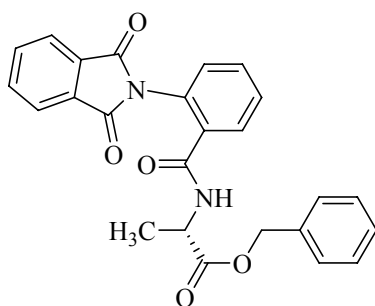
7.5.1 General Procedure (I):

2-phthalimidobenzoic acid (3.0 mmol), desired benzyl ester salt (3.0 mmol) and DCM (30 ml) were placed in a 100 ml round bottom flask. TEA (3.0 mmol) was added and the solution cooled to 0°C in an ice bath. EDC (3.0 mmol) was then added and the solution stirred at 0°C for 1 hr, and then at room temperature overnight. The solvent was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was washed with water (× 3), dilute HCl (× 2), dilute Na₂CO₃ (× 2), and brine (× 1). This was then dried over MgSO₄, filtered and the solvent evaporated. A ¹H-NMR was obtained to confirm the expected product had been formed.

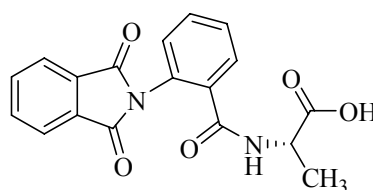
A hydrogenisation was then performed by dissolving the product (2.0 mmol) in methanol (50 ml) and degassing under argon for ~15 min. During this time, Pd/Charcoal (0.50 g) was added. A balloon filled with H₂ gas was then put in place so the solution was under H₂ in a closed system while being stirred overnight. The mixture was then filtered through a celite patch, the solvent evaporated and a ¹H-NMR obtained.

Experiment 120a

(S)-benzyl 2-(2-(1,3-dioxisoindolin-2-yl)benzamido)propanoate and (S)-2-(2-(1,3-dioxisoindolin-2-yl)benzamido)propanoic acid (100a and 100b) (SG-149 and SG-151)



C₂₅H₂₀N₂O₅
Mol. Wt.: 428.44 g/mol



C₁₈H₁₄N₂O₅
Mol. Wt.: 338.31 g/mol

General procedure (I) was followed using 2-phthalimidobenzoic acid (0.8 g; 3.01 mmol), L-alanine-benzylester-*p*-toluenesulfonate salt (1.1 g; 3.0 mmol), TEA (0.3 g; 3.15 mmol) and EDC (0.6 g, 3.03 mmol). The solution was stirred for 48 hr and

following work-up, the $^1\text{H-NMR}$ confirmed the product had been formed as a clear foamy oil with a yield of 0.9 g (2.02 mmol; 67%). The hydrogenisation was then carried out using the phenyl ester **100a** (0.8 g; 1.97 mmol). A $^1\text{H-NMR}$ showed the desired product was present however; a small amount of the methyl ester had also been formed. This was purified by dissolving the product in ethyl acetate (~20 ml) and extracting with saturated NaHCO_3 (2×20 ml). The aqueous layer was then dropped onto acidified ice and the desired product precipitated. This was filtered, washed with water and dried. A $^1\text{H-NMR}$ showed this was the pure product and the yield was found to be 0.5 g (1.56 mmol; 79%). [Overall yield = 52%]. The product was a colourless powder.

100b:

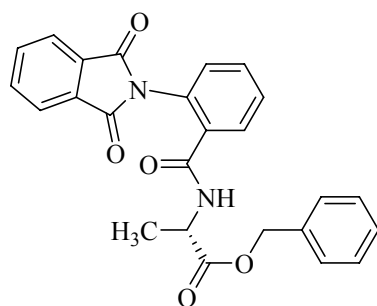
$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 1.43 (d; $^3J = 7.2\text{Hz}$; 3H; CH_3), 4.59 (m; 1H; CH_{asym}), 6.59 (br.d; $^3J = 6.8\text{Hz}$; 1H; NH), 7.40 (dd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.53 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.63 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.70 (dd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.76 (m; 2H; CH_{arom}), 7.92 (m; 2H; CH_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ (ppm) = 17.9 (1C; CH_3), 48.5 (1C; CH_{asym}), 24.8 (1C; CH), 124.0 (2C; Cq), 128.5 (1C; CH_{arom}), 129.3 (1C; CH_{arom}), 129.8 (1C; Cq), 130.0 (1C; CH_{arom}), 131.8 (1C; CH_{arom}), 132.0 (2C; CH_{arom}), 133.6 (1C; Cq), 134.6 (2C; CH_{arom}), 167.0 (1C; C=O), 167.7 (1C; C=O), 176.2 (2C; C=O).

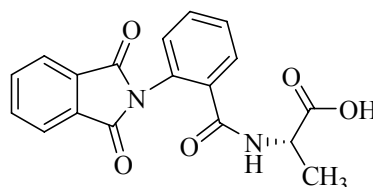
CAS No.: 330434-07-6

Experiment 120b

(S)-benzyl 2-(2-(1,3-dioxoisindolin-2-yl)benzamido)propanoate and (S)-2-(2-(1,3-dioxoisindolin-2-yl)benzamido)propanoic acid (100a and 100b) (SG-214 and SG-217)



$C_{25}H_{20}N_2O_5$
Mol. Wt.: 428.44 g/mol



$C_{18}H_{14}N_2O_5$
Mol. Wt.: 338.31 g/mol

General procedure (I) was followed, using 2-phthalimidobenzoic acid (0.80 g; 3.00 mmol), L-alanine-benzylester-p-toluenesulfonate salt (1.05 g; 3.00 mmol), TEA (0.30 g; 3.01 mmol) and EDC (0.58 g, 3.00 mmol). The $^1\text{H-NMR}$ confirmed the product had been formed as a yellow foamy solid with a yield of 0.91 g (2.12 mmol; 71%). The hydrogenisation was then carried out using the phenyl ester **100a** (0.89 g; 2.07 mmol). A slight modification was applied to this reaction in that ethyl acetate was used as the solvent instead of methanol, which eliminated the problem of the methyl ester being formed along with the desired product. The $^1\text{H-NMR}$ showed this to be the pure product and the yield was found to be 0.63 g (1.86 mmol; 90%). [Overall yield = 62%]. The product was a colourless foamy solid.

