Photodecarboxylative Additions to Phthalimides and their Application in the Synthesis of AKS-186 and its Analogues

Written Dissertation
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PhD of Science
in
CHEMICAL AND PHARMACEUTICAL SCIENCES

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June 2008

Abstract

Photochemical methods have been widely neglected by industry for the search of novel pharmaceutical lead compounds. The photodecarboxylative addition of various carboxylates to phthalimides has been developed in our group as a powerful access to hydroxyl- and methylene-isoindolinones. Likewise, the *intramolecular* version yields the corresponding cyclisation products.

In this thesis the *intermolecular* version, *i.e.* the photodecarboxylative addition of carboxylates to phthalimides, has been further investigated. Various heteroatom-substituted carboxylates have been studied in order to establish a mechanistic understanding of the photoinduced electron transfer processes involved. *N*-methylphthalimide was used as a model substrate and was irradiated at λ = 300 nm in aqueous acetone and in the presence of excess amounts of potassium carboxylates, the latter generated from the corresponding carboxylic acid and potassium carbonate. The evolution of carbon dioxide was tested using barium hydroxide solutions and was deemed positive when barium carbonate precipitation was formed. Among the carboxylates used were alkyl-, benzyl- and heteroatom-substituted carboxylates. Alkylated amino acid derived carboxylates solely underwent photoreduction whereas *N*-acylated amino acid readily furnished the desired addition products. To investigate the possibility of deactivation by certain electron-donors, various phthalimides with potential electron-donor substituents in the *N*-side chain have been studied. In these cases potassium propionate served as model carboxylate.

In an extension of the decarboxylative addition, alkyl benzoylformates were irradiated in the presence of sulphur-containing carboxylates and the corresponding addition products were obtained in moderate to good yields. Due to their less favourable electrochemical properties, these compounds do not undergo photoinduced electron transfer reactions with alkyl-, benzyl- or oxygen-containing carboxylates, respectively.

The optimised irradiation conditions were applied to the synthesis of AKS-186 and its derivatives. AKS-186 has demonstrated promising cardiovascular drug activities

and became readily accessible from *N*-(4-acetoxybenzyl)phthalimide using the developed photochemical method as key-step. Depending on the nature of the chosen carboxylate the addition products were obtained in poor to good yield of 10-76%. Subsequent dehydration/deprotection gave the desired target compounds in good to excellent yield of 70-96%.

Signature Page

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of PhD in Chemical and Pharmaceutical Sciences is entirely my own work, that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed: ……. (Candidate) ID No: 50219022

Date: 07/07/2008

Preface

For a long time, photochemistry was not recognised as a major branch in synthetic organic chemistry. For the last 20 years, however, this view has changed considerably and numerous photochemical transformations have been developed. Products can now be obtained in high chemical yields and with high selectivities. To address climate change and global warming, synthetic solar photochemistry has furthermore been developed. Nowadays, photochemical reactions are widely known and reported in a vast number of publications. Nevertheless, they are still widely neglected by the pharmaceutical, agrochemical and fine-chemical industry.

Declaration:

Two numbering systems have been used in this thesis. Compounds were numbered in *italics* and brackets in the introduction, e.g. *(1)*. In the results, discussion and experimental parts compounds were numbered in **bold**, e.g. **1**

Acknowledgements

I am honoured to present to you this thesis, which is by far the most significant scientific accomplishment in my life to date and it would have been impossible without people who supported me and believed in my capabilities.

Most of all I would like to thank my supervisor, Dr. Michael Oelgemöller from the School of Chemical Sciences in Dublin City University (DCU). He is a very kind person, great scientist with a deep vision and rich knowledge. His scientific excitement and enthusiasm, as well as his commitment and dedication to his work inspired me in the best way possible and in the most important moments of making pivotal decisions and the correct ones, therefore, I am glad to have worked with him and to have known him as a lecturer and friend. I want to thank him as well for patience and professionalism in working under our collaborative project on "Photodecarboxylative additions of carboxylates to phthalimides". I can't forget the best night outs most notably the great Jonny Fox, Maynooth, Galway and Cologne parties, few of many others.

I sincerely thank Dr. Paraic James for his invaluable help and for being the first to offer me a place in this great university and I owe him for this big time. My best regards go to Dr. Kieran Nolan, Dr. Peter Kenny, Dr. Dermot Brougham, Dr. Enda McGlynn and Dr. Mary Pryce for being very helpful and supportive throughout the degree course. Also, I want to thank Dr. Namir Aga for his guidance and support in the most difficult moments, especially before exams time.

My special thanks go to Robert Groarke for being my best friend throughout the years since day one to date and for his patience while editing this thesis which helped me to relax before the presentation. Special thanks go to Sonia Gallagher of being the first project student to work with me and her smiley face made my days better, Michael Ryan who's help was invaluable, particularly when my computer crashed while writing this thesis; Pierre Neureuille, Brian Murphy and Jana Fiedler for their contribution to my project.

As always, it is impossible not to mention everybody who had an impact to this work: Michael Burke, Damien McGuirk, Vincent Hooper, Maurice Burke, Ambrose

May, Veronica Dobbyn, Ann Corcoran for their assistance in keeping me in lab supplies. Lorraine McCormack, Emmet O'Reilly, Steven Finn, Kieran Joyce, Ciaran Smyth, Bill Henry, Saibh Morrissey, Ewa Kowalska and Neil O'Halloran for laughs and chats in the lab.

However, there are those whose spiritual support is even more important. I thank my parents Samir and Charife, my sisters Joumana and Maliha, my brothers Fares, Kifah, Ali and my uncle Maher for being my inspiration in completing this project.

Sincere thanks go to Dr. Kevin Kavanagh and his group at the University of Maynooth, for his assistance in the testing of some of the compounds discussed in this study.

This project was financially supported by a studentship from Dublin City University (DCU) and grants from the National Institute of Cellular Biotechnology (NICB) and Science Foundation Ireland (SFI). I am greatful for this funding.

Mass spectrometry studies were conducted at the University of Bielefeld (Germany) in the group of Prof. Mattay and are greatly acknowledged.

I hope I didn't forget many people I knew during my time here in DCU.

Fadi Hatoum

Dedication

I would like to dedicate this thesis to my Family, source of inspiration to my life. I would like to dedicate it to all people that stood beside me throughout my studies, to all my friends and to my readers.

Table of Contents

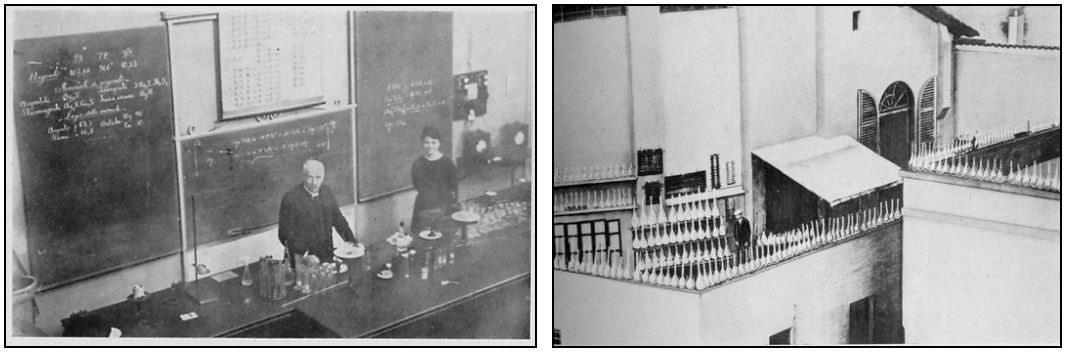
Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
aliph	Aliphatic
arom	Aromatic
BET	Back Electron Transfer
^{o}C	Degree Celsius
^{13}C	Carbon 13
CI	Chemical ion
d.e.	Diastereoisomeric excess
DMSO	Dimethylsulphoxide
EI	Electron Ion
eq.	Equivalent
ES	Excited State
ESI	Electron Spray Ion
ET	Electron Transfer
g	Gram
Gly	Glycine
GP	General Procedure
h, hrs	Hour (s)
^{1}H	Proton
hex	Hexane
hν	Light, radiation
Hz	Hertz
IR	Infrared
J	Coupling constant
kV	Kilovolt
λ	Wavelength
max	Maximum

MHz	Megahertz
µg	Microgram
ml	Millilitre
mm	Millimetre
mmol	Millimol
MS	Mass Spectrometer
MW	Molecular Weight
n	Number of carbon chain
N	Normal
nm	Nanometer
NMP	*N*-methylphthalimide
PDC	Photodecarboxylation
PET	Photoinduced Electron Transfer
Ph	Phenyl
Pht=N	Phthaloyl
ppm	Part per million
r.b.f.	Round bottomed flask
RET	Reverse Electron Transfer
r.t.	Room temperature
Sens	Sensitiser
SET	Single Electron Transfer
T	Tesla
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TsOH	Toluene-4-sulfonic acid
UV	Ultraviolet
V	Volts
vi	Various intensities
VIS	Visible
vs.	Versus

1 Introduction

Giacomo Ciamician (1857-1922) (Picture **1**) is considered as the father of photochemistry and was the first scientist to systematically investigate the chemical effects of light. He has predicted a hundred years ago that photochemistry will dominate chemical production when he stated: "*On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plants and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is. And if in a distant future the supply of coal becomes completely exhausted, civilization will not be checked by that, for life and civilization will continue as long as the sun shines! If our black and nervous civilization, based on coal, shall be followed by a quiter civilization based on the utilization of solar energy, that will not be harmful to progress and to human happiness*".[1]



Picture 1: a) Giacomo Ciamician teaching in Bologna and b) Giacomo Ciamician on the roof of the Chemical Institute in Bologna (surrounded by exposed flasks to the sunlight)[2].

1.1 Photochemistry

According to the *IUPAC* photochemistry is "the branch of chemistry concerned with the chemical effects of light"; it involves the interaction of matter with electro-magnetic radiation shown in its entire spectrum below (Figure **1**).

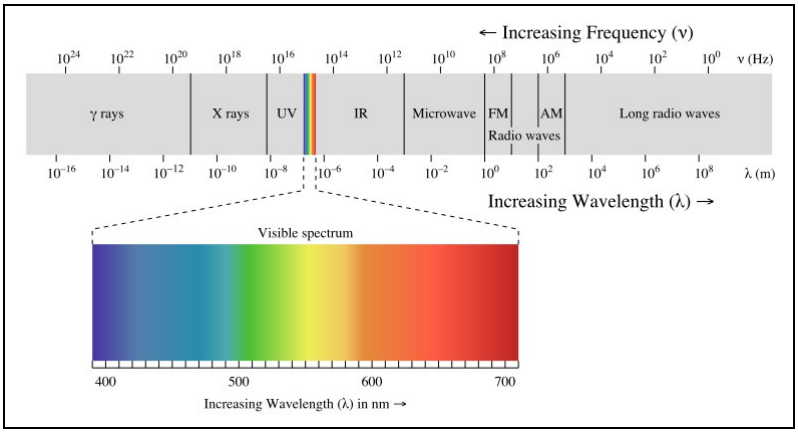


Figure 1: Electromagnetic spectrum[3]

This latter scenario is described by the 1st law of photochemistry, introduced by Grotthus-Draper, which states that only light which is absorbed by a molecule may cause a photochemical change.[4] The interaction of one molecule with one photon of light, where S_o is the ground state of the molecule and S^* is the excited state of the molecule, can be seen below (Figure **2**).

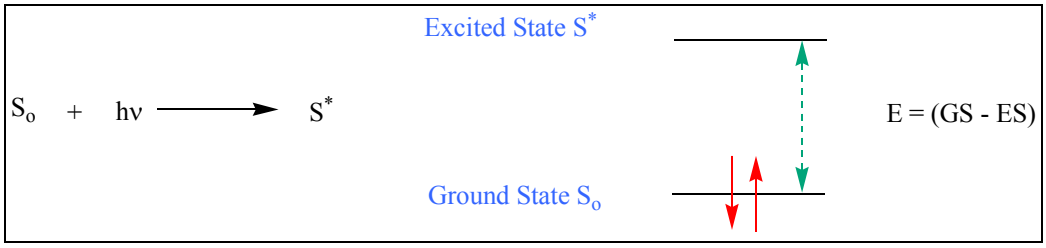


Figure 2: Electron states in the photochemical reactions

The important absorption range for photochemistry lies between 200-700 nm and comprises of the UV region at 200-400 nm and the visible region at 400-700 nm.

The irradiation that was used for this project was 300 ± 25 nm, which is in the UV area, as this is the region that the chosen phthalimide chromophore absorbs in.
Electrons can photochemically exist in the singlet state or triplet state, in the excited singlet state their spin is paired (Figure **3**) whereas in the triplet excited state their spin is parallel (Figure **4**).

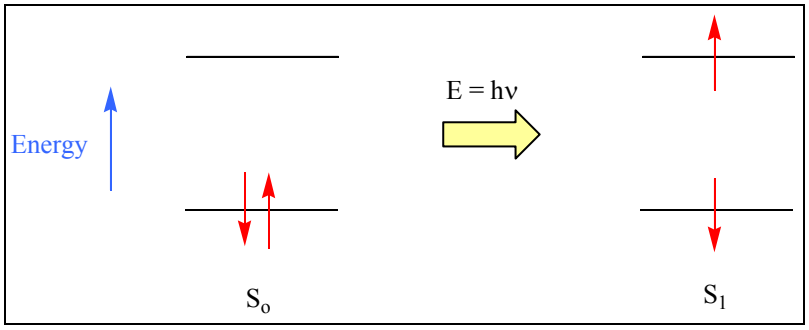


Figure 3: Singlet excited state

Direct transmission of the excited singlet state to the triplet state is energetically favoured but forbidden by Wigner's rule. Triplet states can be populated indirectly via Inter-System Crossing (**ISC**). This allows the excited singlet state to reach the lower energy triplet state. The triplet excited state is important in photochemical reactions as it permits the formation of the product. The lifetime of the triplet state is usually high as $T_1 \rightarrow S_o$ is forbidden.[5]

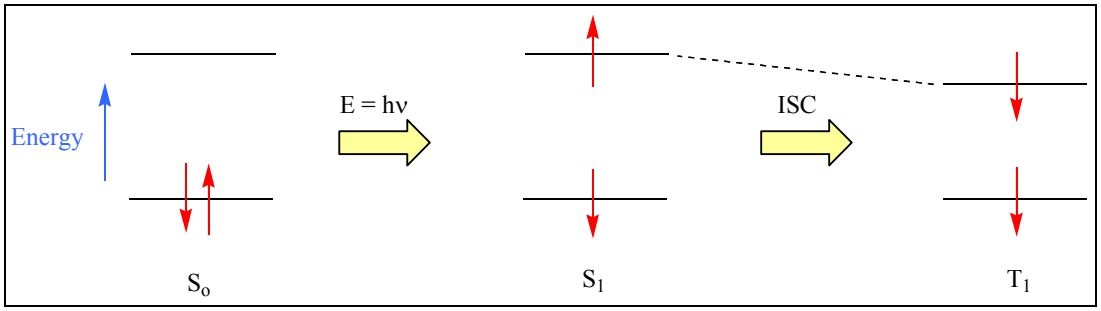


Figure 4: Triplet excited state

There is no direct route for $S_o \rightarrow T_1$. However in the presence of a suitable acceptor molecule a possible indirect route opens up via energy transfer. This takes place between a donor molecule (**D**) and an acceptor molecule (**A**). This process is known

as triplet sensitisation (Figure **5**). During the collision energy transfer occurs from $\mathbf{D}^* \rightarrow \mathbf{A}$ thus generating a triplet excited acceptor molecule.[4,5]

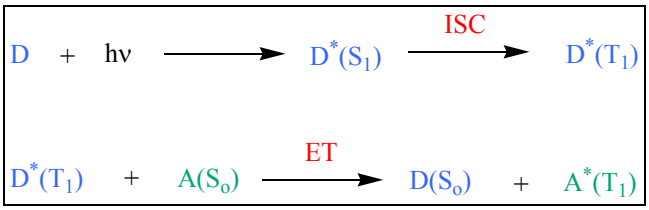


Figure 5: Triplet sensitisation process

This ensures that the reaction proceeds via the triplet state. The one condition that is necessary for these sensitisers is that the triplet energy of the donor is higher than that of the acceptor, *i.e.* E_T (**D**) > E_T (**A**). A typical sensitizer is benzophenone which forms T_1 very efficiently with **ISC** of ~100%. The sensitizer used in this thesis was acetone.

Once a molecule has absorbed energy in the form of electromagnetic radiation, there are a number of routes by which it can return to ground state. The Jablonski diagram shown below (Figure **6**) shows a few of these processes.

If the photon emission occurs between states of the same spin state (*e.g.* $S_1 \rightarrow S_0$) this is termed fluorescence. If the spin states of the initial and final energy levels are different (*e.g.* $T_1 \rightarrow S_0$), the emission is called phosphorescence. Phosphorescence occurs at a longer wavelength (*lower energy*). The lifetimes of fluorescent states are very short ($1 * 10^{-5}$ to 10^{-8} seconds), whereas those of phosphorescence are significantly longer ($1 * 10^{-4}$ seconds to minutes or even hours).

Three nonradiative deactivation processes are also significant here: Internal conversion (**IC**), Intersystem crossing (**ISC**) and vibrational relaxation. Internal conversion is the radiationless transition between energy states of the same spin state (comparable with fluorescence - a radiative process). Intersystem crossing is a radiationless transition between different spin states (comparable to phosphorescence). Vibrational relaxation, the most common of the three usually occurs very quickly ($<1 * 10^{-12}$ seconds) and is enhanced by physical contact of an excited molecule with other particles with which energy, in the form of vibrations and

rotations, can be transferred through collisions. This means that most excited state molecules never emit any energy because in liquid samples the solvent or, in gas phase samples, other gas phase molecules that are present can quench the energy before other deactivation processes can occur.

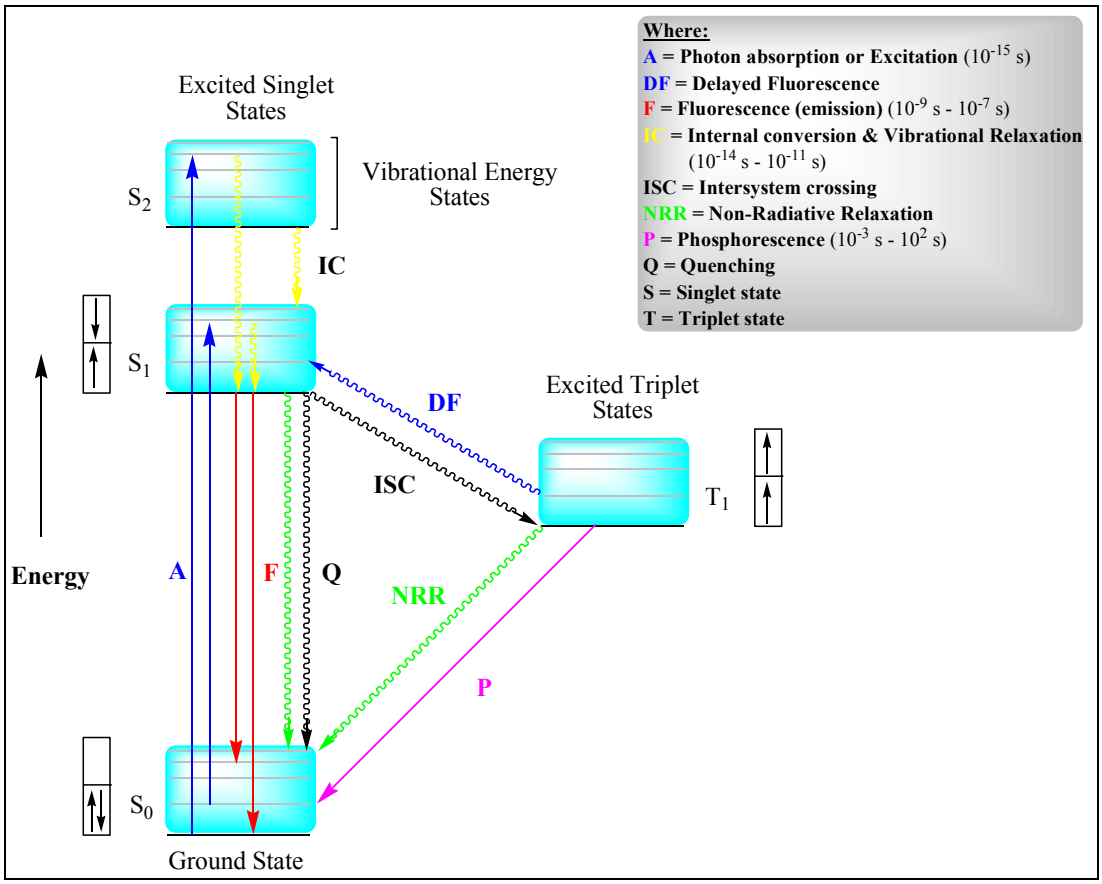


Figure 6: Simplified Jablonski diagram

There are several reaction parameters required for a successful photoreaction. The solvent should be inert, such as hexane, benzene or acetonitrile and it should also be degassed. This is usually achieved by passing a slow steady stream of an inert gas through the solution. The removal of oxygen helps to avoid side reactions and triplet quenching. Absorption overlap of the starting material, solvent and product should be kept to a minimum (Figure **7**). The light used should be in the region where the starting material, solvent and product show distinct differences in their UV spectra.

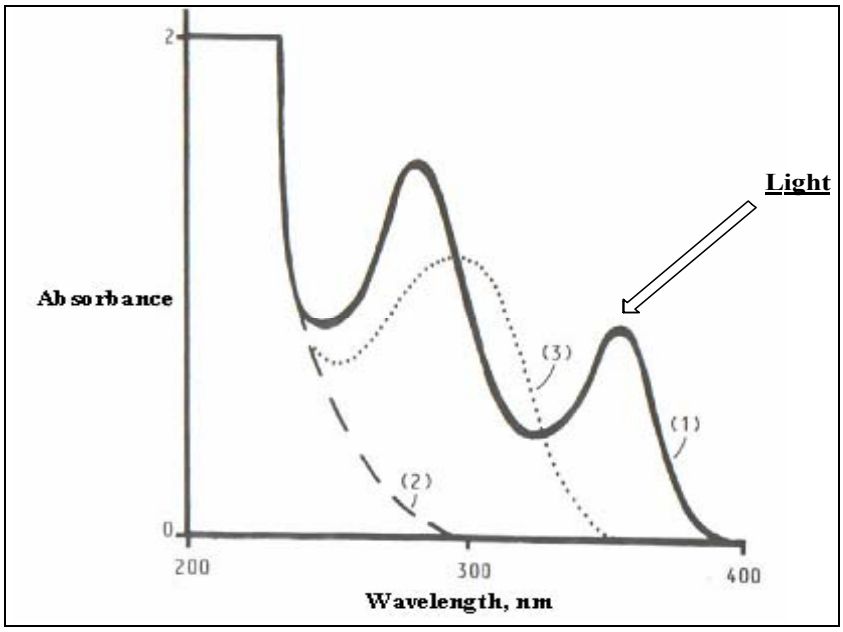


Figure 7: Examples of UV-spectra for: (1) Starting Material, (2) Solvent, (3) Product[6]

The glass used for the photoreactor tube must also allow absorption at the correct wavelength. For example, quartz glass is transparent at $\lambda > 200$ nm, whereas Pyrex glass is transparent at $\lambda > 300$ nm (Figure **8**).

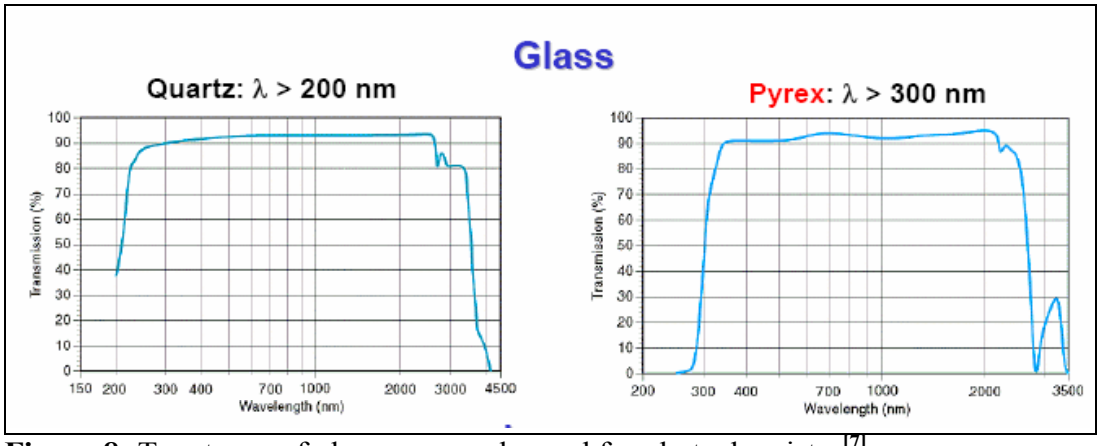
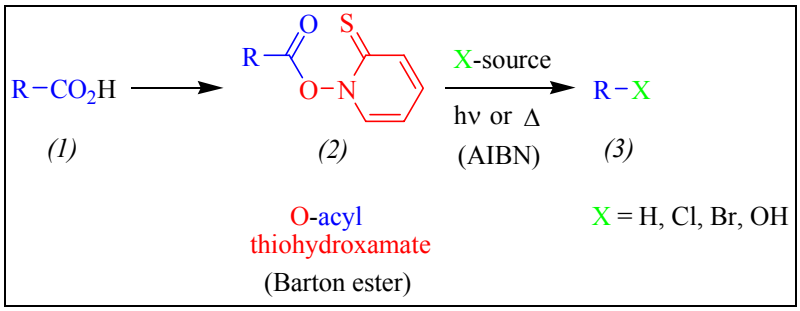


Figure 8: Two types of glass commonly used for photochemistry[7]

1.2 Photodecarboxylations

Photodecarboxylation (**PDC**) reactions are significant in many synthetic areas of chemistry. The classical approach to decarboxylation employs the Barton method (Scheme **1**). This radical reaction has many applications in the pharmaceutical and agricultural industry.[8]



Scheme 1: Cleavage of O-acyl thiohydroxamates (*Barton **II** reaction*)

Barton reported the reaction of *O*-acyl derivatives with many radicals, the latter generated from an X-source (Scheme **1**).[9] The photolysis of *O*-acyl thiohydroxamates *(2)* in the presence of suitable hydrogen donors such as *tert*-butyl mercaptane or tri-butyltin hydride results in the reductive decarboxylation via a radical chain mechanism to give the corresponding alkane *(3)*.[10]

Many disadvantages have been discovered that make tributyltin hydride an unsuitable reagent. For example, the tin residues, which are formed, are hard to remove. Organotin products are furthermore toxic, so these would not be suitable for large scale production.[11] As a result, it is very important to find an alternative route for these significant **PDC** reactions.

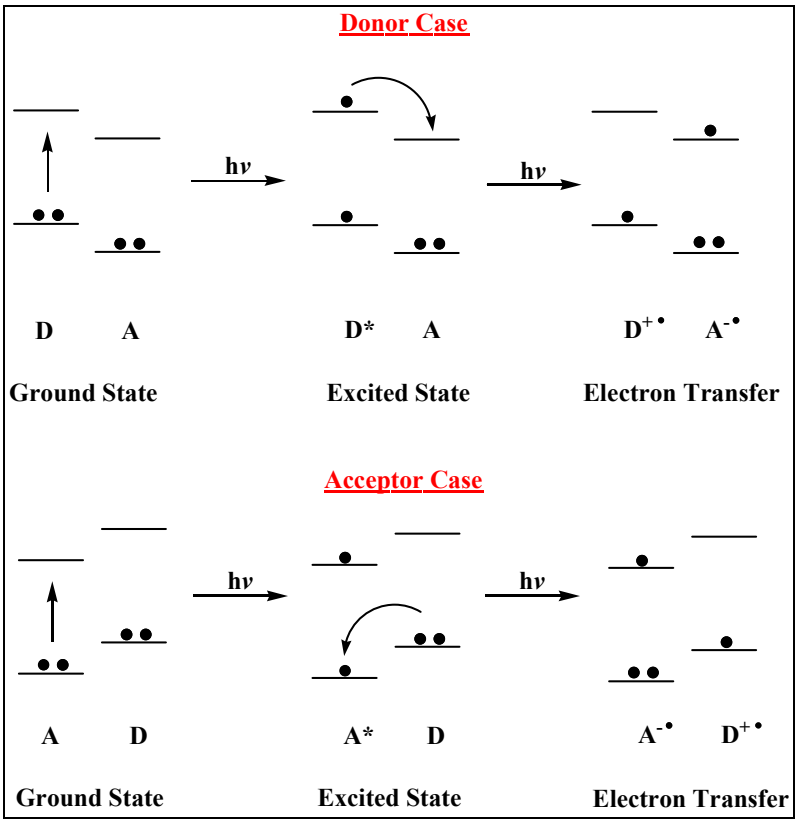
PDC is also the basis of the photo-Kolbe reaction, which involves the decarboxylation of, for example, acetic acid using a metal-liquid interface by irradiation of the metal, most commonly TiO_2.

The photodecarboxylative addition reaction involving phthalimides has been developed over the last decade. Phthalimides are excellent electron acceptors in the excited state and this makes them very applicable for photoinduced decarboxylation

reactions with alkylcarboxylates.[12] This in turn will lead to the formation of carboxy and subsequently alkyl radicals. Over the last few years **PDC**-additions of carboxylates, α-carboxylates and heteroatom substituted carboxylate to phthalimides have been developed as alternative methods to thermal Grignard reactions.[13] This transformation has been used to synthesis bioactive compounds such as *AKS-186* (this work) which possesses inhibitory activity for thromboxane A_2 analogue which induces vasoconstriction.[14]

1.3 Photoinduced Electron Transfer (PET)

This process is central to photochemistry as excited states are stronger oxidants and reductants than their corresponding ground states. This is important as many of the compounds synthesised in this project were found to be the result of photoreduction reactions. Upon irradiation, the electron is prompted to a vacant orbital in the excited state where donation or acceptance of the electron becomes easier in the molecule. Electron transfer (**ET**) normally occurs between two species, the donor (**D**) and the acceptor (**A**) as is illustrated in Scheme **2**.



Scheme 2: Electron donating and accepting scenario

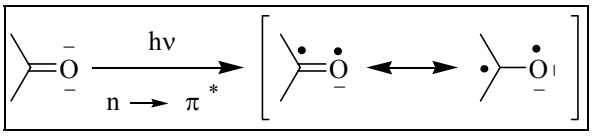
Upon electronic excitation the redox properties of either the electron donor (**D**) or the acceptor (**A**) are enhanced. The feasibility of an electron transfer can be estimated from a simple free reaction energy consideration as customary in the frame of the Rehm-Weller approach (Equation **1**),[15,16] where $E_{1/2}^{Ox}(D)$ and $E_{1/2}^{Red}(A)$ 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.

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

Equation 1:

1.4 Photochemistry of Carbonyl Group

Carbonyl compounds are very interesting in synthetic organic chemistry and particularly in photochemical reactions. They are compounds that contain a functional group composed of a carbon atom double-bonded to an oxygen atom (C=O) (Scheme **3**) and they are commonly used in the restricted sense of aldehydes and ketones, although it actually includes carboxylic acids and their derivatives.



Scheme 3: n→π* transition of the carbonyl group

Aldehydes and ketones show UV-absorption in the region of 275-300 nm which can be allocated to the forbidden $n \rightarrow \pi^*$ transition. There are several possibilities for further reaction after the first excited singlet state or after subsequent intersystem crossing (**ISC**) to the triplet state:

1. *α-Cleavage* of the C-C bond next to the carbonyl group (*Norrish Type **I** Cleavage*).
2. *Intramolecular* H-abstraction from γ-position of carbonyl group with subsequent fragmentation or cyclisation (*Norrish Type **II** Cleavage; Yang cyclisation*).
3. *Intermolecular* H-abstraction and formation of a reduced compound (*Photoreduction*).
4. Addition to a C=C bond of an olefin with formation of a cyclisation adduct (*Paternò-Büchi reaction*).

The *Norrish Type **II** Cleavage* and the cyclisations are, in particular, relevant for the photochemistry of phthalimides.

In the ground state, the carbonyl group can function as both nucleophile and electrophile (Figure **9**).

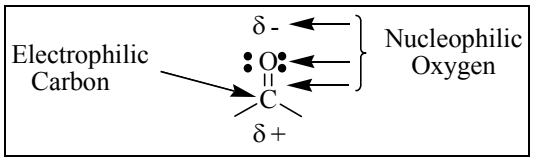


Figure 9: Polar character of a carbonyl group

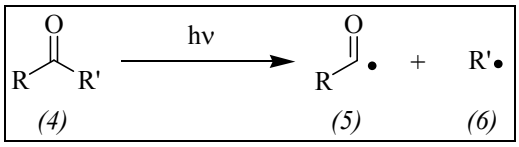
This is due to the fact that carbon is less electronegative than oxygen, so the carbonyl carbon bears a δ^+ charge while the oxygen bears a δ^- charge. This renders the carbonyl carbon electrophilic (reacts with bases and nucleophiles). The combination of oxygen δ^-, oxygen lone pairs, and C=O π bond allow the carbonyl group to function as a nucleophile (reacts with acids and electrophiles).
In the excited state, the carbonyl C=O follows an Umpolung mechanism, which is defined to be any process by which the normal alternating donor and acceptor reactivity pattern is interchanged. The original meaning of the term has been extended to the reversal of any commonly accepted reactivity pattern.[17]

1.5 Norrish Photoreactions

Carbonyl compounds are able to undergo various photochemical reactions, most important the two types of reactions that are named after *Norrish*.[18]

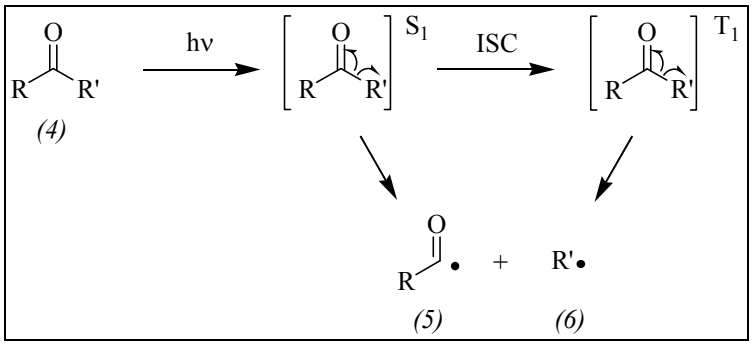
1.5.1 Norrish Type I

The *Norrish type **I*** reaction can be described as a photochemical reaction of a carbonyl compound *(4)*, where the bond between carbonyl group and α-carbon is cleaved homolytically. In doing so, two new radical species *(5)* and *(6)* are generated that can further react by decarbonylation, disproportionation or recombination to yield a variety of products (Scheme **4**).



Scheme 4: *Norrish type **I*** reaction

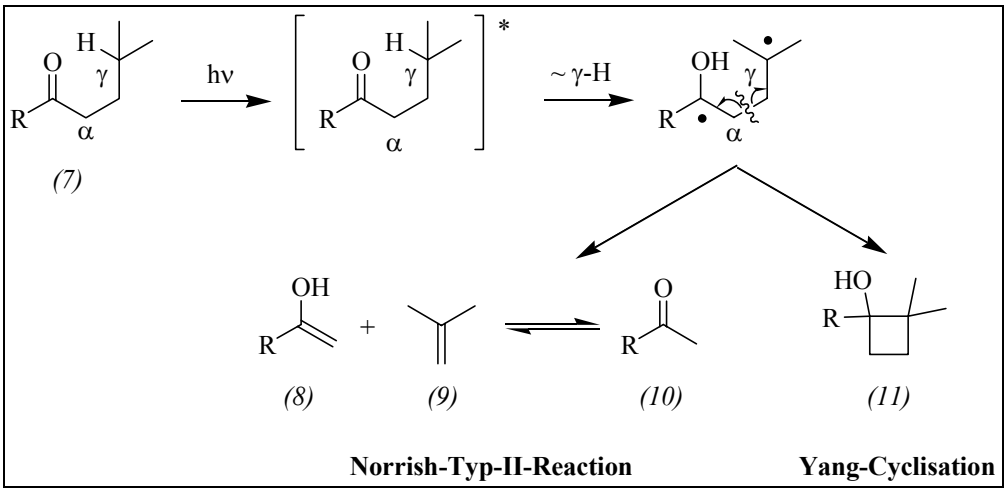
Upon absorption of a photon of light, a carbonyl compound is promoted to the singlet excited (***S*$_1$**) state, and may further reach the triplet excited (***T*$_1$**) state by *inter-system crossing* (***ISC***). *Norrish type **I*** cleavages may occur from either state leading to the formation of an acyl radical *(5)* and an alkyl radical *(6)* (Scheme **5**). In case of aromatic ketones, the photolytic cleavage is preferred from the triplet state due to the favourable *intersystem crossing* (***ISC***) rates of these derivatives.[18-21]



Scheme 5: *Norrish type **I*** mechanisms

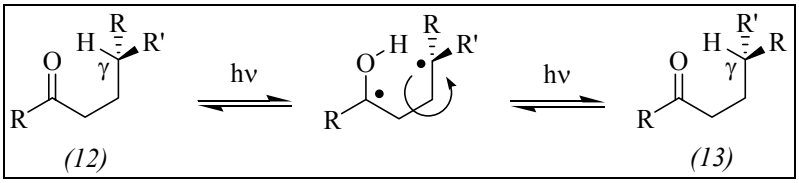
1.5.2 Norrish Type II

The *Norrish type **II*** process is an intramolecular abstraction of a γ-hydrogen by an excited carbonyl compound to produce a 1,4-biradical as the primary photoproduct (Scheme **6**).[22] The latter may either lead to cleavage or cyclisation. The fragmentation / cyclisation ratio is determined by the relative orientation of the respective molecular orbitals, and furthermore by the conformation of the diradical species (Scheme **6**).[23]



Scheme 6: *Norrish type **II*** reaction

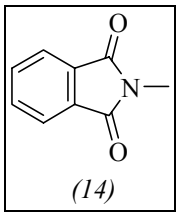
The quantum yield for the formation of these products is generally low. The photochemically initiated 1,5-hydrogen shift from the γ-carbon to the carbonyl oxygen is a reversible process, and may as well proceed back to the starting material. This has been shown with optically active ketones containing a chiral γ-carbon centre. Upon irradiation, the optically active ketone racemises to a mixture of two enantiomeric products *(12)* and *(13)* (Scheme **7**).



Scheme 7: Racemisation via *Norrish type **II***

1.6 Usage of the Phthalimide Group

Phthalimides (*isoindoline-1,3-diones*) are examples of heterocyclic aromatic imides. In this project, *N*-methylphthalimide (**NMP**) *(14)* was predominately used as a starting material (Figure **10**).

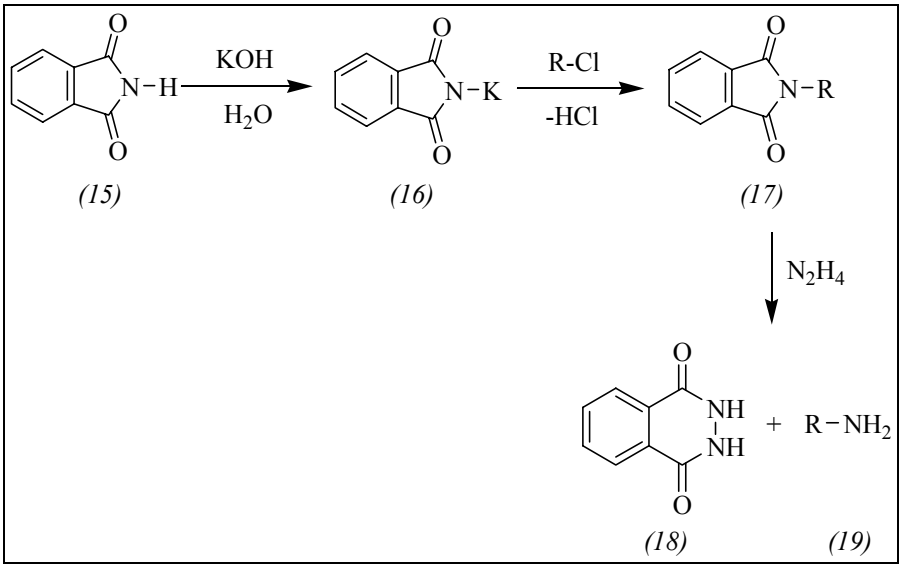


(14)

Figure 10: Structure of *N*-methylphthalimide (**NMP**)

Phthalimides are of great pharmaceutical importance. They are also very useful agrochemicals with anti-fungal and herbicidal activities. They can be used as protecting groups in peptide synthesis and for the formation of primary amines.

The reaction of potassium phthalimides with alkyl halides can be used to prepare primary amines. This useful method is called the Gabriel synthesis and is shown below (Scheme **8**).[24]



(15) *(16)* *(17)* *(18)* *(19)*

Scheme 8: Gabriel Synthesis

Due to the acidity of the phthalimide NH (pK_a = 9), potassium hydroxide can be used to convert it to its corresponding potassium phthalimide *(16)*. The phthalimide ion is a good nucleophile that can react with alkyl halides to produce an *N*-alkylphthalimide *(17)*. The *N*-alkylphthalimide can then be hydrolysed to the corresponding primary amine but this can be a slow and difficult procedure. Alternatively, *N*-alkylphthalimide can be treated with hydrazine (N_2H_4) to give the

corresponding primary amine *(19)*.[25] 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.[26]

1.7 Phthalimides-Synthetic Usage in Photochemistry

The application of the phthalimide system to photochemistry was first introduced by Kanaoka and co-workers in the early 1970's.[27,28] As a result of this early work many transformations of phthalimides in synthetic organic photochemistry have emerged.[27-36] Even though its photochemistry is similar to carbonyl photochemistry in many respects it covers additional reactivity features due to the remarkably high oxidising power of the first excited and the first as well as second excited triplet states of phthalimides.[32] The photochemistry of phthalimides is consequently dominated by **PET** processes. In the presence of energetically feasible electron donor groups, **PET** leads to the generation of radical ions which can undergo non-productive (*back*) electron transfer, direct radical ion combination, or mesolytic extrusion of a suitable leaving group (*e.g.* a proton, silyl cation or carbon dioxide), respectively. The competition between these processes can be controlled by variation of the redox potentials, the stability of the radical cations and the leaving group ability.

There are two main reaction paths that phthalimides can follow (**i**) Photoaddition and (**ii**) Photocyclisation reactions. Photoadditions to phthalimides have been investigated in this thesis. Numerous *intermolecular* applications such as addition reactions of alkenes,[37-40] alcohols,[41,42] ethers,[40,43] thioethers,[44] alkylbenzenes,[45,46] and amines[46] to the phthalimide system have been reported. These reactions often gave poor yields, and mixtures of the desired photoaddition and undesired photoreduction products were obtained.

1.8 Photophysical and Electrochemical Properties of Phthalimides

Intense studies of the photophysical[33-35] and electrochemical[47-49] properties of phthalimides have been reported. In acetonitrile, *N*-alkylphthalimides show relatively simple UV absorption spectra with absorption maxima at λ_{max} = 235 nm (π, π^*) and λ_{max} = 290 nm (n, π^*), respectively.[33] At room temperature, they furthermore exhibit weak fluorescence with low quantum yields ($\Phi_f < 1.10^{-3}$) in ethanol or acetonitrile.[34] In the absence of oxygen in alcohol *N*-alkylphthalimides show a broad structureless phosphorescence centred around λ_{max} = 450 nm with quantum yields between Φ_p = 0.4-0.7 and triplet lifetime between τ_p = 0.7-1.04 s (at 196 ^oC).[33-35] The order of the excited states of phthalimides has been controversially discussed. The level of the (n, π) triplet state is either slightly below or above the lowest singlet state, which accounts for the high intersystem crossing rates. *N*-Methylphthalimide is reversibly reduced to the corresponding radical anion at *ca.* -1.35 V in DMF,[47,48] and at *ca.* -1.5 V in acetonitrile (*vs.* SCE),[48] respectively. The presence of a hydrogen donor site in the side chain has a dramatic effect on the redox properties.[50,51] In particular, anodically shifted pre-waves emerge in the cyclic voltammograms which have been assigned to *intra*- and *intermolecular* hydrogen bonds to the phthalimide electrophore.

Due to their favourable photophysical and electrochemical properties, phthalimides are superior substrates for **PET** reactions.[50,51] The limiting maximum oxidation potential of the electron donor depends on the excited state of the phthalimide electron acceptor,[33] and can be estimated by the Rehm-Weller equation.[15,16] If the excited singlet state is involved (E_{00}=3.8 eV), the limiting oxidising power for an isoenergetic electron transfer is *ca.* 2.4 V (*vs.* SCE). For the first excited triplet state (E_{00}=3.1 eV), the limiting oxidising power decreases to *ca.* 1.7 V (*vs.* SCE). In cases where the second excited triplet state is involved the oxidation power increases by about 0.5 eV (Figure **11**; Table **1**).

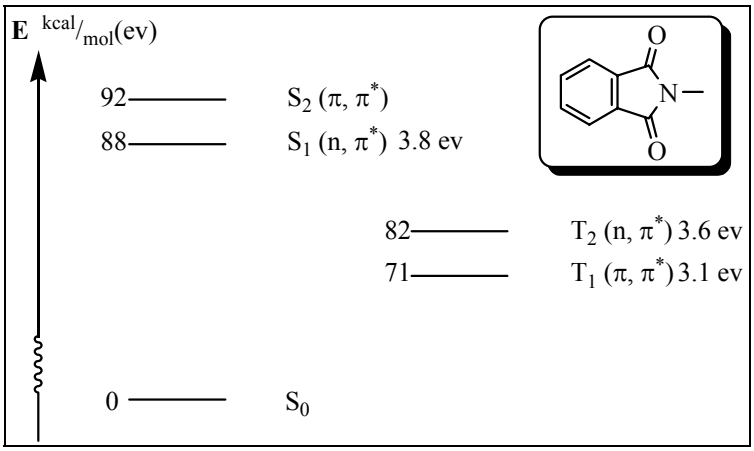


Figure 11: Jablonski-Diagram of *N*-methylphthalimide

τ_s [ns]	Φ_f	k_f [s^{-1}]	Φ_{ISC}	k_{ISC} [s^{-1}]	τ_{ph} [ns]
0.185	0.0008	4×10^6	0.7	3.9×10^9	0.8

Table 1: *N*-methylphthalimide properties

1.9 *Intermolecular* Photoreactions of Phthalimides

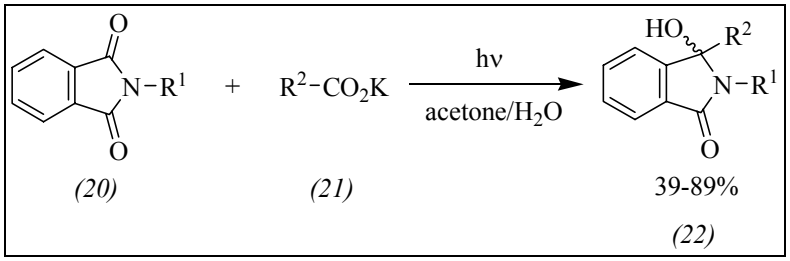
Various aspects of the photochemistry of phthalimides, including *intermolecular* addition reactions and their proposed mechanisms, have been reviewed previously.[29c-f, 52-55]

1.9.1 Photoreactions with Carboxylates

Photodecarboxylation of ω-phthalimido carboxylates was recently published by Griesbeck and co-workers as a strategy for the construction of medium to macrocyclic ring-systems.[56 - 58] Likewise, *intermolecular* counterparts, *i.e.* photodecarboxylative additions, have been described with simple carboxylates, α-ketocarboxylates and heteroatom-containing carboxylates.[59,60] **PET** plays a key role in the *intermolecular* photoaddition where the carboxylate anion acts as electron donating group and the electronically excited imido group as electron acceptor.

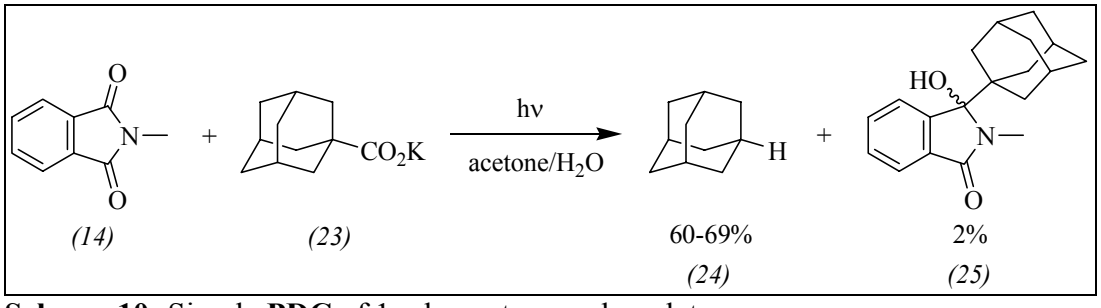
1.9.1.1 Alkylcarboxylates

Alkylcarboxylates *(21)* underwent *intermolecular* addition reactions to form alkylhydroxyphthalimidines *(22)* in good to excellent yields (Scheme **9**).[13,60,61] Several carboxylate / phthalimide systems were investigated in detail by Griesbeck and Oelgemöller, who developed this transformation as a mild and convenient photochemical pathway to hydroxyphthalimidines. The latter compounds were previously commonly synthesised via thermal methods, *e.g.* SmI_2-mediated coupling of organic halides (SmI_2 / R-X)[62] addition of organometallic compounds (R-Mg-X or R-Li),[63-65] or alkylation with organic halides using lithium in liquid ammonia (Li / NH_3 / R-X),[66] respectively.



Scheme 9: PDC-addition of alkyl carboxylates

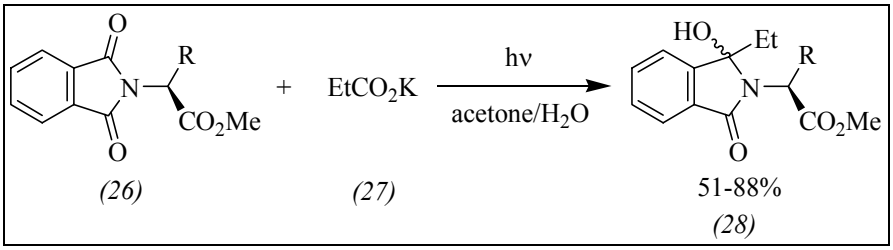
In contrast, photoreaction of the potassium salt of 1-adamantane carboxylic acid *(23)* gave the alkane adamantine *(24)* as the main product in 60-69% yields (Scheme **10**). Most of the *N*-methylphthalimide remained unchanged and could be reisolated. In one particular reaction the photoaddition product *(25)* was also obtained in 2% yield.



Scheme 10: Simple **PDC** of 1-adamantane carboxylate

The irradiation of *N*-methylphthalimide in the presence of sodium formate as the product composition was sensitive to the reaction conditions applied. Therefore, the result was the stepwise domination by *photoreduction* or *photo-dearomatisation*, as it is known in the literature for other phthalimides[46,67-69] and related imide chromophores.[70,71]

One very interesting application for this remarkably efficient photoaddition was the highly *chemoselective* ethylation of *N*-phthaloylamino acid methyl esters.[60] In all cases examined (Scheme **11**), the *intermolecular* decarboxylative gave the wanted products in 51-88% yield and products arising from *intramolecular* hydrogen abstractions[72,73] were not observed.



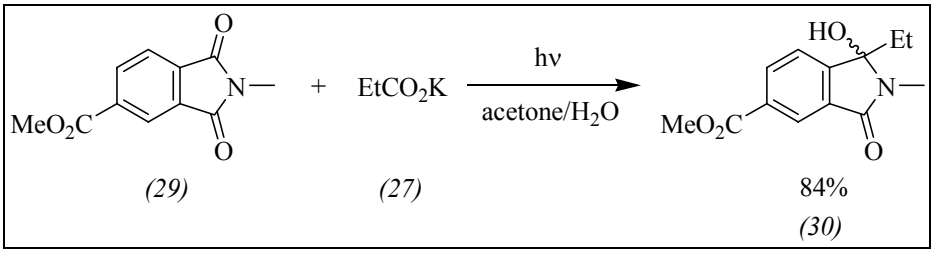
Scheme 11: Ethylation of *N*-phthaloylamino acid methyl esters

R	Amino acid	Yield [%]	*d.e.* [%]
H	Gly	88	—
Me	*L*-Ala	89	4
i-Pr	*L*-Val	51	6
i-Bu	*L*-Leu	55	14
s-Bu	*L*-Ile	63	38
Ph	*D*-Phg	85	30
Bn	*L*-Phe	72	28
CH_2CO_2Me	*L*-Asp	64	14
$C_2H_4CO_2Me$	*L*-Glu	62	28

Table 2: Photodecarboxylative ethylation of *N*-phthaloylamino acid methyl esters

The photoinduced alkylation proceeded selectively at the imide carbonyl group and not the corresponding ester group, the latter commonly observed for alternative nucleophilic additions (*e.g.* Grignard reaction).[63,64] The diastereoselectivity for the ethyl transfer reaction was negligible to moderate (Table **2**).[60]

A highly regioselective alkylation of *N*-methyltrimellitic acid *(29)* has been recently described.[74] Photolysis in the presence of potassium propionate *(27)* solely gave the *para*-addition product *(30)* in 84% yield (Scheme **12**). Its preferred formation was explained on the basis of the differences in spin densities in the corresponding imide radical anions. Looking at the radical anion of *N*-methyltrimellitic acid imide, the spin densities were significantly higher for the imido *para*-carbon atom than for the *meta*-carbon atom thus indicating preferential *para* alkylation. In contrast, *N*-methyl-quinolinic acid imide only showed a slight preference for formation of its *ortho* isomer.

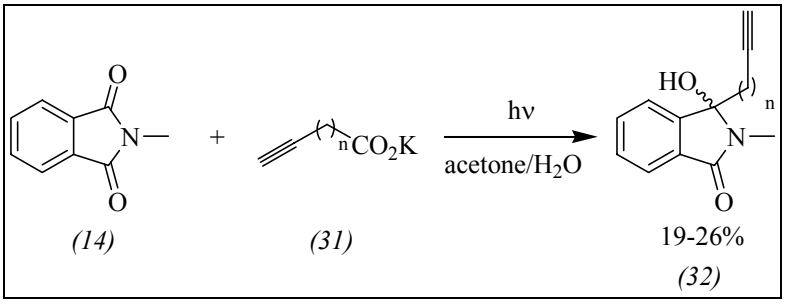


(29) *(27)* *(30)*

Scheme 12: Alkylation of *N*-methyltrimellitic acid imide

Griesbeck and co-workers recently used the photodecarboxylative benzylation of phthalimides as a concise route to *aristolactam* precursors,[75] but there still a problem in the final electrocyclisation step.

Intermolecular addition of alkynoates *(31)* to *N*-methylphthalimide have also been reported (Scheme **13**).[13,60]



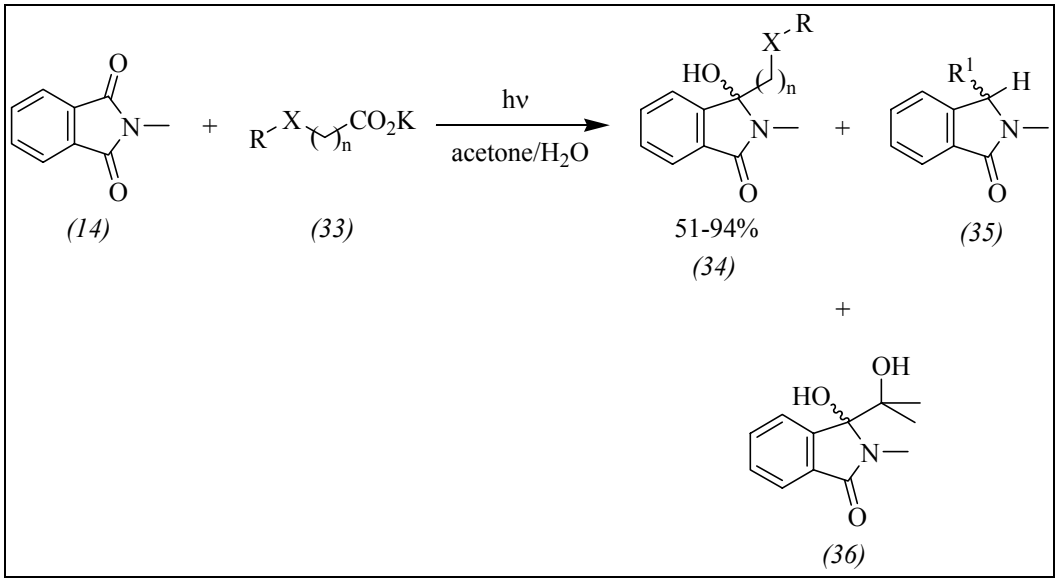
(14) *(31)* *(32)*

Scheme 13: PDC-Photoaddition of alkynoates

The corresponding hydroxyphthalimidines *(32)* were obtained in moderate yields of 19-26% from irradiation of *N*-methylphthalimide in the presence of 5 equivalents of potassium alkynoates in aqueous acetone.

1.9.1.2 Heteroatom substituted carboxylates

The incorporation of a heteroatom in close proximity to the carboxylic group plays a crucial role in the addition efficiency. The presence of the potential electron donor[76] can either strongly increase or decrease the addition efficiency.[12,77,78] When the heteroatom was positioned in the α-position of the carboxylate, the corresponding addition products *(34)* were obtained in moderate to good yield of 51-94% from *N*-methylphthalimide (Scheme **14**). In contrast, β-thioalkyl-substituted carboxylates completely suppressed the photoreaction and no reaction was observed. The related β-oxoalkyl-substituted carboxylates, however, reacted efficiently to give the addition products in 4-67% yield.

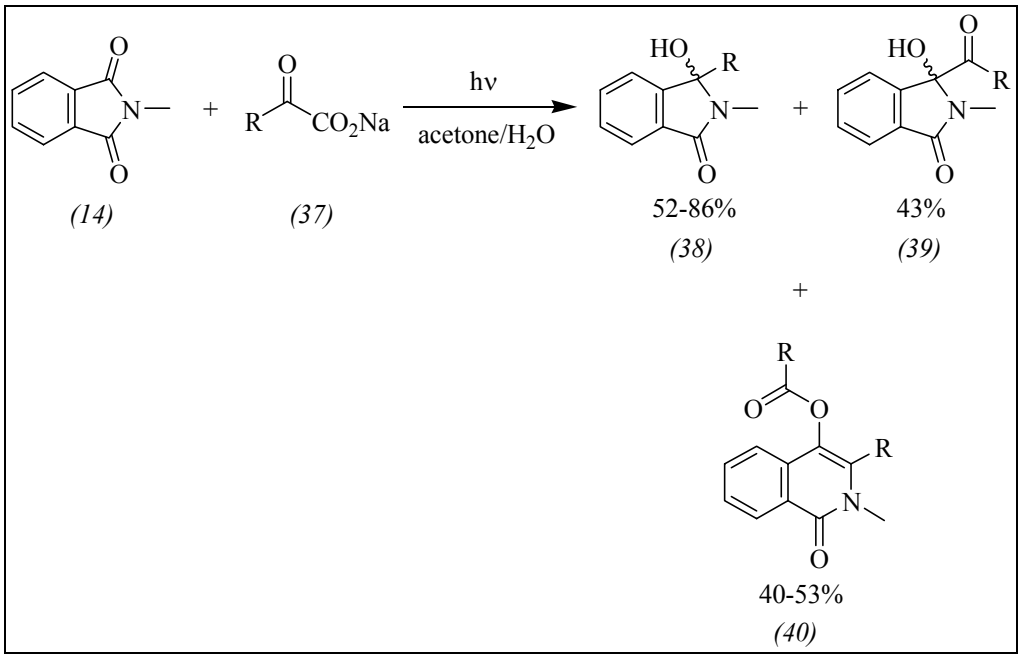


Scheme 14: Photoaddition of heteroatom substituted carboxylates

The comparison of oxygen- vs. sulphur-substituted carboxylates shows that oxidation of the heteroatom dominates in the case of thioethers. Consequently, in case of β-thioalkyl substrate the sulphur atom acts as a hole trap due to the fast non-productive **BET**[79] and prevents oxidation of the carboxylate. Alkylamino-substituted carboxylates gave exclusively photoreduction or trapping of the solvent acetone.[12]

1.9.1.3 α-Keto carboxylates

Irradiation of phthalimides in the presence of α-keto carboxylates *(37)* furnished alkylation *(38)*, acylation *(39)* and ring expansion products *(40)* (Scheme **15**), respectively.[59] Glyoxylate, secondary and tertiary α-keto carboxylates gave the corresponding reduction or alkylation products *(38)* in 52-86% yields. On the other hand, pyruvate and α-keto leucine gave dihydroisoquinolinyl esters as ring expansion products *(40)* in 40-53% yields. The acylated product *(39)* was isolated in 43% yield. After analysis of the results, it was assumed that this reaction course is controlled by the stability of the acyl radical intermediates.[80,81] When more reactive acyl radicals are generated, decarbonylation proceeded C-C bond formation, whereas in the case of less reactive acyl radicals, C-C bond formation successfully competed with decarbonylation.

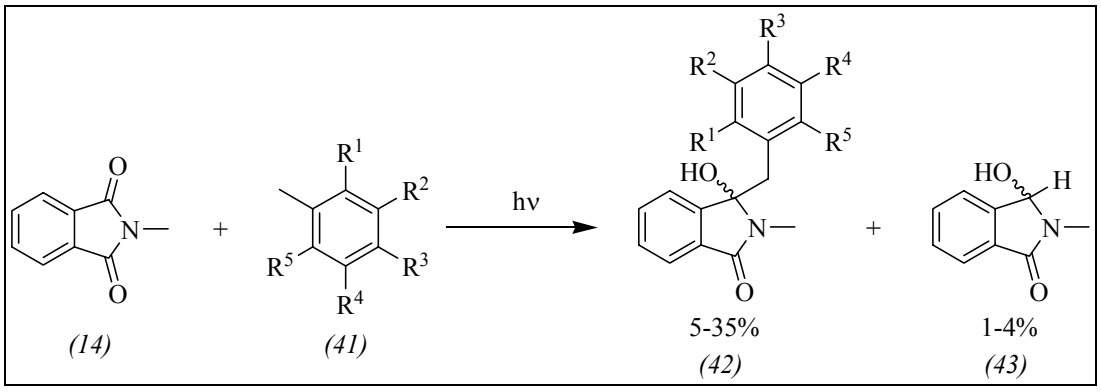


Scheme 15: Photoaddition of α-keto carboxylates

The formation of the unusual ring expansion products was explained by ring opening of the primary monoacylated compounds although the mechanisms remain unclear yet.

1.9.2 Photoreactions with aromatic systems

Kanaoka *et al.* have shown that a series of toluene derivatives *(41)* add to electronically excited *N*-methylphthalimide to produce the corresponding addition products *(42)* in poor to moderate yields of 5-35% (Scheme **16**; Table **3**).[46] As noticeable from the table below, the *p*-xylene derived product was obtained in the highest yield of 35%. The reaction generally proceeded via hydrogen abstraction from the benzylic position. The photoreduction product *(43)* was additionally isolated in low yields 1-4%.

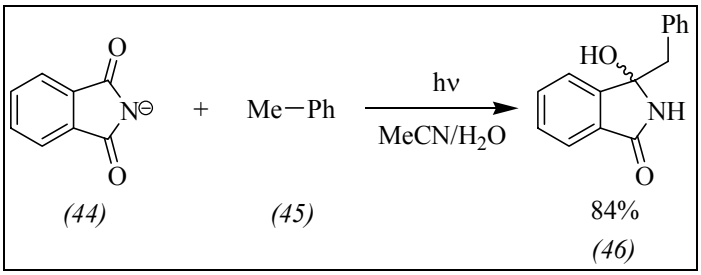


Scheme 16: Photoaddition of toluene derivatives to *N*-methylphthalimide

Arene					Conversion	Product Composition	
R^1	**R^2**	**R^3**	**R^4**	**R^5**	*(14)* **[%]**	*(42)* **[%]**	*(43)* **[%]**
H	H	H	H	H	30	5	2
Me	H	H	H	H	79	23	3
H	Me	H	H	H	59	7	2
H	H	Me	H	H	58	35	4
Me	H	H	Me	H	67	24	1

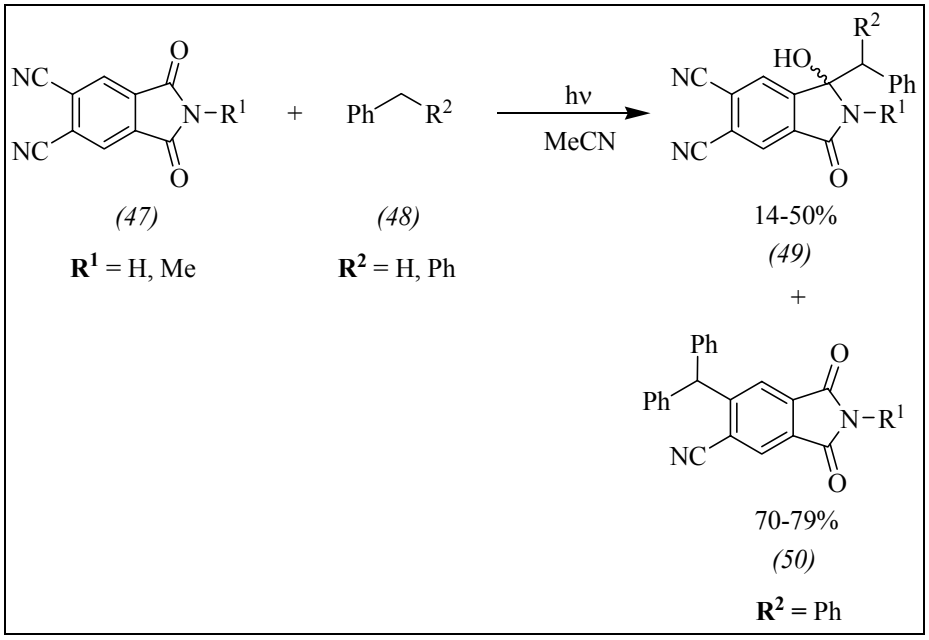
Table 3: Product composition of photoaddition of toluene derivatives to *N*-methyl-phthalimide

In contrast, toluene *(45)* proved to be highly reactive with the phthalimide anion *(44)* giving the corresponding product *(46)* in a high yield of 84% without any side products (Scheme **17**).[82] The use of base was essential and no conversion could be achieved without it. An electron transfer between the anion and the free phthalimide prior to hydrogen abstraction from the aromatic side chain and radical combination was suggested by Suau and co-workers.



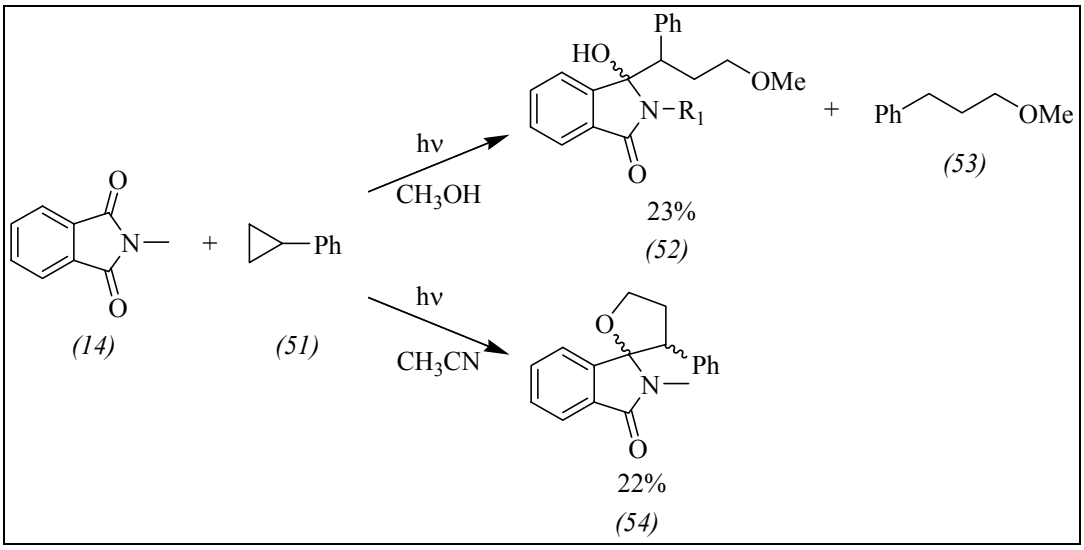
Scheme 17: Photoaddition of toluene to the phthalimide anion

An alternative electron transfer was postulated by Albini *et al.* in 1993 for cyano-substituted phthalimides *(47)*.[45] Two products were observed when diphenylmethane (**R²** = Ph) was used as the toluene derivative (Scheme **18**). The products *(49)* resulting from photoaddition to the carbonyl group were isolated in 14-50% yield and the products *(50)* resulting from substitution of the cyano-group in 70-79% yield.



Scheme 18: Photoaddition with diphenylmethane

Photolysis of phenylcyclopropane *(51)* in the presence of *N*-methylphthalimide depended critically on the use of solvent.[83-85] Irradiation in acetonitrile produced a 1:1 mixture of isomeric spiro-tetrahydrofuranyl lactams *(54)* in 22% yield. When photolysis was performed in methanol, solvent-incorporation was observed to produce the corresponding product *(52)* in 23% yield (Scheme **19**). An *intramolecular* version of this **PET** reaction has also been described.[85]

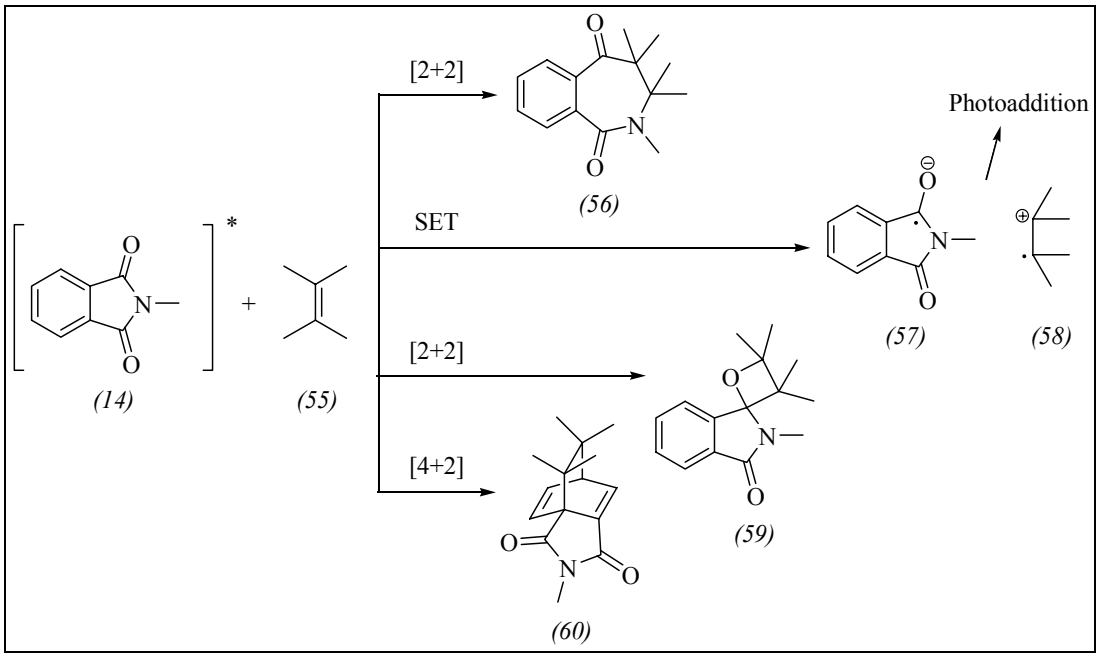


Scheme 19: Solvent dependent photoreactions with diphenylmethane

1.9.3 Photoreactions with alkene systems

Photoreactions with phthalimides in the presence of alkenes *(55)* depends on the conditions being used and the oxidation potential of the C=C double bond (Scheme **20**). Thus, for alkene with oxidation potential higher than 2.1 V,[86 - 91] benz-azepinediones *(56)* were generated from *N*-methylphthalimide via [2+2] photocyclo-addition onto the C-N bond. The triplet excited state of *N*-methylphthalimide[90,92] was shown to be responsible for [4+2] photocycloadditions to the aromatic ring *(60)* [93-95] and Paternò-Büchi reaction to give oxetanes *(59)*. In the case of easily oxidised alkenes, **SET** yields the radical-ion pair *(57)* and *(58)* (**BET** regenerates the starting material) and radical coupling products were obtained.[96,97]

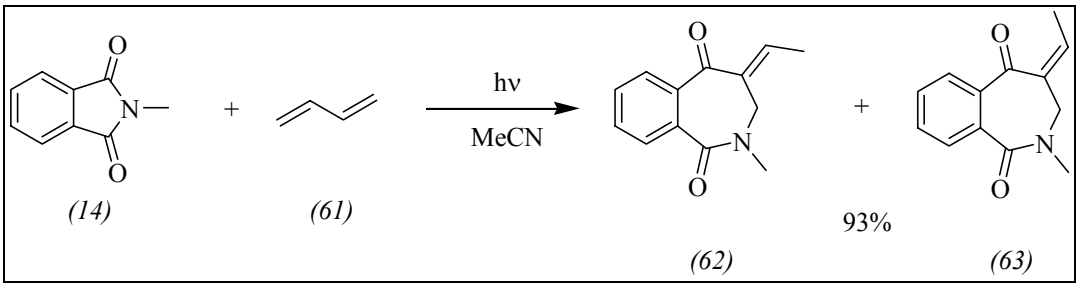
Photoaddition reactions involving alkenes were studied extensively by the groups of Mazzocchi[41, 37] and Kubo.[38]



Scheme 20: Photoaddition reactions with alkenes

1.9.3.1 The formation of benzazepinediones

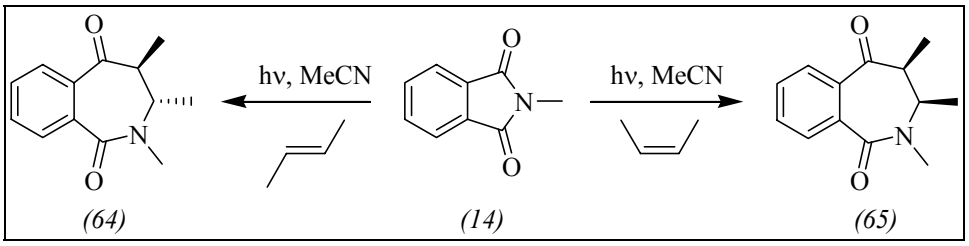
Benzazepinediones were synthesised by irradiation of *N*-methylphthalimide with butadiene *(61)* in acetonitrile (Scheme **21**). The products *(62)* and *(63)* were obtained through $[\pi^2+\sigma^2]$ photocycloaddition in a high yield of 93% (based on recovered starting material) as an isomeric mixture. This reaction took also place in the presence of isoprene and 1,3-pentadiene and the corresponding products were isolated in yields of 49 and 50%, respectively. No product was obtained using cyclopentadiene and 2,5-dimethyl-2,4-hexadiene, or when *N*-phenylphthalimide or phthalimide replaced *N*-methylphthalimide.



Scheme 21: Formation of benzazepinedione

Using various alkenes, Mazzocchi *et al.* concluded that benzazepinediones can be formed using 1-substituted, 1,1-disubstituted and 1,2-disubstituted alkenes but not using tetra-substituted or cyclic ones.[90]

The mechanism of this transformation was studied using the photoaddition reaction of *N*-methylphthalimide with either ***cis***- or ***trans***-2-butene. The stereoselectivity of the corresponding products *(64)* and *(65)* was high > 95% (Scheme **22**) at low conversion rates.



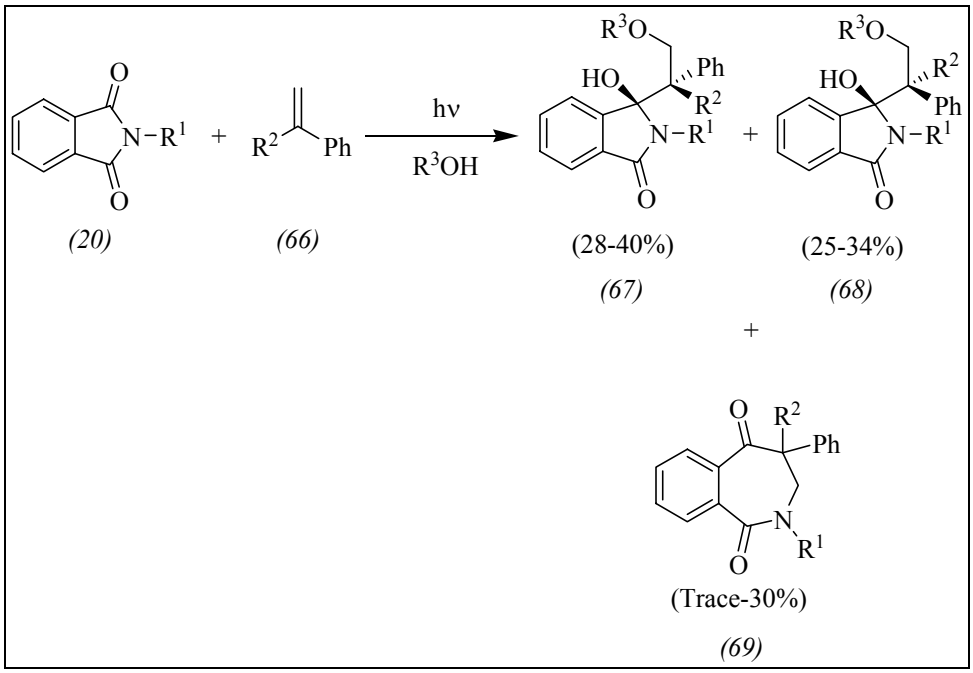
Scheme 22: Formation of benzazepinedione

The regioselectivity of the cycloaddition was studied by Mazzocchi and co-workers for unsymmetrically substituted phthalimides showing that donor substituents direct the incoming alkene preferentially to the *meta*-position, whereas acceptor groups direct to the *para*-position.[89,91]

Irradiations of the phthalimide anion in the presence of alkenes was reported recently by Suau and co-workers.[98,99]

1.9.3.2 Alcohol incorporation

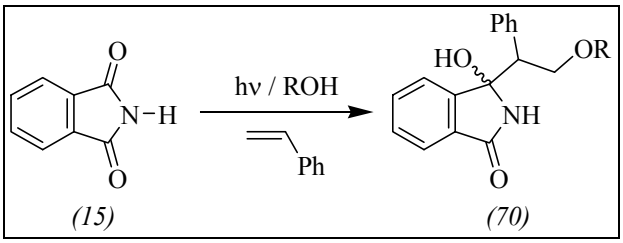
Upon irradiation in alcoholic solvents and in the presence of *N*-methylphthalimide, phthalimide, *N*-acetoxymethylphthalimide various phenylalkenes *(66)* produced diastereoisomeric solvent incorporated addition products *(67)* and *(68)* in good yields of 28-40% and 25-34%, respectively (Scheme **23**).[38,97] Benzazepinedione *(69)* were obtained in 30% yield using other alcohols instead of methanol.



(20) *(66)* *(67)* *(68)* *(69)*

Scheme 23: Alcohol incorporation

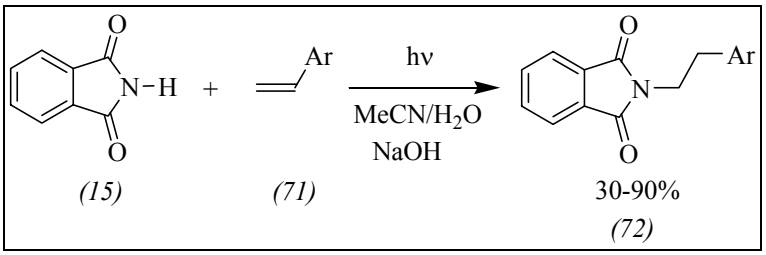
Maruyama and Kubo[38] described the irradiation of phthalimide with styrenes as electron donors in alcoholic solvents to give the corresponding photoaddition products *(70)* (Scheme **24**).



Scheme 24: Intermolecular photochemistry of phthalimide with styrenes

1.9.3.3 Phthalimidations

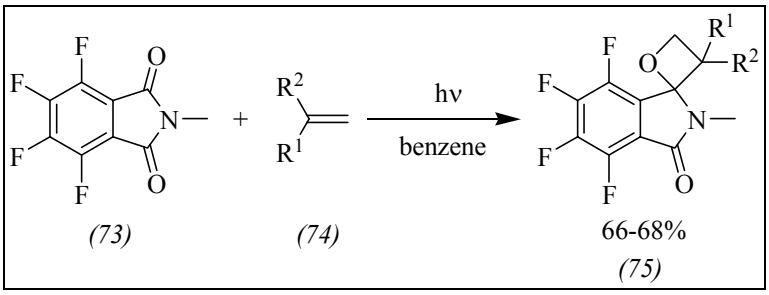
The phthalimide anion was used as trapping agent in the photochemical phthalimidation reaction of inactivated double bonds (Scheme **25**).[100] Variation of the anion concentration controlled the reaction. At higher NaOH concentration [$\pi^2+\sigma^2$] addition was observed,[98,99] while at low NaOH concentration phthalimidation gave the corresponding products *(72)* in 30-90% yield. In the latter case, the phthalimide anion acts as a nucleophile and traps the olefin radical cation intermediate.



Scheme 25: Phthalimidation reaction

1.9.3.4 Paternò-Büchi reactions

The Paternò-Büchi reaction, a [2+2] cycloaddition, generally occurs between excited carbonyl compounds and alkenes yielding oxetanes. This reaction was reported by Kubo and Umehara using 4,5,6,7-tetrafluoro-*N*-methylphthalimide *(73)* as starting material and corresponding oxetane products *(75)* were obtained in 66-68% yield (Scheme **26**).[101]

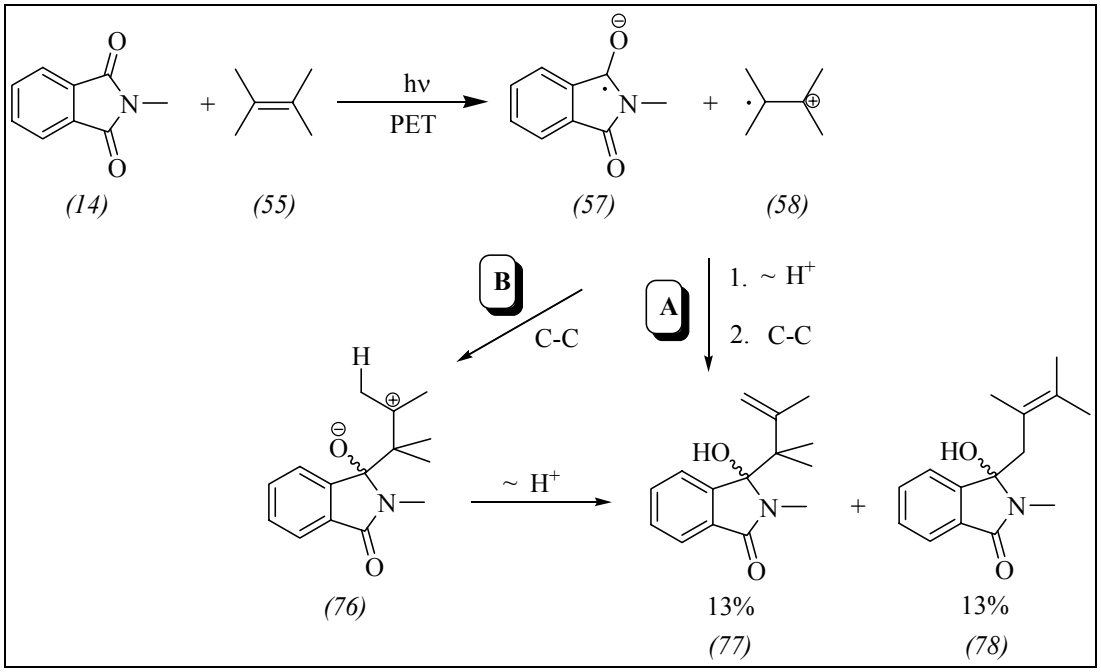


(73) (74) (75)

Scheme 26: Paternò-Büchi reaction of 4,5,6,7-tetrafluoro-*N*-methylphthalimide

1.9.3.5 Photoreductive additions

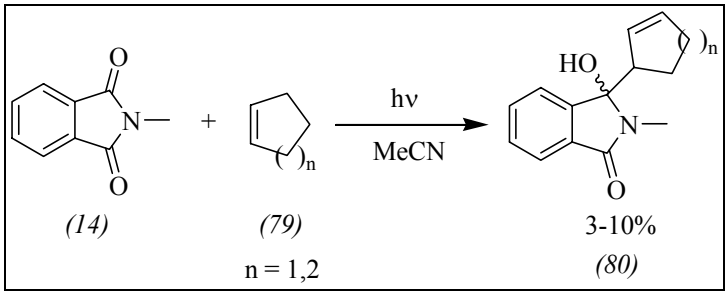
Prolonged irradiation of *N*-methylphthalimide with 2,3-dimethyl-2-butene *(55)* in acetonitrile gave two products *(77)* and *(78)* in equal yields of 13% (Scheme **27**).[41] It was suggested that this reaction proceeds via initial electron transfer. Intermolecular proton transfer and radical combination (Path **A**) gave the regioisomeric pair, whereas radical combination and intramolecular proton transfer produced solely the product carrying a terminal double bound (Path **B**).



(14) (55) (57) (58) (76) (77) (78)

Scheme 27: Photoreduction mechanism

Kanaoka and Hatanaka reported the photolysis of *N*-methylphthalimide with either cyclopentene or cyclohexene *(79)* in acetonitrile giving the addition products *(80)* in low yields of 3-10% (Scheme **28**).[40]

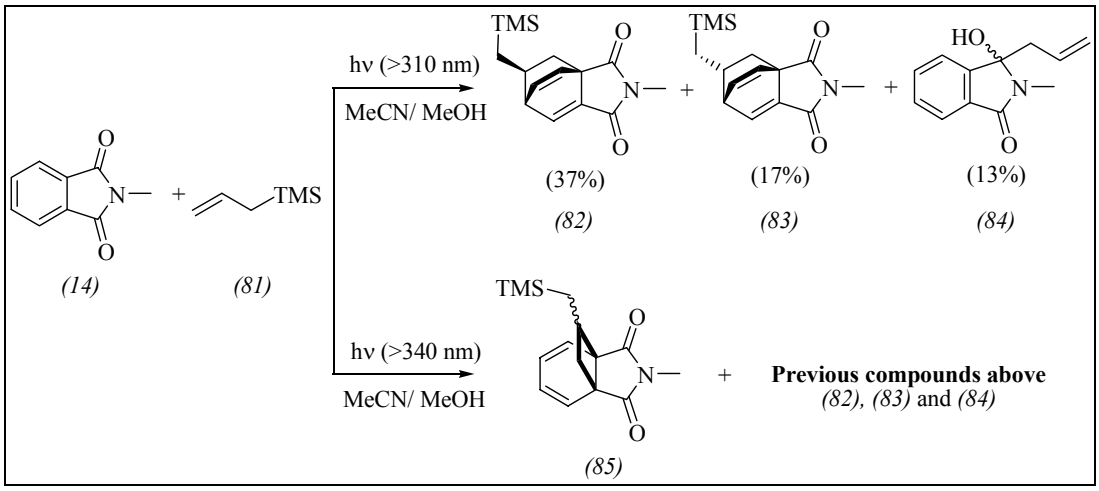


Scheme 28: Photoreduction with cyclo-(pentene or hexane)

The regioselectivity of the photoreduction was investigated by Mazzocchi and co-workers for unsymetrically substituted *N*-methylphthalimides.[91,102]

1.9.3.6 Ortho- and Para-cycloadditions

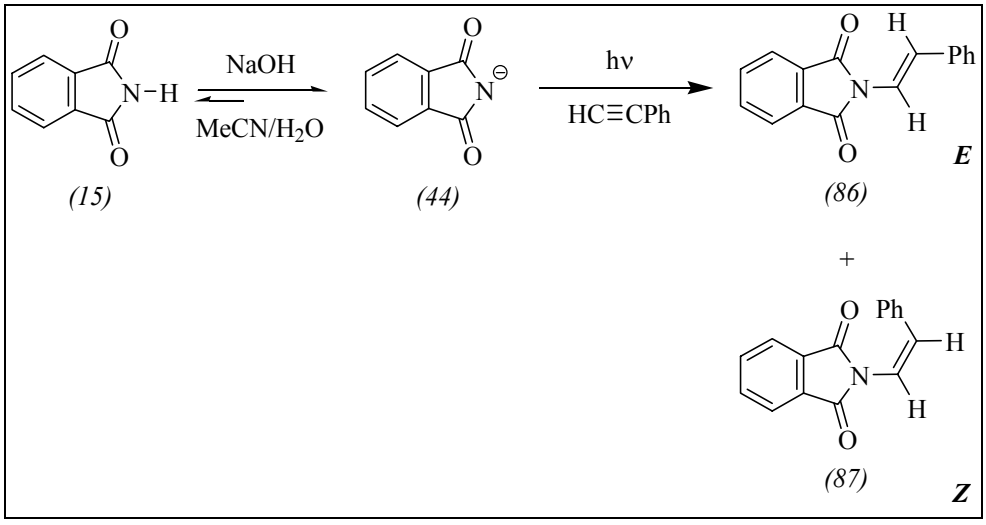
Kubo and co-workers[95] described the irradiation of *N*-methylphthalimide with allyl-trimethylsilane *(81)* in a mixture of acetonitrile and methanol [19:1] using two different wavelengths. At $\lambda > 310$ nm, two stereoisomeric products *(82)* and *(83)* were obtained in 37% and 17% yield, respectively. This reaction occurred through [4+2] *para*-cycloaddition reaction to the benzene moiety of *N*-methylphthalimide. An additional product *(84)* was obtained in 13% yield. At $\lambda > 340$ nm the same products *(82)*, *(83)* and *(84)* were obtained together with an extra compound *(85)* deriving from [2+2] addition at the benzene moiety of *N*-methylphthalimide (Scheme **29**).



Scheme 29: Photoreduction using two different wavelengths (310 and 340 nm)

1.9.4 Photoreactions with alkyne systems

Irradiating of the phthalimide anion in the presence of alkynes gave the corresponding unsaturated *N*-substituted phthalimides *(86)* and *(87)* (Scheme **30**). The reaction was found to be inactive without the use of base (*e.g.* NaOH).[103]



Scheme 30: Irradiation of the phthalimide anion with inactivated alkynes

1.10 Synthesis of 3-(Aryl and Alkyl)methylene-1H-isoindolin-1-ones

The syntheses of methylene-isoindolinones *(89)* have been reported previously in different research groups. These were, for example, accessible using the photo-decarboxylative addition as a key-step.[12,13,75] The benzylation of *N*-methylphthal-imide with phenylacetate is a straightforward and high-yielding process to 3-Aryl-methylene-*1H*-isoindolin-1-ones (Figure **12**).