100a:

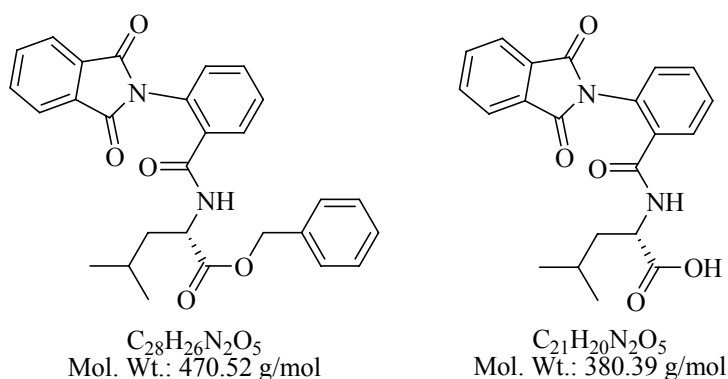
$^1\text{H-NMR}$: (400 MHz, CDCl_3): δ (ppm) = 1.40 (d; $^3J = 7.2\text{Hz}$; 3H; CH_3), 4.64 (m; 1H; CH_{asym}), 5.11 (d; $^3J = 12.4\text{Hz}$; 1H; CH_2), 5.15 (d; $^3J = 12.4\text{Hz}$; 1H; CH_2), 6.63 (br.d; $^3J = 7.6\text{Hz}$; 1H; NH), 7.29-7.38 (m; 5H; CH_{arom}), 7.40 (dd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.51 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.62 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.6\text{Hz}$; 1H; CH_{arom}), 7.70 (dd; $^3J = 7.6\text{Hz}$; $^4J = 1.6\text{Hz}$; 1H; CH_{arom}), 7.76 (m; 2H; CH_{arom}), 7.92 (m; 2H; CH_{arom}).

100b:

For $^1\text{H-NMR}$ data see experiment 120a.

Experiment 121

(S)-benzyl 2-(2-(1,3-dioxisoindolin-2-yl)benzamido)-4-methylpentanoate and (S)-2-(2-(1,3-dioxisoindolin-2-yl)benzamido)-4-methylpentanoic acid (101a and 101b) (SG-145 and SG-150)



General procedure (I) was followed, using 2-phthalimidobenzoic acid (0.8 g; 3.0 mmol), L-leucine-benzylester toluene-4-sulfonate salt (1.2 g; 3.01 mmol), TEA (0.3 g; 3.0 mmol) and EDC (0.6 g, 3.0 mmol). The ¹H-NMR confirmed the product had been formed as a pale yellow oil with a yield of 1.1 g (2.26 mmol; 75%). The hydrogenisation was then carried out using the phenyl ester **101a** (1.0 g; 2.03 mmol). A ¹H-NMR showed the desired product was present however, a small amount of the methyl ester had also been formed. This was purified by dissolving the product in ethyl acetate (~20 ml) and extracting with saturated NaHCO₃ (2 × 20 ml). The aqueous layer was then dropped onto acidified ice and the desired product precipitated. This was filtered, washed with water and dried. A ¹H-NMR showed this was the pure product and the yield was found to be 0.4 g (1.02 mmol; 50%). [Overall yield = 34%]. The product was a colourless powder.

101a:

¹H-NMR: (400 MHz, CDCl₃): δ (ppm) = 0.84 (t; ³J = 6.0 Hz; 6H; 2 × CH₃), 1.54 (m; 1H; CH), 1.59-1.71 (m; 2H; CH₂), 4.70 (m; 1H; CH_{asym}), 5.10 (s; 2H; CH₂), 6.40 (br.d; ³J = 8.4 Hz; 1H; NH), 7.32 (m; 5H; CH_{arom}), 7.39 (dd; ³J = 8.0 Hz; ⁴J = 1.2 Hz; 1H; CH_{arom}), 7.51 (ddd; ³J = 7.6 Hz; ⁴J = 1.2 Hz; 1H; CH_{arom}), 7.61 (ddd; ³J = 7.6 Hz;

$^4J = 1.6\text{Hz}$; 1H; CH_{arom}), 7.68 (dd; $^3J = 7.6\text{Hz}$; $^4J = 1.6\text{Hz}$; 1H; CH_{arom}), 7.76 (m; 2H; CH_{arom}), 7.90 (m; 2H; CH_{arom}).

101b:

$^1\text{H-NMR}$: (400 MHz, CDCl₃): δ (ppm) = 0.87 (t; $^3J = 6.6\text{Hz}$; 6H; 2 \times CH₃), 1.52-1.60 (m; 1H; CH), 1.61-1.71 (m; 2H; CH₂), 4.60 (m; 1H; CH_{asym}), 6.50 (br.d; $^3J = 8.0\text{Hz}$; 1H; NH), 7.38 (dd; $^3J = 7.6\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}), 7.52 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 0.8\text{Hz}$; 1H; CH_{arom}), 7.61 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.69 (dd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.74 (m; 2H; CH_{arom}), 7.90 (m; 2H; CH_{arom}).

$^{13}\text{C-NMR}$: (100 MHz, CDCl₃): δ (ppm) = 21.7 (1C; CH₃), 22.9 (1C; CH₃), 24.8 (1C; CH), 40.9 (1C; CH₂), 51.0 (1C; CH_{asym}), 123.9 (1C; Cq), 128.5 (1C; CH_{arom}), 129.4 (1C; CH_{arom}), 129.7 (1C; Cq), 130.0 (1C; CH_{arom}), 131.7 (1C; CH_{arom}), 132.0 (2C; 2 \times CH_{arom}), 134.0 (1C; Cq), 134.5 (2C; 2 \times CH_{arom}), 147.9 (1C; Cq), 167.1 (1C; C=O), 167.7 (1C; C=O), 170.0 (1C; C=O), 176.4 (1C; C=O).

CAS No.: 330434-09-8

7.5.2 General Procedure (J):

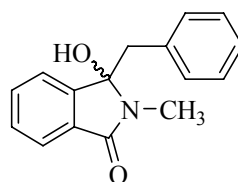
NMP (0.38 mmol) was dissolved in 5 ml of acetone. The addition partner (1.13 mmol) was added to K₂CO₃ (0.57 mmol) and dissolved in 5 ml of distilled H₂O. These solutions were then added together in a conical flask and made up to 25 ml using a mixture of acetone/water (50:50). This solution was sonicated for 5 min and then degassed with a slow stream of N₂ for ~20 min. The microreactor was prepared by pumping the pre-sonicated mobile phase of acetone/water (50:50) through it until all air bubbles had been removed. The solution (10 ml) was then taken up in the syringe and any air bubbles expelled and connected to the syringe pump. The flow rate was then set, the syringe pump and the lamps ($\lambda = 300 \pm 20$ nm) above the microreactor were switched on and the irradiated solution collected in a round-bottomed flask. During the reaction, the reactor was kept cool by pumping cold water through the second cooling channel. When the syringe was empty, the syringe pump and the lamps were switched off simultaneously. The syringe was filled with the mobile phase and replaced on the syringe pump which was then turned on

simultaneously with the lamps. When the reaction was complete, acetone was removed by rotary evaporation at $\sim 50^{\circ}\text{C}$ and the remaining solution was extracted with DCM (3×20 ml). The two layers were separated (organic \rightarrow bottom layer, aqueous \rightarrow top layer) and the organic layer washed with saturated NaHCO_3 (2×20 ml) and then with saturated NaCl (2×20 ml). The organic layer was collected and dried over MgSO_4 , filtered by gravity filtration and the DCM evaporated from the filtrate by rotary evaporation at $\sim 40^{\circ}\text{C}$. A $^1\text{H-NMR}$ was obtained for the crude product. There was not enough product obtained to perform column chromatography.