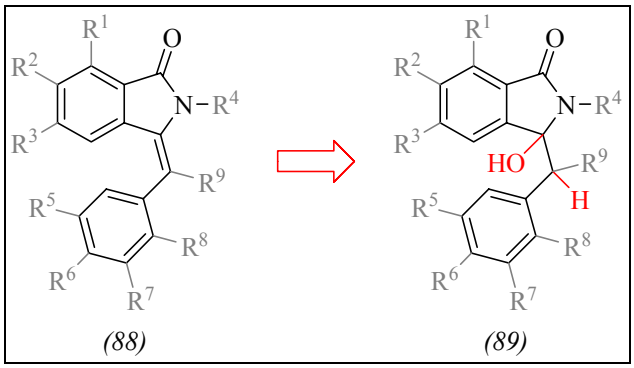
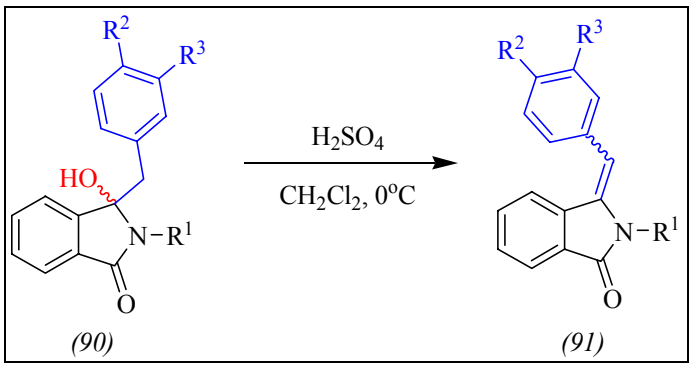


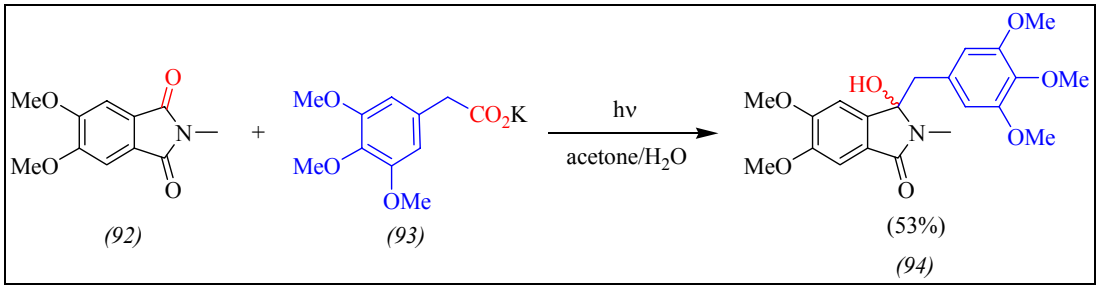
Figure 12: 3-Arylmethylene-*1H*-isoindolin-1-one retrosynthesis

Acid catalysed dehydration of the hydroxyl isoindolines *(90)* has been reported to proceed easily by treatment with trifluoroacetic acid in methylene chloride (small scale) or in a biphasic mixture of $CHCl_3$ / conc. sulphuric acid, resulting in ***E/Z***-mixtures *(91)* with the desired ***E***-diastereoisomers formed in excess (Scheme **31**).[75]



Scheme 31: Acid-catalysed dehydration step

Dimethoxy-substituted *N*-methylphthalimide, which has a highly fluorescent single state (Φ_f = 1.0 in CH_2Cl_2), was investigated but it was not quenched by simple alkyl carboxylates. Previous experimental work showed that 5,6-dimethoxy-2-methyl-isoindoline-1,3-dione was a reactive substrate for the photodecarboxylation with 3,4,5-trimethoxyphenylacetate *(93)* , producing the corresponding addition product *(94)* in good yield (Scheme **32**). In this particular case, electron transfer occurs from the electron-rich aryl group rather than from the carboxylate and this scenario seemed to accelerate the electron transfer process.[75]



Scheme 32: Photoreaction of dimethoxy-substituted *N*-methylphthalimide

1.10.1 AKS-186 and its analogues

Earlier studies on the 3-arylmethylene-*1H*-isoindolin-1-one system lead to our involvement in the *AKS-186* synthesis. Open analogues of aristolactams are known to show cardiovascular activities. *AKS-186*, a higher generation cardiovascular compound, was reported to inhibit vasoconstriction induced by the thromboxane A_2 analogue (U-46619).[104] The structures of *AKS-186 (95)* and one of its active analogues *(96)* are shown below (Figure **13**).

Even though these compounds can be synthesised in many different ways including the addition of an appropriate Grignard reagent [63,104-109] to an *N*-substituted phthalimide followed by subsequent dehydration or directly by the reaction of *N*-substituted phthalimide with a Wittig reagent;[110,111] the photodecarboxylative addition method proposed by Griesbeck and co-workers was used as an environment friendly, efficient and clean alternative.

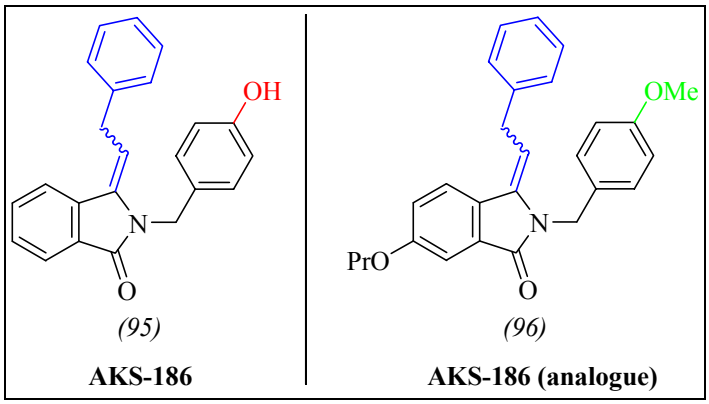


Figure 13: *AKS-186* and its analogue

Generally speaking, 3-methylene-*1H*-isoindolin-1-one-based compounds (Figure **14**) have attracted significant interest over the last years as reflected by different articles dealing with their synthesis and emphasising their pharmaceutical and medicinal activities.[112]

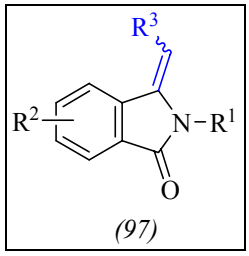
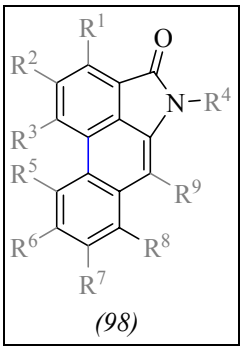


Figure 14: Main structure of 3-methylene-*1H*-isoindolin-1-one compounds

Of these the aristolactams deserve special mentioning since they possess a wide variety of biological activities. Aristolactams *(98)* are a small family of compounds, which have a phenanthrene chromophore (Scheme **15**), and are mainly found in the *Aristolochiaceae* together with the aristolochic acids and 4,5- dioxoaporphines.



(98)

Figure 15: General structure of aristolactams

2 Aims and Objectives

The photochemistry of heteroatom-substituted carboxylates is not fully understood yet. Therefore, the aims of this work were:

1. To further investigate the scope and limitations of photodecarboxylative photoadditions of various carboxylates to phthalimides.
2. To investigate Photoinduced Electron Transfer (**PET**) reactions for NR, O, S, CONH, CONR containing carboxylates.
3. To stepwise modify the heteroatom (X) and the separating carbon chain length between heteroatom and terminal carboxylates (n) (Figure **16**).

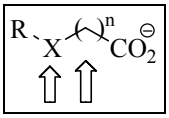


Figure 16: Proposed modifications

4. To investigate amide-linked derivatives for which contradictory mechanistic scenarios have been described for *intramolecular* cyclisations. In particular, Griesbeck assumed electron transfer from the terminal carboxylate while Yoon postulated electron transfer from the amide linker instead (Figure **17**).

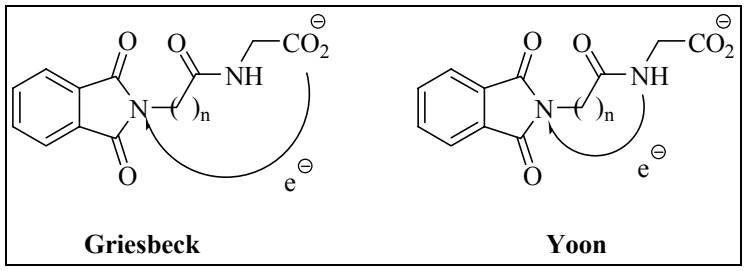


Figure 17: Electron Transfer scenario

5. To synthesis *AKS-186* and selected analogues using the photodecarboxylative addition protocol.

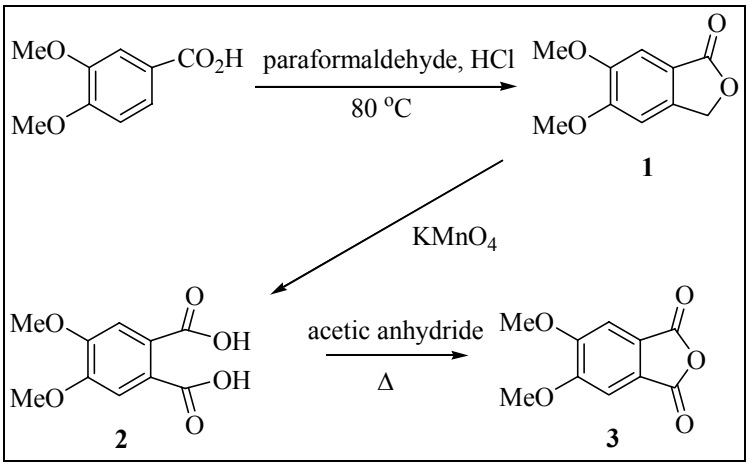
3 Results

3.1 Synthesis of starting material

3.1.1 Synthesis of phthalimides

3.1.1.1 Synthesis of 4,5-dimethoxyphthalic anhydride 3

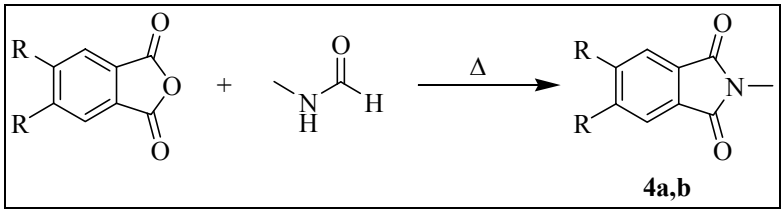
4,5-Dimethoxyphthalic anhydride **3** was synthesised from 3,4-dimethoxybenzoic acid [veratric acid] in a three step sequence following a modified procedure by Barfield and co-workers (Scheme **33**).[113] Veratric acid was converted into *m*-meconine **1** in 83% yield by condensation with paraformaldehyde. Subsequent oxidation with $KMnO_4$ furnished 4,5-dimethoxyphthalic acid **2** in a moderate yield of 22% yield. In contrast to the literature,[113] a prolonged reaction time of 1 week was, however, required. Finally, 4,5-dimethoxyphthalic anhydride **3** was obtained from **2** through treatment with acetic anhydride, which, after recrystallisation, produced **3** as long, colourless needles. The yield of 4,5-dimethoxyphthalic anhydride **3** was 95%. In $CDCl_3$, the MeO groups in compounds **3** showed a singlet at 4.03 ppm in the ^1H NMR, and a peak at 57.2 ppm in the ^{13}C NMR, respectively.



Scheme 33: Synthesis of 4,5-dimethoxyphthalic anhydride (Experiment 1)

3.1.1.2 Synthesis of N-methylphthalimide 4a and 5,6-dimethoxy-N-methylphthalimide 4b

Following a procedure described by Schindlbauer, *N*-methylphthalimide **4a** and 5,6-dimethoxy-*N*-methylphthalimide **4b** were synthesised in good yields of 61 and 75% by heating phthalic anhydride and 4,5-dimethoxyphthalic anhydride, respectively, in *N*-methylformamide (Scheme **34**, Table **4**).[114] In case of **4a**, of NMe group showed a singlet at 3.18 ppm in its ^{1}H NMR and a peak at 24.3 ppm in its ^{13}C NMR in $CDCl_3$. Likewise, the NMe group in **4b** gave a singlet at 3.14 ppm in its ^{1}H NMR and a peak at 24.3 ppm in its ^{13}C NMR in $CDCl_3$.



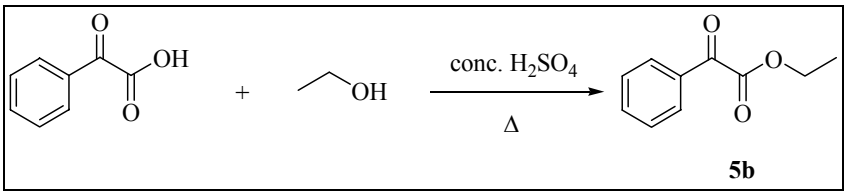
Scheme 34: Synthesis of *N*-methylated phthalimides (Experiment 2 and 3)

No.	Ref.	R	Temp [°C]	Time [h]	M.p. [°C]	Yield [%]
4a	FH-3	H	160	8	128-131	61
4b	FH-48	MeO	190	2	253-256	75

Table 4

3.1.2 Synthesis of ethyl benzoylformate 5b

Ethyl benzoylformate **5b** was synthesised from benzoylformic acid via standard esterification with ethanol and catalytic amounts of concentrated sulphuric acid (Scheme **35**). The product was obtained in 50% yield as a yellow oil. In $CDCl_3$, the ethyl group showed a triplet at 1.35 ppm and a quartet at 4.39 ppm in its ^{1}H NMR, respectively. Partial decarbonylation occurred under the reaction conditions and the ethyl ester of benzoic acid was found as a side product.

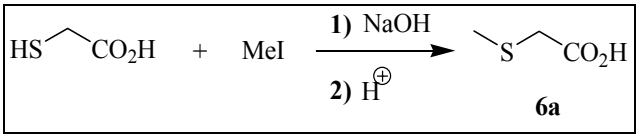


Scheme 35: Synthesis of ethyl benzoylformate (Experiment 4)

3.1.3 Synthesis of selected carboxylic acid

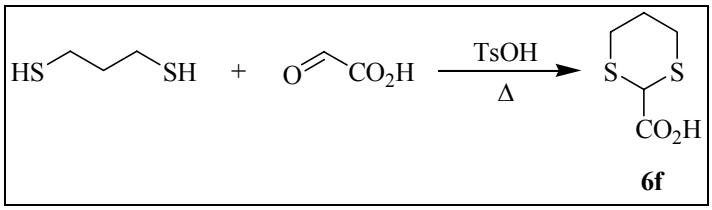
3.1.3.1 Synthesis of methylthioacetic acid 6a and 1,3-dithiane-2-carboxylic acid 6f

Thioglycolic acid was methylated with iodomethane according to a procedure reported by Larsson (Scheme **36**).[115] The desired methylthioacetic acid **6a** was isolated in 57% yield. In $CDCl_3$, the MeS group showed a singlet at 2.19 ppm in the ^1H NMR and a peak at 16.6 ppm in the ^{13}C NMR, respectively.



Scheme 36: Synthesis of methylthioacetic acid (Experiment 5)

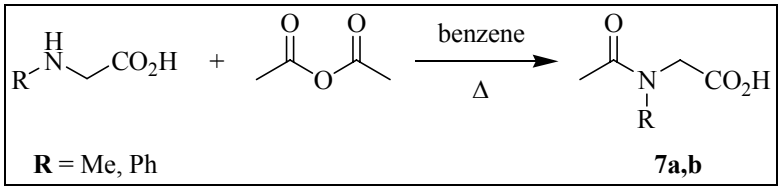
1,3-Dithiane-2-carboxylic acid **6f** was synthesised from 1,3-propanedithiol and glyoxylic acid according to Bates and Ramaswamy (Scheme **37**).[116] The acid was obtained as a colourless solid in 91% yield and gave a melting point of 92-98°C. In $CDCl_3$, the NMR spectra showed the CH group at 4.16 ppm (^1H NMR) and 39.6 ppm (^{13}C NMR), respectively. Likewise, the CO_2H group gave a singlet at 175.5 ppm in the ^{13}C NMR.



Scheme 37: Synthesis of 1,3-dithiane-2-carboxylic acid (Experiment 6)

3.1.3.2 Synthesis of N-acylated amino acids 7a-d

The α-amino acids sarcosine and *N*-phenylglycine were acylated with acetic anhydride following a procedure described by Paulmann (Scheme **38**, Table **5**).[117] 2-(*N*-Methylacetamido)acetic acid **7a** and 2-(*N*-phenylacetamido)acetic acid **7b** were obtained in yields of 39% and 27%, respectively. In the case **7a**, two different rotamers were observed in the ^{1}H NMR spectrum ($CDCl_3$). The ratio of the interconverting rotamers was determined as 2:1 (***Like:Unlike***) (Figure **18**). For **7b**, the transoid-rotamer dominated in the ^{1}H NMR. Thus, a differentiation of the rotamers could not be achieved due to the significant overlap of the signals in the NMR spectrum.



Scheme 38: Synthesis of *N*-acylated amino acids (Experiment 7 and 8)

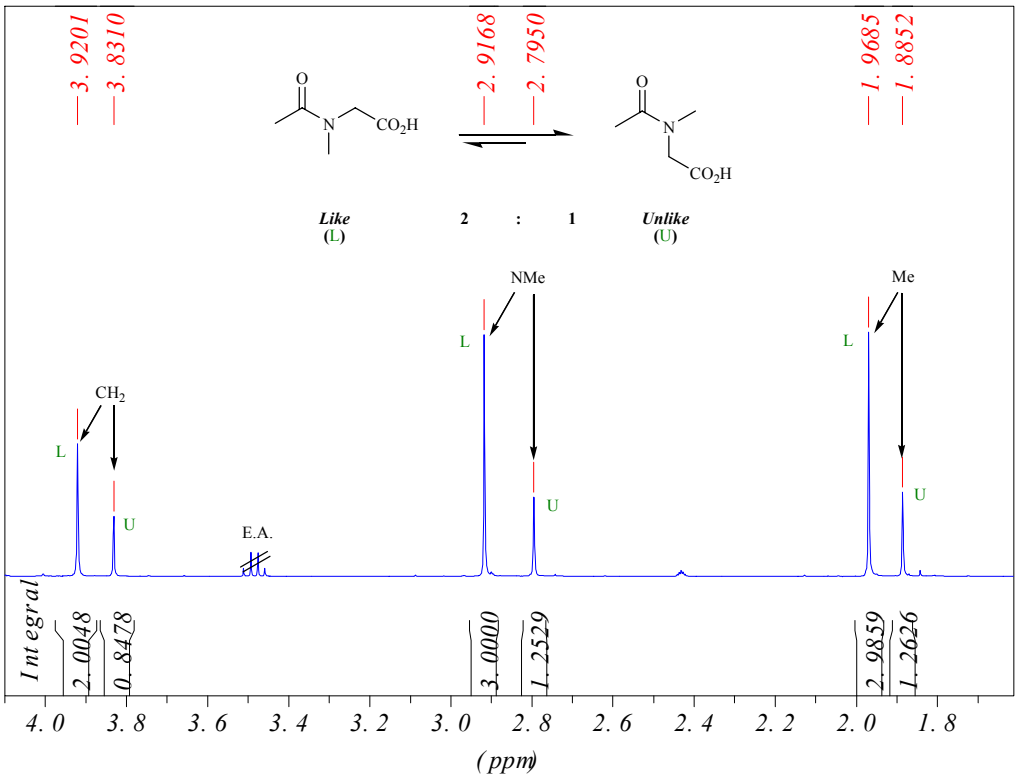
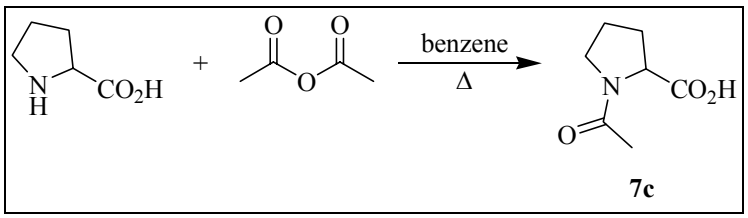


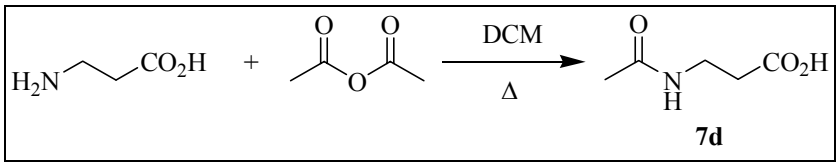
Figure 18: ^{1}H NMR spectrum of ***Unlike***- and ***Like*-7a** in $CDCl_3$

Likewise, racemic proline was acylated with acetic anhydride to yield 1-acetyl-pyrrolidine-2-carboxylic acid **7c** in 96% yield (Scheme **39**).[117] The methyl group showed a singlet at 2.17 ppm in the ^{1}H NMR spectrum and a singlet at 22.5 ppm in the ^{13}C NMR (both values in $CDCl_3$), respectively. In this case the complete assignment of the rotamers was not possible due to the signal broadening and overlap in the ^{1}H NMR. Based on the separated singlets of the COMe groups the rotamer ratio was determined as 3:2 in favour of ***Like*-7c**.



Scheme 39: Formation of 1-acetylpyrrolidine-2-carboxylic acid (Experiment 9)

3-Acetamido propanoic acid **7d** was prepared in a similar manner from *β*-alanine and acetic anhydride (Scheme **40**).[117] The product was isolated as a colourless solid in 97% yield. The acetyl group gave a singlet at 2.00 ppm in its ^{1}H NMR spectrum, while the free NH group showed a broad singlet at 6.43 ppm (both values in $CDCl_3$).



Scheme 40: Synthesis of 3-acetamido propanoic acid (Experiment 10)

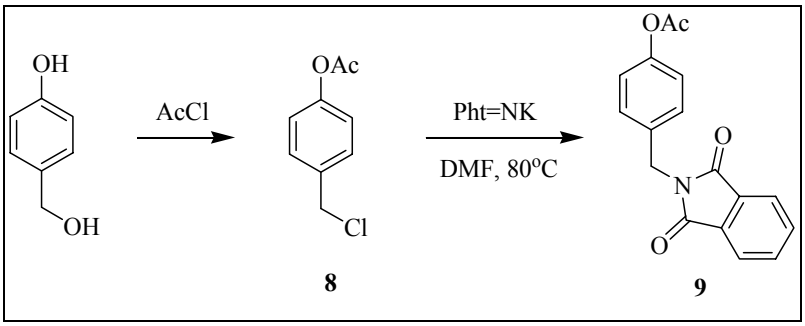
No.	Ref.	Amino Acid	M.p. [°C]	^{1}H-NMR[a)] [ppm]	Yield [%]
7a	FH-70	Sarc	129-131	2.17	39
7b	FH-71	*N*-Ph-Gly	189-191	1.92	27
7c	FH-72	*rac*-Pro	60-65	2.17	96
7d	FH-75	*β*-Ala	52-55	2.00	97

[a)] Signal of the acetyl group $CDCl_3$

Table 5

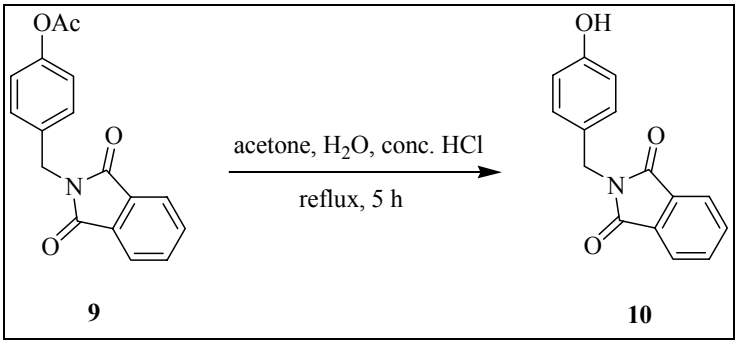
3.1.4 Synthesis of 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9 and 2-(4-hydroxybenzyl)isoindoline-1,3-dione 10

Synthesis of 2-(4-acetoxybenzyl)isoindoline-1,3-dione **9** was achieved from 4-hydroxybenzyl alcohol in two steps following a procedure by Johansson (Scheme **41**).[118] Treatment of 4-hydroxy-benzyl alcohol with acetyl chloride at room temperature gave 4-(chloromethyl)phenyl acetate **8** in an excellent yield of 84% as a pale yellow oil. Subsequent phthalimidation of **8** was achieved using potassium phthalimide and DMF. The desired product 2-(4-acetoxybenzyl)isoindoline-1,3-dione **9** was obtained in a good yield of 71% as a colourless solid. In $CDCl_3$, the OAc group of **9** showed a singlet at 2.27 ppm in the ^{1}H NMR, and a peak at 21.4 ppm in the ^{13}C NMR, respectively.



Scheme 41: Synthesis of 2-(4-acetoxybenzyl)isoindoline-1,3-dione (Experiment 11)

Following a procedure by Griesbeck *et al.*, hydrolysis of **9** in a refluxing mixture of acetone, H_2O and conc. HCl (40:28:12) furnished 2-(4-hydroxybenzyl)isoindoline-1,3-dione **10** in a yield of 95% as a colourless powder (Scheme **42**).[78]



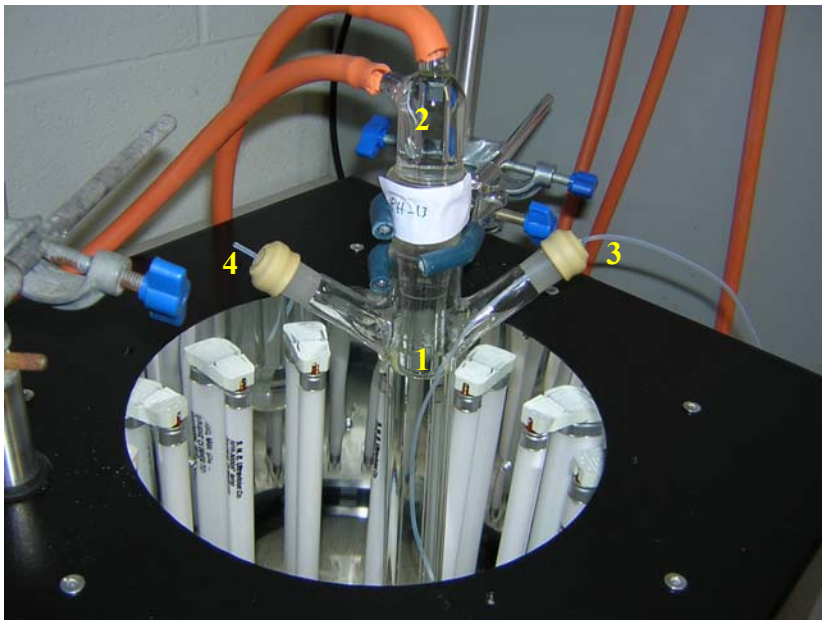
Scheme 42: Synthesis of 2-(4-hydroxybenzyl)isoindoline-1,3-dione (Experiment 12)

3.2 Photoreactions

3.2.1 Photochemical set-up

For the irradiation experiments a Rayonet photochemical chamber reactor fitted with 16 RPR-3000Å lamps ($\lambda = 300 \pm 25$ nm) and Pyrex tubes ($\lambda \geq 300$ nm) were used (Picture **2**). The reaction mixture was constantly purged with a slow stream of N_2 and the leaving gas stream was allowed to exit through a short Teflon tube. To avoid overheating, a cold finger was used (**T** < 25 °C). The reaction process was monitored

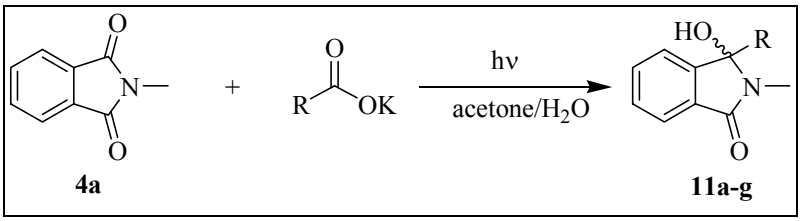
by TLC analysis or by passing the leaving nitrogen stream into a saturated barium hydroxide solution until precipitation of barium carbonate has ceased.



Picture 2: Rayonet photoreactor and experimental set-up (**1:** Pyrex reaction tube, **2:** cold finger, **3:** N_2 inlet, **4:** gas outlet)

3.2.2 Photoreactions of *N*-methylphthalimide 4a with alkyl-carboxylates

In a first series of experiments, *N*-methylphthalimide **4a** was selected as a model substrate. Upon irradiation in aqueous acetone for 3-6 h and in the presence of 3 equivalents of various potassium alkyl carboxylates, the corresponding hydroxy-phthalimidines **11a-d** were obtained in moderate to good yields of 21-78% (Scheme **43**, Table **6**). An excess amount of carboxylate was required in order to drive the reaction to high conversion. For all compounds, the C-OH group gave a characteristic singlet between 90 and 95 ppm in the ^{13}C NMR spectrum.



Scheme 43: Photoreactions with alkyl carboxylates (Experiment 13-19)

No.	Ref.	R	Time [h]	Conv.[a)] [%]	^{13}C-NMR[b)] [ppm]	Yield [%]
11a	FH-34	Et	6	75	91.7	60 (76[c)])
11b	FH-47	*t*-Bu	3	97	95.2	68 (70[c)])
11c	FH-43	Allyl	5	100	90.0	26
11d	FH-10	Bn	3	100	90.9	78
11e	FH-100	$PhCH_2CH_2$	5	100	90.7	67
11f	FH-101	$PhCH_2CH_2CH_2$	5	100	90.8	21
11g	FH-106	*p*-$HOC_6H_4CH_2$	6	70	91.4	67 (96[c)])

[a)] Conversion determined by ^{1}H-NMR, b) Signal of the C-OH group in $CDCl_3$, c) Yield based on conversion

Table 6

The ^{1}H-NMR spectrum of compound **11c** in $CDCl_3$ is exemplarily shown in Figure **19**. The NMe group showed a sharp singlet at 2.73 ppm. The CH_2 group was assigned to two doublets of doublets at 2.72 and 2.90 ppm while OH group was spotted as a singlet at 4.01 ppm. The olefinic protons were found at 4.88, 4.95 and 5.15 ppm, and the aromatic protons between 7.37 and 7.55 ppm, respectively.

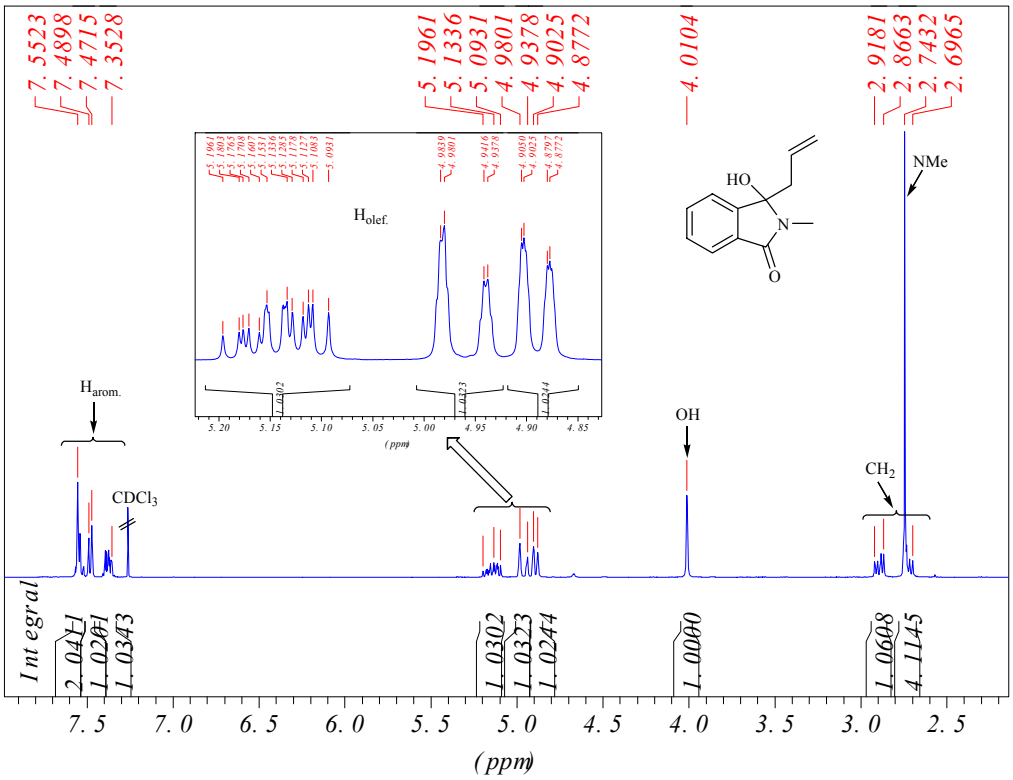


Figure 19: Representative ^{1}H-NMR spectrum of **11c** in $CDCl_3$

The structure of product **11e** was confirmed by X-ray structure analysis (Figure **20**). Remarkably, 2 molecules of the same enantiomeric form of **11e** form dimers, which are connected by hydrogen bonding. A pair with the configuration *S* is depicted in Figure **20**. The same number of *S*, *S* and *R*, *R* dimers are found in the crystal. Hence, the compound crystallised as racemate and not as a colgomerate.

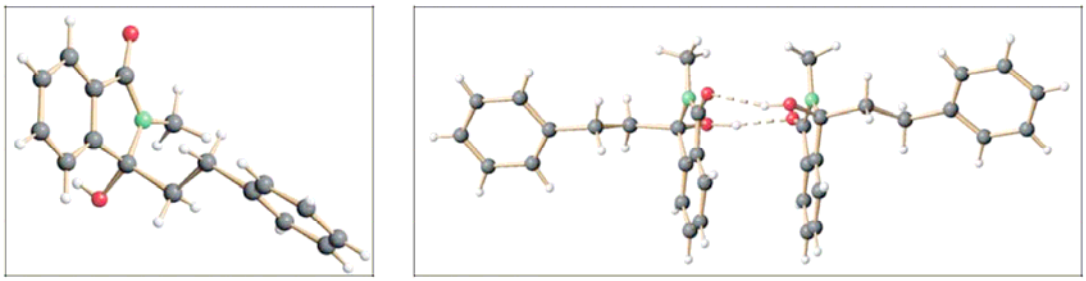
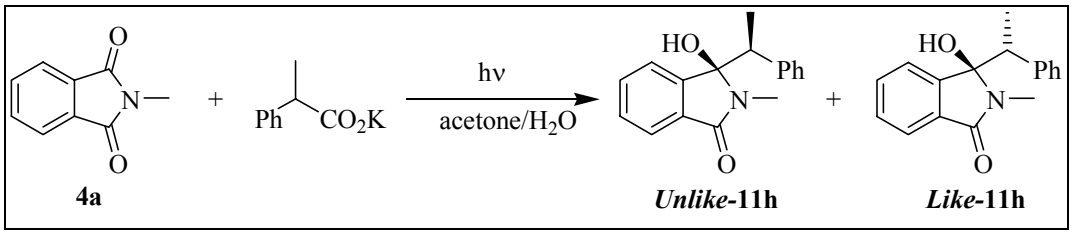


Figure 20: X-ray of **11e**

A special case was the irradiation of 2-phenylpropanoic acid with *N*-methylphthalimide **4a** and a diastereoisomeric mixture of ***Unlike-*** and ***Like*-11h** (with respect to the methyl group) was obtained in 90% yield after just 2 h of irradiation (Scheme **44**). The diastereoisomeric ratio was determined for the crude product by integration of baseline-separated signals in the ^{1}H NMR and was found to be 1:1.6 in favour of the ***Like***-diastereoisomer.

Pure fractions of the diastereoisomers were obtained by column chromatography and suitable crystals for X-ray analysis were obtained by recrystallisation. Interestingly, both compounds from dimers via hydrogen bonding (Figure **21**). In contrast to **11e** these are formed between different enatiomeric forms.



Scheme 44: Photoreaction with 2-phenylpropanoic acid (Experiment 20)

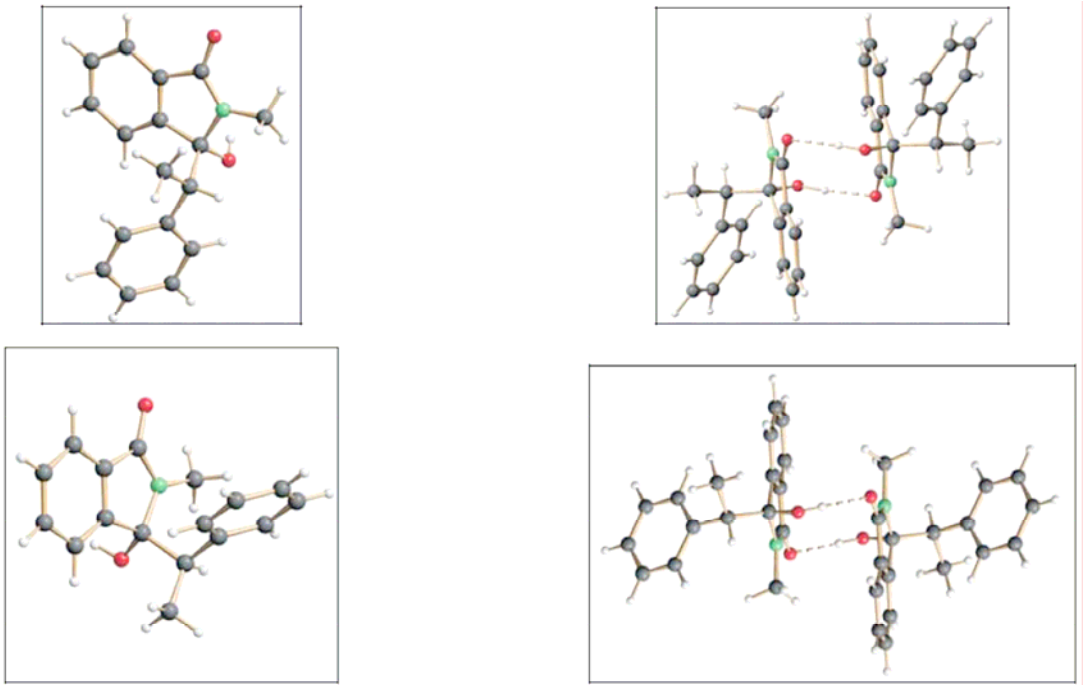


Figure 21: X-ray of ***Unlike-*** (top) and ***Like*-11h** (bottom)

The diastereoisomers could be assigned to the corresponding NMR spectra (Figure **22**). In the ^{1}H NMR recorded in deuterated acetone, the Me-substituent was found at 1.03 ppm for ***Unlike*-11h** and at 1.65 ppm for ***Like*-11h**, respectively.

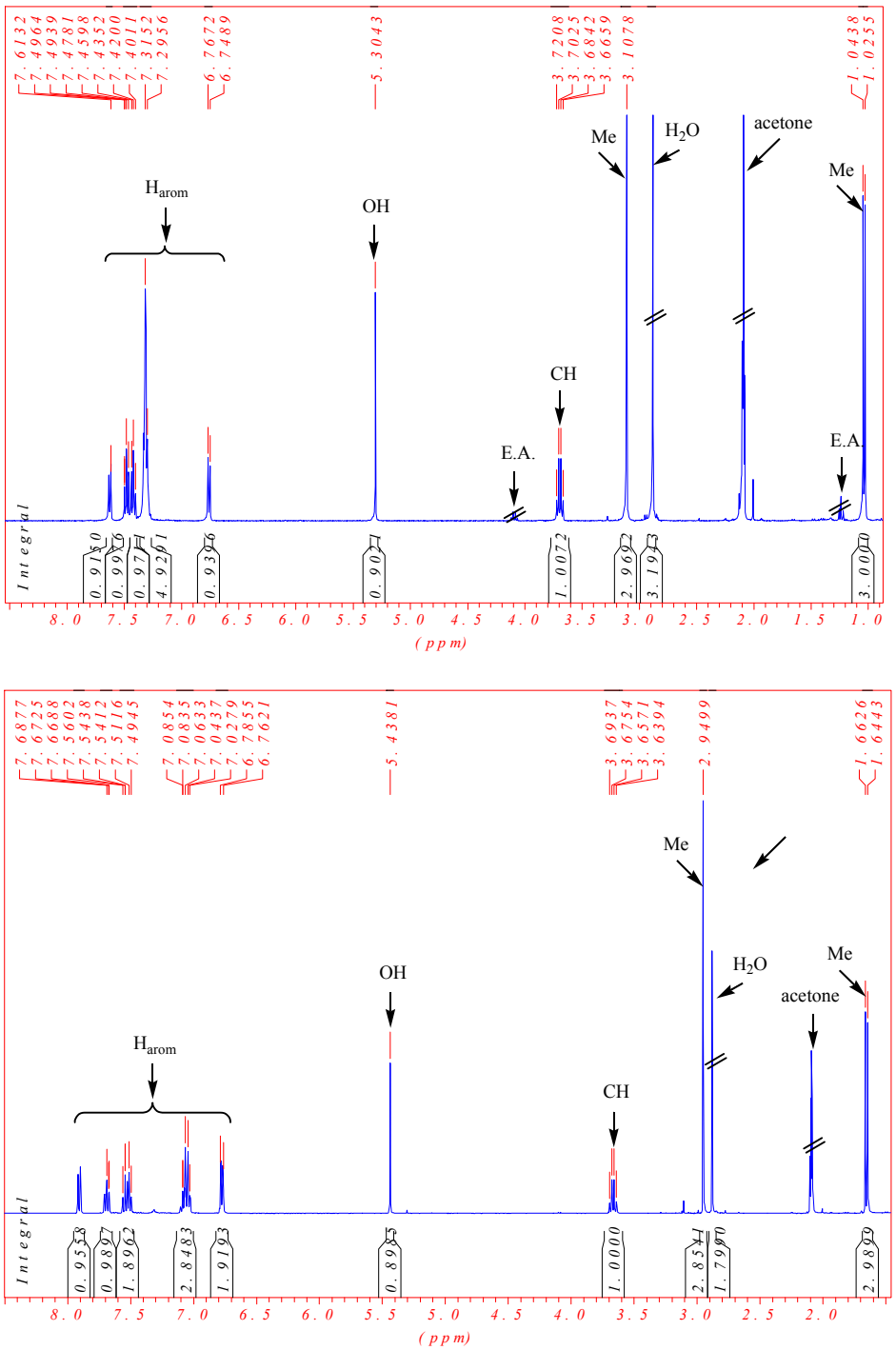
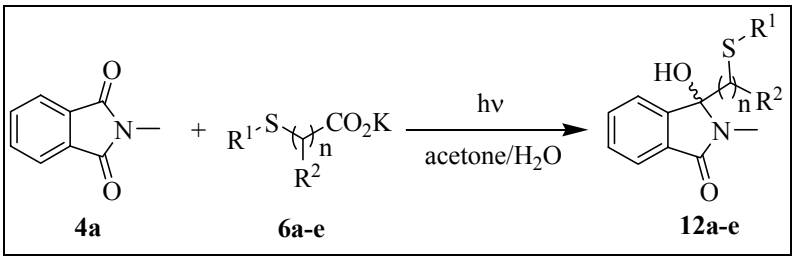


Figure 22: ^{1}H-NMR spectra of ***Unlike*-** (left) and ***Like*-11h** (right) in acetone-d_6

3.2.3 Photoreactions of *N*-methylphthalimides 4a and 5,6-dimethoxy-*N*-methylphthalimide 4b with heteroatom substituted carboxylates

3.2.3.1 With sulphur-containing carboxylates

The sulphur-containing carboxylates **6a-e** readily underwent photoaddition to *N*-methylphthalimide **4a** and furnished the corresponding addition products **12a-e** in moderate to excellent yields of 34-95% (Scheme **45**, Table **7**). In case of **12b** a diastereoisomeric mixture was obtained. The diastereoisomeric ratio was calculated from the ^{1}H-NMR spectrum of the crude product as 4:3 in favour of the ***Unlike***-isomer. The assignment of the diastereoisomers was achieved in comparison with literature data.[78] When the linker between the sulphur atom and the carboxylate group was extended to 2-carbons as in **6e**, no reaction occurred, even after prolonged photolysis, and *N*-methylphthalimide **4a** was reisolated.



Scheme 45: Photoreactions with **S**-containing carboxylates (Experiments 21-25)

No.	Ref.	R^1	R^2	n	Time [h]	Conv.[a] [%]	^{13}C-NMR[b] [ppm]	Yield [%]
12a	FH-180	Me	H	1	2	100	90.7	90
12b	FH-112	Me	Me	1	6	100	93.4 / 93.5	95[c]
12c	FH-15	Ph	H	1	5	84	90.6	57 (68[d])
12d	FH-21	Bn	H	1	4.5	n.d.[e]	90.2	34
12e	FH-24	Ph	H	2	43	n.r.[f]	—	(100[g])

[a] Conversion determined by ^{1}H-NMR, [b] Signal of the C-OH group in $CDCl_3$, [c] Mixture of diastereoisomers, [d] Yields based on conversion, [e] Not determined, [f] No reaction, [g] Reisolated **4a**

Table 7

A representative ^{1}H-NMR spectrum of the photoaddition product **12a** is shown in Figure **23**. The most significant signals are the doublets at 3.06 and 3.17 ppm, respectively, which represent the CH_2 group between the newly formed C-OH and the thiomethyl group. The OH peak is present at 4.12 ppm as a singlet. Likewise, the NMe- and SMe- groups show sharp singlets at 2.75 and 1.77 ppm, respectively. The aromatic protons are found between 7.39 and 7.66 ppm.

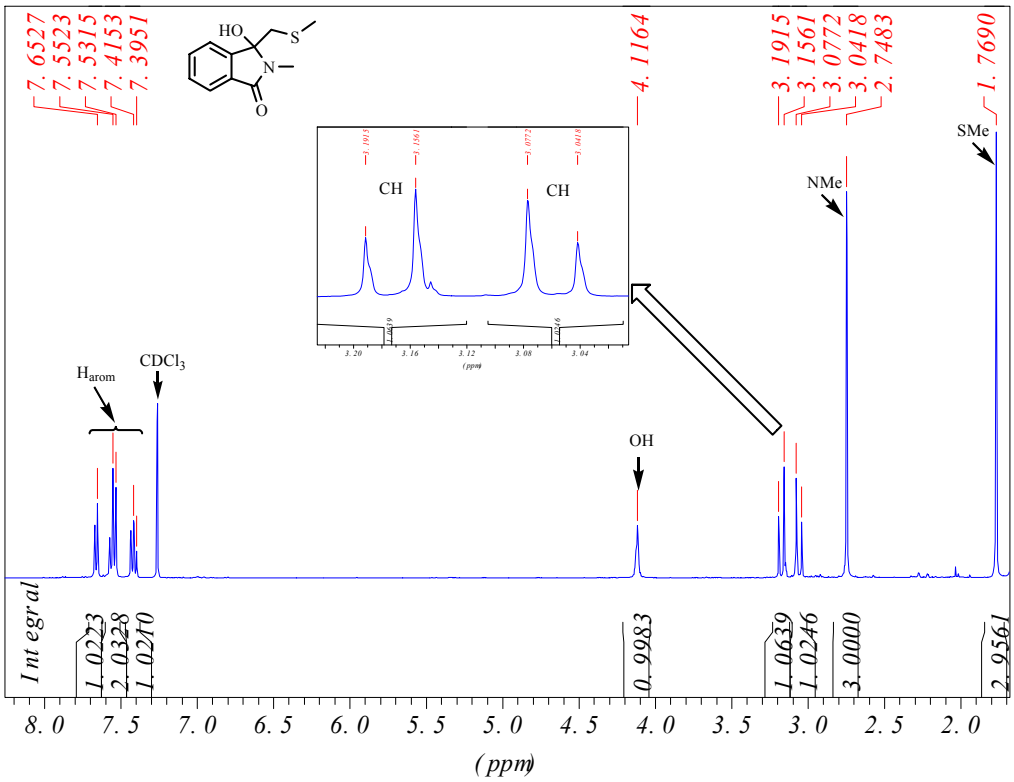
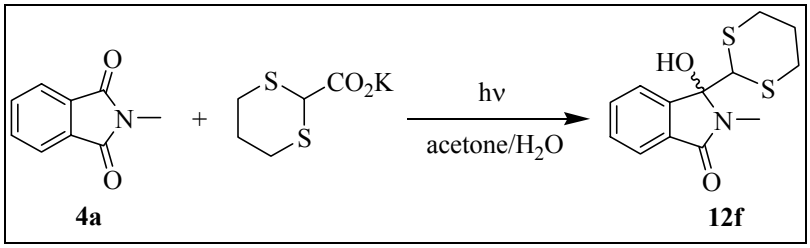


Figure 23: Representative ^{1}H-NMR spectrum of **12a** in $CDCl_3$

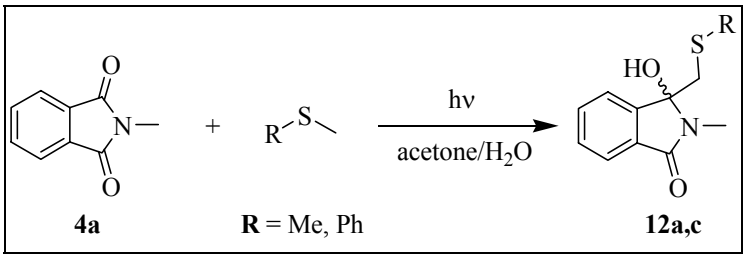
Likewise, the carboxylate of 1,3-dithiane-2-carboxylic acid **6f** gave the corresponding addition product **12f** in 72% yield after just 1 h (Scheme **46**). The yield based on conversion was calculated as 82%. In $CDCl_3$, the quaternary C-OH carbon was found at 90.9 ppm in the ^{13}C-NMR spectrum.



Scheme 46: Photoreaction with 1,3-dithiane-2-carboxylic acid (Experiment 26)

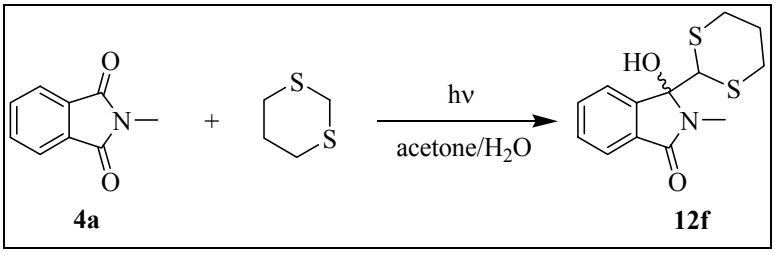
For comparison, *N*-methylphthalimide **4a** was irradiated in the presence of dimethylsulphide and thioanisole (Scheme **47**). In contrast to the corresponding carboxylates **6a** and **c**, the reaction proceeded significantly slower and the addition products **12a**

and **c** were isolated in yields of 69 and 17% after 2 and 4 h of irradiation. In both cases, high conversion ratios of 92 and 84% were determined. However, the unpleasant stench of the thioethers in general and the high volatility of dimethylsulphide in particular proved problematic.



Scheme 47: Photoreactions with dimethylsulphide and thioanisole (Experiments 27 and 28)

Likewise, the reaction of *N*-methylphthalimide **4a** with 1,3-dithiane gave the corresponding addition product **12f** in 12% yield after 15 h of irradiation (Scheme **48**).

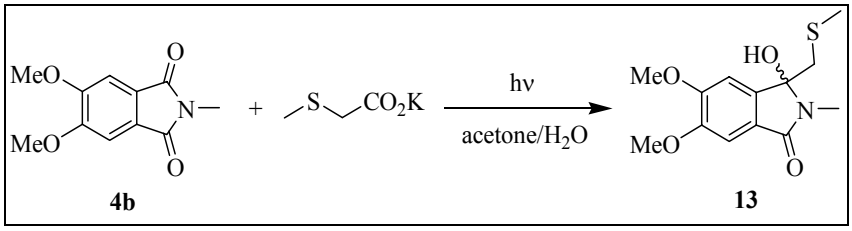


Scheme 48: Photoreaction with 1,3-dithiane (Experiment 29)

To further broaden the product diversity, 5,6-dimethoxy-*N*-methylphthalimide **4b** was irradiated in the presence of carboxylates **6a** (Scheme **49**). The corresponding addition product **13** was obtained in 38% yield. After 14 h of irradiation, the conversion was determined as 52%.

The ^{1}H-NMR spectrum of **13** in $CDCl_3$ is shown in Figure **24**. The most characteristic signals are the doublets at 2.98 ppm and 3.13 ppm, respectively, which represent the CH_2 group between the newly formed C-OH and the thiomethyl group, respectively. The singlet peak present at 3.11 ppm is attributed to the OH moiety, the

two MeO peaks are found at 3.80 and 3.95 ppm, whereas the sharp singlets at 2.79 ppm and 1.82 ppm are assigned to the NMe- and SMe- groups respectively. The aromatic protons are found as singlets at 6.77 and 7.13 ppm.



Scheme 49: Photoreaction of dimethoxyphthalimide with potassium-2-(methylthio) acetate (Experiment 30)

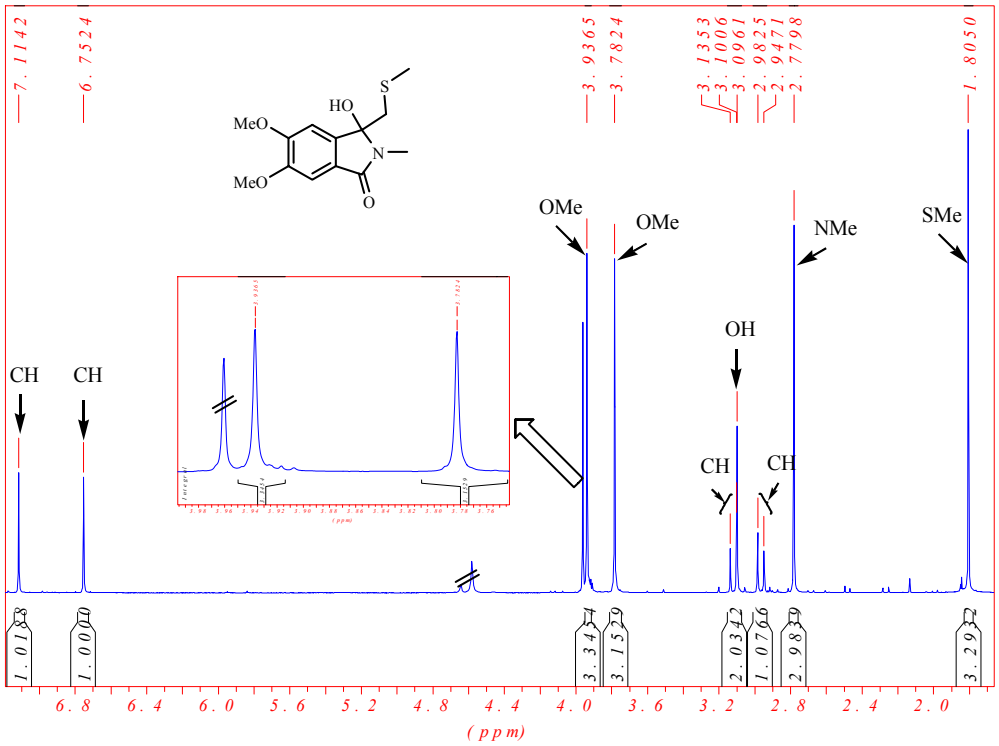
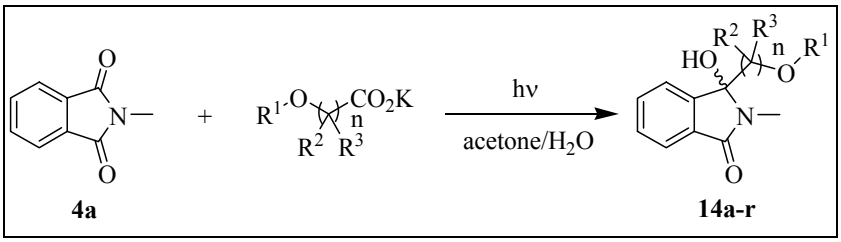


Figure 24: Representative ^{1}H-NMR spectrum of **13**in $CDCl_3$

3.2.3.2 With oxygen-containing carboxylates

A series of different oxygen-containing carboxylates was irradiated in the presence of *N*-methylphthalimide **4a** in aqueous acetone (Scheme **50**, Table **8**). The α-oxo-alkyl-substituted carboxylates readily gave the corresponding addition products **14a-o** and **14r** in moderate to excellent yields of 21-94%. In contrast, the β-oxoalkyl carboxylates **14p** and **14q** reacted significantly slower and the corresponding addition products were obtained after prolonged irradiation in yields of 8 and 26%, respectively.



Scheme 50: Photoreactions with **O**-containing carboxylates (Experiment 31-48)

The ^{1}H-NMR spectrum of compound **14b** is exemplarity shown in Figure **25**. The hydrogens on the methylene bridge between the newly formed C-OH group and the phenoxy moiety gave a pair of doublet peaks at 4.24 and 4.36 ppm, respectively. The OH peak is present as a broad singlet at 4.30 ppm in between these two doublet peaks, while the NMe singlet is observed at 2.84 ppm. The aromatic protons are present as a set of signals between 6.77 and 7.66 ppm.

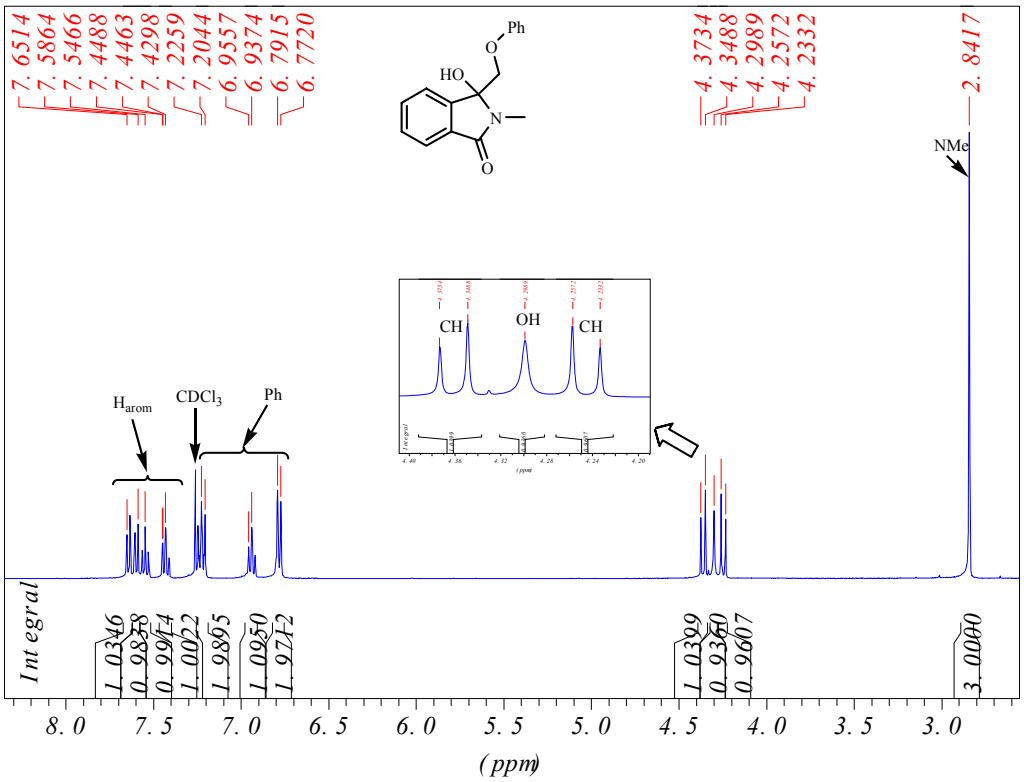


Figure 25: Representative ^{1}H-NMR spectrum of **14b** in $CDCl_3$

The photoreactions involving branched carboxylates furnished diastereoisomeric product mixtures **14k-m** and **14r**. The ^{1}H-NMR of **14k** is depicted in Figure **26** as an example. Two sets of signals are observed which were assigned to the two diastereoisomers. The diastereoisomeric ratio was determined by integration of baseline separated signals in the ^{1}H-NMR and was determined as 46:54. Selectivities were low for compounds **14k-m** with 6%, for **14r** a higher ***d.e.*** of 28% was found. An assignment of the diastereoisomers was not made.

No.	Ref.	R^1	R^2	R^3	n	Time [h]	Conv.[a] [%]	^{13}C-NMR[b] [ppm]	Yield [%]
14a	FH-13	Et	H	H	1	3.5	95	88.8	77 (81[c])
14b	FH-19	Ph	H	H	1	1.5	100	88.9	85
14c	FH-20	Bn	H	H	1	5	100	89.1	38
14d	FH-57		H	H	1	4	n.d.[d]	88.8	48
14e	FH-65		H	H	1	10	29	89.2	21 (72[c])
14f	FH-175		H	H	1	1	100	89.4	93
14g	FH-58		H	H	1	11	61	88.5	53 (87[c])
14h	FH-69		H	H	1	1	100	88.6	71
14i	FH-64		H	H	1	1	90.9	89.2/89.3[e]	55 (61[c])
14j	FH-62		H	H	1	3	87	88.6	51 (64[c])
14k	FH-109	Ph	Me	H	1	2	n.d.[d]	91.6/91.8[f]	87
14l	FH-59		Me	H	1	11	99	91.2/91.3[f]	61 (62[c])
14m	FH-63		Me	H	1	1	100	91.5/91.6[f]	80
14n	FH-16	Me	Me	Me	1	3.5	100	94.0	94
14o	FH-30		Me	Me	1	2	n.d.[d]	93.9	51
14p	FH-22	Me	H	H	2	16	89	89.4	8 (9[c])
14q	FH-23	Ph	H	H	2	16	96	89.7	26 (27[c])
14r	FH-66			H	1	1	n.d.[d]	88.6/89.4[f]	83

[a] Conversion determined by ^{1}H-NMR, [b] Signal of the C-OH group in $CDCl_3$, [c] Yields based on conversion, [d] Not determined, [e] Contains 30% of **14f**, [f] minor/Major product.

Table 8

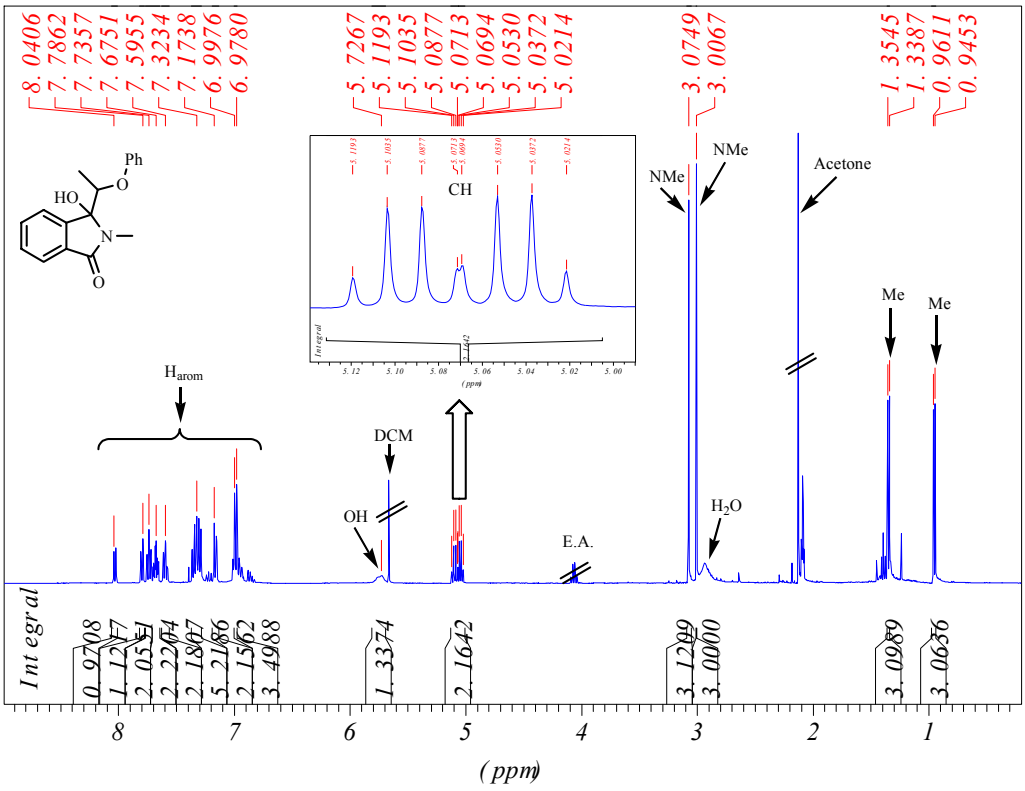


Figure 26: Representative ^{1}H-NMR spectrum of **14k** in acetone-d_6

The photoreaction involving 2-(4-chloro-2-methylphenoxy) acetate with *N*-methyl-phthalimide **4a** surprisingly gave a mixture of the desired compound **14i** and a second, minor product in 30%. Both, the ^{1}H and ^{13}C NMR gave two complete sets of signals, although overlap within the ^{1}H NMR made a complete assignment difficult as depicted in Figure **27**. The purity of the corresponding carboxylic acid was confirmed by NMR spectroscopy and therefore the by-product must have been formed during photolysis. Based on the ^{1}H NMR spectrum, in particular the aromatic region, it was assumed that partial dehalogenation (-Cl ↔ -H exchange) had occurred. Hence, compound **14f** was independently synthesised and a mixed NMR was recorded. Following this strategy, the pair of doublets for the methylene bridge from the impurity increased in height, thus proving that it was indeed identical with **14f**.

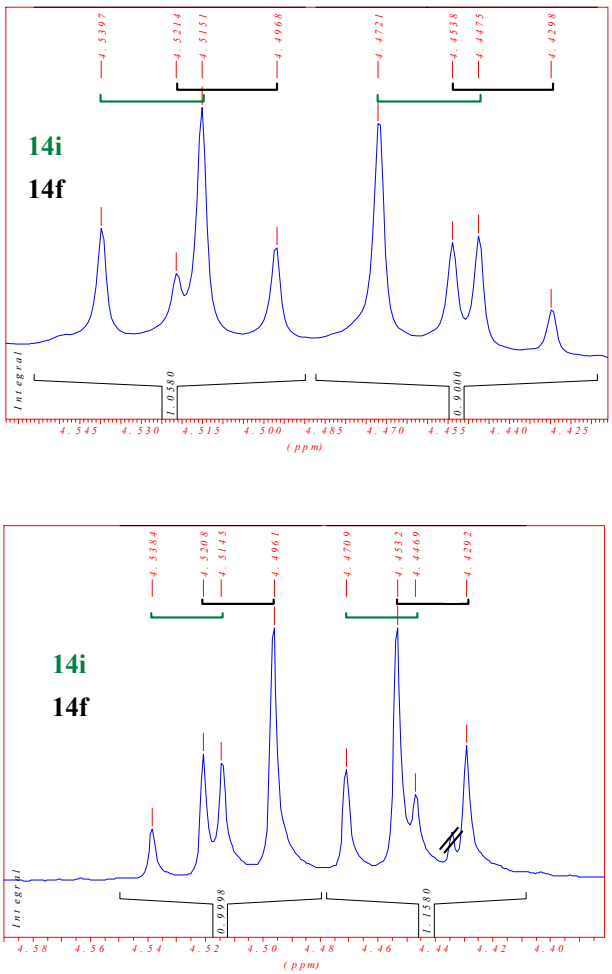
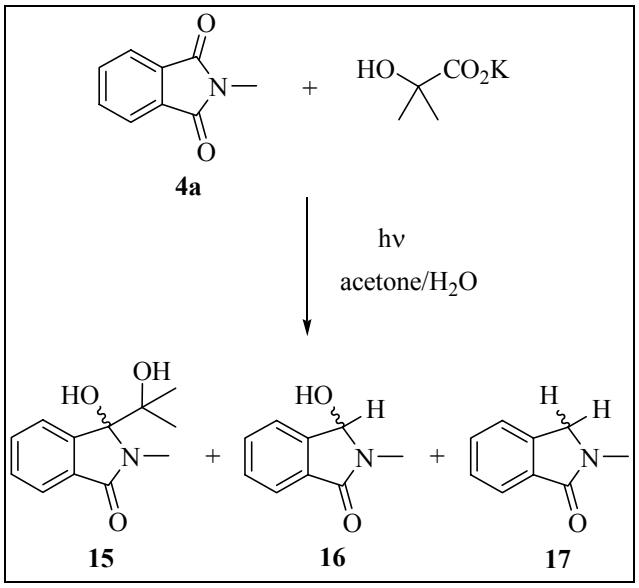


Figure 27: ^{1}H-NMR comparison: a) original mixture (*top*) and b) after addition of **14f** (*bottom*).

In contrast to the ether-linked carboxylates, the irradiation of *N*-methylphthalimide **4a** with 2-hydroxy-2-methylpropionate was less selective and resulted in the isolation of a complex mixture. Besides the desired addition product **15**, the photo-reduction products **16** and **17** were obtained (Scheme **51**). The composition of the crude product was determined from the ^{1}H-NMR by integration of baseline separated signals and was found to be 22:67:11 (**15**:**16**:**17**).

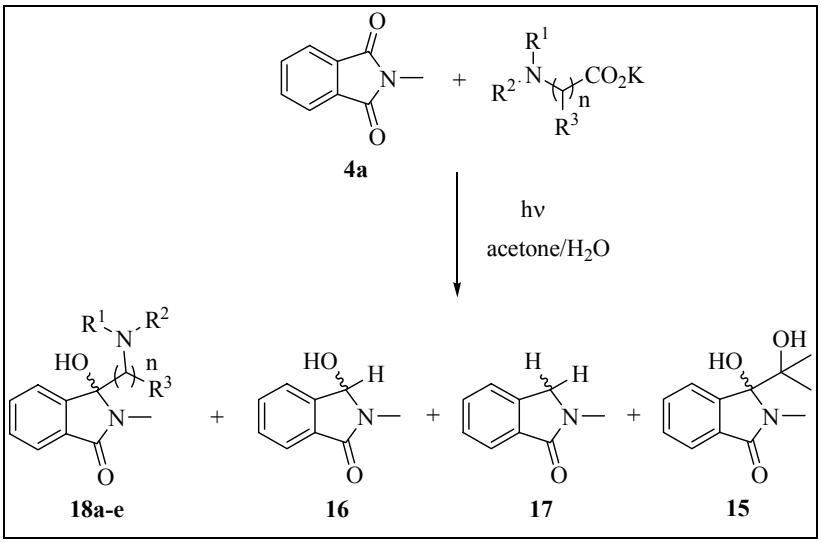


Scheme 51: Irradiation of **NMP** in the presence of 2-hydroxy-2-methylpropionate (Experiment 49)

3.2.3.3 With nitrogen-containing carboxylates

Due to the low oxidation potentials of tertiary amines (R_3N: $E_{Ox.}$ = 0.7-1.3 vs. SCE[32]), PET reactions of amines and phthalimides are highly exergonic.[76] Additionally, amines are potent hydrogen donors and consequently photoreductions are commonly observed as side reactions.[119, 46]

A series of nitrogen-containing carboxylates was irradiated at 300 nm in aqueous acetone and in the presence of *N*-methylphthalimide **4a**. In all cases involving *N*-bis-alkylated amino acids, solely photoreduction to **16** and **17**, and acetone trapping to **15** was observed (Scheme **52**, Table **9**). The product ratios varied after purification and especially the amount of **16** decreased. This indicates that most of **16** remained on silica gel. By comparison of the product ratios prior and after purification an elution order of **17** > **15** > **16** was established.



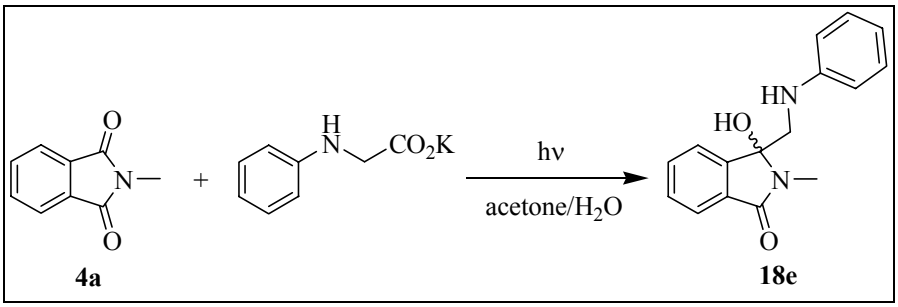
Scheme 52: Photoreactions with **N**-containing carboxylates (Experiments 50-54)

No.	Ref.	R^1	R^2	R^3	n	Time [h]	Conv.[a] [%]	Composition/Yields [%]			
								18	**15**	**16**	**17**
18a	FH-67	Me	Me	H	1	1	100	—	37 (48[b])	34 (4[b])	29 (48[b])
18b	FH-29	Me	Me	Bn	1	3	67	—	53 (63[b])	32 (0[b])	15 (37[b])
18c	FH-68	Me	Me	H	2	1	67	—	39 (29[b])	29 (0[b])	32 (71[b])
18d	FH-28	$(CH_2)_5$		H	2	1	84	—	68 (66[b])	23 (10[b])	9 (24[b])
18e	JF-16	Ph	H	H	1	4	n.d.[c]	30[b]	n.d.[c]	n.d.[c]	n.d.[c]

[a] Conversion determined by ^{1}H-NMR, [b] Isolated yield, [c] Not determined.

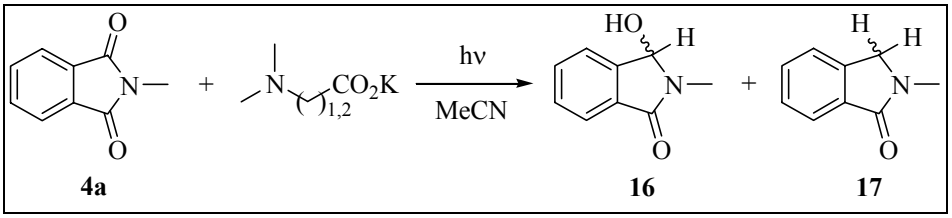
Table 9

The desired photoaddition product could only be isolated when *N*-phenyl glycine was used as starting material (Scheme **53**). The reaction remained sluggish, but the addition product **18e** was isolated in a yield of 30% after column chromatography.



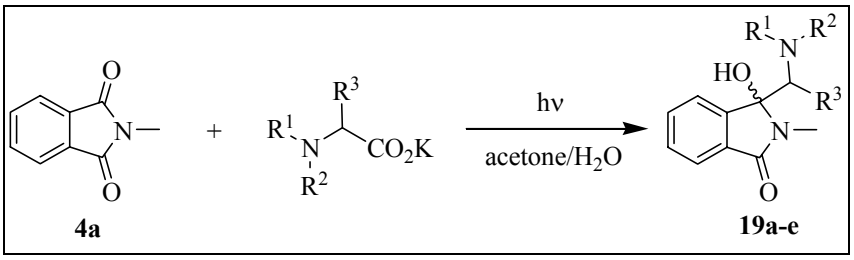
Scheme 53: Photoreaction with *N*-phenyl glycine (Experiment 54)

In order to study the influence of the co-solvent water on the photoreaction, two specific reactions involving 2-(dimethylamino)acetic acid and 3-(dimethylamino) propionic acid were carried out using acetonitrile as solvent. Again, no photo-addition product could be detected and the photoreduction products **16** and **17** dominated instead (Scheme **54**).



Scheme 54: Photoreactions with 2-(dimethylamino)acetic acid and 3-(dimethyl amino) propanoic acid (Experiments 55 and 56)

Likewise, a set of *N*-protected amino acid salts was irradiated under the conditions of the photodecarboxylative addition (Scheme **55**, Table **10**). In contrast to their *N*-alkylated counterparts, all experiments proceeded readily and the corresponding products **19a-e** were collected in good to excellent yields of 71-97% after just 1-3 h.



Scheme 55: Photoreactions with *N*-protected amino acid salts (Experiments 57-61)

No.	Ref.	R^1	R^2	R^3	Time [h]	Conv.[a)] [%]	^{13}C-NMR[b)] [ppm]	Yield [%]
19a	FH-41	Ac	H	H	2	95	89.6	71
19b	FH-73	Ac	Me	H	1	100	90.0	73
19c	FH-74	Ac	Ph	H	1	100	90.0	97
19d	FH-78	Ac	$(CH_2)_3$		1	100	92.2/92.6[c)]	76
19e	FH-44	Boc	H	H	3	100	89.9	74

[a)] Conversion determined by ^{1}H-NMR, [b)] Signal of the C-OH group in $CDCl_3$, [c)] Major/minor product.

Table 10

A representative ^{1}H-NMR spectrum is shown in Figure **28** for **19c**. A pair of doublets at 4.18 and 4.66 ppm represents the two non-equivalent methylene protons. The OH signal is observed at 4.51 ppm as a broad singlet peak, whereas the NMe-group is found at 2.57 ppm. The COMe group is present as a singlet at 1.63 ppm. The aromatic protons appear as a set of signals between 6.68 and 7.57 ppm.

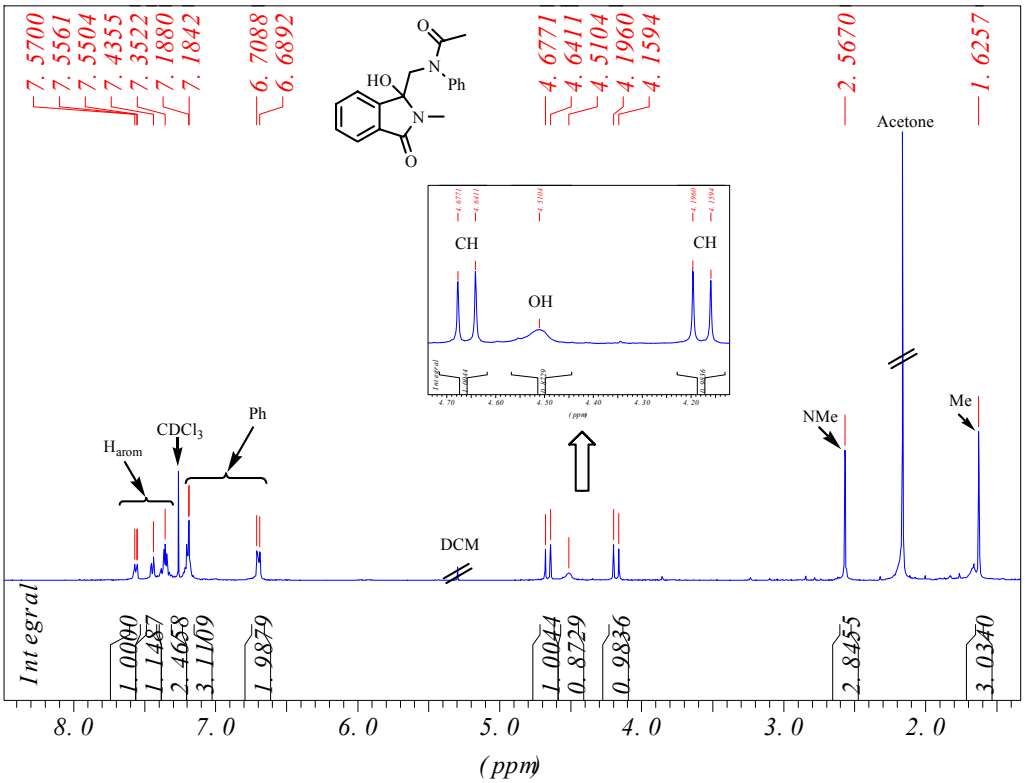


Figure 28: Representative ^{1}H-NMR spectrum of **19c** in $CDCl_3$

The irradiation involving the proline derivative **7c** gave a mixture of diastereoisomers **19d**. A diastereoisomeric ratio of 3:1 was determined although no assignment has been achieved so far. The ^{1}H-NMR spectrum of the isolated mixture is depicted in Figure **29**.

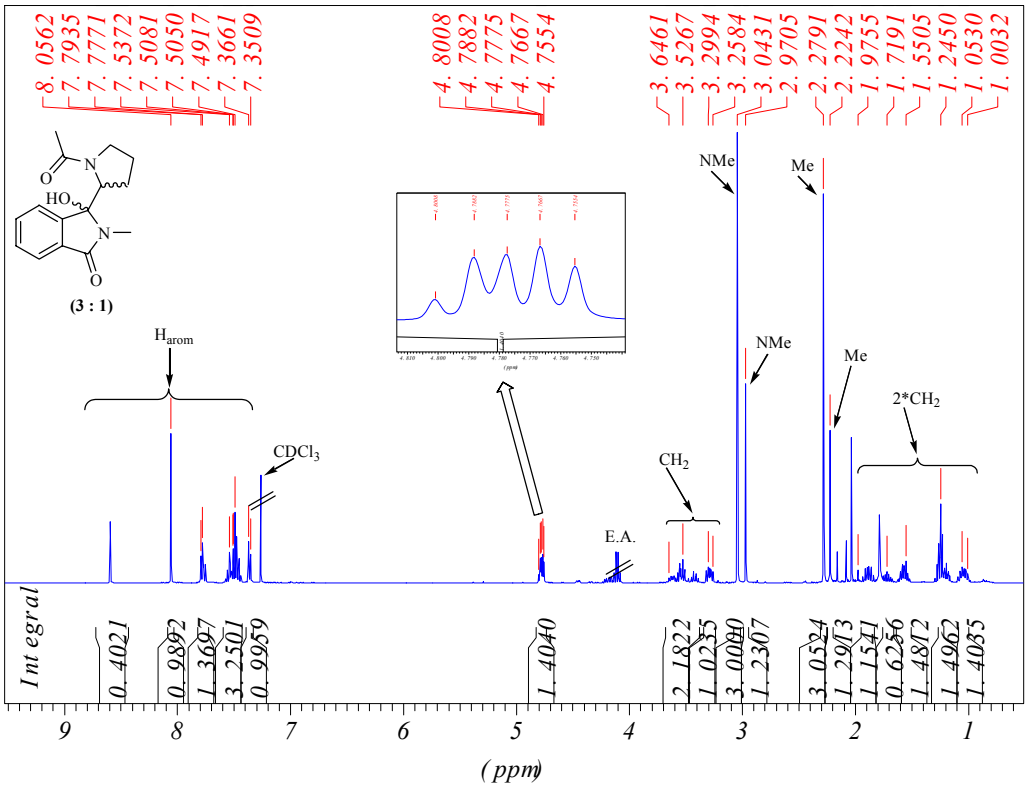
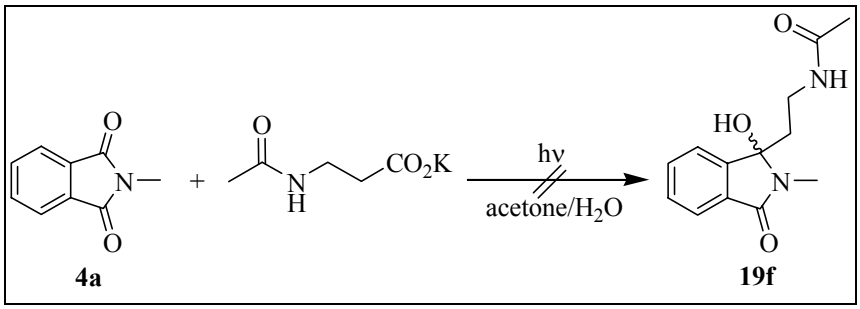


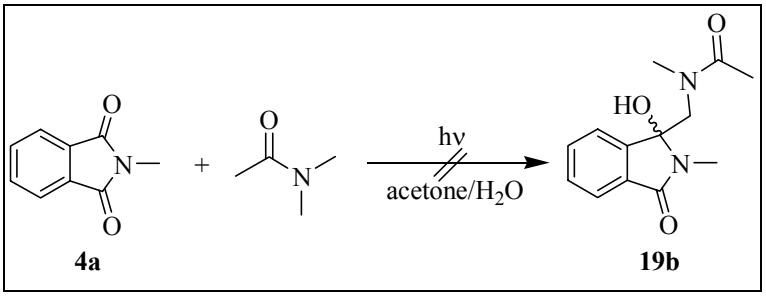
Figure 29: Representative ^{1}H-NMR spectrum of **19d** in $CDCl_3$

In contrast to the α-amino acids, the chain extended β-alanine derivative gave, however, no photoaddition product **19f** (Scheme **56**) even after prolonged irradiation of up to 100 hrs. A conducted $Ba(OH)_2$-test for CO_2 evolution remained negative. Instead, *N*-methylphthalimide **4a** was recovered in 59% yield.



Scheme 56: Photoreaction involving β-alanine (Experiment 62)

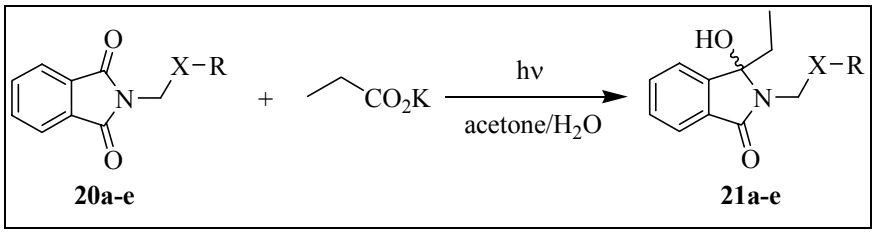
Likewise, *N*-methylphthalimide **4a** and dimethylacetamide gave no reaction and **4a** was reisolated quantitatively after 5 hours of irradiation (Scheme **57**).



Scheme 57: Dimethylacetamide photoaddition to **NMP** (Experiment 63)

3.2.3.4 Irradiation of donor-substituted phthalimides with potassium propionate

The phthalimides **20a-e** carrying potential donor substituents in the *N*-side chain were used as replacements of *N*-methylphthalimide **4a** (Scheme **58**, Table **11**). Potassium propionate was chosen as a simple model carboxylate. Upon irradiation the corresponding addition products **21** were only obtained with the amide and ether derived starting materials **20c-e**. In contrast, compounds **20a** and **b** remained photo-stable. Although **20a** showed some photodecomposition, as noticeable from the recovery of 23%, no cyclisation products arising from competing *intramolecular* CH-activations or PET-reactions were alternatively detected.



Scheme 58: Photoreactions of donor-substituted phthalimides with potassium propionate (Experiments 64-68)

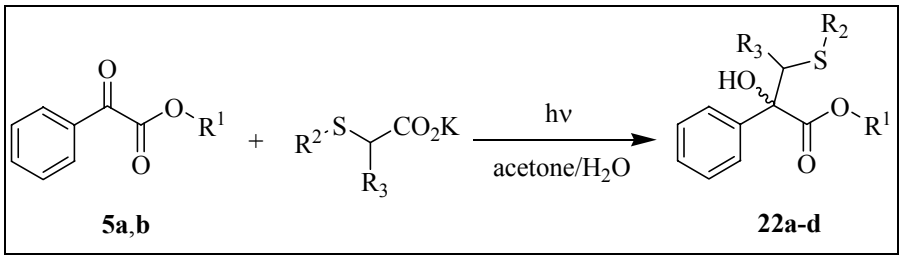
No.	Ref.	X	R	Time [h]	Conv.[a)] [%]	^{13}C-NMR[b)] [ppm]	Yield [%]
21a	FH-50	NMe	Me	4	n.r.[c)]	—	(23 [d)])
21b	FH-49	S	Me	10	n.r.[c)]	—	(96[d)])
21c	FH-35	O	Me	2	98	91.9	51 (52[e)])
21d	FH-56	CONH	Me	4	95	92.1	43 (45[e)])
21e	FH-36	CONMe	Me	21	95	91.6	51 (54[e)])

[a)] Conversion determined by ^{1}H-NMR, [b)] Signal of the C-OH group in $CDCl_3$, [c)] No reaction, [d)] Reisolated **4a**, e) Yields based on conversion.

Table 11

3.2.4 Photoreactions of alkyl benzoylformates with sulphur-containing carboxylates

Benzoylformates **5a** and **5b** were used as starting material instead of the usual *N*-methylphthalimide **4a** and potassium 2-mercaptoacetate ($RSCH_2CO_2K$) were used as model carboxylate (Scheme **59**, Table **12**). Upon irradiation for 3-10 hrs under the usual photoaddition conditions, products **22b-d** were obtained in moderate to good yields of 28-84%. The newly formed C-OH bond was found in the ^{13}C NMR spectra between 80.5-84.1 ppm and the conversion was obtained at 70-100%.



Scheme 59: Photoreactions of alkyl benzoylformates with **S**-containing carboxylates (Experiments 69-72)

No.	Ref.	R^1	R^2	R^3	Time [h]	Conv.[a)] [%]	^{13}C-NMR[b)] [ppm]	Yield [%]
22a	JF-12	Me	Me	H	10	100	81.4	31
22b	JF-13	Me	Ph	H	9	100	80.5	44
22c	JF-8	Me	Me	Me	4	100	83.7/84.1[c)]	84
22d	FH-133	Et	Me	H	3	70	81.1	28

[a)] Conversion determined by ^{1}H-NMR, [b)] Signal of the C-OH group in $CDCl_3$, [c)] Major/minor product.

Table 12

3.3 Screening results

3.3.1 Antifungal screening

The effect of compounds **3**, **6e**, **7a**, **11a**, **12c**, **12g**, **14c**, **14p**, **18a** and **21c** was investigated on the pulmonary pathogen *Aspergillus fumigatus* and with the pathogenic yeast *Candida albicans*. The compounds were dissolved to a working concentration of 500 µg/ml to which serial dilutions were performed. The final concentration of the dissolving agent DMSO was maintained at less then 5% as concentrations greater then this are reported to inhibit fungal growth.

Unfortunately, the compounds investigated did not result in any reduction in growth when compared to the untreated control at the concentrations investigated.

3.3.2 Antibacterial screening

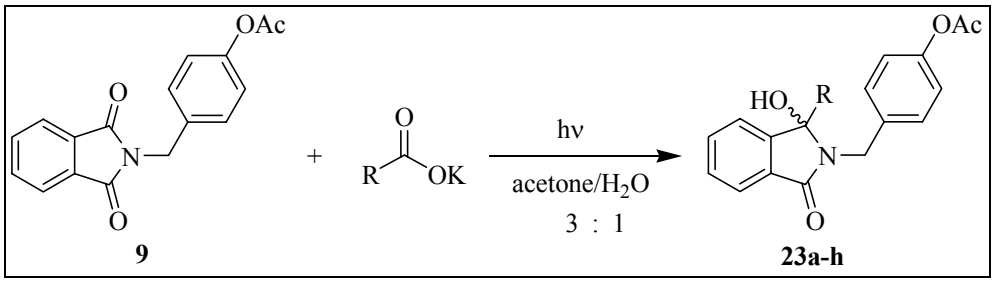
The effect of compounds **3**, **6e**, **11a**, **12g**, **14c**, **14p** and **21c** were investigated on *E. coli, Enterococcus sp., P. aeruginosa, Salmonella sp., Klebsiella sp., S. aureus* and *B. subtilis*. The compounds were dissolved to a working concentration between 1.3 to 500 μg/ml to which serial dilutions were performed. The dissolving agent used in this case was MeOH.

Unfortunately, the compounds investigated did not result in any reduction in growth when compared to the untreated control at the concentrations investigated but in opposite helped the growth of these bacteria.

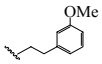
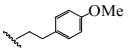
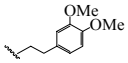
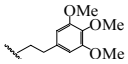
3.4 Synthesis of *AKS-186* and its analogues

3.4.1 Photoreactions involving 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9

2-(4-Acetoxybenzyl)isoindoline-1,3-dione **9** was irradiated in the presence of 3 equivalents of different potassium alkyl carboxylates. Due to its reduced solubility of **9**, all photoaddition experiments were conducted in a 3:1 mixture of acetone and water. After 2-20 hrs the corresponding addition products **23a-h** were obtained in poor to good yields of 10-76% (Scheme **60**; Table **13**). In the ^{13}C NMR spectra, the characteristic singlet of the C-OH group was detected in the region of 91.8-92.9 ppm. Only in case of the *di*- and *tri*-methoxy substituted carboxylic acids **23f** and **g** no reactions occurred and the starting material **9** was recovered in 69 and 89%, respectively.



Scheme 60: Photoreactions involving 2-(4-acetoxybenzyl)isoindoline-1,3-dione (Experiment 73-80)

No.	Ref.	R	Time [h]	Conv.[a] [%]	^{13}C-NMR[b] [ppm]	Yield [%]
23a	JF-02	Bn	5	100	92.2	44
23b	FH-86	$PhCH_2CH_2$	2	52	92.5	44
23c	FH-150		3	63	92.0	21
23d	FH-151		2	84	91.8	76
23e	FH-152		2	100	91.8	55
23f	FH-153		20	n.r.[c]	—	69[d]
23g	FH-154		20	n.r.[c]	—	89[d]
23h	FH-143		10	69	92.7	10

[a] Conversion determined by ^{1}H-NMR, [b] Signal of the C-OH group in acetone & $CDCl_3$, [c] No reaction., [d] Reisolated S.M.

Table 13:

Recrystallisation of the *AKS-186* precursor **23b** gave suitable crystals for X-ray analysis (Figure **30**). The compound forms a dimer via hydrogen bonding between the C-OH and the C=O group and crystallised as a racemate.