Experiment 122

Comparison of Experiment 4

3-benzyl-3-hydroxy-2-methylisoindolin-1-one (67a) (SG-204)



$\text{C}_{16}\text{H}_{15}\text{NO}_2$
Mol. Wt.: 253.3 g/mol

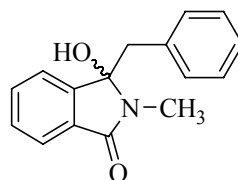
General procedure (J) was followed, with the slight variation of doubling amounts used and dissolving in 50 ml instead of the usual 25 ml, using NMP (0.12 g; 0.75 mmol), phenylacetic acid (0.31 g, 2.26 mmol) and K_2CO_3 (0.16 g, 1.13 mmol). The flow rate used was 0.12 ml/min; residence time: 14 min. The composition of NMP to product was calculated from the $^1\text{H-NMR}$ to be 75:25.

For $^1\text{H-NMR}$ data see experiment 4.

Experiment 123

Comparison of Experiment 4

3-benzyl-3-hydroxy-2-methylisoindolin-1-one (67a) (SG-205)



$C_{16}H_{15}NO_2$
Mol. Wt.: 253.3 g/mol

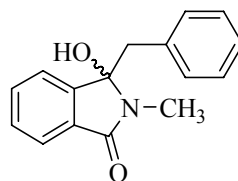
General procedure (J) was followed using the same stock solution as used in experiment 122. The flow rate used was 0.08 ml/min; residence time: 21 min. The composition of NMP to product was calculated from the 1H -NMR to be 60:40.

For 1H -NMR data see experiment 4.

Experiment 124

Comparison of Experiment 4

3-benzyl-3-hydroxy-2-methylisoindolin-1-one (67a) (SG-206)



$C_{16}H_{15}NO_2$
Mol. Wt.: 253.3 g/mol

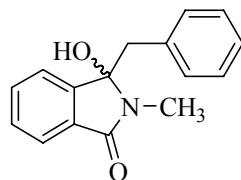
General procedure (J) was followed using the same stock solution as used in experiment 122. The flow rate used was 0.06 ml/min; residence time: 28 min. The composition of NMP to product was calculated from the 1H -NMR to be 58:42.

For 1H -NMR data see experiment 4.

Experiment 125

Comparison of Experiment 4

3-benzyl-3-hydroxy-2-methylisoindolin-1-one (67a) (SG-195)



$C_{16}H_{15}NO_2$
Mol. Wt.: 253.3 g/mol

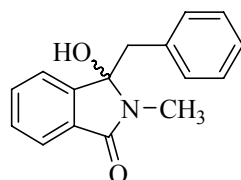
The general procedure (J) was followed using the same stock solution as used in experiment 126. The flow rate used was 0.05 ml/min; residence time: 33 min 36sec. The composition of NMP to product was calculated from the 1H -NMR to be 41:59.

For 1H -NMR data see experiment 4.

Experiment 126

Comparison of Experiment 4

3-benzyl-3-hydroxy-2-methylisoindolin-1-one (67a) (SG-194)



$C_{16}H_{15}NO_2$
Mol. Wt.: 253.3 g/mol

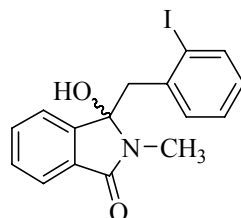
General procedure (J) was followed using NMP (0.06 g, 0.37 mmol), phenylacetic acid (0.15, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate used was 0.04 ml/min; residence time: 42 min. The conversion was found to be 100% and the yield was found to be 0.04 g (0.15 mmol; 100%). The 1H -NMR showed this to be the desired pure product.

For 1H -NMR data see experiment 4.

Experiment 127a-c

Comparison of Experiment 64

3-(2-iodobenzyl)-3-hydroxy-2-methylisoindolin-1-one (82a) (SG-103)



$C_{16}H_{14}INO_2$
Mol. Wt.: 379.19 g/mol

General procedure (J) was followed, with slight variation, using NMP (0.06 g, 0.39 mmol), 2-iodophenylacetic acid (0.3 g, 1.13 mmol) and K_2CO_3 (0.1 g, 0.56 mmol). The reactant solution was made up to 25 ml and was pumped through the microreactor in its entirety. The flow rate used was varied 3 times throughout the reaction and all 3 fractions were collected and TLCs performed. In each the starting material was visible. The fractions were then worked up in the usual way, 1H -NMRs obtained and the ratio of NMP to product calculated.

a) Fraction 1 used a flow rate of 0.249 ml/min; residence time: 6 min 42 sec. The ratio was 95:5.

b) Fraction 2 used a flow rate of 0.162 ml/min; residence time: 10 min 24 sec. The ratio was 92:8.

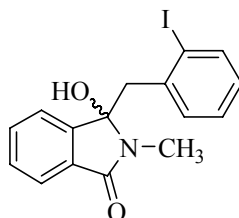
c) Fraction 3 used a flow rate of 0.129 ml/min; residence time: 14 min. The ratio was 90:10.

For 1H -NMR data see experiment 64.

Experiment 128

Comparison of Experiment 64

3-(2-iodobenzyl)-3-hydroxy-2-methylisoindolin-1-one (82a) (SG-168)



$C_{16}H_{14}INO_2$
Mol. Wt.: 379.19 g/mol

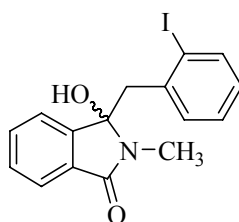
General procedure (J) was followed, with slight variation, using NMP (0.12 g, 0.75 mmol), 2-iodophenylacetic acid (0.59, 2.25 mmol) and K_2CO_3 (0.16 g, 1.13 mmol). The flow rate used was 0.08 ml/min; residence time: 21 min. The ratio of NMP to product was calculated from the 1H -NMR to be 86:14.

For 1H -NMR data see experiment 64.

Experiments 129 and 130

Comparison of Experiment 64

3-(2-iodobenzyl)-3-hydroxy-2-methylisoindolin-1-one (82a) (SG-174)



$C_{16}H_{14}INO_2$
Mol. Wt.: 379.19 g/mol

General procedure (J) was followed using NMP (0.06 g, 0.39 mmol), 2-iodophenylacetic acid (0.30 g, 1.14 mmol) and K_2CO_3 (0.08 g, 0.57 mmol). The flow rate was initially set at 0.01 ml/min; residence time: 2 hr 48 min. This fraction was collected and worked up as usual and the ratio of NMP to product was calculated from the 1H -NMR to be 77:23.

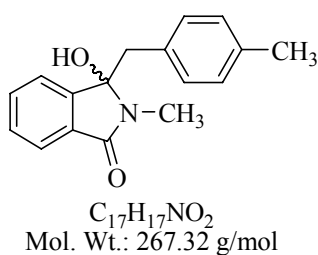
The flow rate was then changed to 0.04 ml/min; residence time: 42 min, the reaction continued and the second fraction collected and worked up. This time the ratio of NMP to product was calculated from the $^1\text{H-NMR}$ to be 81:19.