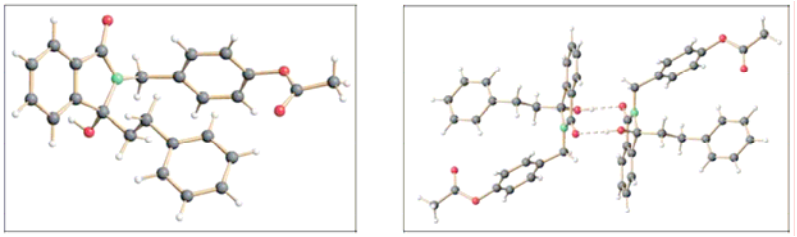
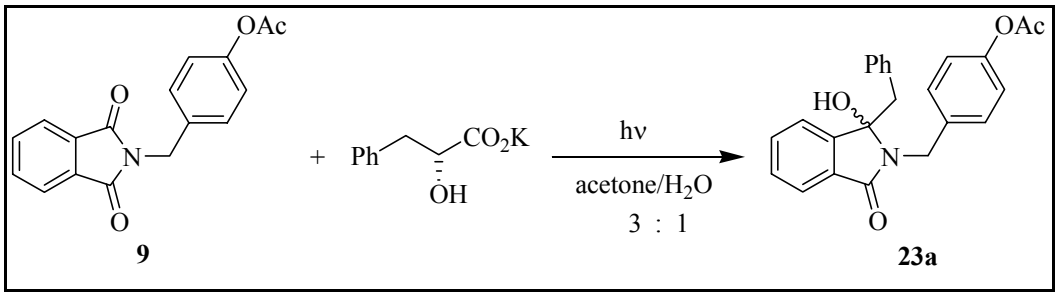


Figure 30: X-ray of **23b**

Irradiation of the α-hydroxy substituted *L*-3-phenyllactic acid did not yield the expected diastereoisomeric mixture of the corresponding addition product. The ^{1}H NMR spectrum revealed that compound **23a** was formed instead (Scheme **61**). Hence, decarboxylation is followed by retro-Aldol fragmentation, *i.e.* loss of formaldehyde.



Scheme 61: Photoreactions with *L*-3-phenyllactic acid (Experiment 81)

In acetone-d_6, the OH group was found in the ^{1}H-NMR at 5.65 ppm as a sharp singlet (Figure **31**). Likewise, the presence of two doublets at 3.34 and 3.57 ppm confirmed the presence of an isolated CH_2 group (no ^{3}J coupling). The *N*-CH_2 group appeared as two close doublets with a strong roof effect at around 4.8 ppm, whereas the aromatic protons were in the region of 6.88 and 7.60 ppm, respectively. The integration of 23 hydrogens in total furthermore confirmed the suggested structure **23a**.

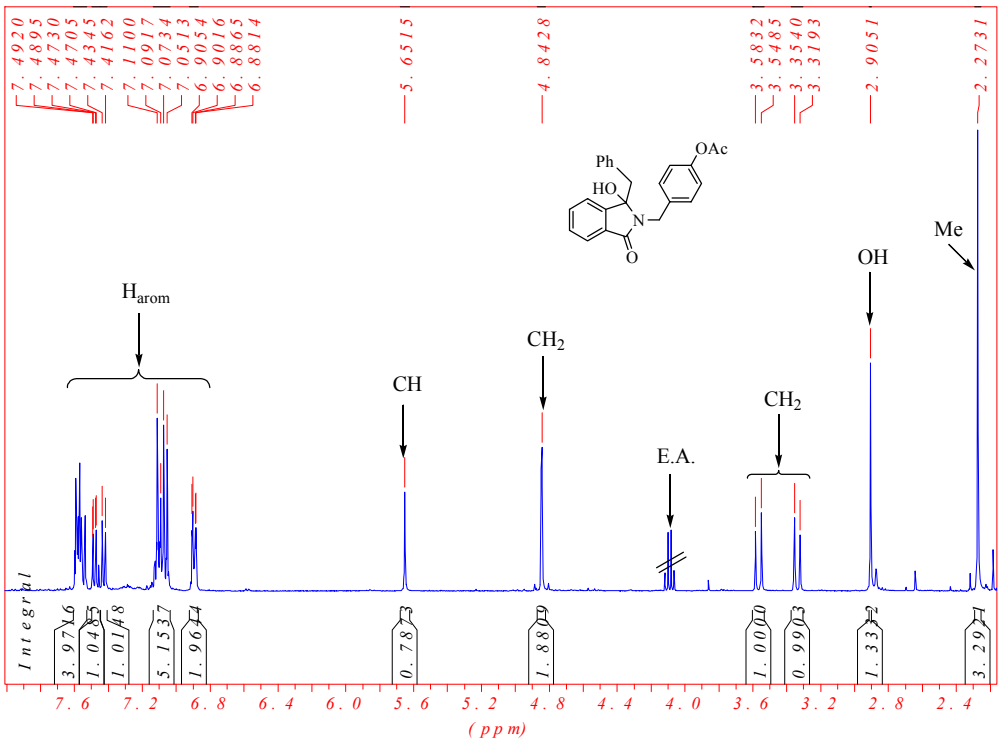
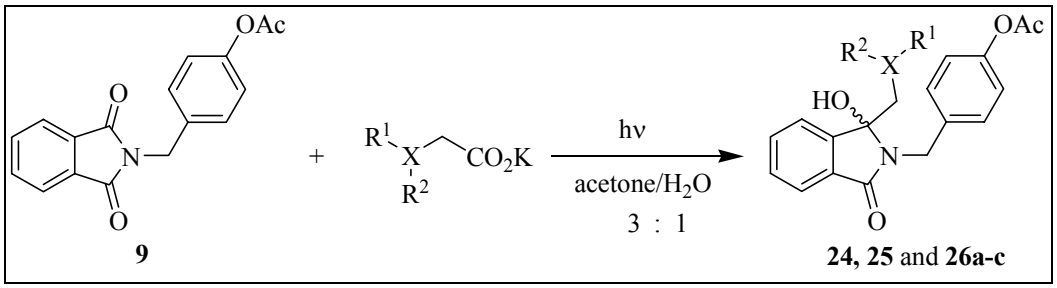


Figure 31: ^{1}H-NMR spectrum of **23a** (originating from *L*-3-phenyllactic acid) in acetone-d_6

In order to synthesise *AKS-186* isosteres, the photoaddition protocol was extended to heteroatom-derived carboxylates (Scheme **62**; Table **14**). Irradiations involving sulphur- and oxygen-containing carboxylates resulted in the formation of the corresponding addition products **24** and **25** in yields of 44 and 34%. Likewise, *N*-protected amino acid potassium salts furnished compounds **26a-c** in moderate to good yields of 55-89%. All photoproducts showed the characteristic singlet of the C-OH group around 90.0 ppm in their ^{13}C NMR spectra.



Scheme 62: Photosynthesis of AKS-186 and its analogues (Experiments 82-86)

No.	Ref.	X	R^1	R^2	Time [h]	Conv.[a] [%]	^{13}C-NMR[b] [ppm]	Yield [%]
24	FH-92	S	Ph	—	9	75	91.9	44 (59[c])
25	FH-87	O	Ph	—	4	54	89.5	34 (52[c])
26a	FH-158	N	Ph	H	5	89	90.9	88
26b	FH-159	N	OAc	H	2	100	91.6	89
26c	FH-164	N	OAc	Ph	5	90	91.8	55

[a] Conversion determined by ^{1}H-NMR, [b] Signal of the C-OH group in acetone, [c] Based on conversion.

Table 14:

The ^{1}H-NMR spectrum of compound **24** in acetone-d_6 is shown below (Figure **32**). The Me-group appeared as a singlet at 2.27 ppm, whereas the OH-group showed a broad singlet at 3.05 ppm, The SCH_2 group gave a pair of doublets at 3.62 and 3.74 ppm. In contrast, the NCH_2 group was found as two doublets at 4.54 and 4.62 ppm. The aromatic protons appeared as various, partly overlapping, signals in the region of 7.05 and 7.74 ppm.

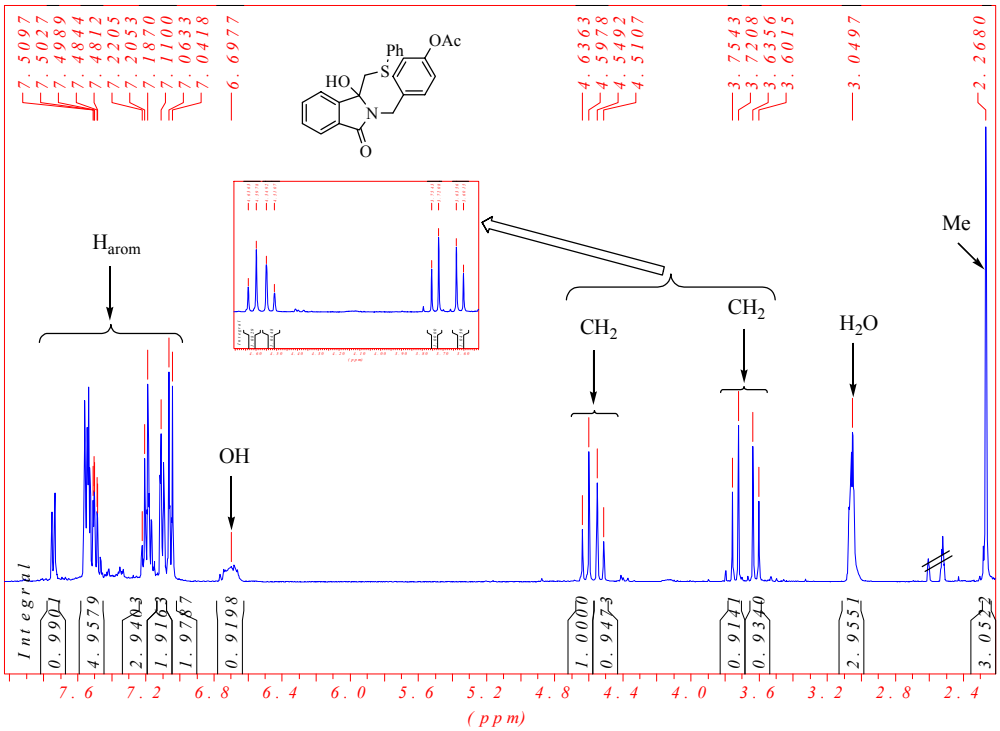
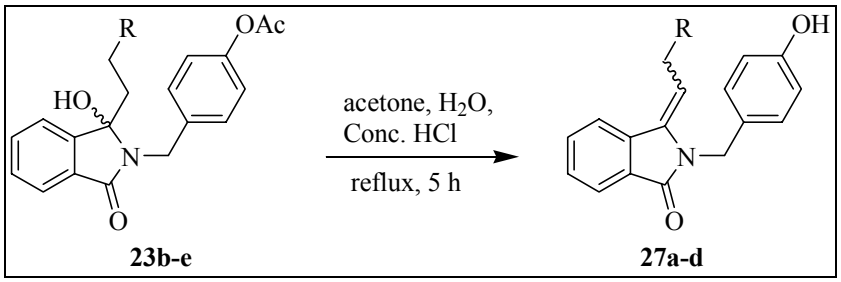


Figure 32: ^{1}H NMR spectrum of **24** in acetone-d_6

3.4.2 Dehydration/deprotection reactions

The synthesis of AKS-186 and its analogues require subsequent dehydration and deprotection. This was conveniently achieved by refluxing a solution of the photo-product in a mixture of acetone, water and conc. HCl (10:7:3). Subsequent workup and purification gave the desired unsaturated isoindolinones **27a-d** in yields of 70-96% (Scheme **63**, Table **15**).



Scheme 63: Dehydration/deprotection reactions (Experiments 87-90)

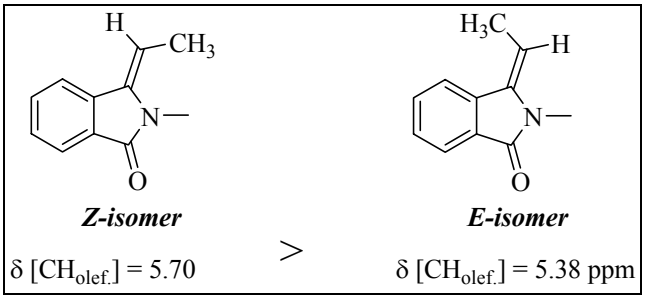
No.	Ref.	R^1	*Z/E*-ratio[a)]	^{13}C-NMR[b)] [ppm]	Yield [%]
27a	FH-147	Ph	*E*-only	96.0[c)]	70
27b	FH-155		1:14	111.3/110.8	96
27c	FH-156		1:15	94.3[c)]	76
27d	FH-157		1:16	113.3[c)]	88

[a)] Ratio determined by ^{1}H-NMR, [b)] Signal of the olefinic C-H groups in acetone, [c)] Main isomer only.

Table 15:

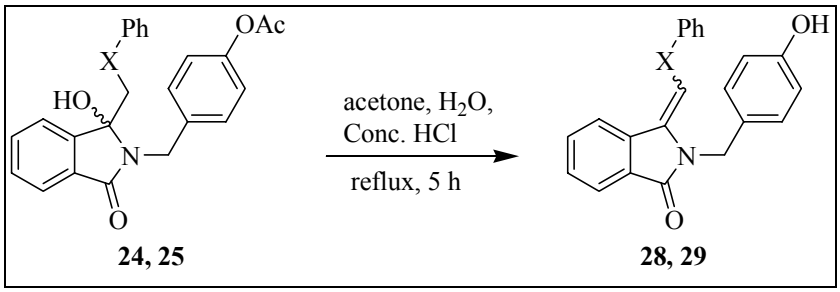
The stereoselectivities were determined by ^{1}H NMR analysis of the crude products and varied between 1:14 and 1:16. The configurations of the two isomers (***E/Z***) were assigned by comparison with known analogues reported by Ang and Halton.[63] The olefinic hydrogen of the *Z*-isomer is influenced by the anisotropy effect of the

aromatic ring (Scheme **64**) and is found at higher chemical shifts than its *E*-counterpart. Applying this general trend for compounds **27a-d**, the *E*-isomer was preferentially formed. In case of AKS-186 itself (**27a**) the *E*-isomer was found exclusively as proven by comparison with literature data.[1104] The main or exclusive *E*-isomer showed the characteristic $=CH_{olef.}$ peak between 5.77-5.80 in the ^{1}H- and 94.3-113.3 ppm in the ^{13}C-NMR spectrum, respectively.



Scheme 64: Assignment of ***Z-*** and ***E-***isomers according to Ang and Halton

Likewise, the dehydration/deprotection reactions of the heteroatom containing photoaddition products **24** and **25** gave the AKS-186 isosteres **28** and **29** in high yields of 88 and 89% (Scheme **65**; Table **16**). Both, compounds were obtained as stereoisomeric mixtures (***E/Z***) in ratios of 4:1 (in favour of the *E*-isomer) and 1:1, respectively. In the ^{1}H-NMR, the typical olefinic CH signals were observed as singlets at 6.71 (**28**) and 7.41 (**29**) ppm for the ***E***-isomer and at 6.35 (**28**) and 7.12 (**29**) ppm for the ***Z***-isomer. In the ^{13}C-NMR spectra, the group was found for the ***E***-isomer at 105.6 (**28**) and 120.6 (**29**) ppm, respectively. The ***Z***-isomer of **29** appeared at 124.6 ppm; the corresponding isomer of **28** was not detected due to its low content.



Scheme 65: Dehydration/deprotection reactions (Experiments 91 and 92)

No.	Ref.	X	*Z/E*-ratio[a)]	^{13}C-NMR[b)] [ppm]	Yield [%]
28	FH-145	S	1:4	105.6/n.d.[c)]	88
29	FH-144	O	1:1	120.6/124.6	89

[a)] Ratio determined by ^{1}H-NMR, [b)] Signal of the olefinic C-H groups in acetone, [c)] Not determined.

Table 16

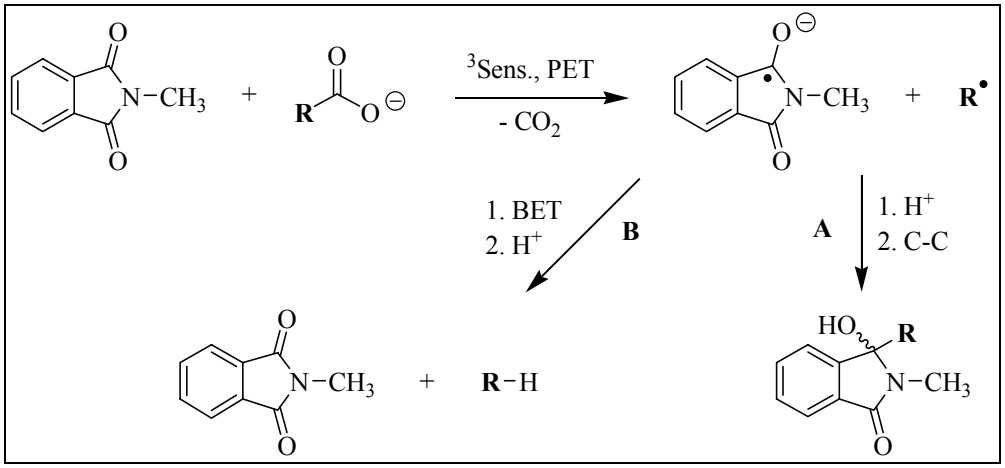
4 Discussions

4.1 *Intermolecular* photoreaction of *N*-alkylphthalimides with alkyl carboxylates

Photoadditions of alkyl carboxylates to *N*-methylphthalimide **4a** furnished alkyl-phthalimidines as the only products. In line with the stability of the intermediately formed alkyl radicals,[120] *tert*-butylation and benzylation were the most efficient reactions and the addition products **11b, d** and **h** were obtained in high yields after short irradiation times. Accounting for the less favourable stability of the ethyl radical, ethylation proceeded less satisfactory and **11a** was isolated in a lower yield even after prolonged photolysis. Despite complete consumption of the phthalimide, the yields for the phenylalkly-derived acids remained low. Hydrogen-abstraction from the benzylic position may successfully compete with photodecarboxylative addition in these cases. The resulting products would all incorporate the intact carboxylate function and thus, would have been removed during work-up. Despite the stability of the corresponding allyl radical, vinyl acetate gave a significantly lower yield and required extended irradiation. 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.[121] Owing for their carboxylic acid functionalities, the resulting products would have been water soluble and extracted during work-up.

The mechanistic scenario for the photodecarboxylative addition is depicted in Scheme **66**.[57,122] 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: $E_{Ox.} = 1.54$ V in MeCN, 2.65 V in H_2O *vs.* SCE[123]) *intramolecular* electron transfer *via* the excited $^3\pi,\pi^*$ triplet state ($E_{00} = 3.1$ eV) or the higher $^3n,\pi^*$ state ($E_{00} \approx 3.6$ eV) are both energetically feasible. Subsequent decarboxylation of the carboxy radical yields the corresponding C-radical. The rate

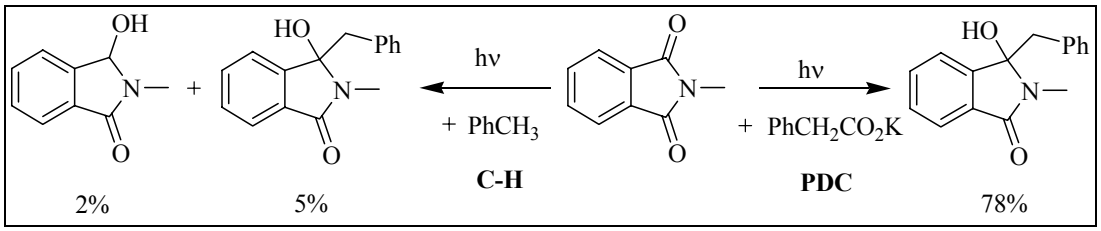
for CO_2 loss is controlled by the stability of the corresponding alkyl radical and is estimated to be in the range of 10^9-10^{10} s^{-1} for simple alkyl acyloxy radicals.[120] Protonation, intersystem crossing and C-C bond formation result in the desired photoaddition products (path **A**). Alternatively, back electron transfer (**BET**) generates the corresponding carbanions, which are protonated by water (path **B**).[124] In the later case, the simple decarboxylation products (-CO_2H ↔ -H exchange) are formed. 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 case, they were removed during drying in vacuum due to their volatility. However, in case of 1-adamantane carboxylic acid, the **PDC** product was found to be the dominant product.[13]



Scheme 66: Mechanism of photodecarboxylative addition of carboxylates to phthalimide

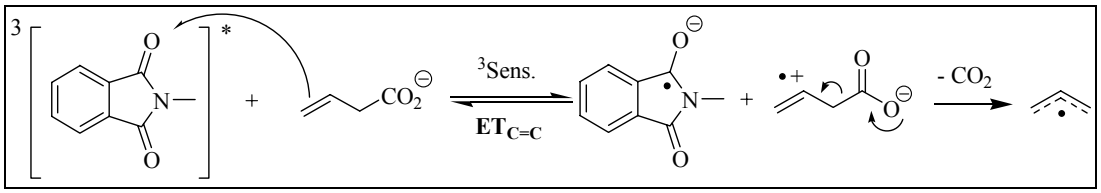
Major advantages of the photodecarboxylation protocol are its simple procedure and the usage of carboxylic acids. These starting materials are easily accessible in large quantities and with broad structural diversity, and are additionally stable. In contrast to other PET additions involving phthalimides,[32] loss of carbon dioxide proceeds irreversibly and regioselectively. This becomes especially apparent when comparing the benzylation of *N*-methylphthalimide with toluene or phenyl acetate (Scheme **67**). As reported by Kanaoka and co-workers, simple hydrogen abstract gives the

corresponding benzylated product in low yield (5%) and with poor selectivity and conversion (30%).[46] In contrast, **PDC** exclusively yields the benzylation product in high yield and purity.



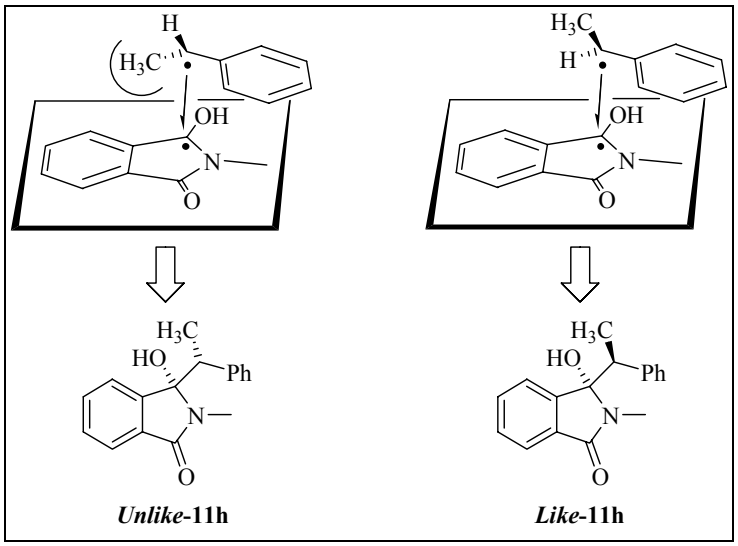
Scheme 67: Alternative benzylation procedures

For vinyl acetate, an alternative mechanism involving electron transfer from the C=C double bond can be postulated (Scheme **68**). Subsequent α-decarboxylation leads to the common allyl radical. A similar competitive mechanistic scenario has been described by Kurauchi and co-workers for the decarboxylative addition to 1-methyl-2-phenyl-1-pyrrolinium perchlorate.[125] 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 68: Alternative mechanisms of allylation

The photodecarboxylative addition of 2-phenylpropanoic acid gave a mixture of two diastereoisomers in a ration of 1:1.6 in favour of the ***Like***-compound. The diastereoselectivity can be explained during the crucial C-C bond formation step (Scheme **69**) and the methyl group favours the radical approach that minimises steric clashing.[126] Although the diastereoselectivity was marginal, photoreactions with high stereoselectivities are known today.[127,128]

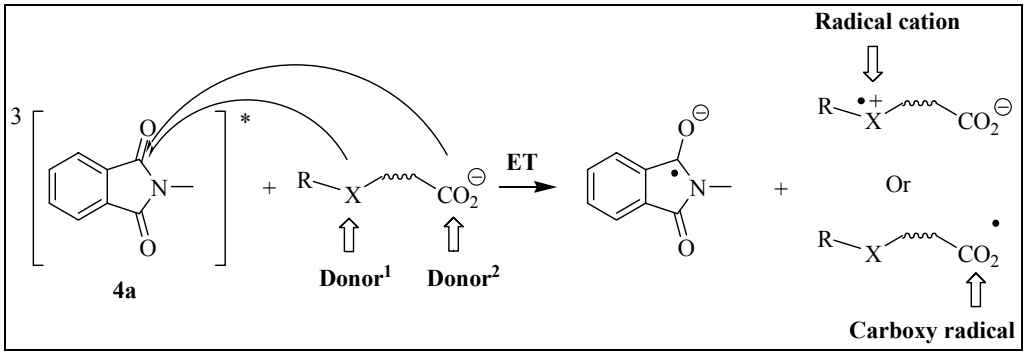


Scheme 69: Simplified radical approach leading to ***Unlike-*** and ***Like*-11h**

4.2 Photoreactions of heteroatom-substituted phthalimides

For photoadditions involving heteroatom-substituted carboxylates, two limiting mechanistic scenarios are possible (Scheme **70**):

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 activation and leaving group.[129]

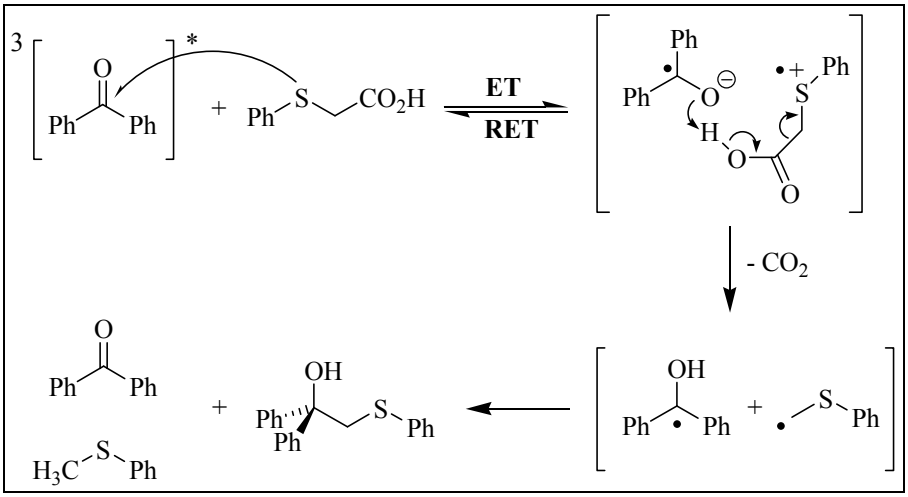


Scheme 70: Competitive scenario for heteroatom substituted carboxylates

The experimental results from this work allow a clear distinction between these scenarios. Based on the oxidation behaviour of the heteroatom,[130] the following reactivity order was expected:

$$NR > S > CO_2^- \geq CONR > O$$

Benzophenone photosensitised decarboxylations of thiophenoxyacetic acid (Scheme **71**) and *N*-phenyl glycine have been described earlier by Davidson and co-workers.[131 - 133] The authors postulated a charge-transfer complex between the carboxylic acid and the benzophenone triplet state.[134] After electron transfer, the radical ion pair can undergo a proton transfer-decarboxylation cascade reaction. The resulting radical pair can either combine or undergo hydrogen transfer.

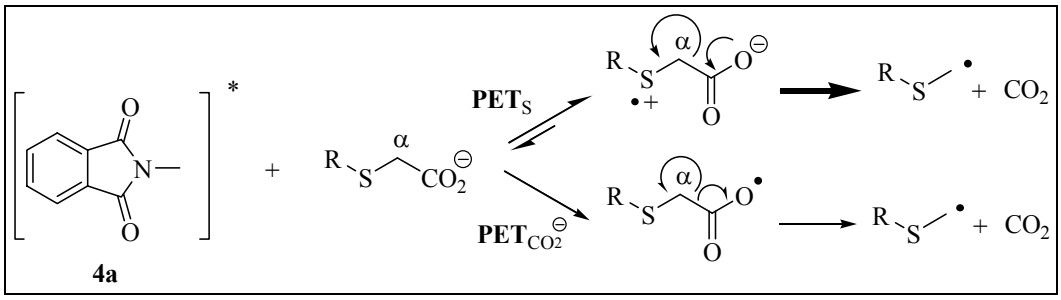


Scheme 71: Photosensitised decarboxylation of thiophenoxyacetic acid

4.2.1 Sulphur-containing carboxylates

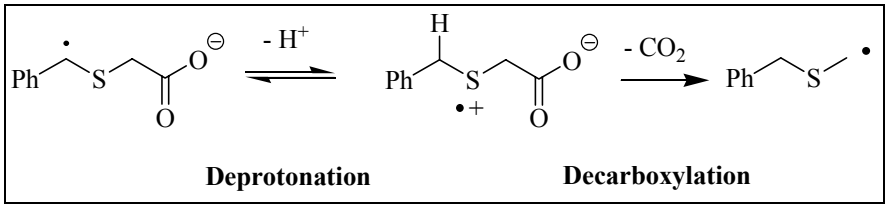
The incorporation of sulphur in the alkylcarboxylate and especially its position with respect to the carboxylate function had a critical effect on the addition efficiency. Whereas α-thioalkyl-substituted carboxylates readily underwent addition in high yields, the corresponding β-thioalkyl-substituted carboxylates remained inert even after prolonged irradiation. This activation/deactivation process can be explained based on the oxidation properties of the competing donors ($E_{Ox.}$ S > $E_{Ox.}$ CO_2^-).

Due to the favourable low oxidation potentials of thioethers (Me_2S: $E_{Ox.}$ = 1.25 V in MeCN *vs.* SCE[76]), the photoreactions involving sulphur-containing carboxylates are initiated by electron transfer from the heteroatom and not from the carboxylate. The resulting sulphur centred radical cation subsequently eliminates carbon dioxide irreversibly from its α-position.[135] The resulting terminal carbon-radical undergoes, after intersystem crossing, C-C bond formation to yield the product (Scheme **72**). The function of the carboxylate is therefore that of an efficient leaving and directing group. An alternative electron transfer from the carboxylate would result in the same product, but is energetically disfavoured due to the high oxidation potential of the carboxylate group.



Scheme 72: Mechanism of α-decarboxylation reaction

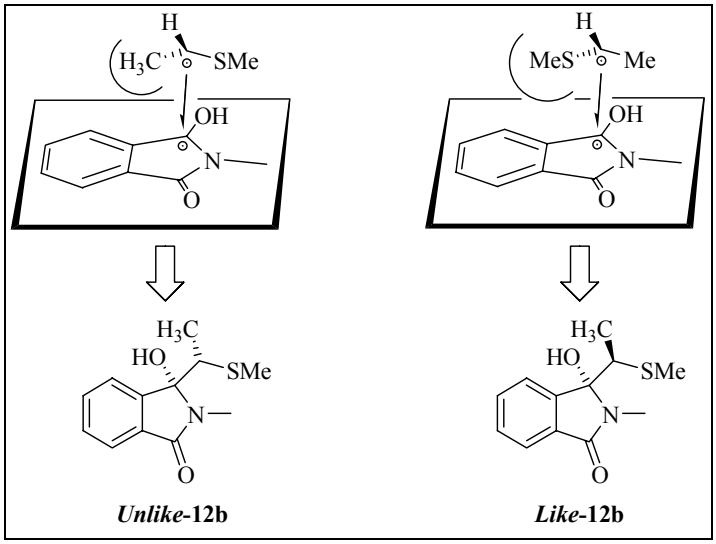
The *S*-benzyl derived carboxylate gave a somewhat lower yield compared to the *S*-methylated or *S*-phenylated analogues. In this case, proton transfer from the benzylic position of the radical cationic intermediate may compete with α-decarboxylation (Scheme **73**). This reversible deprotonation would give a stabilised benzylic radical.



Scheme 73: Alternative mechanisms for the *S*-benzyl derived carboxylate

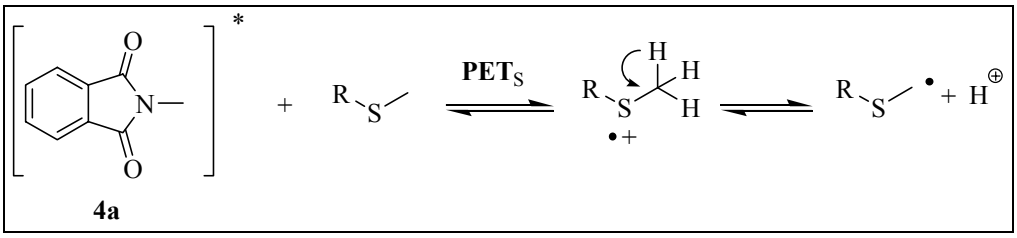
2-(Methylsulfanyl) propionic acid furnished a mixture of diastereoisomers with a slight preference for the ***Unlike***-isomer (10% *d.e.*). In contrast to the photodecarboxylative addition of 2-phenylpropanoic acid, the difference in size

between the thiomethyl and methyl groups is rather small. Hence, diastereo differentiation remains low during the competing C-C bond formation step (Scheme **74**).[126]



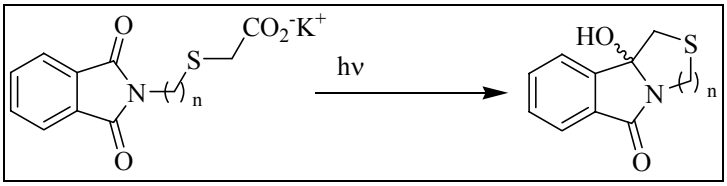
Scheme 74: Simplified radical approaches leading to ***Unlike-*** and ***Like*-12b**

In contrast to the corresponding thioethers, irradiations involving α-thioalkyl-substituted carboxylates gave higher yields and conversions. They furthermore avoided the usage of unpleasant starting materials. Especially dimethylsulphide is problematic due to the low boiling point and thus high volatility of this compound. The higher efficiency of the addition can be explained by comparing the crucial departure of the leaving group. In case of thioethers (Scheme **75**), both, electron transfer and deprotonation are reversible and hence, prolonged irradiation times are required. In case of the corresponding α-thioalkyl-substituted carboxylates, the loss of carbon dioxide is irreversible and thus significantly reduces the back electron transfer step and ultimately increases the quantum efficiency.



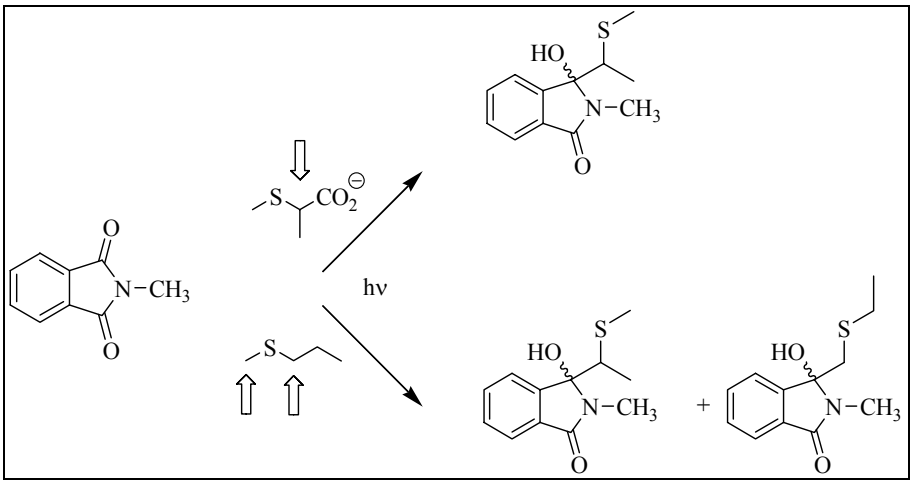
Scheme 75: Mechanistic key-steps for the addition of thioethers

Quantum yields have been determined for the related *intramolecular* counterparts, *i.e.* photocyclisation.[78] Thus, phthalimidoalkylsulfanyl acetates were regio-selectively converted into the corresponding tricyclic ring systems with high quantum yields (Φ *ca.* 0.1)[136] and in good to excellent isolated yields of 60 to 98% (Scheme **76**). The cyclisation efficiency was dramatically reduced for the free acids or for substrates with the carboxylate group in the β-position, and cyclisation consequently occurred with much lower quantum yields (Φ < 0.03).[136]



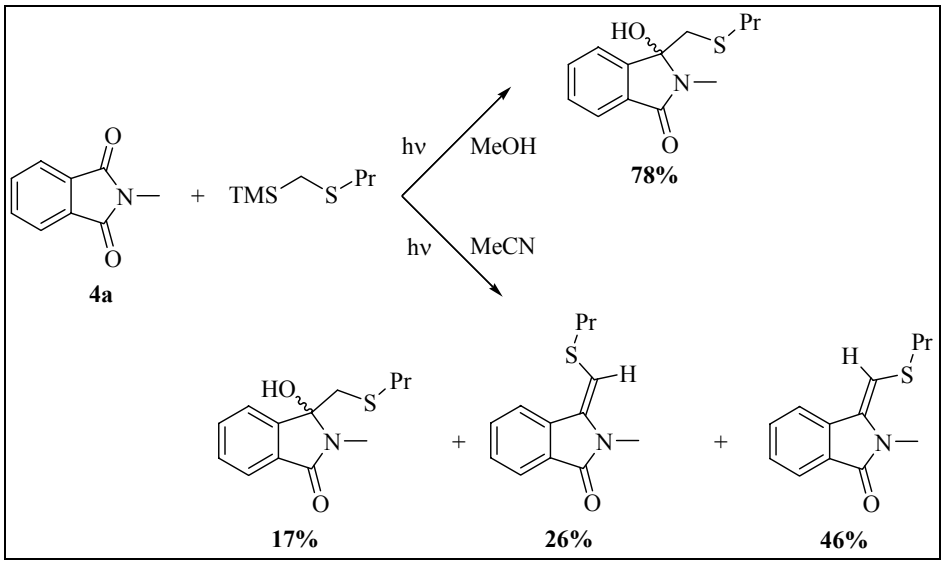
Scheme 76: Photocyclisation of phthalimidoalkylsulfanyl acetate

The directing effect of the carboxylate function becomes apparent when comparing the branched 2-methylthiopropionate with ethylmethylsulphide (Scheme **77**). Addition exclusively occurred at the position of the leaving group carbon dioxide. In contrast, the thioether gives a mixture of regioisomers.



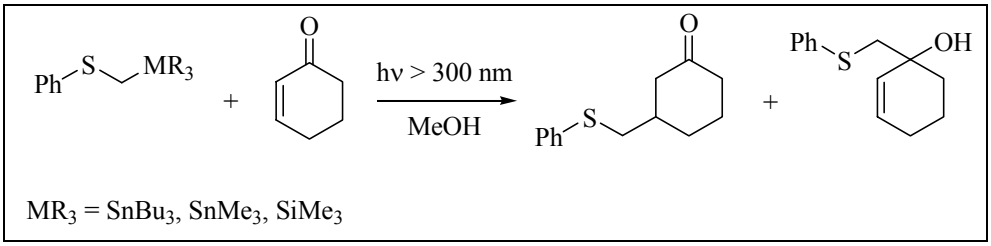
Scheme 77: Directing effect of the carboxylate function

The photoadditions involving α-thioalkyl carboxylates convincingly mirrors those of α-trialkylsilylmethyl- or α-trialkylstannylmethyl-substituted thioethers. Yoon *et al.* have reported the photoreaction of *N*-methylphthalimide **4a** with trimethylsilylmethyl *n*-propyl thioether and isolated the corresponding product in a good yield of 78% when irradiated in methanol (Scheme **78**). In acetonitrile, the reaction proceeded with much lower conversion and larger amounts of "formal dehydration" products were obtained.[119]



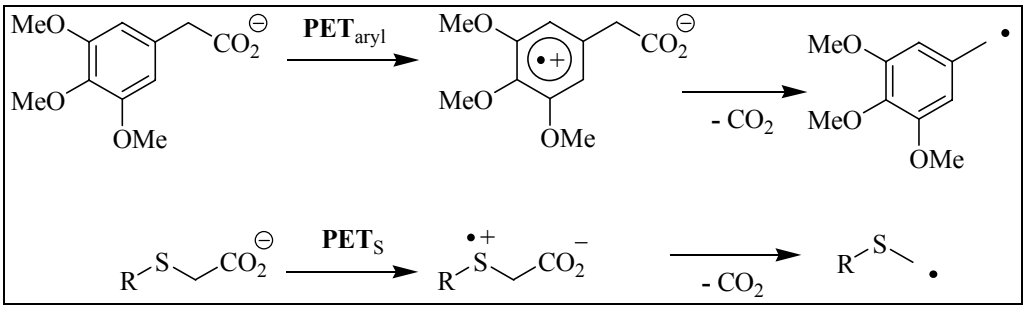
Scheme 78: Photoaddition involving trimethylsilylmethyl *n*-propyl thioether

Related addition reactions of α-silyl- and α-stannyl-sulphides to 2-cyclohexen-1-one were reported by Narasaka *et al.* (Scheme **79**).[137] In general, the α-stannyl-derived sulphides gave good yields of the regioisomeric products. In contrast, the silyl-analogous solely furnished the C=C addition product although in low yield and after longer irradiation times.[138]



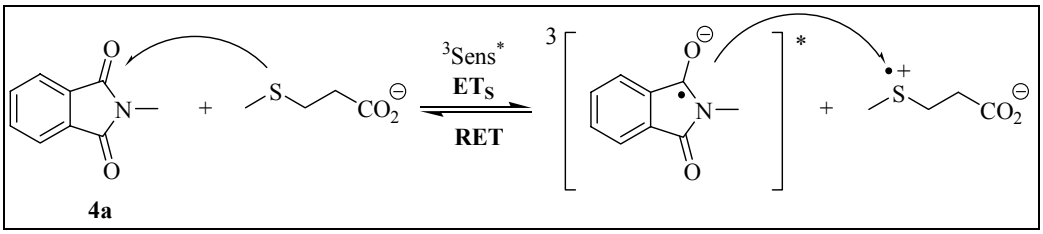
Scheme 79: Addition of α-silyl- and α-stannyl-sulphides to 2-cyclohexen-1-one

The photoreaction of the dimethoxy-substituted *N*-methylphthalimide furthermore supports the assumption that electron transfer occurs exclusively from the hetero-atom. Since the highly fluorescent single state of this phthalimide is not quenched by simple alkyl carboxylates, electron transfer from the carboxylate function is not operating (Scheme **80**). The sulphur heteroatom thus parallels the electron-rich 3,4,5-trimethoxyphenyl-group, which is known to operate as an electron donor in the photodecarboxylative addition.[75] The oxidation strength of the excited dimethoxy-lated phthalimide is thus lower than that of the excited phthalimide analogue. Based on literature data and the successful addition of the α-thioalkyl carboxylate, photo-additions to dimethoxy phthalimide do not operate for simple carboxylates and require either a heteroatom with low oxidation potential or electron-rich aryl groups in the α-position to the carboxylate.



Scheme 80: Comparison of **PET**-activity of dimethoxy-substituted *N*-methyl-phthalimide

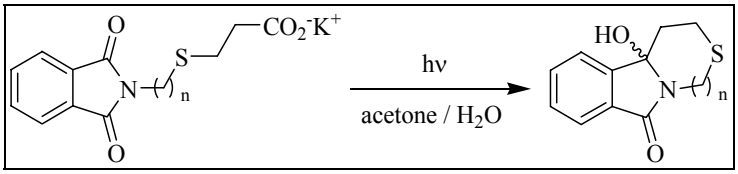
A special case was the irradiation of *N*-methylphthalimide in the presence of 3-(phenylthio) propanoic acid as the reaction did not yield any addition product. This and the lack of carbon dioxide formation, as proven by a negative $Ba(OH)_2$ test, indicates that return electron transfer is the most efficient process (Scheme **81**). In contrast to the corresponding α-thioalkyl-substituted carboxylates, decarboxylation from the more remote β-position of the sulphur-centred radical cation is not possible here. Product formation can only arise from electron transfer from the carboxylate function but due to its higher oxidation potential, this competing process is energetically less feasible. Hence, β-thioalkyl-substituted carboxylates function as a *hole trap* and completely prevent product formation.



Scheme 81: Deactivation process for β-thioalkyl-substituted carboxylates

This deactivating is in line with quantum yield determinations for analogue cyclisation reactions.[78,136] In contrast to phthalimidoalkylsulfanyl acetates, conversions and yields dropped drastically for the related 3-mercaptopropionic acid derived compounds, and the photoreactions became more sluggish. Even after prolonged irradiation the isolated yields were poor with 11-20% (Scheme **82**). In contrast to the

photoaddition process, however, electron transfer from the carboxylate does operate, although very inefficient. This is reflected by low cyclisation quantum yields of $\Phi < 0.03$.[136]

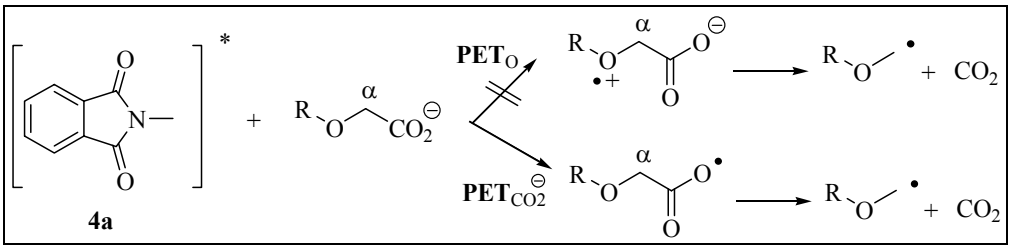


Scheme 82: Photocyclisation of 3-phthalimidoalkylsulfanyl propionate

4.2.2 Oxygen-containing carboxylates

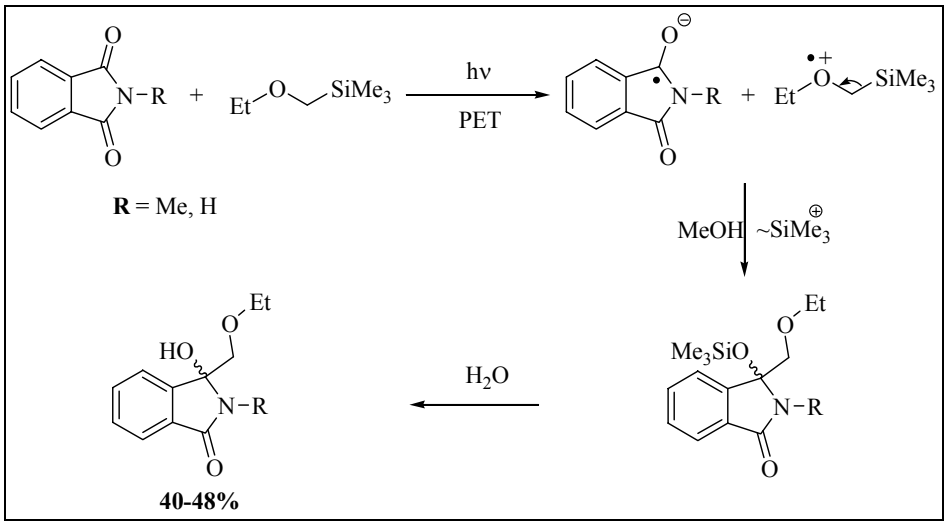
Photoreactions involving oxygen-containing carboxylates were less sensitive towards the position of the heteroatom along the carbon chain. Both, α- and β-oxo-alkyl-substituted carboxylates gave decarboxylative addition products, although in lower yields and after prolonged irradiation in the latter case. When comparing the oxidation potentials of the competing donors ($E_{Ox.}$ CO_2^- >> $E_{Ox.}$ O), the electron transfer activity is dominated by the carboxylate function.