For $^1\text{H-NMR}$ data see experiment 64.

Experiment 131

Comparison of Experiment 5

3-(4-methylbenzyl)-3-hydroxy-2-methylisoindolin-1-one (67b) (SG-252)



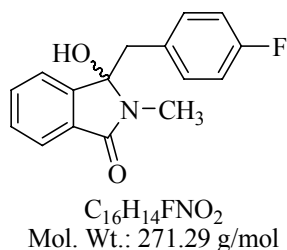
General procedure (J) was followed using NMP (0.06 g; 0.38 mmol), *p*-tolylacetic acid (0.17 g, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate was set at 0.007 ml/min; residence time: 4 hr. The $^1\text{H-NMR}$ showed the product was formed in its pure state. The yield was found to be 0.04 g (0.14 mmol; 93%).

For $^1\text{H-NMR}$ data see experiment 5.

Experiment 132

Comparison of Experiment 8

3-(4-fluorobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67e) (SG-253)



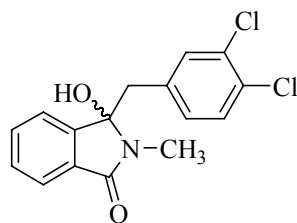
General procedure (J) was followed using NMP (0.06 g; 0.38 mmol), 4-fluorophenylacetic acid (0.17 g, 1.13 mmol) and K₂CO₃ (0.08 g, 0.57 mmol). The flow rate was set at 0.007 ml/min; residence time: 4 hr. The ¹H-NMR showed the product was formed in its pure state. The yield was found to be 0.02 g (0.08 mmol; 53%).

For ¹H-NMR data see experiment 8.

Experiment 133

Comparison of Experiment 10

3-(3,4-dichlorobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67 g) (SG-257)



C₁₆H₁₃Cl₂NO₂
Mol. Wt.: 322.19 g/mol

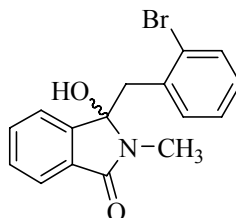
General procedure (J) was followed using NMP (0.06 g; 0.38 mmol), 3,4-dichlorophenylacetic acid (0.23 g, 1.13 mmol) and K₂CO₃ (0.08 g, 0.56 mmol). The flow rate was set at 0.009 ml/min; residence time: 3 hr. The NMR showed the product was formed in its pure state. The yield was found to be 0.04 g (0.14 mmol; 93%).

For ¹H-NMR data see experiment 10.

Experiment 134

Comparison of Experiment 11

3-(2-bromobenzyl)-3-hydroxy-2-methylisoindolin-1-one (67h) (SG-260)



C₁₆H₁₄BrNO₂
Mol. Wt.: 332.19

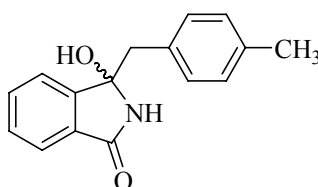
General procedure (J) was followed using NMP (0.06 g; 0.38 mmol), 2-bromophenylacetic acid (0.24 g, 1.14 mmol) and K₂CO₃ (0.08 g, 0.56 mmol). The flow rate was set at 0.006 ml/min; residence time: 4 hr 40 min. The NMR showed the product was formed with some minor impurities present. The crude product was purified by adding a small amount of acetone to dissolve the impurities and then removing the solvent. The ¹H-NMR obtained showed this to be the pure product, and the yield was found to be 0.04 g (0.09 mmol; 60%).

For ¹H-NMR data see experiment 11.

Experiment 135

Comparison of Experiment 17

3-(4-methylbenzyl)-3-hydroxyisoindolin-1-one (68a) (SG-290)



C₁₆H₁₅NO₂
Mol. Wt.: 253.3 g/mol

General procedure (J) was followed, with slight variation, using phthalimide (0.06 g; 0.38 mmol), *p*-tolylacetic acid (0.17 g, 1.13 mmol) and K₂CO₃ (0.08 g, 0.56 mmol). The flow rate was set at 0.014 ml/min; residence time: 2 hr. The product was found

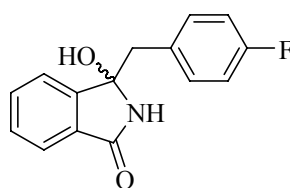
to have a yield of 0.04 g, (0.15 mmol; 97%). The $^1\text{H-NMR}$ showed the desired product had been formed.

For $^1\text{H-NMR}$ data see experiment 17.

Experiment 136

Comparison of Experiment 19

3-(4-fluorobenzyl)-3-hydroxyisoindolin-1-one (68b) (SG-288)



$\text{C}_{15}\text{H}_{12}\text{FNO}_2$
Mol. Wt.: 257.26 g/mol

General procedure (J) was followed, with slight variation, using phthalimide (0.06 g; 0.37 mmol), 4-fluorophenylacetic acid (0.17 g, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate was set at 0.014 ml/min; residence time: 2 hr. The product was found to have a yield of 0.04 g, (0.15 mmol; 100%). The $^1\text{H-NMR}$ showed the desired product had been formed.

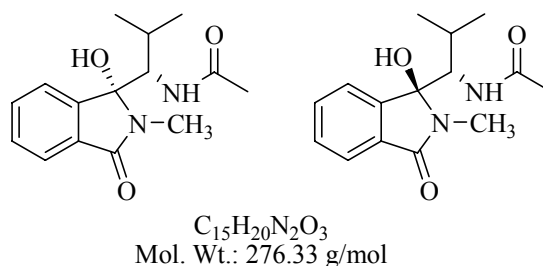
For additional $^1\text{H-NMR}$ data see experiment 19.

$^{19}\text{F-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}/\text{C}_6\text{F}_6$): δ (ppm) = -118.5 (s; 1F; CF).

Experiment 137

Comparison of Experiment 42

***N*-((*S*)-1-(*Like* and *Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-methylpropyl)acetamide (78c) (SG-189)**



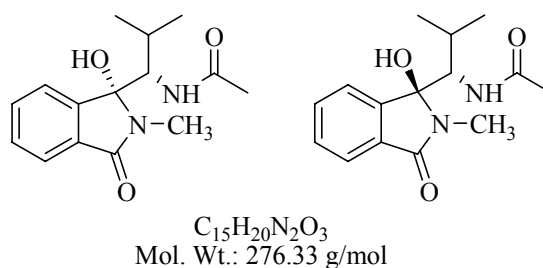
General procedure (J) was followed using NMP (0.06 g, 0.39 mmol), acetyl-valine (0.18 g, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate was set at 0.04 ml/min; residence time: 42 min. The 1H -NMR showed the crude product to be mainly NMP, however both isomers of the product were also present. The composition of NMP to product was calculated from the 1H -NMR to be 96:4, and the ratio of the isomers was found to be 62:38.

For 1H -NMR data see experiment 42.