Although product formation for α-oxoalkyl-substituted carboxylates can be explained by two electron transfer routes, the high oxidation potential of dialkyl-ethers (> 2.5 V vs. SCE[139]) makes an electron transfer from the heteroatom highly unfavourable (Scheme **83**). Instead, electron transfer occurs from the carboxylate function, generating an unstable carboxy radical that subsequently eliminates carbon dioxide. The resulting carbon centred radical furnishes the observed addition product. This mechanistic behaviour is thus opposite to photodecarboxylations involving sulphur-containing carboxylates.



Scheme 83: Mechanism of addition of α-substituted heteroatom in the oxygen case

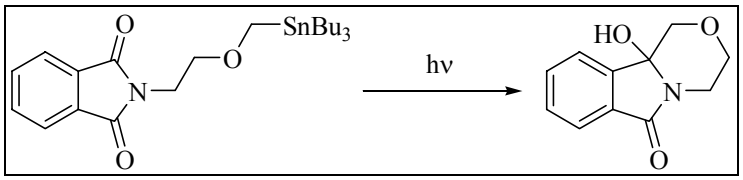
The photodecarboxylative addition reaction appears to mirror analogue photo-additions involving trimethylsilylmethyl ethyl ether described by Yoon *et al.* (Scheme **84**).[119] However, the presence of an α-TMS group greatly effects the oxidation potential of the ether oxygen, which decreases by about 0.5 V.[129,140] Hence, the reactivity order changes to -OCH_2TMS > -$OCH_2CO_2^-$ > -OCH_2R and electron transfer occurs from the heteroatom to the excited phthalimide. As for the α-oxo-alkyl-substituted carboxylate function, the silyl group enhances the efficiency and regioselectivity of the photoaddition (Scheme **84**).



Scheme 84: Intermolecular mechanism of alkoxysilyl compounds

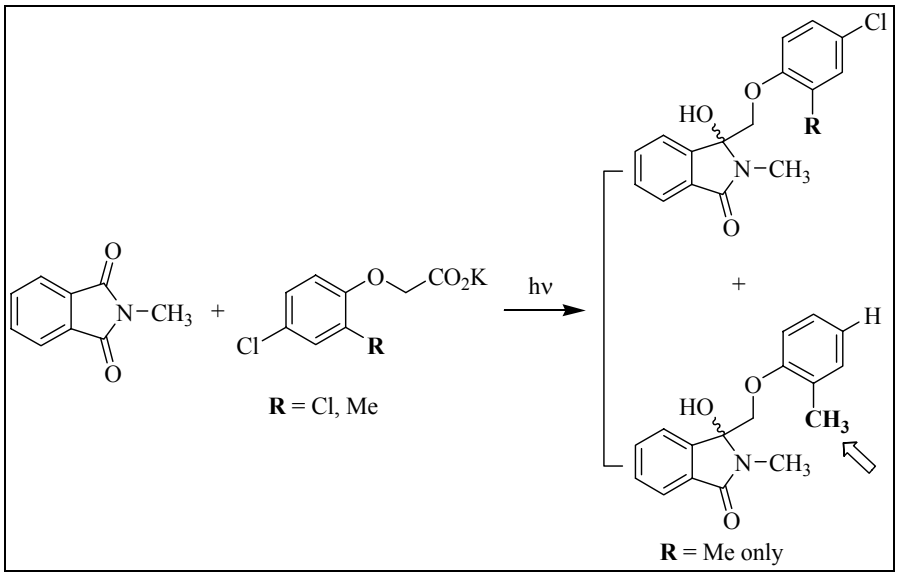
Yoon and co-workers have furthermore studied *intramolecular* cyclisation reactions involving trimethylsilyl- and tributylstannyl-terminated phthalimido-ethers.[141] The authors noted that the **PET**-destannation reaction proceeded more efficiently than the desilylation route (Scheme **85**). In both cases, the macrocyclisation is initiated by

electron transfer from the ether bridge followed by solvent mediated exclusion of the cationic terminal leaving group (Me_3Si^+ or Bu_3Sn^+).



Scheme 85: Intermolecular cyclisations of alkoxystannyl compounds

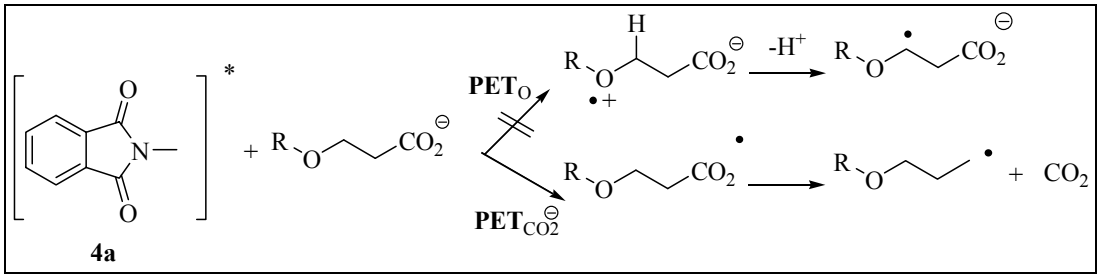
The partial dehalogenation (-Cl ↔ -H exchange) observed with 2-phenylpropanoic acid as starting material remains unclear (Scheme **86**).



Scheme 86: Photoadditions involving 2,4-disubstituted α-oxoalkyl-substituted carboxylates

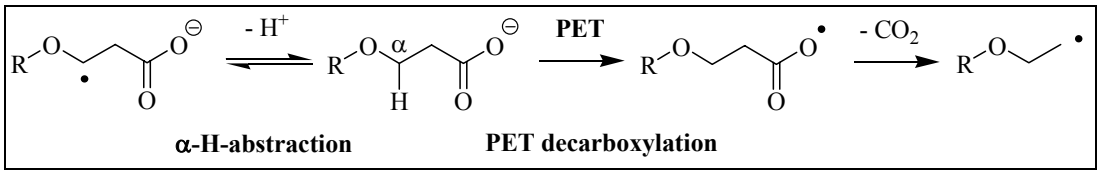
Since this reaction was not observed for the related 2,4-dichlorinated carboxylic acid, the electronic nature of the *ortho*-substituent may play a crucial role in photo-dehalogenation. The electron-donating methyl group thus favours dehalogenation, whereas the *chloro*-substituent shows no effect. Several photodehalogenation reactions have been described in the literature.[142,143]

The mechanistic scenario for β-oxoalkyl-substituted carboxylates is depicted in Scheme **87**. 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 in agreement with the compared to the ether oxygen lower oxidation potential of carboxylates.



Scheme 87: Mechanism of addition of β-substituted heteroatom in the oxygen case

Although reactivity prevailed for the β-oxoalkyl-substituted carboxylates, the efficiency of these reactions drastically decreased, as noticeable from yields and required irradiation times. Possibly, hydrogen abstraction from the α-position of the oxygen atom may compete with electron transfer mediated decarboxylation (Scheme **88**). Similar hydrogen-abstractions are known for irradiations involving simple dialkylethers.[40,43]



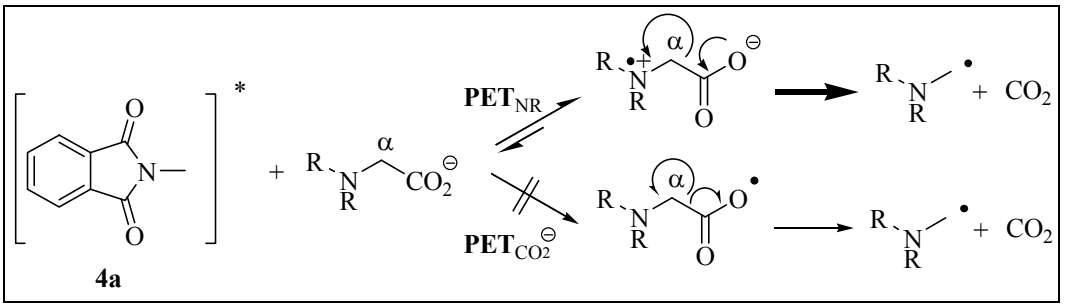
Scheme 88: Alternative mechanisms for the β-oxoalkyl-substituted carboxylates

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 ether yield similar products.

The photoreaction of the hydroxy-substituted carboxylate proceeded rather sluggish and photoreduction dominated over photoaddition. The poor efficiency of the photo-addition thus parallels that of analogue reactions with alcohols.[42,144]

4.2.3 Nitrogen-containing carboxylates

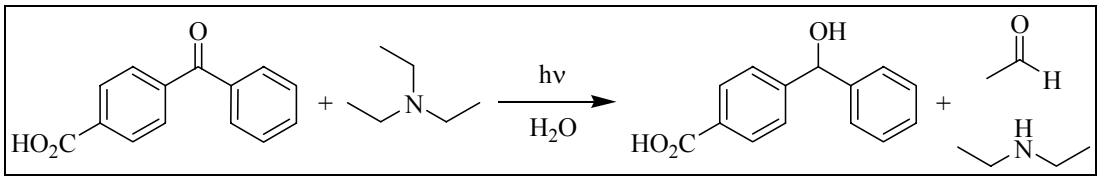
With the exception of *N*-phenyl glycine, photodecarboxylative addition of nitrogen-containing carboxylates to *N*-methylphthalimide solely gave photoreduction and acetone trapping products. The lack of carbon dioxide formation, *i.e.* missing $BaCO_3$ precipitation, for *N*, *N*-dimethylated amino acids strongly suggests that decarboxylation does not operate for these substrates. However, due the low oxidation potentials of tertiary amines (R_3N: $E_{Ox.}$ = 0.7-1.3 vs. SCE[76]) PET reactions involving phthalimides are highly exergonic. Consequently, electron transfer involving amino acids should occur entirely from the nitrogen heteroatom ($E_{Ox.}$ N >> $E_{Ox.}$ CO_2^-) as illustrated in Scheme **89**. At the same time, however, amines are potent hydrogen donors and consequently photoreductions are commonly observed as side reactions.[119, 46]



Scheme 89: Mechanistic scenario for nitrogen-containing carboxylates

Photoreductions by amines are known to be solvent dependant and in particular to be sensitive towards the presence of water.[145] Oxidative *N*-dealkylation is commonly observed, in particular for methyl and other small groups.[146] As an example, irradiation of triethylamine in water and in the presence of 4-benzoylbenzoic acid yields diethylamine and acetaldehyde in yields of 85 and 90%, respectively (Scheme

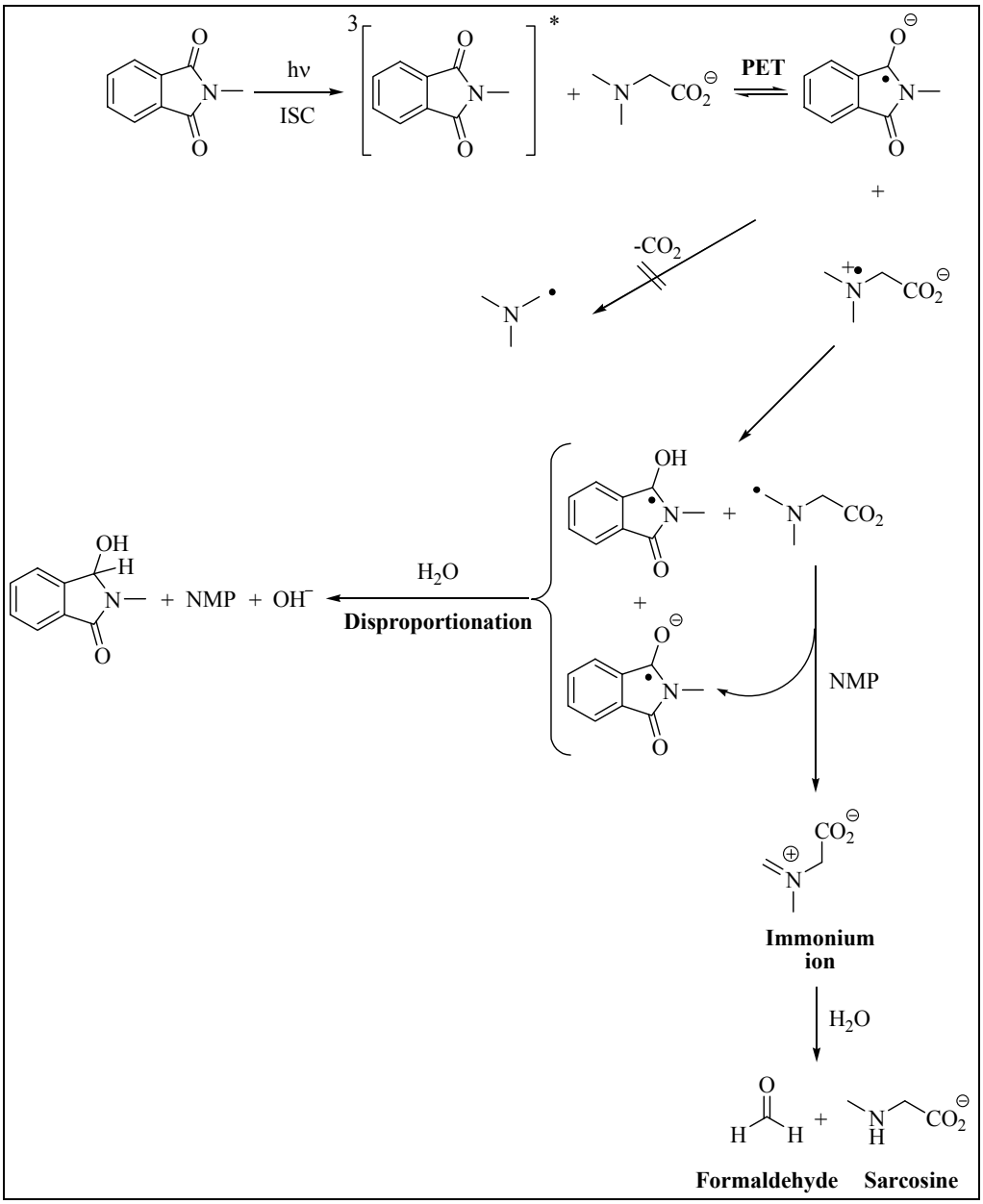
90). Likewise, photolysis of *N*, *N*-dimethyl-2-butylamine furnishes formaldehyde and *N*-methyl-2-butylamine. In both cases, the benzophenone derivative is reduced to its corresponding benzhydrol.[146]



Scheme 90: Photosensitised decarboxylation of thiophenoxyacetic acid

For irradiation of *N*, *N*-dialkylated amino acid salts in the presence of *N*-methyl phthalimide in aqueous acetone, an analogue scenario can be postulated. The mechanism is outlined in Scheme **91** using *N*, *N*-dimethylglycine as model compound. Electron transfer from the amine function to the triplet excited phthalimide yields the corresponding radical ion pair. In contrast to α-thioalkyl carboxylates, subsequent decarboxylation does not occur. Instead, rapid hydrogen transfer from the *N*-methyl group gives the corresponding ketyl and α-alkylamino radical pair. Hydrogen transfer from the latter to a ground state phthalimide leads to the formation of an immonium ion, which is subsequently hydrolysed to formaldehyde and sarcosine. Disproportionation of the phthalimide derived ketyl radical and ketyl radical anion yields the photoreduction product and regenerates *N*-methyl phthalimide. The mechanism for both, acetone trapping and secondary reduction remains unknown at present. However, it has been shown that *N*-methyl phthalimide can undergo stepwise photoreduction.[13] In addition, similar photoreductions have been reported by Kubo and co-workers for irradiations of other imide chromophores in the presence of secondary amines.[70,71] Likewise, acetone trapping has been described in the literature and clearly demonstrates the specific role of acetone as a sensitiser.[12] In contrast, the photoreaction of *N*-phenyl glycine follows the mechanism of the photodecarboxylative addition (Scheme **91**) and the lack of a suitable *N*-alkyl substituent protects amino acid from dealkylation. The sluggish outcome of the transformation can be explained by photoreactions arising from the

secondary amino function. An analogue reduction has been reported for *N*-methyl-phenanthrene-9,10-dicarboximide.[71]



Scheme 91: Mechanism of nitrogen-containing carboxylates in aqueous acetone

In acetonitrile, photoreduction was again observed as the only reaction pathway. Hence, the outcome of the photoreactions involving nitrogen-containing carboxylic acids or carboxylates predominantly depends on the structure of the acid, in

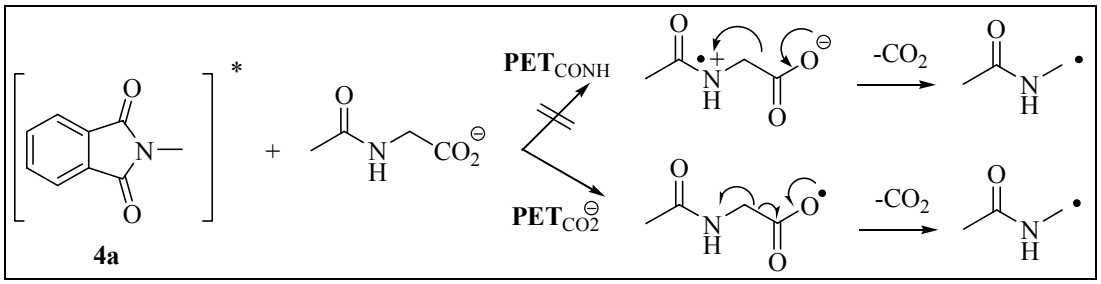
particular the substituents at the nitrogen, and not on the presence of water. Decarboxylation was again not observed as shown by negative $Ba(OH)_2$ tests. Hence, a similar mechanism as outlined for irradiations in aqueous acetone can be postulated (Scheme **91**). Differences arise from direct excitation of the phthalimide and from the obviously not possible hydrolysis of the immonium ion.

Although the photoreactions with nitrogen-containing carboxylates proceeded rather disappointing, photoreactions with amines are known to give sluggish reaction mixtures as well. Depending on the reaction conditions, photoaddition products were obtained in low to moderate yields.[46] Better results were achieved with *N*-trimethylsilylmethyl-*N*, *N*-diethylamine and the corresponding addition product was isolated in 41% yield when irradiated in acetonitrile. The primary photoreduction product was obtained as by-product (22%).[119] However, the latter transformation was critically depending on the solvent applied.

4.2.4 Amide-containing carboxylates

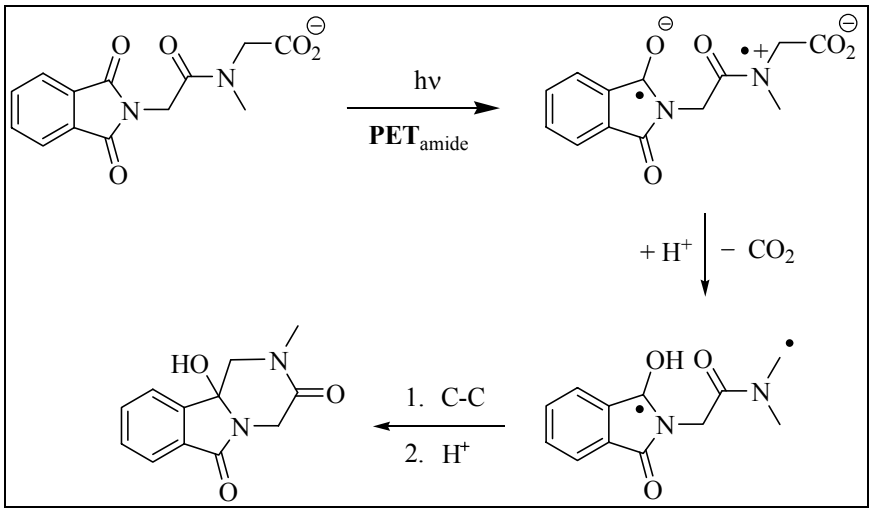
N-acylation of amino acids restored photoreactivity and the corresponding addition products were obtained in good to high yields after short irradiation times. This suggests that the crucial electron transfer step occurs primarily from the carboxylate function as supported by the oxidation potentials ($E_{Ox.}$ CONR ≥ $E_{Ox.}$ CO_2^-). The difference of the oxidation potentials of the competing donors is, however, rather small (*N*-methylacetamide: $E_{Ox.}$ = 1.81 V in MeCN[130] and acetate: $E_{Ox.}$ = 1.54 V in MeCN vs. SCE[123]).

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 **92**). Subsequent C-C bond formation yields the isolated photoproducts.

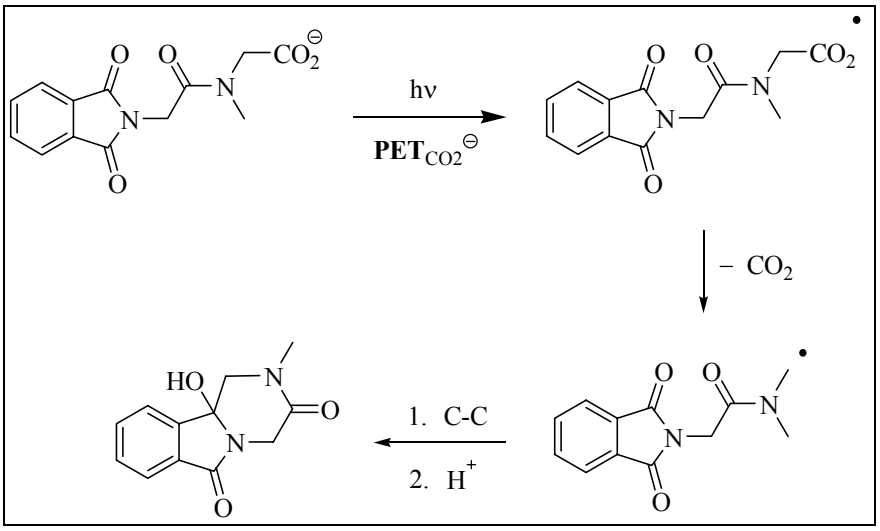


Scheme 92: Mechanism of amide-containing carboxylates

Analogue photocyclisations of phthaloyl dipeptides have been described by the groups of Yoon/Mariano[147] and Griesbeck/Oelgemöller.[148] Both groups favour different **PET** scenarios. Whereas Yoon and Mariano postulated electron transfer from the amide linker (Scheme **93**), Griesbeck and Oelgemöller suggested electron transfer from the carboxylate function instead (Scheme **94**). 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.

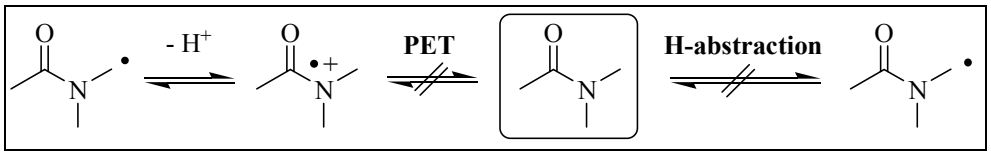


Scheme 93: Mechanistic scenario for the photocyclisation of Pht=Gly-Sarc by Yoon and Mariano



Scheme 94: Mechanistic scenario for the photocyclisation of Pht=Gly-Sarc by Griesbeck and Oelgemöller

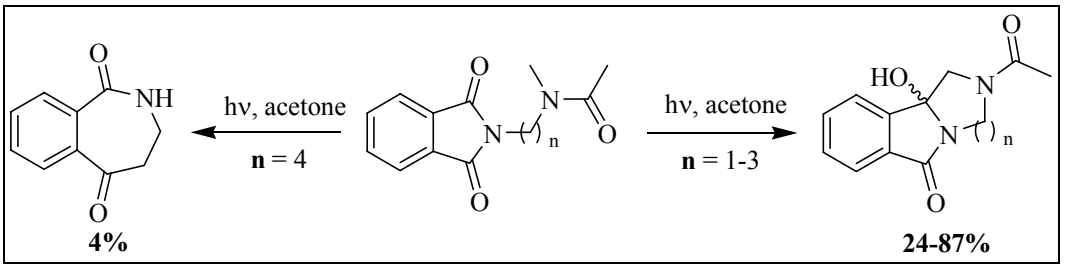
An additional argument for the latter scenario comes from the attempted photoaddition of dimethylacetamide to *N*-methylphthalimide. Since no addition product, either formed through photoinduced electron transfer or hydrogen abstract (Scheme **95**), could be detected, electron transfer from the amide function appears energetically not feasible.



Scheme 95: Possible scenarios for dimethylacetamide

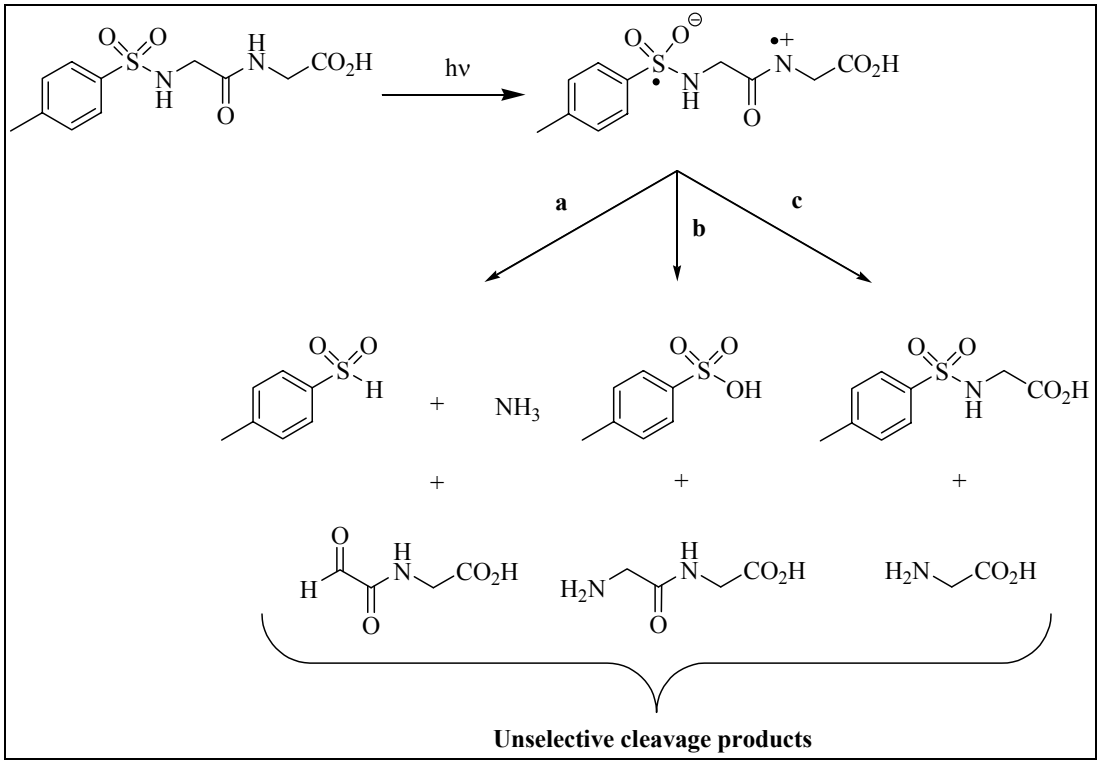
This is also supported by *intramolecular* cyclisation reactions of *N*-acyl containing phthalimides (Scheme **96**).[149] Upon irradiation in acetone, the methylene, ethylene and propylene bridges derivatives regioselectively cyclised towards the *N*-methyl group. The crucial experiment that unambiguously proved a hydrogen-abstraction rather than an electron-transfer mechanism was the irradiation of the butylene bridged starting material. After prolonged irradiation, solely the unsubstituted benzazepinedione was isolated. Its formation can be explained by γ-hydrogen abstrac-

tion followed by ring-expansion and subsequent *Norrish-**II*** cleavage. Similar results were obtained for photocyclisations of related succinimide derivatives.[149, 150]



Scheme 96: Photocyclisation of 3-phthalimidoalkylsulfanyl propionate

In contrast, photoreactions arising from electron transfer from the amide function have been reported by Hill and co-workers (Scheme **97**).[151]

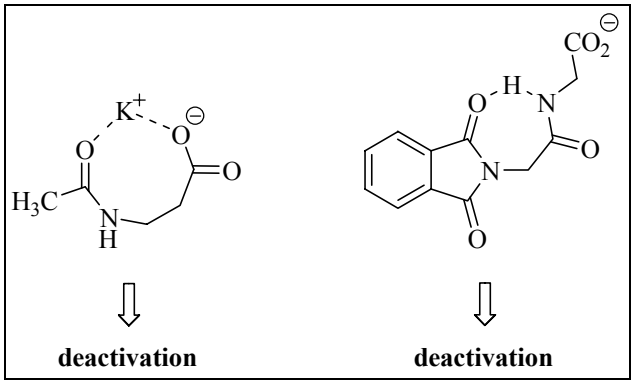


Scheme 97: Photochemistry of *N*-*p*-tosyldiglycine

The authors investigated the photochemistry of *N*-*p*-toluenesulfonyl amino acids and peptides in aqueous media and obtained various cleavage products. The formation of

these products was most consistently explained by initial electron transfer from the peptide bond to the *p*-toluenesulfonyl chromophore followed by S-N or C-C cleavage. When amino acids with aryl substituents in their side-chains, as for example in phenylalanine, were employed competitive electron transfer was postulated.

The photodecarboxylative addition of *N*-acetyl β-alanine remained, however, unsuccessful. Since no carbon dioxide formation was observed, this photoreaction somewhat parallels that of β-thioalkyl-substituted carboxylates. In line with this argument, electron transfer/back transfer from and to the amide function would create a hole trap. This scenario, however, contradicts to the oxidation potentials of the competing donors and also of the previously discussed results and literature findings. It is therefore assumed that in this case deactivation is caused by geometric or steric factors. A possible explanation is presented in Scheme **98**. *Intramolecular* chelation would prevent any photochemical activity. Analogue models based on deactivating hydrogen-bonding have been used to explain the unselective photocyclisation efficiency of phthaloyl α, α-dipeptides.[58]



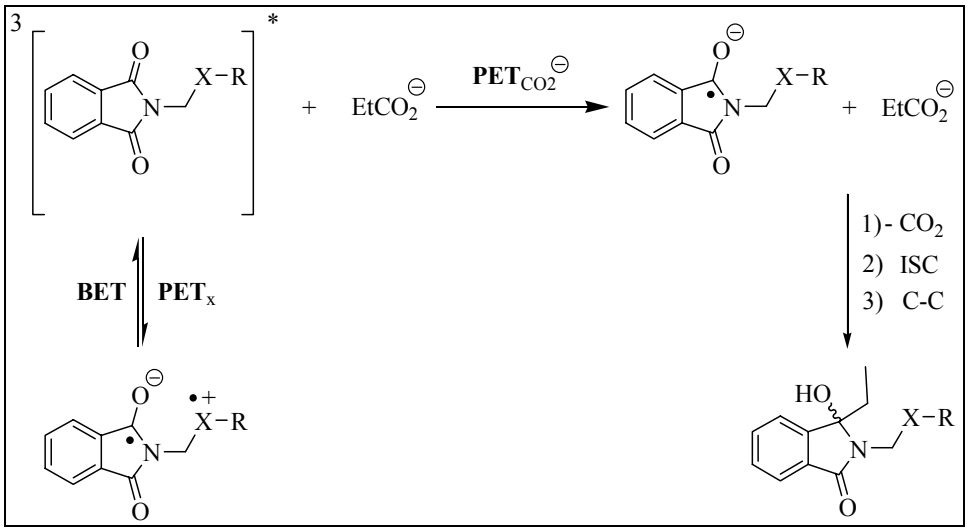
Scheme 98: Possible deactivation for *N*-acyl β-alanine and phthaloyl α, α-dipeptides

In conclusion, the results from this work demonstrate that the photoaddition efficiencies of heteroatom-containing carboxylates to phthalimides strongly depend on the nature and the position of the heteroatom relative to the terminal carboxylate. Two extreme scenarios have been identified and the incorporation of a heteroatom can either dramatically increase the efficiency and regioselectivity of the addition or can result in complete deactivation. Oxidation potentials can be used as a measure to

evaluate the origin, *i.e.* heteroatom *vs.* carboxylate, of the initial electron transfer step.

4.2.5 Photoreactions of donor-substituted phthalimides with potassium propionate

The photoreactivity of donor-substituted phthalimides completely agrees with the corresponding photoaddition reactions involving heteroatom-substituted phthalimides (Scheme **99**).



Scheme 99: Mechanistic scenarios for **PDC**-ethylation of donor-substituted phthalimides

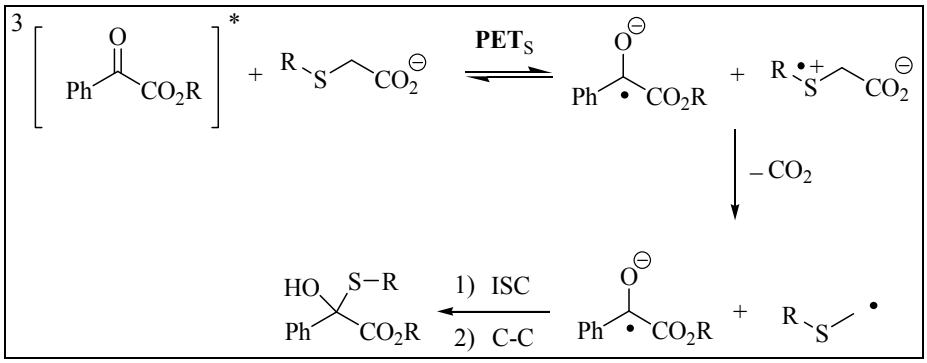
The incorporation of amide or ether groups in the *N*-side chain has no influence on the ethylation and electron transfer thus occurs exclusively from the propionate. In contrast, amine- and thioether-derived phthalimides completely prevent photodecarboxylative addition. In line with their, compared to the carboxylate function, lower oxidation potentials, electron transfer dominates for both heteroatoms. In case of the sulphur-containing phthalimide, this electron transfer is completely non-productive. *Intramolecular* **PET**-cyclisation for this compound is also known to be very inefficient (1% upon exhaustive irradiation in benzene).[44, 152]

In contrast, the nitrogen-containing analogue showed extensive photodecomposition. Photocyclisation products were again not detected and such cyclisations are known to critically depend on the structure of the amino-derived phthalimide.[153,154]

4.3 Photoaddition reactions involving phenylglyoxolates

The **PET**-photochemistry of phenylglyoxolates has been intensively investigated by Neckers and co-workers.[155] Photoadditions of thioethers and amines give the corresponding addition products in moderate to high yields. In contrast, phenylacetate does not undergo photodecarboxylative addition to the phenylglyoxolate chromophore. Hence and in line with dimethoxy *N*-methylphthalimide, the oxidation power of the excited phenylglyoxolate is too low to allow electron transfer from the carboxylate function. When α-thioalkyl-substituted carboxylates were applied, irradiations in aqueous acetone furnished the desired decarboxylative addition products in moderate to good yields. This activation process for carbon dioxide extrusion can be explained based on the lower oxidation potential of the thioether fragment ($E_{Ox.}$ S > $E_{Ox.}$ CO_2^-).

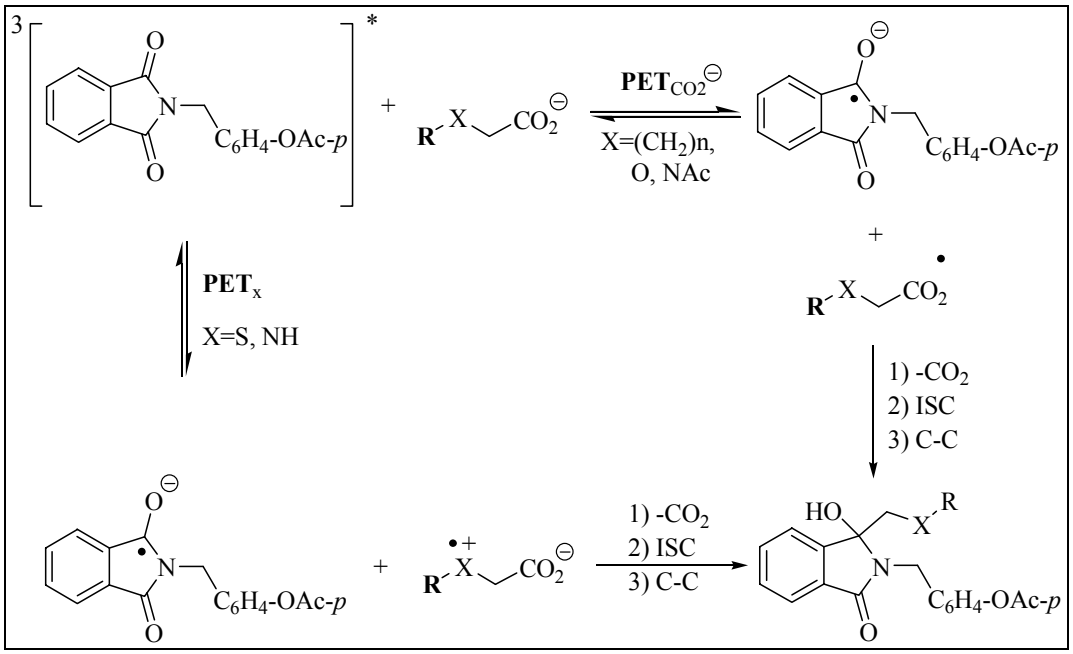
Triplet sensitisation generates the triplet state of phenylglyoxolate, which after electron transfer yields the corresponding radical ion pair. Subsequent loss of the α-carboxy group gives the carbon centred radical, which after intersystem crossing undergoes C-C bond formation to the photoproduct (Scheme **100**). The overall mechanism is thus identical to that involving phthalimides.



Scheme 100: Mechanism for the addition of α-thioalkyl carboxylates to phenylglyoxolates

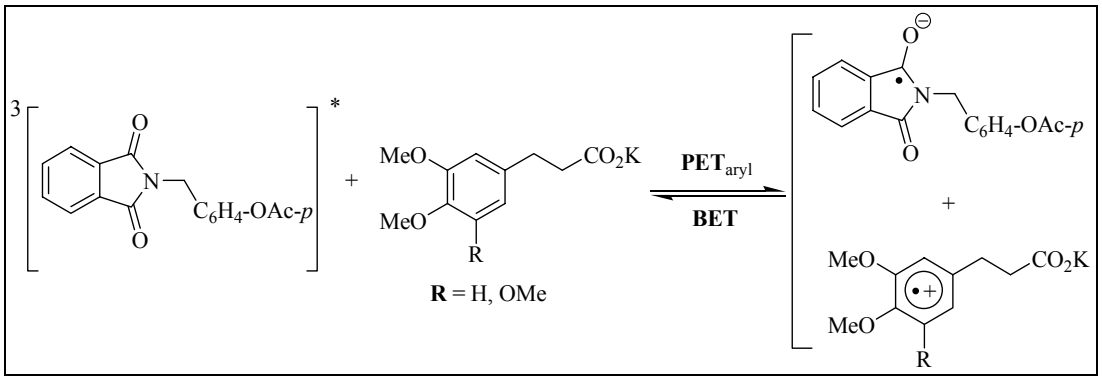
4.4 Photoreactions of 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9 with alkyl and heteroatom-substituted carboxylates

With a few exceptions, the mechanisms for the photoadditions of alkyl- and heteroatom-substituted carboxylates to 2-(4-acetoxybenzyl)isoindoline-1,3-dione mirrors those involving *N*-methylphthalimide (Scheme **101**). In case of nitrogen- and sulphur-derived carboxylates, initial electron transfer occurs from the heteroatom, followed by α-decarboxylation. In contrast, alkyl-, oxygen-and amide-containing carboxylates react via electron transfer from the carboxylate function. Both pathways efficiently yield the desired addition products in moderate to good yields.



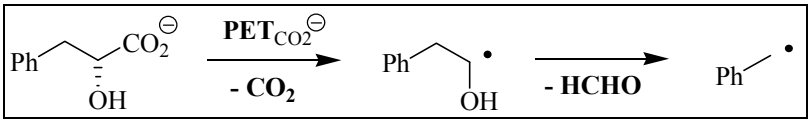
Scheme 101: Mechanistic scenario for the addition of various carboxylates to 2-(4-acetoxybenzyl)phthalimide.

The lack of photoreactivity for the di- and trimethoxyphenyl-substituted 3-propanoic acids can be convincingly explained based on the electronic nature of the aryl-groups. Competing electron transfer from the electron-rich aryl groups remains unproductive as decarboxylation cannot occur from the remote position of the carboxylate. Instead, back electron transfer regenerates the starting materials. Similar to β-thioalkyl-groups, remote electron-rich aryl-substituents therefore function as hole traps (Scheme **102**).



Scheme 102: Deactivation by remote electron-rich aryl-substituents

The photoaddition involving *L*-3-phenyllactic acid exclusively gave the benzylated photoadduct. This can be explained by a rapid sequence of decarboxylation and retro-Aldol fragmentation (Scheme **103**). Obviously, *unimolecular* loss of formaldehyde can successfully compete with intersystem crossing and C-C bond formation in this case. The resulting benzyl radical is highly stabilised and subsequently undergoes addition to the benzylated product. In contrast, mandelic acid is known to add to *N*-methylphthalimide without loss of formaldehyde.[60a] The formation of the resulting phenyl radical disfavours retro-Aldol fragmentation in this case. Follow-up fragmentation, *i.e.* decarbonylations (loss of CO), are also known for the addition of α-keto carboxylates.[59b]



Scheme 103: Decarboxylation/retro-Aldol cascade for *L*-3-phenyllactic acid

5 Outlook

The protocol of the photodecarboxylative addition can be applied to a variety of additional carboxylic acid libraries. In particular *N*-protected amino acids and peptides may be of interest due to their biological importance.

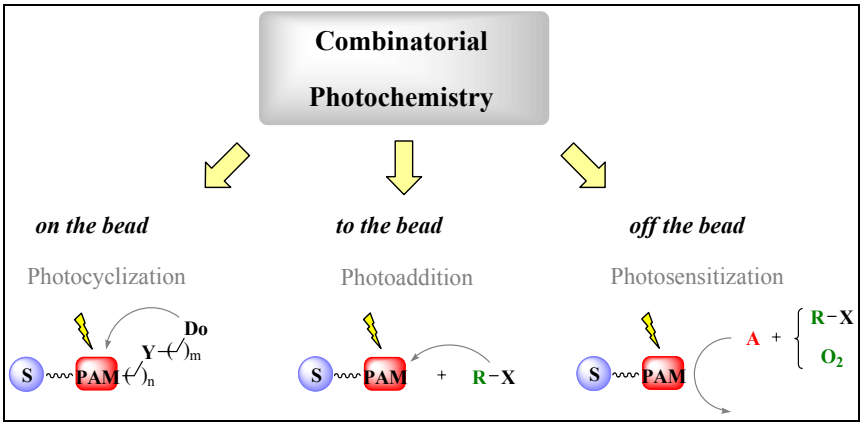
The regioselectivity of the photoaddition could be investigated either by carboxylates bearing multiple carboxylic acid functions or by using unsymmetrically substituted phthalimides. The latter strategy is important for the synthesis of known, active *AKS-186* analogues (Figure **13**).

To allow further transformation of the photoproducts, the incorporation of reactive functional groups, either in *terminal* position or in a side-chain, such as halides or thiols may also be considered.

Photoadditon reactions on smaller (*micro*) or larger (*macro*) scale could be a way to investigate newly emerging photochemical technologies. This would also allow a way to produce larger amounts of bioactive compounds for future screening and toxicology studies. This would ultimately overcome the current neglect of synthetic photochemistry in industry. Most conventional "*thermal*" synthetic strategies have reached their limits and consequently new approaches in drug design have to be developed in order to identify new chemical lead structures in the future.

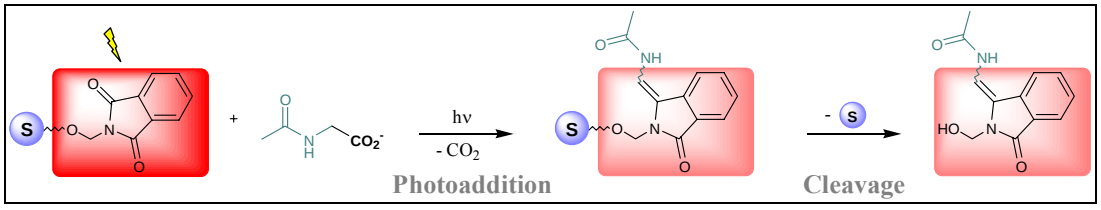
A new synthetic R&D approach might be the development of *combinatorial photochemistry* - an innovative combination of combinatorial chemistry and synthetic organic photochemistry. Three main synthetic strategies have been recently defined by Oelgemöller: photoinduced macrocyclisations (*photochemistry on the bead*), photoadditions (*photochemistry to the bead*) and sensitised phototransformations (*photochemistry off the bead*). The general concepts are outlined below (Scheme **104**) where **PAM** = Photoactive Moiety; **S** = Solid Support; **Y** = Linker; **Do** = Donor and **A**, **R-X** = Substrates. For *intermolecular* addition reactions like those presented in this thesis, solely the photoactive component is attached to the solid resin via a proper functional group. An excess amount of the reaction partner (**R-X**) is added and this mixture is irradiated using the same techniques for conventional photoadditions. Solvent volumes can be significantly reduced, and excess or

unreactive additive can be easily removed by filtration and subsequent washing. The latter procedures are the main advantages of *combinatorial chemistry* and will drastically simplify and shorten the purification and isolation process. In comparison to the time consuming *conventional* synthesis *in solution*, the combinatorial approach allows rapid synthesis of a broad number of target compounds in one single run by simply varying **R-X**.



Scheme 104: Combinatorial Photochemistry

The *photo-Kolbe* decarboxylation involving phthalimides could serve as a model transformation to prove the feasibility of the concept. The large number of commercially available carboxylic acids would allow rapid generation of broad libraries.
Attachment of the *photoactive moiety* to the solid support could be achieved either *via* substituents at the chromophore (*head-to-resin* alignment), or more conveniently through suitable side-chains at the *N*-terminus. A representative example is shown below (Scheme **105**) in which *N*-acetylglycine is added to solid-supported *N*-hydroxymethyl phthalimide.



Scheme 105: *Photo-Kolbe* reaction to the bead

6 Experimental

6.1 General

6.1.1 Spectroscopic methods

NMR: NMR spectra were recorded on a *Bruker 400 Ultrashield*^{TM} instrument (400 MHz for ^{1}H; 100 MHz for ^{13}C) using the *XWin-NMR 2.6* software. Chemical shift values are referred to solvent residual resonances: $CDCl_3$ (7.26/77.36 ppm), DMSO-d_6 (2.54/40.45 ppm) and acetone-d_6 (2.09/30.60 and 206.3 ppm). Chemical shifts δ are given in ppm, coupling constants *J* in Hz.

IR–Spectroscopy: IR spectra were recorded on a *Perkin-Elmer system 2000 FT-IR* spectrophotometer as KBr discs.

Mass-spectrometry: All MS-spectra were recorded in the group of Prof. Mattay at the University of Bielefeld (Germany).

ESI was performed using a *Bruker APEX III* Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer equipped with a 7.0 T, 160 mm bore superconducting magnet, infinity cell, and interfaced to an external (nano) ESI ion source. Nitrogen served both as the nebuliser gas and the dry gas for ESI. Nitrogen was generated by a *Bruker nitrogen generator NGM 11*. Argon served as cooling gas in the infinity cell and collision gas for MS^n experiments. Scan accumulation and data processing were performed with *XMASS NT V. 5.0* on a PC Workstation.

EI and CI mass spectra were recorded using an *Autospec X* magnetic sector mass spectrometer with EBE geometry equipped with a standard EI or CI source. Samples were introduced by push rod in aluminium

crucibles if not otherwise noted. Ions were accelerated by 8 kV in EI mode and 6 kV in CI mode. The spectra shown here are recorded and processed with *OPUS software V. 3.6* by the accumulation and averaging of several single spectra.

ESI/APCI mass spectra were recorded using a *Bruker Esquire 3000* ion trap mass spectrometer equipped with a standard ESI/APCI source. Samples were introduced by direct infusion with a syringe pump. Nitrogen served both as the nebuliser gas and the dry gas. Nitrogen was generated by a *Bruker nitrogen generator NGM 11*. Helium served as cooling gas for the ion trap and collision gas for MS^n experiments. The spectra shown here are recorded with the *Bruker Daltonik esquire NT 5.1 esquire Control software* by the accumulation and averaging of several single spectra (as cited). Data Analysis software 3.1 was used for processing the spectra.

6.1.2 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.

6.1.3 Analytical Methods

Melting points: Melting points were determined using a *Griffin Melting Point Apparatus* and are uncorrected.

6.1.4 Photolysis

Glassware: All photoreactions were performed in *Pyrex*® tubes (150 and 350 ml).

Reactors: Photochemical reactions were performed in a *RPR–200 Rayonet photochemical chamber reactor* (Southern New England Ultraviolet Company) equipped with *RPR 3000 Å lamps* (λ_{max} = 300 ± 25 nm). All reactions were carried out under an atmosphere of nitrogen.

6.1.5 Solvents and reagents

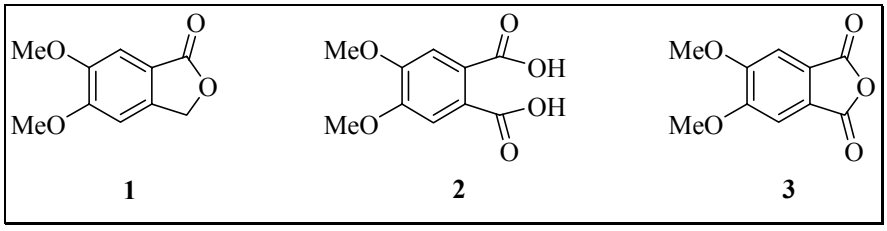
All solvents and starting materials were obtained from commercial suppliers (*Sigma-Aldrich* and *Fluka*) and were used without purification.

6.2 Synthesis of starting materials

6.2.1 Synthesis of phthalimides

Experiment 1

6.2.1.1 Synthesis of 4,5-dimethoxyphthalic anhydride 3 (FH-38)



6.2.1.1.1 Synthesis of m-meconine 1

A solution of 15 g (82.34 mmol) 3,4-dimethoxybenzoic acid [veratric acid] and 23 ml (20.24 mmol) paraformaldehyde in 500 ml conc. HCl was stirred for 6 h at 80°C. The clear, brownish solution was cooled to room temperature and *ca.* 500 ml of ice-cooled NH_4OH were added until a beige precipitate was formed (pH changed from 1 to 7). Vacuum filtration gave a beige solid, which was washed with water. After drying 13.32 g (68.59 mmol; 83%) of *m*-meconine **1** were obtained as beige solid.

Melting point: 148-153°C (Lit:[156] 154-156°C).

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 3.84 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.28 (s, 2 H, CH_2), 7.23 (s, 1 H, H_{arom}), 7.26 (s, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 56.9 (s, 1 C, OCH_3), 57.1 (s, 1 C, OCH_3), 70.2 (s, 1 C, CH_2), 105.7 (s, 1 C, CH_{arom}), 106.7 (s, 1 C, CH_{arom}), 117.4 (s, 1 C, Cq), 142.8 (s, 1 C, Cq), 150.9 (s, 1 C, Cq), 155.6 (s, 1 C, Cq), 171.9 (s, 1 C, C=O).

6.2.1.1.2 Synthesis of 4,5-dimethoxyphthalic acid 2

A solution of 4.89 g (25.18 mmol) of *m*-meconine **1**, 3.96g (25.06 mmol) of $KMnO_4$ and 2.65 g (25.00 mmol) of Na_2CO_3 in 250 ml of water was stirred at room temperature for 1 week. 50 ml of 27.5% H_2O_2 were carefully added upon which the colour changed to brownish and a precipitation occurred. The solid was filtered off and the clear filtrate was washed twice with EA. The aqueous layer was acidified to pH 1 with conc. HCl and extracted with EA (2 × 150 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated and the solid residue was dried in vacuum. 1.27 g (5.62 mmol; 22%) of 4,5-dimethoxyphthalic acid **2** were obtained as a colourless solid. The crude material was used without further purification.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 4.00 (s, 6 H, OCH_3), 7.68 (s, 2 H, H_{arom}), >10 (s, 2 H, OH).

6.2.1.1.3 Synthesis of 4,5-dimethoxyphthalic anhydride 3

A solution of 1.25 g (5.53 mmol) of 4,5-dimethoxyphthalic acid in 100 ml of acetic anhydride was refluxed for 1 hour. Most of the acetic anhydride was distilled off. Upon standing, colourless needle formed which were filtered off. Drying gave 30 mg (0.14 mmol; 4%) of compound **3**. The mother liquor was evaporated to dryness. After drying, an additional 1.1 g (5.28 mmol; 95%) of 4,5-dimethoxyphthalic anhydride **3** were obtained as a colourless solid. The combined material was used without further purification.

^{1}H–NMR: (400 MHz, $CDCl_3$)

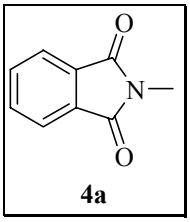
δ (ppm) = 4.03 (s, 6 H, OCH_3), 7.36 (s, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 57.2 (s, 2 C, OCH_3), 106.4 (s, 2 C, CH_{arom}), 125.2 (s, 2 C, Cq), 156.1 (s, 2 C, Cq), 163.4 (s, 2 C, C=O).

Experiment 2

6.2.1.2 Synthesis of N-methylphthalimide 4a (FH-03)



4a

A solution of 10.04 g (67.78 mmol) of phthalic anhydride in 80 ml of *N*-methylformamide was heated to 160°C for 8 h. The reaction mixture was cooled down to room temperature and was placed in an ice-bath upon which colourless needles formed. The solid material was filtered off, carefully washed with 10 ml of EtOH and dried. Recrystallisation from EtOH yielded 6.62 g (41.08 mmol; 61%) of *N*-methylphthalimide **4a** as colourless needles.

Melting point: 128-131°C (Lit:[157] 135°C).

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 3.18 (s, 3 H, NCH_3), 7.70 (dd, ^{3}J = 5.3, ^{4}J = 3.1 Hz, 2 H, H_{arom}), 7.84 (dd, ^{3}J = 5.3, ^{4}J = 3.1 Hz, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

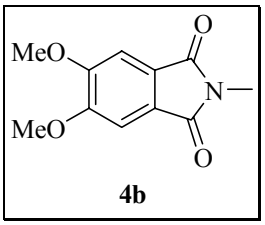
δ (ppm) = 24.3 (s, 1 C, NCH_3), 123.5 (s, 2 C, CH_{arom}), 132.6 (s, 2 C, Cq_{arom}), 134.2 (s, 2 C, CH_{arom}), 168.8 (s, 2 C, C=O).

IR: (KBr, disk)

ν (cm^{-1}) = 2896 (vi, CH_{aliph}), 2344 (w, CN), 1720.59 (s, C=O), 1527.31 (w, $C=C_{arom}$), 717.33 (s, CH_{arom}).

Experiment 3

6.2.1.3 Synthesis of 5,6-dimethoxy-N-methylphthalimide 4b (FH-48)



4b

A solution of 1.10 g (5.28 mmol) of 4,5-dimethoxyphthalic anhydride in 50 ml of *N*-methylformamide was heated to 190°C for 2 h. Upon standing overnight at room

temperature yellow needles crystallised. The solid material was collected by vacuum filtration. Drying furnished 0.88 g (3.98 mmol; 75%) of 5,6-dimethoxy-*N*-methylphthalimide **4b** as yellow needles.

Melting point: 253-256°C (Lit:[158] 266°C).

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 3.14 (s, 3 H, NCH_3), 3.99 (s, 6 H, 2 * OCH_3), 7.30 (s, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

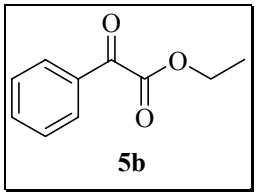
δ (ppm) = 24.3 (s, 1 C, NCH_3), 56.9 (s, 2 C, OCH_3), 105.6 (s, 2 C, CH_{arom}), 125.9 (s, 2 C, Cq_{arom}), 154.0 (s, 2 C, Cq_{arom}), 169.0 (s, 2 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 2952.05 (vi; CH_{aliph}), 2345.6 (w; CN), 1708.29 (s; C=O), 1600.11 (w; $C=C_{arom}$), 1012.95 (s; CO), 744.15 (s; CH_{arom}).

Experiment 4

6.2.2 Synthesis of ethyl benzoylformate 5b (FH-06)



5b

1 ml of conc. H_2SO_4 was added to a solution of 2.06 g (13.72 mmol) of benzoylformic acid in 50 ml of EtOH. The reaction mixture was refluxed for 5 h, cooled down to room temperature and stirred overnight. 50 ml of H_2O were added and the EtOH was removed by rotary evaporation. On standing a colourless solid precipitated. The solid material was extracted from the reaction mixture with DCM (3 × 50 ml). Evaporation gave a yellow oil which was dried in vacuum. Column chromato-

graphy (SiO_2, DCM) gave 1.22 g (6.85 mmol; 50%) of ethyl benzoylformate **5b** as a yellow oil.

^{1}H–NMR: (400 MHz, $CDCl_3$)

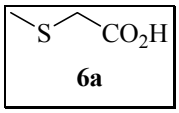
δ (ppm) = 1.35 (t, 3 H, CH_3), 4.39 (q, 2 H, CH_2), 7.45 (m, 2 H, H_{arom}), 7.58 (m, 1 H, H_{arom}), 7.95 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 14.1 (s, 1 C, CH_3), 62.4 (s, 1 C, CH_2), 129.0 (s, 2 C, CH_{arom}), 130.0 (s, 2 C, CH_{arom}), 132.5 (s, 1 C, CH_{arom}), 135.0 (s, 1 C, Cq), 164.0 (s; 1 C, C=O), 186.6 (s, 1 C, C=O).

Experiment 5

6.2.3 Synthesis of methylthio acetic acid 6a (FH-09)



6a

7 ml (100.68 mmol) Thioglycolic acid was dissolved in 200 ml 1N NaOH and to this solution 10 ml (160.63 mmol) of iodomethane (MeI) was added and the reaction mixture was left to stir at room temperature for 3 days. This solution was washed with diethyl ether (2 × 100 ml), then Conc. H_2SO_4 was added until the solution acidity was (pH = 1), at this stage the solution colour turned from colourless to yellow orange after addition of sulphuric acid.

This solution was extracted with diethyl ether (5 × 50 ml) and the organic layer was washed with saturated NaCl it was dried over $MgSO_4$/Charcoal and was filtered by vacuum filtration and the filtrate was evaporated by rotary evaporator to give the red product 6.10 g (57.47 mmol; 57%) of **6a**.

^{1}H–NMR: (400 MHz, $CDCl_3$)

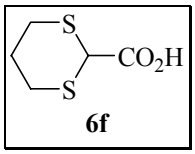
δ (ppm) = 2.19 (s, 3 H, CH_3), 3.19 (s, 2 H, CH_2), 9.27 (s, 1 H, OH).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 16.6 (s, 1 C, CH_3), 35.9 (s, 1 C, CH_2), 176.6 (s, 1 C, C=O).

Experiment 6

6.2.4 Synthesis of 1,3-dithiane-2-carboxylic acid 6f (FH-37)



6f

1.84 g (19.99 mmol) Glyoxylic acid monohydrate, 2.20 ml (21.91 mmol) 1,3-propanedithiol and 0.38 g (2.20 mmol) Toluene-4-sulfonic acid (TsOH) in 50 ml (559.46 mmol) benzene was refluxed for 2 h. The reaction was cooled to 25°C and the organic layer was extracted with saturated $NaHCO_3$ (3 × 10 ml). The aqueous layer was washed with diethyl ether [Et_2O] (25 ml) then cautiously acidified with HCl and finally extracted with ethyl acetate [E.A.] (4 × 50 ml). The organic layer was dried over $MgSO_4$ and was filtered by gravity filtration and the filtrate was evaporated by rotary evaporator to give a colourless solid product 2.98 g (18.14 mmol; 91%) of **6f**.

Melting point: 92-98°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

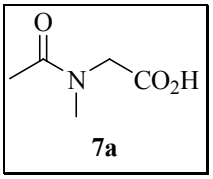
δ (ppm) = 2.03 (m, 1 H, CH_2), 2.16 (m, 1 H, CH_2), 2.60 (m, 2 H, CH_2), 3.42 (m, 2 H, CH_2), 4.16 (s, 1 H, CH).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 25.1 (s, 1 C, CH_2), 26.0 (s, 2 C, CH_2), 39.6 (s, 1 C, CH), 175.5 (s, 1 C, C=O).

Experiment 7

6.2.5 Synthesis of 2-(*N*-methylacetamido) acetic acid 7a (FH-70)



7a

4.16 g (46.69 mmol) Sarcosine was dissolved in 5.8 ml (61.47 mmol) acetic anhydride [Ac_2O] and 25 ml (279.73 mmol) benzene; this solution mixture was refluxed for 6 h. The solvent was evaporated by rotary evaporation and the product was yellowish viscous liquid which was cooled in an ice bath until a yellow solid was formed (glass rod was used to help the crystallisation formed by scratching the flask walls). This product was then recrystallised from hot ethanol [EtOH] and was filtered by vacuum filtration and the filtrate was cooled in an ice bath and the colourless solid in the funnel was washed with EtOH. The pure product 2.40 g (18.30 mmol; 39%) of **7a** was colourless solid.

Melting point: 129-131°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

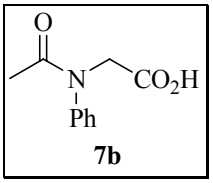
δ (ppm) = 2.17 (s, 3 H, CH_3), 3.11 (s, 3 H, NCH_3), 3.49 (s, 1 H, OH), 4.14 (s, 2 H, CH_2).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.6 (s, 1 C, CH_3), 31.3 (s, 1 C, NCH_3), 37.9 (s, 1 C, CH_2), 172.3 (s, 1 C, C=O), 172.7 (s, 1 C, C=O).

Experiment 8

6.2.6 Synthesis of 2-(*N*-phenylacetamido) acetic acid 7b (FH-71)



7b

4.02 g (26.59 mmol) *N*-Phenylglycine was dissolved in 5.6 ml (59.35 mmol) acetic anhydride [Ac_2O] and 25 ml (279.73 mmol) benzene; this solution mixture was refluxed for 6 h. The solvent was evaporated by rotary evaporation and the product was brown viscous liquid which was cooled in an ice bath until a brown solid was formed. This product was then recrystallised from hot ethanol [EtOH] and was filtered by vacuum filtration and the solid product in the funnel was washed with EtOH. The pure product 1.37 g (7.09 mmol; 27%) of **7b** was yellow solid.

Melting point: 189-191°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

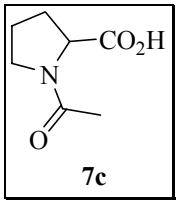
δ (ppm) = 1.92 (s, 3 H, CH_3), 3.60 (s, 1 H, OH), 4.35 (s, 2 H, CH_2), 7.35 (m, 3 H, H_{arom}), 7.41 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 22.5 (s, 1 C, CH_3), 51.1 (s, 1 C, CH_2), 128.1 (s, 2 C, CH_{arom}), 128.7 (s, 1 C, CH_{arom}), 130.2 (s, 2 C, CH_{arom}), 143.6 (s, 1 C, Cq), 172.0 (s, 1 C, C=O), 172.1 (s, 1 C, C=O).

Experiment 9

6.2.7 Synthesis of 1-acetylpyrrolidine-2-carboxylic acid 7c (FH-72)



7c

4.01 g (34.83 mmol) *D,L*-Proline was dissolved in 5.6 ml (59.35 mmol) acetic anhydride [Ac_2O] and 25 ml (279.73 mmol) benzene; this solution mixture was refluxed for 6 h. The solvent was evaporated by rotary evaporation and the product was yellowish viscous liquid which was cooled in an ice bath until a yellow viscous liquid was formed. This product was then recrystallised from hot ethanol [EtOH] and was filtered by vacuum filtration and the colourless solid product 5.25 g (33.41 mmol; 96%) of **7c** was washed with hexane and was left out in the fridge overnight.

Melting point: 60-65°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

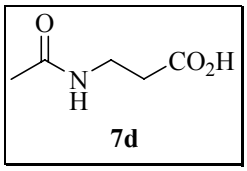
δ (ppm) = 2.04 (m, 3 H, CH_2), 2.17 (s, 3 H, CH_3), 2.40 (m, 1 H, CH_2), 3.54 (m, 2 H, CH_2), 4.57 (m, 1 H, CH).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 22.5 (s, 1 C, CH_3), 25.1 (s, 1 C, CH_2), 28.1 (s, 1 C, CH_2), 48.9 (s, 1 C, CH_2), 60.1 (s, 1 C, CH), 172.9 (s, 1 C, C=O), 173.0 (s, 1 C, C=O).

Experiment 10

6.2.8 Synthesis of 3-acetamido propanoic acid 7d (FH-75)



7d

0.89 g (9.99 mmol) 3-Amino propanoic acid [β-Alanine] was dissolved in 1.05 ml (11.12 mmol) acetic anhydride [Ac_2O] and 35 ml (546.03 mmol) dichloromethane [DCM]; this solution mixture was refluxed for 24 h. The colour was clear, colourless. The solvent was evaporated by rotary evaporation and the product 1.27 g (9.68 mmol; 97%) of **7d** was colourless solid.

Melting point: 52-55°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

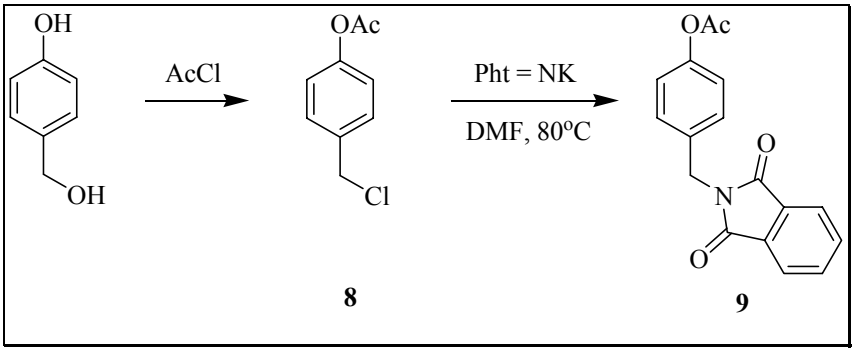
δ (ppm) = 2.00 (s, 3 H, CH_3), 2.58 (dd, ^3J = 12.0, ^4J = 6.1 Hz, 2 H, CH_2), 3.51 (dd, ^3J = 12.0, ^4J = 6.1 Hz, 2 H, CH_2), 6.43 (br. s, 1 H, NH), 8.69 (br. s, 1 H, OH).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.4 (s, 1 C, CH_3), 34.1 (s, 1 C, NCH_2), 35.3 (s, 1 C, CCH_2), 171.6 (s, 1 C, NC=O), 177.1 (s, 1 C, CC=O).

Experiment 11

6.2.9 Synthesis of 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9 (FH-84)



6.2.9.1 Synthesis of 4-(chloromethyl)phenyl acetate 8 (FH-83)

4-hydroxy-benzyl alcohol, 5.00 g (40.32 mmol) was added in small portions to a stirred solution of acetyl chloride (AcCl) (20 ml). The addition was done at such a rate so as to keep the evolution of HCl gas at a moderate rate. The resulting solution was stirred at ambient temperature overnight. Excess of acetyl chloride was removed with a water pump (rotary evaporator). The resulting liquid was diluted with diethyl ether (Et_2O) (50 ml) and then treated with a saturated solution of $NaHCO_3$. After the CO_2 evolution had ceased, the solution was transferred to a separatory funnel and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 * 25 ml). The combined organic phase was washed with brine (saturated NaCl) (2 * 25 ml) and dried over $MgSO_4$ (2 spatulas).

Removal of solvent by rotary evaporator after gravity filtration gave 6.24 g (33.80 mmol; 84%) of product **8** as pale yellow oil.

^{1}H-NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.29 (s, 3 H, CH_3CO), 4.57 (s, 2 H, CH_2Cl), 7.08 (d, 2 H, *J*= 8.6 Hz, H_{arom}), 7.39 (d, 2 H, *J* = 8.6 Hz, H_{arom}).

^{13}C-NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.3 (s, 1 C, CH_3CO), 45.8 (s, 1 C, CH_2Cl), 122.1 (s, 2 C, CH_{arom}), 130.0 (s, 2 C, CH_{arom}), 135.2 (s, 1 C, Cq), 150.8 (s, 1 C, Cq), 169.6 (s, 1 C, C=O).

6.2.9.2 Synthesis of 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9 (FH-84)

A solution of 4-(chloromethyl)phenyl acetate, 6.24 g (33.80 mmol) and potassium phthalimide, 7.50g (40.49 mmol) in DMF (50 ml) was heated by reflux at 80 °C for 3 hours under nitrogen (N_2). The cooled reaction mixture was diluted with $CHCl_3$ (70 ml) and H_2O (100 ml) was added. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (3 * 25 ml). The combined organic phase was washed with cold 0.1 M NaOH (50 ml) and H_2O (2 * 50 ml). The solvent was evaporated until a white solid started to precipitate.

A total of Et_2O (100 ml) was added to get complete precipitation. After, 1 hour, the solid was collected by suction filtration, washed with Et_2O, and dried to give 2-(4-acetoxybenzyl)isoindoline-1,3-dione, 7.09 g (24.01 mmol, 71%) of **9** as white solid.

Melting point: 162-163 °C.

^{1}H-NMR: (400 MHz, $CDCl_3$)

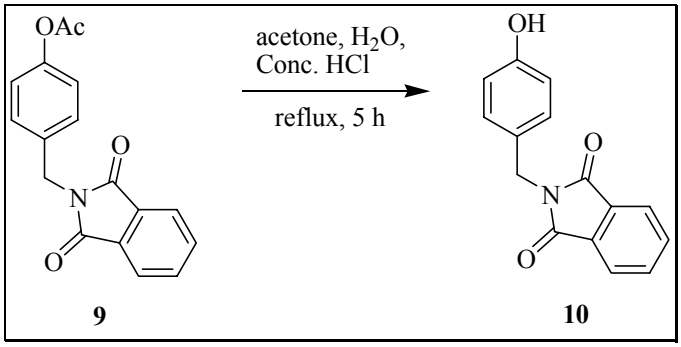
δ (ppm) = 2.27 (s, 3 H, CH_3CO), 4.82 (s, 2 H, CH_2N), 7.03 (d, ^{3}J = 8.6 Hz, 2 H, H_{arom}), 7.47 (d, ^{3}J = 8.6 Hz, 2 H, H_{arom}), 7.71 (m, 2 H, H_{arom}), 784 (m, 2 H, H_{arom}).

^{13}C-NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.4 (s, 1 C, CH_3CO), 41.3 (s, 1 C, CH_2N), 122.1 (s, 2 C, CH_{arom}), 123.7 (s, 2 C, CH_{arom}), 130.4 (s, 2 C, CH_{arom}), 132.4 (s, 2 C, CH_{arom}), 134.3 (s, 2 C, CH_{arom}), 134.4 (s, 1 C, Cq), 150.6 (s, 1 C, Cq), 168.3 (s, 1 C, C=O), 169.8 (s, 1 C, C=O).

Experiment 12

6.2.10 Synthesis of 2-(4-hydroxybenzyl)isoindoline-1,3-dione 10 (FH-88)



2-(4-acetoxybenzyl)isoindoline-1,3-dione, 3.51 g (11.89 mmol) was dissolved in acetone (40ml), H_2O (28 ml) and Conc. HCl (12 ml), then it was refluxed for 5 h. This reaction was monitored by TLC. This solution was left to stir at r.t. overnight. H_2O (50 ml) was added, acetone was evaporated and the solution was left to settle down for 5 minutes. The white precipitate occurred was washed with H_2O and dried to give the product, 2.87 g (11.33 mmol; 95%) of **10** as white powder.

TLC: R_f = 0.51 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 150-153 °C.

^{1}H-NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 4.83 (s, 2 H, CH_2), 7.03 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 7.47 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 7.71 (dd, ^3J = 5.4, ^4J = 3.1 Hz, 2 H, H_{arom}), 784 (dd, ^3J = 5.4, ^4J = 3.1 Hz, 2 H, H_{arom}).

^{13}C-NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 41.3 (s, 1 C, CH_2), 122.2 (s, 2 C, CH_{arom}), 123.7 (s, 2 C, CH_{arom}), 130.4 (s, 2 C, CH_{arom}), 130.7 (s, 1 C, Cq), 132.4 (s, 1 C, Cq), 134.3 (s, 1 C, Cq), 134.4 (s, 2 C, CH_{arom}), 150.6 (s, 1 C, Cq), 168.3 (s, 1 C, C=O), 169.8 (s, 1 C, C=O).

6.3 Photoreactions

6.3.1 General procedure for photoreactions involving *N*-methylphthalimide 4a (GP-1)

N-Methylphthalimide **4a** (or analogues) (1.5 mmol) was dissolved in 10 ml acetone. The carboxylic acid (4.5 mmol) and K_2CO_3 (2.25 mmol) were dissolved in 15 ml H_2O and 5 ml acetone and were sonicated using an Ultrasound bath until the formation of CO_2 has ceased. The solutions were poured into a Pyrex tube, which was filled up to 150 ml with a 1:1 mixture of acetone and H_2O. The solution was further sonicated for 10 minutes and was degassed with a slow stream of N_2 for 5 minutes. This solution was irradiated in a Photoreactor ($\lambda = 300 \pm 25$ nm) and the progress of the reaction was monitored by TLC. After complete conversion, most of the acetone was removed in vacuo. The remaining solution was extracted with DCM (3 × 25 ml). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 25 ml) and saturated NaCl (2 × 25 ml), dried over $MgSO_4$ and evaporated at a rotary evaporator to dryness. The crude product was purified by column chromatography.

6.3.2 General procedure for photoreactions involving *N*-methylphthalimide 4a (GP-2)

N-Methylphthalimide **4a** (1.5 mmol) was dissolved in 10 ml acetone. The carboxylic acid (4.5 mmol) was dissolved in acetone and the solution mixture was sonicated using an Ultrasound bath until the formation of CO_2 has ceased. The solutions were poured into a Pyrex tube, which was filled up to 150 ml with acetone. The solution was further sonicated for 10 minutes and was degassed with a slow stream of N_2 for 5 minutes. This solution was irradiated in a Photoreactor ($\lambda = 300 \pm 25$ nm) and the progress of the reaction was monitored by TLC. After complete conversion, most of the acetone was removed in vacuo. The remaining solution was extracted with DCM

(3 × 25 ml). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 25 ml) and saturated NaCl (2 × 25 ml), dried over $MgSO_4$ and evaporated at a rotary evaporator to dryness. The crude product was purified by column chromatography.

6.3.3 General procedure for photoreactions involving 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9 (GP-3)

2-(4-Acetoxybenzyl)isoindoline-1,3-dione **9** (1.50 mmol) was dissolved in acetone (10 ml); Carboxylic acid (4.50 mmol) and K_2CO_3 (2.25 mmol) were dissolved in H_2O (15 ml) and acetone (5 ml). This solution was sonicated using an Ultrasound bath until the formation of CO_2 has ceased. The solutions were poured into a Pyrex tube, which was filled up to 150 ml with a 1 : 1 mixture of acetone and H_2O. The solution was further sonicated for 10 minutes and was degassed with a slow stream of N_2 for 5 minutes. This solution was irradiated in a Photoreactor ($\lambda = 300 \pm 25$ nm) and the progress of the reaction was monitored by TLC. After complete conversion, most of the acetone was removed in vacuo. The remaining solution was extracted with DCM (3 × 25 ml). The combined organic layers were washed with saturated $NaHCO_3$ (3 × 25 ml) and saturated NaCl (3 × 25 ml), dried over $MgSO_4$ and evaporated at a rotary evaporator to dryness. The crude product was purified by column chromatography.

6.3.4 General procedure for photoreactions involving 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9 (GP-4)

2-(4-Acetoxybenzyl)isoindoline-1,3-dione **9** (1.50 mmol) was dissolved in acetone (10 ml); Carboxylic acid (4.50 mmol) and K_2CO_3 (2.25 mmol) were dissolved in H_2O (15 ml) and acetone (5 ml). This solution was sonicated using an Ultrasound bath until the formation of CO_2 has ceased. The solutions were poured into a Pyrex

tube, which was filled up to 150 ml with a 3 : 1 mixture of acetone and H_2O. The solution was further sonicated for 10 minutes and was degassed with a slow stream of N_2 for 5 minutes. This solution was irradiated in a Photoreactor ($\lambda = 300 \pm 25$ nm) and the progress of the reaction was monitored by TLC. After complete conversion, most of the acetone was removed in vacuo. The remaining solution was extracted with DCM (3 × 25 ml). The combined organic layers were washed with saturated $NaHCO_3$ (3 × 25 ml) and saturated NaCl (3 × 25 ml), dried over $MgSO_4$ and evaporated at a rotary evaporator to dryness. The crude product was purified by column chromatography.

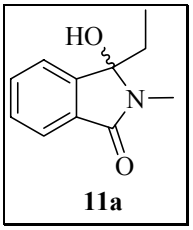
6.3.5 General procedure for dehydration (GP-5)

Phenyl acetate compounds, 0.10 g was dissolved in acetone (10 ml); H_2O (7 ml) and Conc. HCl (3 ml). This solution was refluxed for 5 hrs at 60 ^oC. The reaction was left to stir overnight at r.t. Afterwards, H_2O (50 ml) was added and acetone was evaporated by rotary evaporator. The reaction was left to settle down for 5 minutes. Product was collected as precipitate but in some cases it was extracted from E.A (3 × 25 ml). The combined organic layers were washed with saturated $NaHCO_3$ (3 × 25 ml) and saturated NaCl (3 × 25 ml), dried over $MgSO_4$ and evaporated at a rotary evaporator to dryness.

6.3.6 Photoreactions of *N*-methylphthalimide with carboxylates

Experiment 13

6.3.6.1 Synthesis of 3-ethyl-3-hydroxy-2-methylisoindolin-1-one 11a (FH-34)



11a

Following the general procedure (GP-1), 0.24 g (1.49 mmol) of *N*-methylphthalimide **4a**, 0.34 ml (4.55 mmol) of propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 6 h in 150 ml of water/acetone [50:50]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.17 g (0.89 mmol; 60%) of **11a** as a yellow oil.

TLC: R_f = 0.30 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, $CDCl_3$)

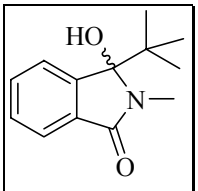
δ (ppm) = 0.38 (t, 3 H, CH_3), 2.05 (m, 2 H, CH_2), 2.67 (s, 3 H, NCH_3), 4.49 (s, 1 H, OH), 7.34 (ddd, ^3J = 6.8, ^4J = 1.5 Hz, 1 H, H_{arom}), 7.44 (d, ^3J = 7.6, 1 H, H_{arom}), 7.51 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 7.8 (s, 1 C, CH_3), 23.4 (s, 1 C, NCH_3), 28.6 (s, 1 C, CH_2), 91.7 (s, 1 C, COH), 122.0 (s, 1 C, CH_{arom}), 123.2 (s, 1 C, CH_{arom}), 129.6 (s, 1 C, CH_{arom}), 131.5 (s, 1 C, Cq), 132.5 (s, 1 C, CH_{arom}), 146.7 (s, 1 C, Cq), 167.8 (s, 1 C, C=O).

Experiment 14

6.3.6.2 Synthesis of 3-tert-butyl-3-hydroxy-2-methylisoindolin-1-one 11b (FH-47)



11b

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methylphthalimide **4a**, 0.47 g (4.60 mmol) of pivalic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.22 g (1.01 mmol; 68%) of **11b** as a yellow solid.

TLC: R_f = 0.47 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 144-146°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.04 (s, 9 H, 3 * CH_3), 2.98 (s, 3 H, NCH_3), 4.67 (s, 1 H, OH), 7.43 (ddd, ^3J = 7.5, ^4J = 1.4 Hz, 1 H, H_{arom}), 7.50 (ddd, ^3J = 7.5, ^4J = 1.4 Hz, 1 H, H_{arom}), 7.61 (m, 1 H, H_{arom}), 7.72 (m, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

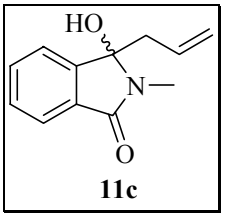
δ (ppm) = 26.6 (s, 3 C, 3 * CH_3), 27.9 (s, 1 C, NCH_3), 39.9 (s, 1 C, Cq), 95.2 (s, 1 C, COH), 123.3 (s, 1 C, CH_{arom}), 124.2 (s, 1 C, CH_{arom}), 129.7 (s, 1 C, CH_{arom}), 131.4 (s, 1 C, CH_{arom}), 132.6 (s, 1 C, Cq), 147.4 (s, 1 C, Cq), 168.3 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3188.48 (b, OH), 2969.54 (vi; CH_{aliph}), 2346.62 (w; CN), 1685.71 (s; C=O), 1612.61 (w; $C{=}C_{arom}$), 1073.52 (s, CO), 759.68 (s; CH_{arom}).

Experiment 15

6.3.6.3 Synthesis of 3-allyl-3-hydroxy-2-methylisoindolin-1-one 11c (FH-43 & SG-22)



11c

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.38 g (4.50 mmol) of vinyl acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 5 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.08 g (0.39 mmol; 26%) of **11c** as a bright yellow solid.

^{1}H–NMR: (400 MHz, $CDCl_3$)

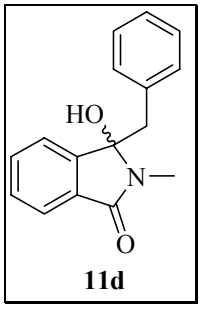
δ (ppm) = 2.72 (dd, ^3J = 14.4, ^4J = 7.1 Hz, 1 H, CH_2), 2.74 (s, 3 H, NCH_3), 2.89 (dd, ^3J = 14.4, ^4J = 7.1 Hz, 1 H, CH_2), 4.01 (br. s, 1 H, OH), 4.89 (dd, ^3J = 13.5, ^4J = 1.2 Hz, 1 H, CH_2), 4.96 (dd, ^3J = 13.5, ^4J = 1.2 Hz, 1 H, CH_2), 5.14 (m, 1 H, CH), 7.37 (m, 1 H, H_{arom}), 7.48 (d, ^3J = 7.3 Hz, 1 H, H_{arom}), 7.54 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.4 (s, 1 C, NCH_3), 40.3 (s, 1 C, CH_2), 90.0 (s, 1 C, COH), 119.6 (s, 1 C, CH), 122.1 (s, 1 C, CH), 123.0 (s, 1 C, CH_{arom}), 129.5 (s, 1 C, CH_{arom}), 130.6 (s, 1 C, CH_{arom}), 131.1 (s, 1 C, Cq), 132.1 (s, 1 C, CH_{arom}), 146.3 (s, 1 C, Cq), 167.3 (s, 1 C, C=O).

Experiment 16

6.3.6.4 Synthesis of 3-benzyl-3-hydroxy-2-methylisoindolin-1-one 11d (FH-10)



11d

The general procedure (GP-1) was followed and 0.49 g (3.04 mmol) of *N*-methyl-phthalimide **4a**, 1.37 g (10.06 mmol) of 2-phenyl acetic acid and 0.69 g (4.99 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 h. The photosolution was clear and yellow. Then, it was crashed out solid from hexane and gave colourless precipitate 0.60 g (2.37 mmol; 78%) of **11d** which was washed twice with hexane for further purification.

TLC: R_f = 0.28 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 148-152°C (Lit:[64] 165-168°C)

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.85 (s, 3 H, NCH_3), 3.08 (d, ^2J = 13.9 Hz, 1 H, CH_2), 3.45 (d, ^2J = 13.9 Hz, 1 H, CH_2), 3.86 (s; 1 H; OH), 6.85 (dd, ^3J = 7.8, ^4J = 2.0 Hz, 2 H, H_{arom}), 7.09 (m, 3 H, H_{arom}), 7.25 (d, ^3J = 7.2 Hz, 1 H, H_{arom}), 7.31 (ddd, ^3J = 7.6 Hz, ^4J = 1.2 Hz , 1 H, H_{arom}), 7.38 (d, ^3J = 7.2 Hz, 1 H, H_{arom}), 7.45 (ddd, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.2 (s, 1 C, NCH_3), 42.7 (s, 1 C, CH_2), 90.9 (s, 1 C, COH), 123.0 (s, 1C, CH_{arom}), 123.2 (s, 1 C, CH_{arom}), 127.3 (s, 1 C, CH_{arom}), 128.3 (s, 1 C, CH_{arom}), 129.8

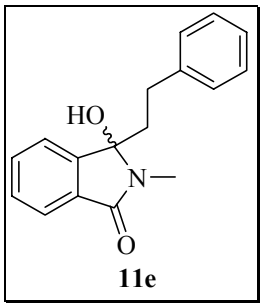
(s, 1 C, CH_{arom}), 130.3 (s, 1 C, CH_{arom}), 131.4 (s, 1 C, CH_{arom}), 132.0 (s, 1 C, Cq), 134.7 (s, 1 C, Cq), 146.5 (s, 1 C, Cq), 167.4 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3276.95 (s, OH), 2937.05 (vi; CH_{aliph}), 2345 (w; CN), 1683.5 (s; C=O), 1618.55 (w; $C=C_{arom}$), 703.37 (s; CH_{arom}).

Experiment 17

6.3.6.5 Synthesis of 3-hydroxy-2-methyl-3-phenethylisoindolin-1-one <u>11e</u> (FH-100)



11e

The general procedure (GP-1) was followed and 0.24 g (1.50 mmol) of *N*-methyl-phthalimide **4a**, 0.68 g (4.51 mmol) of hydrocinnamic acid and 0.31 g (2.27 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 5 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.27 g (1.01 mmol; 67%) of **11e** as a yellowish solid.

TLC: R_f = 0.32 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 65-70°C

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 2.02 (m, 1 H, CH_2), 2.25 (m, 1 H, CH_2), 2.43 (m, 1 H, CH_2), 2.54 (m, 1 H, CH_2), 2.98 (s, 3 H, NCH_3), 5.33 (s, 1 H, OH), 7.13 (d, ^3J = 7.2 Hz, 2 H, H_{arom}), 7.17

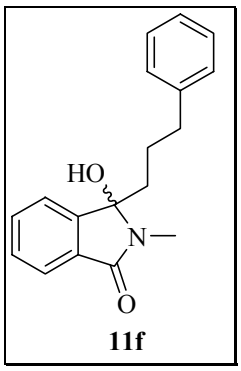
(m, 1 H, H_{arom}), 7.26 (m, 2 H, H_{arom}), 7.57 (ddd, ^{2}J = 1.2, ^{3}J = 7.4 Hz, ^{4}J = 14.6 Hz , 1 H, H_{arom}), 7.68 (ddd, ^{2}J = 1.2, ^{3}J = 7.4 Hz, ^{4}J = 14.6 Hz , 1 H, H_{arom}), 7.73 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 23.3 (s, 1 C, CH_2), 30.7 (s, 1 C, NCH_3), 38.5 (s, 1 C, CH_2), 90.7 (s, 1 C, COH), 122.9 (s, 1C, CH_{arom}), 123.3 (s, 1 C, CH_{arom}), 126.7 (s, 1 C, CH_{arom}), 129.0 (s, 2 C, CH_{arom}), 129.2 (s, 2 C, CH_{arom}), 130.1 (s, 1 C, CH_{arom}), 132.8 (s, 1 C, CH_{arom}), 133.1 (s, 1 C, Cq), 142.0 (s, 1 C, Cq), 148.1 (s, 1 C, Cq), 166.9 (s, 1 C, C=O).

Experiment 18

6.3.6.6 Synthesis of 3-hydroxy-2-methyl-3-(3-phenylpropyl) isoindolin-1-one 11f (FH-101)



11f

The general procedure (GP-1) was followed and 0.24 g (1.50 mmol) of *N*-methyl-phthalimide **4a**, 0.74 g (4.51 mmol) of 4-phenylbutyric acid and 0.31 g (2.27 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 5 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.09 g (0.32 mmol; 21%) of **11f** as a colourless oil.

TLC: R_f = 0.35 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 81-83°C

^{1}H–NMR: (400 MHz, acetone-d_6)

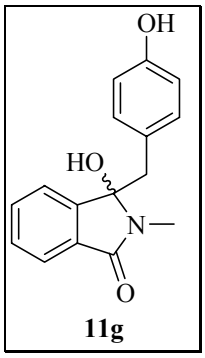
δ (ppm) = 0.98 (m, 1 H, CH_2), 1.24 (m, 1 H, CH_2), 2.19 (m, 2 H, CH_2), 2.57 (m, 2 H, CH_2), 2.88 (s, 3 H, NCH_3), 5.20 (s, 1 H, OH), 7.12 (d, ^{3}J = 4.4 Hz, 2 H, H_{arom}), 7.17 (m, 1 H, H_{arom}), 7.26 (m, 2 H, H_{arom}), 7.52 (ddd, ^{2}J = 1.2, ^{3}J = 7.2 Hz, ^{4}J = 14.4 Hz , 1 H, H_{arom}), 7.59 (m, 1 H, H_{arom}), 7.65 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 23.1 (s, 1 C, CH_2), 26.4 (s, 1 C, NCH_3), 35.8 (s, 1 C, CH_2), 35.9 (s, 1 C, CH_2), 90.8 (s, 1 C, COH), 122.8 (s, 1C, CH_{arom}), 123.1 (s, 1 C, CH_{arom}), 126.6 (s, 1 C, CH_{arom}), 129.1 (s, 2 C, CH_{arom}), 129.2 (s, 2 C, CH_{arom}), 129.9 (s, 1 C, CH_{arom}), 132.7 (s, 1 C, CH_{arom}), 133.9 (s, 1 C, Cq), 142.8 (s, 1 C, Cq), 149.0 (s, 1 C, Cq), 167.2 (s, 1 C, C=O).

Experiment 19

6.3.6.7 Synthesis of 3-(4-hydroxybenzyl)-3-hydroxy-2-methyl isoindolin-1-one 11g (FH-106)



11g

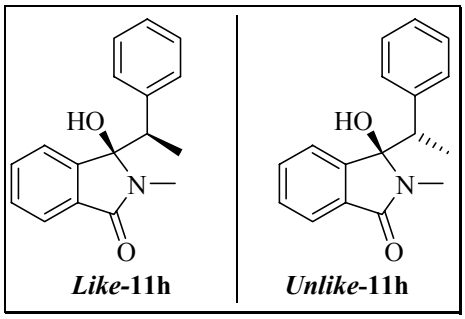
The general procedure (GP-1) was followed and 0.24 g (1.50 mmol) of *N*-methyl-phthalimide **4a**, 0.68 g (4.51 mmol) of 2-(4-hydroxyphenyl)acetic acid and 0.31 g (2.27 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 6 h. The photosolution was clear and yellowish. Column

chromatography (SiO_2; EA:Hex = 1:1) gave 0.27 g (1.00 mmol; 67%) of **11g** as a yellow solid.