Experiment 138

Comparison of Experiment 42

***N*-((*S*)-1-(*Like* and *Unlike*-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-methylpropyl)acetamide (78c) (SG-215)**



General procedure (J) was followed using NMP (0.06 g, 0.38 mmol), acetyl-valine (0.18 g, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate was set at 0.008

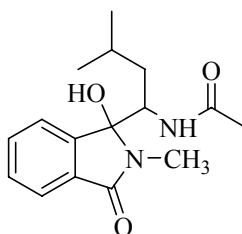
ml/min; residence time: 3 hr 30 min. The composition of NMP to product was calculated from the $^1\text{H-NMR}$ to be 58:42. The ratio of the isomers was calculated from the $^1\text{H-NMR}$ to be 62:38.

For $^1\text{H-NMR}$ data see experiment 42.

Experiment 139

Comparison of Experiment 44

***N*-(1-(1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-3-methylbutyl)acetamide (78d)**
(SG-171)



$\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3$
Mol. Wt.: 290.36 g/mol

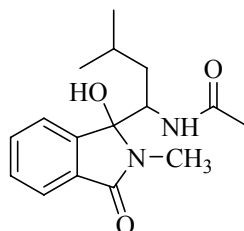
General procedure (J) was followed using NMP (0.12 g, 0.75 mmol), acetyl-leucine (0.39, 2.25 mmol) and K_2CO_3 (0.16 g, 1.13 mmol). The flow rate used was 0.08 ml/min; residence time: 21 min. The composition of NMP to product was calculated from the $^1\text{H-NMR}$ to be 74:26. The ratio of the isomers was calculated from the $^1\text{H-NMR}$ to be 46:54.

For $^1\text{H-NMR}$ data see experiment 44.

Experiment 140

Comparison of Experiment 44

***N*-(1-(1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-3-methylbutyl)acetamide (78d)**
(SG-191)



$C_{16}H_{22}N_2O_3$
Mol. Wt.: 290.36 g/mol

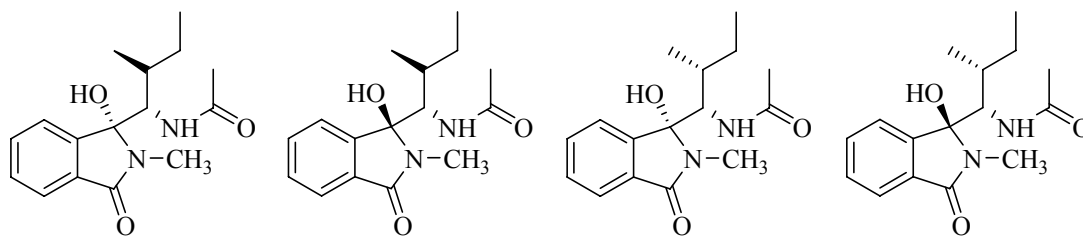
General procedure (J) was followed using NMP (0.06 g, 0.37 mmol), acetyl-leucine (0.20, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate used was 0.04 ml/min; residence time: 42 min. The composition of NMP to product was calculated from the 1H -NMR to be 82:18. The ratio of isomers was calculated from the 1H -NMR to be 43:57.

For 1H -NMR data see experiment 44.

Experiment 141

Comparison of Experiment 46

***N*-(1*S*,2*S*) and (1*S*,2*R*)-1-((*R*) and (*S*)-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-methylbutyl)acetamide (78e)** (SG-170)



$C_{16}H_{22}N_2O_3$
Mol. Wt.: 290.36 g/mol

General procedure (J) was followed using NMP (0.06 g, 0.40 mmol), acetyl-isoleucine (0.20 g, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate used

was 0.08 ml/min; residence time: 21 min. TLC showed the product was formed, however some NMP was also present showing that the residence time was not sufficient for the reaction to go to completion. The $^1\text{H-NMR}$ obtained confirmed the product was formed and the ratio of NMP to product was calculated to be 73:27. The $^1\text{H-NMR}$ also confirmed that four diastereoisomers were formed in a ratio of 26:26:26:22.

For additional $^1\text{H-NMR}$ data see experiment 46.

$^1\text{H-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) =

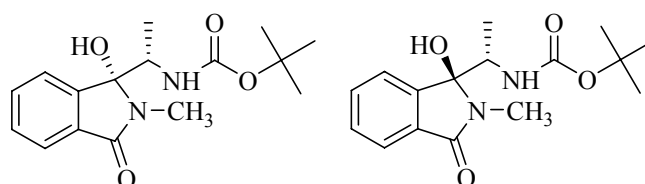
Selected peaks for CH(NH):

4.48 (dd; $^3J = 10.0\text{Hz}$; $^3J = 6.0\text{Hz}$; 1H; CH), 4.53 (dd; $^3J = 9.2\text{Hz}$; $^3J = 3.6\text{Hz}$; 1H; CH), 4.67 (dd; $^3J = 7.2\text{Hz}$; $^3J = 3.2\text{Hz}$; 1H; CH), 4.69 (dd; $^3J = 6.8\text{Hz}$; $^3J = 2.8\text{Hz}$; 1H; CH).

Experiment 142

Comparison of Experiment 50

***tert*-butyl (*S*)-1-(*Like and Unlike*- 1-hydroxy-2-methyl-3-oxoisindolin-1-yl)ethylcarbamate (78i) (SG-192)**



$\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_4$
Mol. Wt.: 306.36 g/mol

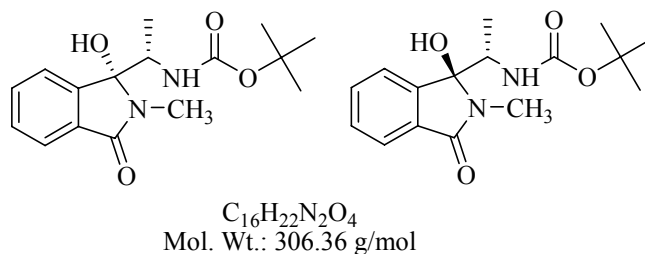
General procedure (J) was followed using NMP (0.06 g, 0.38 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-alanine (0.21, 1.13 mmol) and K_2CO_3 (0.08 g, 0.57 mmol). The flow rate used was 0.04 ml/min; residence time: 42 min. The composition of NMP to product was calculated from the $^1\text{H-NMR}$ to be 68:32. The ratio of isomers could not be calculated from the $^1\text{H-NMR}$.

For $^1\text{H-NMR}$ data see experiment 50.

Experiment 143

Comparison of Experiment 50

***tert*-butyl (S)-1-(Like and Unlike- 1-hydroxy-2-methyl-3-oxoisindolin-1-yl)ethylcarbamate (78i)** (SG-199)



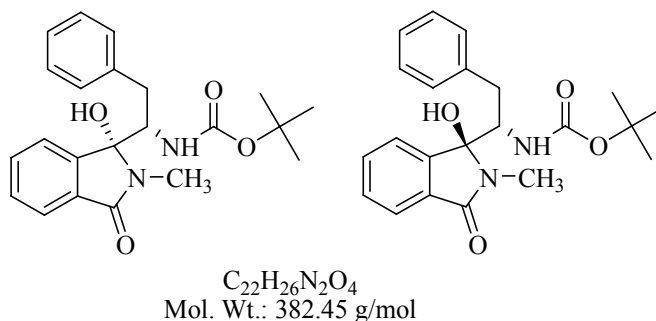
General procedure (J) was followed using NMP (0.06 g, 0.38 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-alanine (0.21, 1.13 mmol) and K_2CO_3 (0.08 g, 0.57 mmol). The flow rate used was 0.01 ml/min; residence time: 2 hr 48 min. The composition of NMP to product was calculated from the 1H -NMR to be 7:93. The ratio of isomers was calculated from the 1H -NMR to be 56:44.

For 1H -NMR data see experiment 50.

Experiment 144

Comparison of Experiment 52

***tert*-butyl (S)-1-(Like and Unlike-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-phenylethylcarbamate (78j)** (SG-193)



General procedure (J) was followed using NMP (0.06 g, 0.38 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-phenylalanine (0.30, 1.13 mmol) and K_2CO_3 (0.08 g, 0.57 mmol).

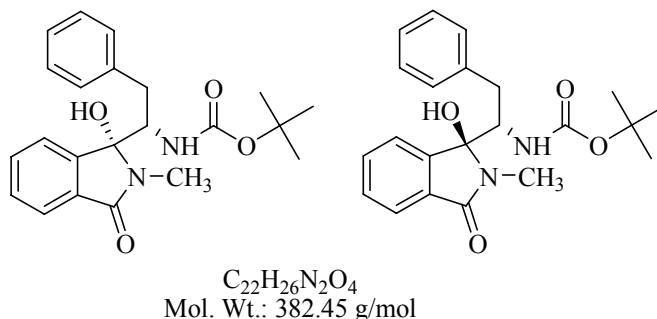
The flow rate used was 0.04 ml/min; residence time: 42 min. The composition of NMP to product was calculated from the $^1\text{H-NMR}$ to be 72:28. The ratio of isomers was calculated from the $^1\text{H-NMR}$ to be 24:76.

For $^1\text{H-NMR}$ data see experiment 52.

Experiment 145

Comparison of Experiment 52

***tert*-butyl (S)-1-(Like and Unlike-1-hydroxy-2-methyl-3-oxoisindolin-1-yl)-2-phenylethylcarbamate (78j) (SG-212)**



General procedure (J) was followed using NMP (0.06 g, 0.38 mmol), *N*-(*tert*-butoxycarbonyl)-*L*-phenylalanine (0.30, 1.13 mmol) and K_2CO_3 (0.08 g, 0.56 mmol). The flow rate used was 0.01 ml/min; residence time: 2 hr 48 min. The composition of NMP to product was calculated from the $^1\text{H-NMR}$ to be 47:53. The ratio of isomers was calculated from the $^1\text{H-NMR}$ to be 28:72.

For $^1\text{H-NMR}$ data see experiment 52.

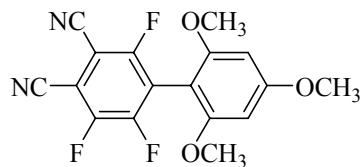
7.5.3 General Procedure (J1):

As in General Procedure (J), with the variation of using TFPN (0.08 g; 0.38 mmol) and 1,3,5-Trimethoxybenzene (0.19 g; 1.13 mmol). DCM was used as the sole solvent and work-up consisted of removing the DCM by rotary evaporation.

Experiment 146

Comparison of Experiment 106

Trimethoxy-substituted phthalonitrile derivative (95c) (SG-314)



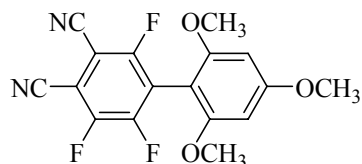
$C_{17}H_{11}F_3N_2O_3$
Mol. Wt.: 348.28 g/mol

General procedure (J1) was followed using TFPN (0.08 g; 0.38 mmol) and 1,3,5-trimethoxybenzene (0.19 g; 1.13 mmol). The flow rate was set at 0.007 ml/min; residence time: 4 hr. The crude yield was found to be 0.10 g. Both the 1H and ^{19}F NMR spectra showed this to be starting material.

Experiment 147

Comparison of Experiment 106

Trimethoxy-substituted phthalonitrile derivative (95c) (SG-315)



$C_{17}H_{11}F_3N_2O_3$
Mol. Wt.: 348.28 g/mol

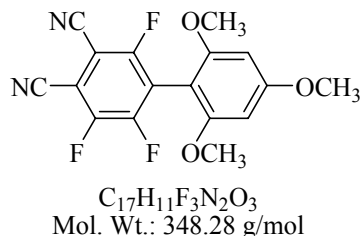
General procedure (J1) was followed using TFPN (0.08 g; 0.38 mmol) and 1,3,5-trimethoxybenzene (0.19 g; 1.14 mmol). The flow rate was set at 0.002 ml/min; residence time: 14 hr. The crude yield was found to be 0.10 g. Both the 1H and ^{19}F NMR spectra showed this to be mainly starting material, however there was also some product present. The ratio of TFPN to product was calculated from the ^{19}F -NMR to be 82:18.

For 1H -NMR data see experiment 106.

Experiment 148

Comparison of Experiment 106

Trimethoxy-substituted phthalonitrile derivative (95c) (SG-320)



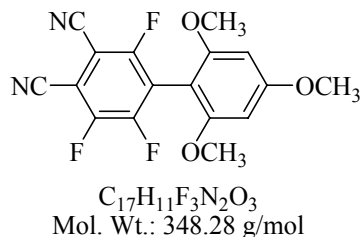
General procedure (J1) was followed, with slight variation, using TFPN (0.02 g; 0.08 mmol) and 1,3,5-trimethoxybenzene (0.04 g; 0.23 mmol). The flow rate was set at 0.002 ml/min; residence time: 14 hr. The crude yield was found to be 0.02 g. Both the 1H and ^{19}F -NMR spectra showed this to be mainly product, however there was also some starting material remaining. The ratio of TFPN to product was calculated from the ^{19}F -NMR to be 16.84.

For 1H -NMR data see experiment 106.

Experiment 149

Comparison of Experiment 106

Trimethoxy-substituted phthalonitrile derivative (95c) (SG-326)



General procedure (J1) was followed, with slight variation, using TFPN (0.02 g; 0.11 mmol) and 1,3,5-trimethoxybenzene (0.04 g; 0.21 mmol). The flow rate was set at 0.001 ml/min; residence time: 28 hr. The crude yield was found to be 0.06 g. Both the 1H and ^{19}F NMR spectra showed this to be mainly product, however there was

also some starting material remaining. The ratio of TFPN to product was calculated from the ^{19}F -NMR to be 39.61.

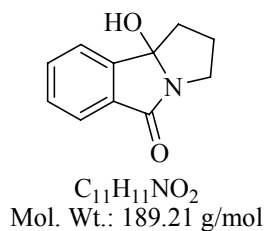
For ^1H -NMR data see experiment 106.

7.5.4 General Procedure (K):

The desired phthalimide (1.50 mmol) was dissolved in 10 ml of acetone and K_2CO_3 (0.75 mmol) was dissolved in 10 ml of distilled H_2O . These two solutions were sonicated separately before being mixed together, transferred to a 100 ml Schlenk flask and sonicated again. The reaction was then carried out as in general procedure (A) for photoreactions in solution.

Experiment 150

9b-hydroxy-1, 2, 3, 9b-tetrahydro-pyrrolo[2,1-a]isoindol-5-one (102) (SG-156)



General procedure (K) was followed using **99a** (0.3 g, 1.50 mmol) and K_2CO_3 (0.1 g, 0.85 mmol). After 5.5 hr the TLC showed the product was formed. The solution was clear and yellow at this point. The product was found to be a yellow-brown solid and the ^1H -NMR obtained confirmed this was the pure product. The yield was found to be 0.2 g (1.23 mmol, 82%).

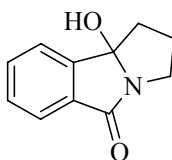
^1H -NMR: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 1.54 (m; 1H; CH_2), 2.30 (m; 2H; CH_2), 2.57 (m; 1H; CH_2), 3.35 (m; 1H; CH_2), 3.61 (m; 1H; CH_2), 5.26 (br.s; 1H; OH), 7.50 (m; 1H; CH_{arom}), 7.60 (m; 3H; CH_{arom}).

^{13}C -NMR: (100 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 28.2 (1C; CH_2), 36.0 (1C; CH_2), 42.0 (1C; CH_2), 96.7 (1C; C-OH), 123.5 (1C; CH_{arom}), 123.5 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 132.9 (1C; Cq), 133.0 (1C; CH_{arom}), 149.3 (1C; Cq), 170.0 (1C; C=O).

CAS No.: 162971-82-6

Experiment 151

9b-hydroxy-1, 2, 3, 9b-tetrahydro-pyrrolo[2,1-a]isoindol-5-one (102) (SG-146)



C₁₁H₁₁NO₂
Mol. Wt.: 189.21 g/mol

General procedure (K) was followed, with slight variation of using the starting materials in a ratio of 1:1 instead of the usual 2:1, using **99b** (0.4 g, 1.52 mmol) and K₂CO₃ (0.2 g, 1.55 mmol). After 2 hr the TLC showed the product was formed. The solution was clear and yellow at this point. The product was found to be a light brown powder and the ¹H-NMR obtained confirmed this was the pure product. The yield was found to be 0.1 g (0.64 mmol, 42%). The reaction was stopped after 2 hr to prevent any unwanted side reactions from occurring, however due to the low yield a longer irradiation time appears necessary.

¹H-NMR: (400 MHz, C₂D₆CO): δ (ppm) = 1.50 (m; 1H; CH₂), 2.30 (m; 2H; CH₂), 2.57 (m; 1H; CH₂), 3.35 (m; 1H; CH₂), 3.60 (m; 1H; CH₂), 7.50 (m; 1H; CH_{arom}), 7.60 (m; 3H; CH_{arom}).

¹³C-NMR: (100 MHz, C₂D₆CO): δ (ppm) = 28.2 (1C; CH₂), 36.0 (1C; CH₂), 41.9 (1C; CH₂), 96.6 (1C; C-OH), 123.4 (1C; CH_{arom}), 123.5 (1C; CH_{arom}), 129.8 (1C; CH_{arom}), 132.8 (1C; Cq), 133.0 (1C; CH_{arom}), 149.4 (1C; Cq), 169.9 (1C; C=O).

7.5.5 General Procedure (J2):

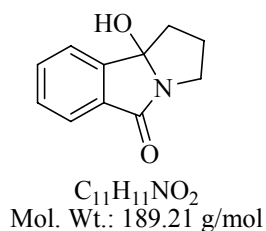
The desired phthalimide (0.75 mmol), was dissolved in 10 ml of acetone and K₂CO₃ (0.38 mmol), was dissolved in 10 ml of distilled H₂O. These two solutions were sonicated separately before being mixed together. These solutions were then added

together in a conical flask and made up to 50 ml using a mixture of acetone/water (50:50). The reaction was then carried out as in general procedure (J).

Experiment 152

Comparison of Experiment 150

9b-hydroxy-1, 2, 3, 9b-tetrahydro-pyrrolo[2,1-a]isoindol-5-one (102) (SG-162)



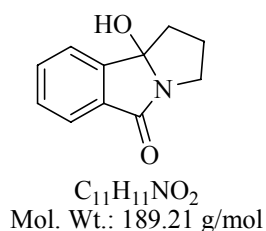
General procedure (J2) was followed using **99a** (0.2 g, 0.75 mmol) and K₂CO₃ (0.1 g, 0.43 mmol). The flow rate used was 0.080 ml/min; residence time: 21 min. The product was found to be a light brown oily solid and the ¹H-NMR showed the desired product was present and pure. The yield was found to be 0.02 g (0.09 mmol; 60%).

For ¹H-NMR data see experiment 150.

Experiment 153

Comparison of Experiment 151

9b-hydroxy-1, 2, 3, 9b-tetrahydro-pyrrolo[2,1-a]isoindol-5-one (102) (SG-163)

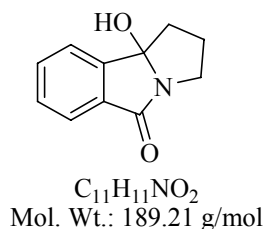


General procedure (J2) was followed, with the slight variation of using a ratio of 1:1 for the reagents, using **99b** (0.2 g, 0.76 mmol), and K₂CO₃ (0.1 g, 0.80 mmol). The flow rate used was 0.080 ml/min; residence time: 21 min. The crude material was found to be an orange solid and the ¹H-NMR showed the product was present and pure. The yield was found to be 0.01 g (0.05 mmol; 33%).

For $^1\text{H-NMR}$ data see experiment 151.

Experiment 154

9b-hydroxy-1, 2, 3, 9b-tetrahydro-pyrrolo[2,1-a]isoindol-5-one (102) (SG-166)

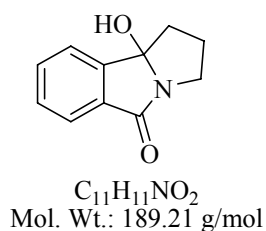


General procedure (K) was followed using **99a** (0.4 g; 1.52 mmol) and K_2CO_3 (0.1 g; 0.77 mmol), however was only irradiated for 21 minutes in order to compare with the microreactor results. The product was found to be a colourless solid and the $^1\text{H-NMR}$ obtained confirmed this was the pure product. The yield was found to be 0.2 g (0.97 mmol, 64%).

For $^1\text{H-NMR}$ data see experiment 150.

Experiment 155

9b-hydroxy-1, 2, 3, 9b-tetrahydro-pyrrolo[2,1-a]isoindol-5-one (102) (SG-167)

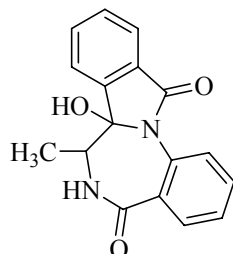


General procedure (K) was followed, with the slight variation of using a ratio of 1:1 for the reagents, using **99b** (0.4 g; 1.50 mmol) and K_2CO_3 (0.2 g; 1.56 mmol), however was only irradiated for 21 minutes in order to compare with the microreactor results. The product was found to be a light brown solid and the $^1\text{H-NMR}$ obtained confirmed this was the pure product. The yield was found to be 0.05 g (0.25 mmol, 17%).

For $^1\text{H-NMR}$ data see experiment 151.

Experiment 156

(103) (SG-224)



$\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$
Mol. Wt.: 294.3 g/mol

General procedure (K) was followed, with the slight variation of halving the amounts used and performing the reaction in a 50 ml Schlenk flask, using **100b** (0.29 g, 0.87 mmol) and K_2CO_3 (0.06 g, (0.44 mmol). After 4 hr the TLC showed the product was formed. The product was found to be a pale yellow solid and the $^1\text{H-NMR}$ obtained confirmed this was the pure product. The yield was found to be 0.10 g (0.35 mmol, 40%).

$^1\text{H-NMR}$: (400 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 1.50 (d; $^3J = 7.2\text{Hz}$; 3H; CH_3), 3.68 (m; 1H; CH), 6.96 (s; 1H; OH), 7.39 (m; 2H; CH_{arom}), 7.48 (br.d; $^3J = 5.6\text{Hz}$; 1H; NH), 7.58 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.63 (m; 1H; CH_{arom}), 7.67 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.75 (m; 2H; CH_{arom}), 8.57 (m; 1H; CH_{arom}).

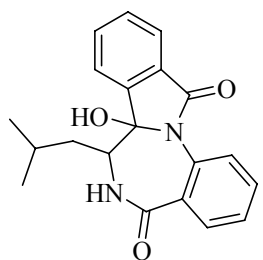
$^{13}\text{C-NMR}$: (100 MHz, $\text{C}_2\text{D}_6\text{CO}$): δ (ppm) = 15.3 (1C; CH_3), 54.4 (1C; CH), 97.5 (1C; COH), 123.4 (1C; CH_{arom}), 125.6 (1C; CH_{arom}), 129.4 (1C; CH_{arom}), 129.9 (1C; CH_{arom}), 130.1 (1C; CH_{arom}), 131.4 (1C; CH_{arom}), 132.2 (1C; CH_{arom}), 132.8 (1C; CH_{arom}), 133.4 (1C; Cq), 135.3 (1C; Cq), 135.5 (1C; Cq), 144.5 (1C; Cq), 167.8 (1C; C=O), 169.7 (1C; C=O).

Literature reference No.: [154]

CAS No.: 331814-59-6

Experiment 157

(104) (SG-157)



$C_{20}H_{20}N_2O_3$
Mol. Wt.: 336.38 g/mol

General procedure (K) was followed, with the slight variation of smaller amounts being used as not enough acid was available, using **99b** (0.37 g, 0.97 mmol) and K_2CO_3 (0.25 g, 1.81 mmol) (calculation error). After 2.5 hr the TLC showed the product was formed. The product was found to be a brown crystalline solid and the 1H -NMR obtained confirmed the product was formed; however a small amount of side product was also present. The yield was found to be 0.19 g (0.56 mmol, 58%).

1H -NMR: (400 MHz, C_2D_6CO): δ (ppm) = 0.83 (d; $^3J = 6.4\text{Hz}$; 3H; CH_3), 0.98 (d; $^3J = 6.4\text{Hz}$; 3H; CH_3), 1.81 (m; 1H; CH), 3.68 (m; 1H; CH_{asym}) 6.08 (s; 1H; OH), 6.89 (d; $^3J = 5.4\text{Hz}$; 1H; NH), 7.38 (dd; $^3J = 8.0\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.59 (ddd; $^3J = 7.6\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.62 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.68 (ddd; $^3J = 7.2\text{Hz}$; $^4J = 1.2\text{Hz}$; 1H; CH_{arom}), 7.74 (m; 3H; CH_{arom}), 7.78 (dd; $^3J = 7.6\text{Hz}$; $^4J = 1.6\text{Hz}$; 1H; CH_{arom}).

^{13}C -NMR: (100 MHz, C_2D_6CO): δ (ppm) = 21.3 (1C; CH_3), 23.9 (1C; CH_3), 26.0 (1C; CH), 38.8 (1C; CH_2), 57.8 (1C; CH), 97.5 (1C; COH), 123.8 (1C; CH_{arom}), 126.0 (1C; CH_{arom}), 130.0 (1C; CH_{arom}), 130.2 (1C; CH_{arom}), 130.6 (1C; CH_{arom}), 132.0 (1C; CH_{arom}), 132.7 (1C; CH_{arom}), 133.2 (1C; CH_{arom}), 133.9 (1C; Cq), 135.6 (1C; Cq), 135.8 (1C; Cq), 144.7 (1C; Cq), 168.2 (1C; C=O), 170.4 (1C; C=O).

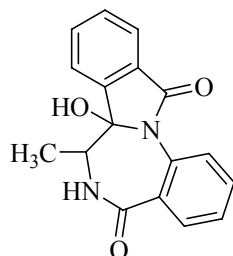
Literature reference No.: [154]

CAS No.: 331814-61-0

Experiment 158

Comparison of experiment 156

(103) (SG-221)



$C_{17}H_{14}N_2O_3$
Mol. Wt.: 294.3 g/mol

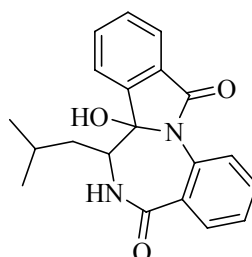
The general procedure (J2) was followed, with the slight variation of halving the amounts used and diluting to 25 ml, using **100b** (0.15 g, 0.43 mmol) and K_2CO_3 (0.03 g, 0.19 mmol). The flow rate was set at 0.01 ml/min; residence time: 2 hr 48 min. The 1H -NMR showed the product was formed (both isomers were present in a ratio of 81:19) and the yield was found to be 0.02 g (0.06 mmol; 35%).

For 1H -NMR data see experiment 156.

Experiment 159

Comparison of experiment 157

(104) (SG-200)



$C_{20}H_{20}N_2O_3$
Mol. Wt.: 336.38 g/mol

The general procedure (J2) was followed, with the slight variation of halving the amounts used and diluting to 25 ml, using **101b** (0.14 g, 0.38 mmol) and K_2CO_3

(0.03 g, 0.19 mmol). The flow rate was set at 0.03 ml/min; residence time: 56 min. The $^1\text{H-NMR}$ showed the product was formed in a yield of 0.04 g (0.13 mmol; 87%).

For $^1\text{H-NMR}$ data see experiment 157.

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Appendix