TLC: R_f = 0.15 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 145-148°C
^{1}H–NMR: (400 MHz, acetone-d_6)
δ (ppm) = 3.08 (s, 3 H, NCH_3), 3.25 (d, ^2J = 14.0 Hz, 1 H, CH_2), 3.43 (d, ^2J = 14.0 Hz, 1 H, CH_2), 5.38 (s, 1 H, OH), 6.56 (d, ^3J = 8.4 Hz, 2 H, H_{arom}), 6.76 (d, ^3J = 8.4 Hz, 2 H, H_{arom}), 7.44 (m, 1 H, H_{arom}), 7.49 (m, 1 H, H_{arom}), 7.58 (m, 2 H, H_{arom}), 8.20 (s, 1 H, OH).
^{13}C–NMR: (100 MHz, acetone-d_6)
δ (ppm) = 23.9 (s, 1 C, NCH_3), 42.2 (s, 1 C, CH_2), 91.4 (s, 1 C, COH), 115.4 (s, 2C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 126.8 (s, 1 C, Cq), 129.7 (s, 1 C, CH_{arom}), 132.1 (s, 2 C, CH_{arom}), 133.0 (s, 1 C, CH_{arom}), 133.8 (s, 1 C, Cq), 135.6 (s, 1 C, CH_{arom}), 148.1 (s, 1 C, Cq), 156.9 (s, 1 C, C=O).

Experiment 20

6.3.6.8 Synthesis of 3-hydroxy-2-methyl-3-(1-phenylethyl) isoindolin-1-one 11h (FH-98)



***Like*-11h** ***Unlike*-11h**

The general procedure (GP-1) was followed and 0.24 g (1.50 mmol) of *N*-methyl-phthalimide **4a**, 0.68 g (4.53 mmol) of 2-phenylpropionic acid and 0.31 g (2.27

mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 2 h. The photosolution was clear and colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.36 g (1.35 mmol; 90%) of **11h** as a white solid.

Diastereoisomers:

***Unlike*-3-hydroxy-2-methyl-3-(1-phenylethyl)isoindolin-1-one (*Unlike*-11h)**

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 1.65 (d, ^2J = 7.1 Hz, 3 H, CH_3), 2.95 (s, 3 H, NCH_3), 3.67 (q, ^2J = 7.3, ^3J = 14.6, ^4J = 21.8 Hz, 1 H, CH), 7.05 (m, 2 H, H_{arom}), 7.31 (m, 2 H, H_{arom}), 7.42 (ddd, ^2J = 1.5, ^3J = 7.6, ^4J = 15.1 Hz , 1 H, H_{arom}), 7.50 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 7.54 (ddd, ^2J = 1.0, ^3J = 7.6, ^4J = 14.6 Hz , 1 H, H_{arom}), 7.69 (ddd, ^2J = 1.5, ^3J = 7.1, ^4J = 14.6 Hz , 1 H, H_{arom}), 7.90 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 10.0 (s, 1 C, CH_3), 27.0 (s, 1 C, NCH_3), 47.2 (s, 1 C, CH_2), 96.4 (s, 1 C, COH), 125.4 (s, 1 C, CH_{arom}), 126.0 (s, 1 C, CH_{arom}), 126.3 (s, 2 C, CH_{arom}), 127.0 (s, 1 C, CH_{arom}), 128.0 (s, 1 C, CH_{arom}), 128.5 (s, 2 C, CH_{arom}), 129.9 (s, 1 C, CH_{arom}), 132.2 (s, 1 C, Cq), 144.0 (s, 1 C, Cq), 148.4 (s, 1 C, Cq), 169.0 (s, 1 C, C=O).

***Like*-3-hydroxy-2-methyl-3-(1-phenylethyl)isoindolin-1-one (*Like*-11h)**

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 1.66 (d, ^2J = 7.1 Hz, 3 H, CH_3), 2.96 (s, 3 H, NCH_3), 3.69 (q, ^2J = 7.3, ^3J = 14.6, ^4J = 21.8 Hz, 1 H, CH), 7.07 (m, 2 H, H_{arom}), 7.32 (m, 2 H, H_{arom}), 7.48 (ddd, ^2J = 1.2, ^3J = 7.6, ^4J = 14.9 Hz , 1 H, H_{arom}), 7.51 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 7.55 (ddd, ^2J = 1.0, ^3J = 7.6 Hz, ^4J = 14.6 Hz , 1 H, H_{arom}), 7.70 (ddd, ^2J = 1.5, ^3J = 7.1, ^4J = 14.6 Hz , 1 H, H_{arom}), 7.91 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

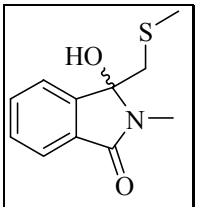
^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 12.0 (s, 1 C, CH_3), 27.0 (s, 1 C, NCH_3), 47.4 (s, 1 C, CH_2), 96.5 (s, 1 C, COH), 125.8 (s, 1 C, CH_{arom}), 126.1 (s, 1 C, CH_{arom}), 126.5 (s, 2 C, CH_{arom}), 127.3 (s, 1 C, CH_{arom}), 128.1 (s, 1 C, CH_{arom}), 128.9 (s, 2 C, CH_{arom}), 130.4 (s, 1 C, CH_{arom}), 132.5 (s, 1 C, Cq), 144.3 (s, 1 C, Cq), 148.6 (s, 1 C, Cq), 169.3 (s, 1 C, C=O).

6.3.7 Photoreactions of *N*-methylphthalimide with sulphur-containing carboxylates

Experiment 21

6.3.7.1 Synthesis of 3-hydroxy-2-methyl-3-(methylthiomethyl) isoindolin-1-one 12a (FH-180)



12a

The general procedure (GP-1) was followed and 0.24 g (1.50 mmol) of *N*-methyl-phthalimide **4a**, 0.50 g (4.7 mmol) of 2-(methylthio) acetic acid and 0.33 g (2.39 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 2 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.40 g (1.8 mmol; 90%) of **12a** as a yellowish solid.

TLC: R_f = 0.22 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 105-108°C (Lit:[44] 114-116°C)
^{1}H–NMR: (400 MHz, $CDCl_3$)
δ (ppm) = 1.77 (s, 3 H, SCH_3), 2.75 (s, 3 H, NCH_3), 3.06 (d, ^2J = 14.2 Hz, 1 H, CH_2), 3.17 (d, ^2J = 14.2 Hz, 1 H, CH_2), 4.12 (s, 1 H, OH), 7.41 (ddd, ^3J = 7.8, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.55 (ddd, ^3J = 7.8, ^4J = 1.0 Hz, 2 H, H_{arom}), 7.66 (dd, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

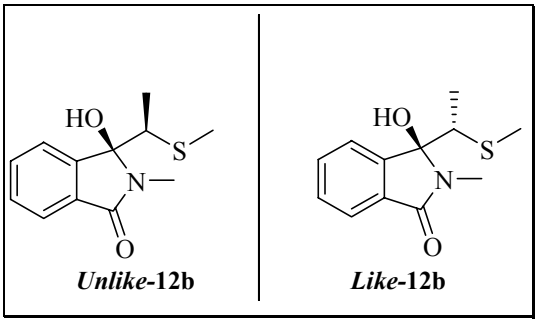
δ (ppm) = 17.3 (s, 1 C, SCH_3), 23.8 (s, 1 C, NCH_3), 40.6 (s, 1 C, CH_2), 90.7 (s, 1 C, Cq, COH), 122.5 (s, 1 C, CH_{arom}), 123.4 (s, 1 C, CH_{arom}), 130.2 (s, 1 C, CH_{arom}), 131.7 (s, 1 C, Cq), 132.4 (s, 1 C, CH_{arom}), 146.3 (s, 1 C, Cq), 167.8 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3299.31 (b, OH), 2922.34 (vi; CH_{aliph}), 2346.71 (w; CN), 1674.6 (s; C=O), 1617.71 (w; $C=C_{arom}$), 1072.43 (s, CO), 696.27 (s; CH_{arom}).

Experiment 22

6.3.7.2 Synthesis of 3-hydroxy-2-methyl-3-(1-(methylthio)ethyl) isoindolin-1-one <u>12b</u> (FH-112)



***Unlike*-12b** ***Like*-12b**

The general procedure (GP-1) was followed and 0.24 g (1.50 mmol) of *N*-methyl-phthalimide **4a**, 0.55 g (4.56 mmol) of 2-(methylthio)propanoic acid and 0.31 g (2.27 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 6 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.34 g (1.43 mmol; 95%) of **12b** as a yellow solid.

TLC: R_f = 0.34 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 85-89°C

Diastereoisomers:

***Unlike*-3-hydroxy-2-methyl-3-(1-(methylthio)ethyl)isoindolin-1-one (*Unlike*-12b)**

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 0.88 (d, ^{3}J = 7.0 Hz, 3 H, CH_3), 1.54 (s, 3 H, SCH_3), 2.98 (s, 3 H, NCH_3), 3.48 (q, ^{3}J = 7.0 Hz, 1 H, CHS), 5.52 (s, 1 H, OH), 7.57 (m, 1 H, H_{arom}), 7.68 (m, 2 H, H_{arom}), 8.09 (d, ^{3}J = 7.5 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 16.6 (q, 1 C, SCH_3), 17.5 (q, 1 C, CH_3), 23.7 (q, 1 C, NCH_3), 48.2 (d, 1 C, CHS), 93.5 (s, 1 C, COH), 122.9 (d, 1 C, CH_{arom}), 124.9 (d, 1 C, CH_{arom}), 130.3 (d, 1 C, CH_{arom}), 132.1 (d, 1 C, CH_{arom}), 133.6 (s, 1 C, Cq), 146.5 (s, 1 C, Cq), 166.8 (s, 1 C, C=O).

***Like*-3-hydroxy-2-methyl-3-(1-(methylthio)ethyl)isoindolin-1-one (*Like*-12b)**

^{1}H–NMR: (400 MHz, acetone-d_6)

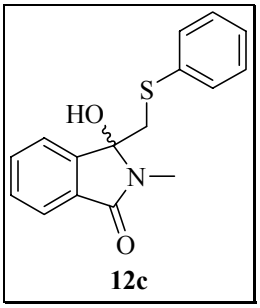
δ (ppm) = 0.86 (d, ^{3}J = 7.0 Hz, 3 H, CH_3), 1.53 (s, 3 H, SCH_3), 2.99 (s, 3 H, NCH_3), 3.49 (q, ^{3}J = 7.0 Hz, 1 H, CH), 5.56 (s, 1 H, OH), 7.62 (ddd, ^{3}J = 7.5 Hz, 1 H, H_{arom}), 7.69 (m, 2 H, H_{arom}), 7.71 (d, ^{3}J = 7.5 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 14.3 (q, 1 C, SCH_3), 24.1 (q, 1 C, CH_3), 38.3 (q, 1 C, NCH_3), 47.6 (d, 1 C, CH), 93.4 (s, 1 C, COH), 123.1 (d, 1 C, CH_{arom}), 123.9 (d, 1 C, CH_{arom}), 130.2 (d, 1 C, CH_{arom}), 132.2 (d, 1 C, Cq), 134.0 (s, 1 C, CH_{arom}), 148.8 (s, 1 C, Cq), 170.8 (s, 1 C, C=O).

Experiment 23

6.3.7.3 Synthesis of 3-hydroxy-2-methyl-3-(phenylthiomethyl) isoindolin-1-one 12c (FH-15)



12c

The general procedure (GP-1) was followed and 0.17 g (1.05 mmol) of *N*-methyl-phthalimide **4a**, 0.52 g (3.09 mmol) of 2-(phenylthio) acetic acid and 0.21 g (1.52 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 5 h. The photosolution was cloudy, smelly and yellow. Then, the product 0.17 g (0.60 mmol; 57%) of **12c** was yellow oily.

Melting point: 99-105°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.61 (s, 3 H, NCH_3), 3.47 (d, ^2J = 14.0 Hz, 1 H, CH_2), 3.62 (d, ^2J = 14.0 Hz, 1 H, CH_2), 3.88 (s, 1 H, OH), 7.11 (m, 5 H, H_{arom}), 7.37 (m, 3 H, H_{arom}), 7.56 (m, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

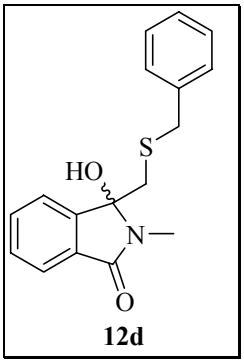
δ (ppm) = 23.7 (s, 1 C, NCH_3), 41.5 (s, 1 C, CH_2), 90.6 (s, 1 C, COH), 122.3 (s, 1 C, CH_{arom}), 123.2 (s, 1 C, CH_{arom}), 127.4 (s, 1 C, CH_{arom}), 129.2 (s, 2 C, CH_{arom}), 130.1 (s, 1 C, CH_{arom}), 131.7 (s, 2 C, CH_{arom}), 132.4 (s, 1 C, CH_{arom}), 134.2 (s, 1 C, Cq), 135.3 (s, 1 C, Cq), 145.7 (s, 1 C, Cq), 167.9 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3280.38 (b, OH), 2927.32 (vi; CH_{aliph}), 2346.38 (w; CN), 1686.58 (s; C=O), 1617.47 (w; $C=C_{arom}$), 745.49 (s; CH_{arom}).

Experiment 24

6.3.7.4 Synthesis of 3-((benzylthio)methyl)-3-hydroxy-2-methyl) isoindolin-1-one 12d (FH-21)



12d

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.82 g (4.50 mmol) of 2-(benzylthio) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 4 ½ h. The photosolution was cloudy, smelly and yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.15 g (0.50 mmol; 34%) of **12d** as a yellow brownish oil.

TLC: R_f = 0.31 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, $CDCl_3$)

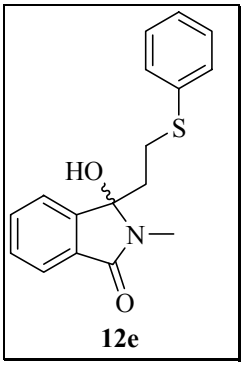
δ (ppm) = 2.61 (s, 3 H, NCH_3), 3.46 (d, ^2J = 14.1 Hz, 1 H, CH_2S), 3.60 (d, ^2J =14.1 Hz, 1 H, CH_2S), 3.64 (br. s, 1 H, OH), 7.11 (br. m, 5 H, H_{arom}), 7.37 (br. m, 3 H, H_{arom}), 7.57 (m, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.3 (q, 1 C, NCH_3), 41.1 (t, 1 C, CH_2S), 90.2 (s, 1 C, COH), 122.0 (d, 1 C, CH_{arom}), 122.8 (d, 1 C, CH_{arom}), 127.0 (d, 1 C, CH_{arom}), 128.8 (d, 2 C, CH_{arom}), 129.7 (d, 1 C, CH_{arom}), 131.3 (d, 2 C, CH_{arom}), 131.4 (s, 1 C, Cq), 132.0 (d, 1 C, CH_{arom}), 135.0 (s, 1 C, Cq), 145.4 (s, 1 C, Cq), 167.6 (s, 1 C, C=O).

Experiment 25

6.3.7.5 Attempted synthesis of 3-hydroxy-2-methyl-3-(2-(phenylthio)ethyl) isoindolin-1-one 12e (FH-24)



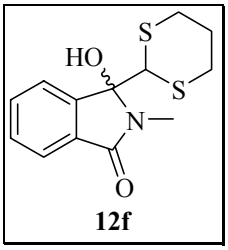
12e

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.83 g (4.55 mmol) of 3-(phenylthio) propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 43 h. The photosolution was cloudy and yellow. Then, the product 0.27 g (100% reisolated S.M.) of **12e** was yellow brownish oily.

*No product was observed therefore the original S.M. **4a** was reisolated.*

Experiment 26

6.3.7.6 Synthesis of 3-(1,3-dithian-2-yl)-3-hydroxy-2-methyl isoindolin-1-one 12f (FH-39)



12f

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.74 g (4.50 mmol) of 1,3-dithiane-2-carboxylic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear and colourless. Then, the product 0.30 g (1.07 mmol; 72%) of **12f** was colourless solid.

TLC: R_f = 0.28 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 177-185°C

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 0.86 (m; 1 H; CH_2), 1.76 (m; 1 H; CH_2), 2.04 (m; 1 H; CH_2), 2.80 (m; 3 H; CH_2), 2.92 (s, 3 H, NCH_3), 3.88 (s, 1 H, OH), 4.80 (s, 1 H, CH), 7.48 (ddd, ^3J = 7.6, ^4J = 1.1 Hz, 1 H, H_{arom}), 7.59 (ddd, ^3J = 7.6, ^4J = 1.1 Hz, 1 H, H_{arom}), 7.66 (d, ^3J = 7.5 Hz, 1 H, H_{arom}), 7.86 (d, ^3J = 7.5 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.3 (s, 1 C, NCH_3), 25.6 (s, 1 C, CH_2), 30.0 (s, 1 C, CH_2), 31.0 (s, 1 C, CH_2), 62.8 (s, 1 C, Cq), 90.9 (s, 1 C, COH), 123.4 (s, 1 C, CH_{arom}), 130.6 (s, 1 C, CH_{arom}), 131.8 (s, 1 C, CH_{arom}), 132.5 (s, 1 C, CH_{arom}), 134.2 (s, 1 C, Cq), 144.6 (s, 1 C, Cq), 167.5 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 281 (M^+, <1), 265 (M^{+1}-OH, 11), 263 (M^+-H_2O, 98), 222 (M^+- $C_2H_4S^+$, 5), 189 (M^+-$C_6H_5O^-$, 100), 162 (M^+-$C_4H_7S_2$, 34), 133 (M^+-$C_5H_8OS_2$, 7), 120 (M^{+1}-$C_9H_8NO_2$, 16), 77 (C_6H_5, 13), 57 (M^+-$C_{11}H_{12}OS_2$, 6).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 282.06170 g/mol for $C_{13}H_{16}NO_2S_2 + H^+$.

Found [M + H]$^+$: 282.06180 g/mol for $C_{13}H_{16}NO_2S_2 + H^+$.

Electronspray: (ESI, Positive ions)

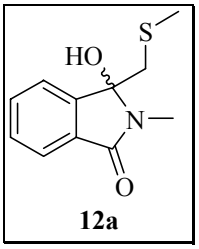
m/z (%) = 282 $(M + H)^+$, 563 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3248.57 (b, OH), 2899.56 (vi; CH_{aliph}), 2347.13 (w; CN), 1677.06 (s; C=O), 1613.21 (w; $C=C_{arom}$), 800.46 (s; CH_{arom}).

Experiment 27

6.3.7.7 Synthesis of 3-hydroxy-2-methyl-3-(methylthiomethyl) isoindolin-1-one <u>12a</u> (FH-53)



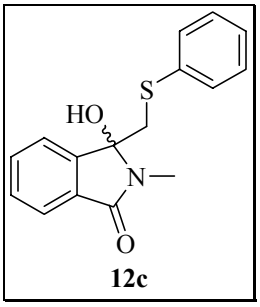
12a

The general procedure (GP-2) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a** and 0.47 g (7.56 mmol) of dimethyl sulphide, anhydrous were dissolved in 150 ml acetone and the reaction was irradiated for 2 h. The photo-solution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.23 g (1.03 mmol; 69%) of **12a** as a yellow solid.

*<u>Analytical data identical to that of previous **12a**</u>.*

Experiment 28

6.3.7.8 Synthesis of 3-hydroxy-2-methyl-3-(phenylthiomethyl) isoindolin-1-one 12c (FH-54)



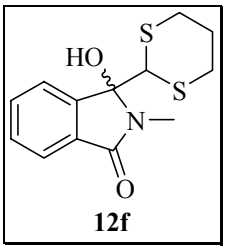
12c

The general procedure (GP-2) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a** and 0.56 g (4.50 mmol) of thioanisole were dissolved in 150 ml acetone and the reaction was irradiated for 4 h. The photosolution was clear and yellowish. Then, the product 0.07 g (0.25 mmol; 17%) of **12c** which was purified by column chromatography was brown viscous liquid.

*Analytical data identical to that of previous **12c**.*

Experiment 29

6.3.7.9 Synthesis of 3-(1,3-dithian-2-yl)-3-hydroxy-2-methyl isoindolin-1-one 12f (FH-55)



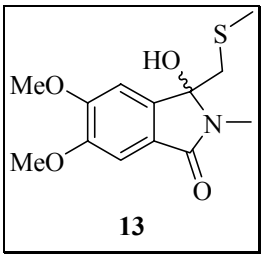
12f

The general procedure (GP-2) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a** and 0.54 g (4.49 mmol) of 1,3-dithiane were dissolved in 150 ml acetone and the reaction was irradiated for 15 h. The photosolution was clear and yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.05 g (0.18 mmol; 12%) of **12f** as a yellow solid.

*Analytical data identical to that of previous **12f**.*

Experiment 30

6.3.7.10 Synthesis of 3-hydroxy-5,6-dimethoxy-2-methyl-3-(methyl thiomethyl) isoindolin-1-one 13 (FH-52)



13

The general procedure (GP-1) was followed and 0.33 g (1.49 mmol) of 5,6-dimethoxy-2-methylisoindoline-1,3-dione, 0.49 g (4.62 mmol) of 2-(methylthio) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 14 h. The photosolution was clear and yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.16 g (0.57 mmol; 38%) of **13** as a green solid.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.82 (s, 3 H, SCH_3), 2.79 (s, 3 H, NCH_3), 2.98 (d, ^2J = 14.0 Hz, 1 H, CH_2), 3.11 (s, 1 H, OH), 3.13 (d, ^2J = 14.0 Hz, 1 H, CH_2), 3.80 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.77 (s, 1 H, H_{arom}), 7.13 (s, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 17.3 (s, 1 C, SCH_3), 24.0 (s, 1 C, NCH_3), 40.7 (s, 1 C, CH_2), 56.3 (s, 1 C, OCH_3), 56.7 (s, 1 C, OCH_3), 90.2 (s, 1 C, COH), 104.8 (s, 1 C, CH_{arom}), 105.6 (s, 1 C, CH_{arom}), 123.9 (s, 1 C, Cq), 139.8 (s, 1 C, Cq), 150.7 (s, 1 C, Cq), 152.9 (s, 1 C, Cq), 168.1 (s, 1 C, C=O).

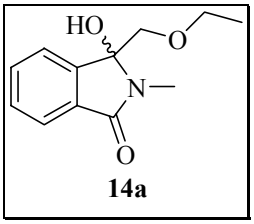
IR: (KBr, disk)

ν (Cm^{-1}) = 3188.48 (b, OH), 2969.54 (vi; CH_{aliph}), 2346.62 (w; CN), 1685.71 (s; C=O), 1612.61 (w; $C=C_{arom}$), 1073.52 (s, CO), 759.68 (s; CH_{arom}).

6.3.8 Photoreactions of *N*-methylphthalimide with oxygen-containing carboxylates

Experiment 31

6.3.8.1 Synthesis of 3-(ethoxymethyl)-3-hydroxy-2-methyl isoindolin-1-one <u>14a</u> (FH-13)



14a

The general procedure (GP-1) was followed and 0.17 g (1.05 mmol) of *N*-methyl-phthalimide **4a**, 0.32 g (3.07 mmol) of 2-ethoxy acetic acid and 0.21 g (1.52 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 ½ h. The photosolution was clear and colourless. Then, it was crashed out solid from hexane and gave colourless solid. 0.18 g (0.81 mmol; 77%) of **14a**.

Melting point: 82-86°C

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.13 (t, ^{3}J = 14.2, ^{4}J = 7.1 Hz, 3 H, CH_3), 2.92 (s, 3 H, NCH_3), 3.49 (q, ^{3}J = 14.0, ^{4}J = 7.0 Hz, 2 H, CH_2), 3.71 (d, ^{2}J = 9.8 Hz, 1 H, CH_2), 3.77 (d, ^{2}J = 9.8 Hz, 1 H, CH_2), 3.91 (s, 1 H, OH), 7.44 (ddd, ^{3}J = 7.4, ^{4}J = 1.0 Hz, 1 H, H_{arom}), 7.54 (ddd, ^{3}J = 7.4, ^{4}J = 1.1 Hz, 1 H, H_{arom}), 7.60 (d, ^{2}J = 7.4 Hz, 1 H, H_{arom}), 7.65 (d, ^{2}J = 7.4 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 15.3 (s, 1 C, CH_3), 24.6 (s, 1 C, NCH_3), 67.7 (s, 1 C, CH_2), 73.0 (s, 1 C, CH_2), 88.8 (s, 1 C, COH), 122.7 (s, 1C, CH_{arom}), 123.5 (s, 1 C, CH_{arom}), 130.1 (s, 1 C, CH_{arom}), 131.9 (s, 1 C, CH_{arom}), 132.3 (s, 1 C, Cq), 145.7 (s, 1 C, Cq), 167.8 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 222 (M^{+1}, 18), 203 (M^{+}-H_2O, 12), 174 (203-C_2H_5, 19), 162 (M^{+}-CH_2OEt , 100), 146 (M^{+1}-C_6H_4, 12), 133 (M^{+}-$C_4H_8O_2^{\cdot}$, 9), 105 (M^{+1}-$C_5H_{11}NO_2$, 7), 77 (M^{+1}-$C_6H_{11}NO_3$, 13).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^{+}$: 222.11247 g/mol for $C_{12}H_{16}NO_3 + H^{+}$.

Found [M + H]$^{+}$: 222.11236 g/mol for $C_{12}H_{16}NO_3 + H^{+}$.

Electronspray: (ESI, Positive ions)

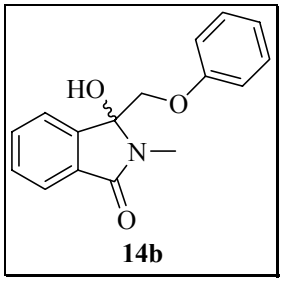
m/z (%) = 221 $(M)^{+}$, 443 $(M_2)^{+}$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3256.56 (b, OH), 2979.56 (vi; CH_{aliph}), 2343 (w; CN), 1683.37 (s; C=O), 1617.07 (w; $C{=}C_{arom}$), 1089.57 (s, CO), 702.65 (s; CH_{arom}).

Experiment 32

6.3.8.2 Synthesis of 3-hydroxy-2-methyl-3-(phenoxymethyl) isoindolin-1-one 14b (FH-19)



14b

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.68 g (4.47 mmol) of phenoxy acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 ½ h. The photosolution was clear and colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.34 g (1.26 mmol; 85%) of **14b** as a yellow solid.

TLC: R_f = 0.32 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 122-129°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.84 (s, 3 H, NCH_3), 4.24 (d, ^2J = 9.7 Hz, 2 H, CH_2), 4.30 (s, 1 H, OH), 4.36 (d, ^2J = 9.7 Hz, 2 H, CH_2), 6.78 (dd, ^3J = 8.84, ^4J = 1.0 Hz, 2 H, H_{arom}), 6.94 (m, 1 H, H_{arom}), 7.22 (m, 2 H, H_{arom}), 7.43 (ddd, ^3J = 7.6, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.55 (ddd, ^3J = 7.6, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.60 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 7.64 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

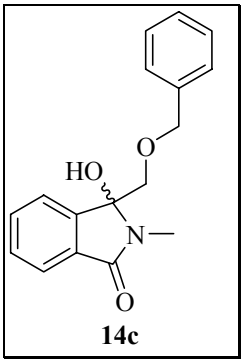
δ (ppm) = 24.3 (s, 1 C, NCH_3), 69.3 (s, 1 C, CH_2), 88.9 (s, 1 C, COH), 115.0 (s, 2 C, CH_{arom}), 121.9 (s, 1 C, CH_{arom}), 122.6 (s, 1 C, CH_{arom}), 123.5 (s, 1 C, CH_{arom}), 129.8 (s, 1 C, CH_{arom}), 130.2 (s, 2 C, CH_{arom}), 131.8 (s, 1 C, CH_{arom}), 132.6 (s, 1 C, Cq), 145.4 (s, 1 C, Cq), 158.3 (s, 1 C, Cq), 168.2 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3289.33 (b, OH), 2939.44 (vi; CH_{aliph}), 2346.53 (w; CN), 1681.41 (s; C=O), 1617.03 (w; $C=C_{arom}$), 1063.43 (s, CO), 765.35 (s; CH_{arom}).

Experiment 33

6.3.8.3 Synthesis of 3-(benzyloxymethyl)-3-hydroxy-2-methyl isoindolin-1-one 14c (FH-20)



14c

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.70 ml (4.50 mmol) of 2-(benzyloxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 5 h. The photosolution was clear, light yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.16 g (0.56 mmol; 38%) of **14c** as a light yellow oil.

^{1}H–NMR: (400 MHz, $CDCl_3$)

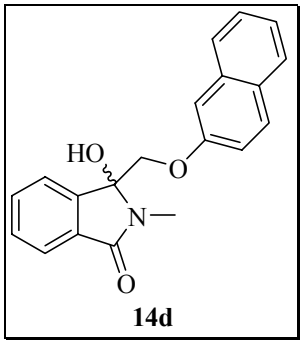
δ (ppm) = 2.74 (s, 3 H, NCH_3), 3.72 (d, ^2J = 10.0 Hz, 1 H, CH_2), 4.24 (s, 1 H, OH), 3.78 (d, ^2J = 10.0 Hz, 1 H, CH_2), 4.43 (s, 2 H, CH_2), 6.84 (dd, ^3J = 7.8, ^4J = 2.0 Hz, 1 H, H_{arom}), 7.10 (m, 3 H, H_{arom}), 7.24 (m, 1 H, H_{arom}), 7.38 (m, 3 H, H_{arom}), 7.49 (d, ^3J = 1.0, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.2 (s, 1 C, NCH_3), 71.4 (s, 1 C, CH_2), 73.8 (s, 1 C, CH_2), 89.1 (s, 1 C, COH), 122.5 (s, 1 C, CH_{arom}), 123.3 (s, 1 C, CH_{arom}), 128.0 (s, 2 C, CH_{arom}), 128.2 (s, 1 C, CH_{arom}), 128.3 (s, 1 C, CH_{arom}), 128.7 (s, 2 C, CH_{arom}), 129.7 (s, 1 C, CH_{arom}), 129.9 (s, 1 C, Cq), 130.3 (s, 1 C, Cq), 145.8 (s, 1 C, Cq), 168.1 (s, 1 C, C=O).

Experiment 34

6.3.8.4 Synthesis of 3-hydroxy-2-methyl-3-((naphthalene-2-yloxy) methyl)isoindolin-1-one 14d (FH-57)



14d

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.91 g (4.50 mmol) of 2-(naphthalen-2-yloxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 4 h. The photosolution was cloudy and yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.23 g (0.72 mmol; 48%) of **14d** as a colourless solid.

TLC: R_f = 0.33 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 171-175°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.99 (s, 3 H, NCH_3), 3.69 (s, 1 H, OH), 4.39 (d, ^{2}J = 9.6 Hz, 1 H, CH_2), 4.49 (d, ^{2}J = 9.6 Hz, 1 H, CH_2), 6.99 (dd, ^{3}J = 8.8, ^{4}J = 2.5 Hz, 1 H, H_{arom}), 7.11 (d, ^{4}J = 2.5 Hz, 1 H, H_{arom}), 7.32 (ddd, ^{3}J = 7.0, ^{4}J = 1.0 Hz, 1 H, H_{arom}), 7.42 (ddd, ^{3}J = 7.0, ^{4}J = 1.0 Hz, 1 H, H_{arom}), 7.47 (ddd, ^{3}J = 7.3, ^{4}J = 0.9 Hz, 1 H, H_{arom}), 7.56 (ddd, ^{3}J = 7.3, ^{4}J = 0.9 Hz, 1 H, H_{arom}), 7.68 (m, 3 H, H_{arom}), 7.72 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.4 (s, 1 C, NCH_3), 69.5 (s, 1 C, CH_2), 88.8 (s, 1 C, COH), 107.5 (s, 1 C, CH_{arom}), 118.8 (s, 1 C, CH_{arom}), 122.6 (s, 1 C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 124.4 (s, 1 C, CH_{arom}), 126.9 (s, 1 C, CH_{arom}), 127.1 (s, 1 C, CH_{arom}), 128.0 (s, 1 C, CH_{arom}), 129.6 (s, 1 C, CH_{arom}), 129.9 (s, 1 C, Cq), 130.4 (s, 1 C, CH_{arom}), 131.9 (s, 1 C, Cq), 132.7 (s, 1 C, CH_{arom}), 134.5 (s, 1 C, Cq), 145.2 (s, 1 C, Cq), 156.2 (s, 1 C, Cq), 168.0 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 319 (M^+, <1), 317 (M^+-C_4H_8, <1), 301 (M^+-H_2O, 100), 244 (M^+-$C_6H_4^+$, 7), 162 (M^+-$C_{11}H_9O$, 32), 144 (M^+-$C_{10}H_{10}NO_2^-$, 30), 117 (M^+-$C_{10}H_{10}NO_2^-$, 82), 76 (M^+-$C_{14}H_{13}NO_3^-$, 15).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 320.12812 g/mol for $C_{20}H_{17}NO_3 + H^+$.

Found [M + H]$^+$: 320.12793 g/mol for $C_{20}H_{17}NO_3 + H^+$.

Calc. [M + Na]$^+$: 342.11006 g/mol for $C_{20}H_{17}NO_3 + Na^+$.

Found [M + Na]$^+$: 342.10997 g/mol for $C_{20}H_{17}NO_3 + Na^+$.

Electronspray: (ESI, Positive ions)

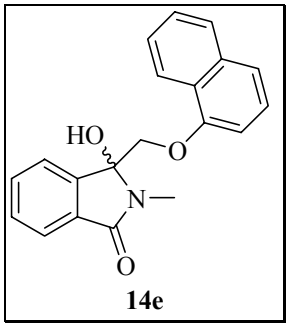
m/z (%) = 320 $(M + H)^+$, 639 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3233.11 (b, OH), 2926 (vi; CH_{aliph}), 2346.46 (w; CN), 1675.22 (s; C=O), 1628.89 (w; $C{=}C_{arom}$), 1049.35 (s, CO), 748.58 (s; CH_{arom}).

Experiment 35

6.3.8.5 Synthesis of 3-hydroxy-2-methyl-3-((naphthalene-1-yloxy) methyl)isoindolin-1-one 14e (FH-13)



14e

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.91 g (4.50 mmol) of 2-(naphthalene-1-yloxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 10 h. The photosolution was cloudy and yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.10 g (0.31 mmol; 21%) of **14e** as a yellow solid.

TLC: R_f = 0.39 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 177-182°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.91 (s, 3 H, NCH_3), 4.17 (s, 1 H, OH), 4.47 (d, ^2J = 9.6 Hz, 1 H, CH_2), 4.55 (d, ^2J = 9.6 Hz, 1 H, CH_2), 6.79 (d, ^3J = 7.3 Hz, 1 H, H_{arom}), 7.32 (m, 2 H, H_{arom}), 7.42 (m, 2 H, H_{arom}), 7.46 (ddd, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.55 (ddd, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.69 (m, 4 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.2 (s, 1 C, NCH_3), 68.8 (s, 1 C, CH_2), 89.2 (s, 1 C, COH), 105.3 (s, 1 C, CH_{arom}), 121.6 (s, 1 C, CH_{arom}), 121.8 (s, 1 C, CH_{arom}), 122.4 (s, 1 C, CH_{arom}), 123.6 (s, 1 C, CH_{arom}), 125.5 (s, 1 C, CH_{arom}), 125.8 (s, 1 C, CH_{arom}), 125.9 (s, 1 C, CH_{arom}), 126.9 (s, 1 C, CH_{arom}), 127.7 (s, 1 C, CH_{arom}), 130.4 (s, 1 C, CH_{arom}), 131.9 (s, 1 C,

Cq), 132.8 (s, 1 C, Cq), 134.7 (s, 1 C, Cq), 145.6 (s, 1 C, Cq), 153.9 (s, 1 C, Cq), 168.3 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 319 (M^+, 6), 301 (M^+-H_2O, 100), 272 (301-COH, 18), 244 (M^{+1}-C_6H_4, 7), 162 (M^+-$C_{11}H_9O$, 84), 77 (C_6H_5, 23).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 320.12812 g/mol for $C_{20}H_{17}NO_3 + H^+$.

Found [M + H]$^+$: 320.12783 g/mol for $C_{20}H_{17}NO_3 + H^+$.

Calc. [M + Na]$^+$: 342.11006 g/mol for $C_{20}H_{17}NO_3 + Na^+$.

Found [M + Na]$^+$: 342.10988 g/mol for $C_{20}H_{17}NO_3 + Na^+$.

Electronspray: (ESI, Positive ions)

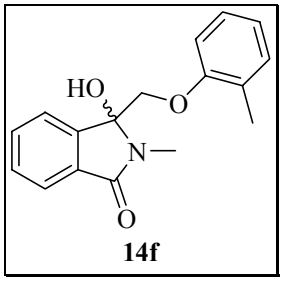
m/z (%) = 320 $(M + H)^+$, 639 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3294.9 (b, OH), 2944.89 (vi; CH_{aliph}), 2346.63 (w; CN), 1675.95 (s; C=O), 1617.52 (w; $C=C_{arom}$), 1070.37 (s, CO), 873.62 (s; CH_{arom}).

Experiment 36

6.3.8.6 Synthesis of 3-((2-methylphenoxy)methyl)-3-hydroxy-2-methylisoindolin-1-one <u>14f</u> (FH-175)



14f

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.74 g (4.50 mmol) of (2-methylphenoxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the

reaction was irradiated for 1 h. The photosolution was cloudy and white. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.42 g (1.48 mmol; 99%) of **14f** as a yellow oil.

TLC: R_f = 0.26 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, $CDCl_3$)

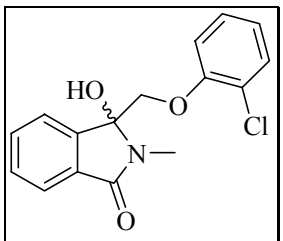
δ (ppm) = 1.81 (s, 3 H, CH_3), 3.03 (s, 3 H, NCH_3), 4.44 (d, ^2J = 9.6 Hz, 1 H, CH_2O), 4.51 (d, ^2J = 9.6 Hz, 1 H, CH_2O), 5.79 (s, 1 H, OH), 6.83 (ddd, ^2J = 14.8; ^3J = 7.2, ^4J = 0.8 Hz, 1 H, H_{arom}), 6.97 (d, ^3J = 8.0 Hz, 1 H, H_{arom}), 7.05 (dd, ^3J = 6.4, ^4J = 0.4 Hz, 1 H, H_{arom}), 7.14 (ddd, ^2J = 16.8; ^3J = 9.2, ^4J = 1.6 Hz, 1 H, H_{arom}), 7.56 (ddd, ^2J = 14.8; ^3J = 7.2, ^4J = 0.8 Hz, 1 H, H_{arom}), 7.63 (ddd, ^2J = 14.8; ^3J = 7.2, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.75 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 15.8 (s, 1 C, CH_3), 23.7 (s, 1 C, NCH_3), 69.1 (s, 1 C, CH_2), 89.4 (s, 1 C, COH), 112.4 (s, 1 C, CH_{arom}), 121.7 (s, 1 C, CH_{arom}), 123.1 (s, 1 C, CH_{arom}), 123.2 (s, 1 C, CH_{arom}), 127.2 (s, 1 C, Cq), 127.7 (s, 1 C, CH_{arom}), 130.3 (s, 1 C, CH_{arom}), 131.3 (s, 1 C, CH_{arom}), 133.6 (s, 1 C, CH_{arom}), 134.3 (s, 1 C, Cq), 147.2 (s, 1 C, Cq), 157.2 (s, 1 C, Cq), 167.4 (s, 1 C, C=O).

Experiment 37

6.3.8.7 Synthesis of 3-((2-chlorophenoxy)methyl)-3-hydroxy-2-methylisoindolin-1-one <u>14g</u> (FH-58)



14g

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.84 g (4.50 mmol) of 2-(2-chlorophenoxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 11 h. The photosolution was clear and yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.24 g (0.79 mmol; 53%) of **14g** as a colourless solid.

TLC: R_f = 0.38 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 159-164°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 3.03 (s, 3 H, NCH_3), 4.27 (d, ^2J = 9.6 Hz, 1 H, CH_2), 4.39 (d, ^2J = 9.6 Hz, 1 H, CH_2), 4.67 (s, 1 H, OH), 6.85 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1 H, H_{arom}), 6.92 (ddd, ^3J = 7.7, ^4J = 1.6 Hz, 1 H, H_{arom}), 7.18 (ddd, ^3J = 7.7, ^4J = 1.6 Hz, 1 H, H_{arom}), 7.33 (dd, ^3J = 8.1, ^4J = 1.5 Hz, 1 H, H_{arom}), 7.49 (ddd, ^3J = 7.4, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.58 (ddd, ^3J = 7.4, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.75 (dd, ^3J = 13.9, ^4J = 7.1 Hz, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.7 (s, 1 C, NCH_3), 71.4 (s, 1 C, CH_2), 88.5 (s, 1 C, COH), 114.3 (s, 1 C, CH_{arom}), 122.9 (s, 1 C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 128.1 (s, 1 C, CH_{arom}), 130.1 (s, 1 C, Cq), 130.5 (s, 1 C, CH_{arom}), 130.8 (s, 1 C, CH_{arom}), 132.0 (s, 1 C, Cq), 132.6 (s, 1 C, CH_{arom}), 144.9 (s, 1 C, Cq), 153.8 (s, 1 C, CH_{arom}), 167.0 (s, 1 C, Cq), 167.9 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 287 (M^{+1}-OH, 22), 285 (M^+-H_2O, 67), 251 (M^+-C_4H_4, 5), 174 (M^+-C_6H_4Cl"O, 33), 162 (M^+-C_7H_6ClO, 22), 146 (M^{+1}-$C_7H_7ClO_2$, 29), 128 (M^{+1}-$C_{10}H_{10}NO_2$, 7), 77 (C_6H_5, 13), 51 ($C_4H_4^+$, 7).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 304.07350 g/mol for $C_{16}H_{14}ClNO_3 + H^+$.

Found [M + H]$^+$: 304.07357 g/mol for $C_{16}H_{14}ClNO_3 + H^+$.

Electronspray: (ESI, Positive ions)

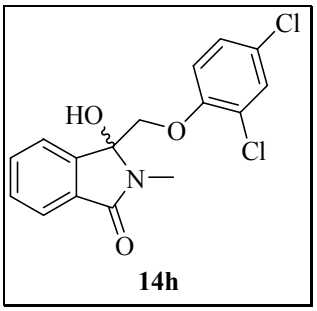
m/z (%) = 304 $(M + H)^+$, 607 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3291.49 (b, OH), 2926.46 (vi; CH_{aliph}), 2339 (w; CN), 1678.33 (s; C=O), 1617.44 (w; $C=C_{arom}$), 1146.48 (s, CO), 756.44 (s; CH_{arom}).

Experiment 38

6.3.8.8 Synthesis of 3-((2,4-dichlorophenoxy)methyl)-3-hydroxy-2-methylisoindolin-1-one 14h (FH-69)



14h

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.99 g (4.48 mmol) of 2-(2,4-dichlorophenoxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was cloudy and colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.36 g (1.06 mmol; 71%) of **14h** as a colourless solid.

TLC: R_f = 0.31 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 148-150°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.90 (s, 3 H, NCH_3), 4.11 (s; 1 H, OH), 4.18 (d, ^2J = 9.6 Hz, 1 H, CH_2), 4.37 (d, ^2J = 9.6 Hz, 1 H, CH_2), 6.76 (d, ^3J = 8.8 Hz, 1 H, H_{arom}), 7.13 (dd, ^3J = 8.8, ^4J = 2.5 Hz, 1 H, H_{arom}), 7.30 (d, ^3J = 2.5 Hz, 1 H, H_{arom}), 7.46 (ddd, ^3J = 7.4, ^4J =

1.0 Hz, 1 H, H_{arom}), 7.57 (ddd, ^{3}J = 7.4, ^{4}J = 1.0 Hz, 1 H, H_{arom}), 7.64 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 7.72 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

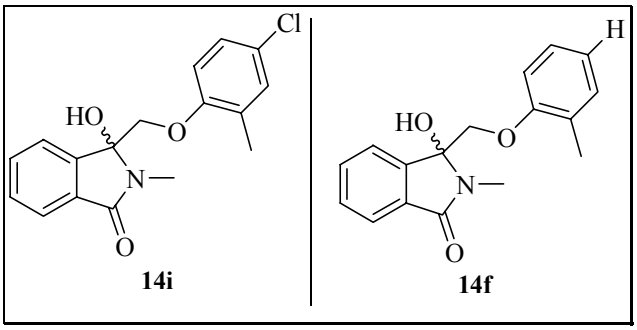
δ (ppm) = 24.4 (s, 1 C, NCH_3), 71.2 (s, 1 C, CH_2), 88.6 (s, 1 C, COH), 115.1 (s, 1 C, CH_{arom}), 122.8 (s, 1 C, CH_{arom}), 123.6 (s, 1 C, CH_{arom}), 124.6 (s, 1 C, Cq), 127.3 (s, 1 C, Cq), 127.9 (s, 1 C, CH_{arom}), 130.4 (s, 1 C, CH_{arom}), 130.5 (s, 1 C, CH_{arom}), 131.8 (s, 1 C, Cq), 132.7 (s, 1 C, CH_{arom}), 144.9 (s, 1 C, Cq), 152.7 (s, 1 C, Cq), 168.0 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3285.52 (b, OH), 2924.34 (vi; CH_{aliph}), 2345.12 (w; CN), 1678.19 (s, C=O), 1615.52 (w; $C=C_{arom}$), 822.56 (s; CH_{arom}).

Experiment 39

6.3.8.9 Synthesis of 3-((4-chloro-2-methylphenoxy)methyl)-3-hydroxy-2-methylisoindolin-1-one 14i (FH-64)



The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.91 g (4.53 mmol) of 2-(4-chloro-2-methylphenoxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was cloudy and colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.26 g (0.82 mmol; 55%) of **14i** together with **14f** as a yellow solid.

TLC: R_f = 0.37 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 110-115°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.74 (s, 3 H, CH_3), 2.76 (s, 3 H, NCH_3), 4.27 (dd, ^3J = 14.4, ^4J = 2.0 Hz, 2 H, CH_2), 4.51 (s, 1 H, OH), 6.65 (d, ^3J = 8.56 Hz, 1 H, H_{arom}), 6.97 (dd, ^3J = 7.2, ^4J = 2.4 Hz, 1 H, H_{arom}), 7.05 (dd, ^3J = 7.2, ^4J = 2.4 Hz, 1 H, H_{arom}), 7.55 (m, 3 H, H_{arom}), 7.61 (m, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 15.9 (s, 1 C, CH_3), 23.9 (s, 1 C, NCH_3), 68.9 (s, 1 C, CH_2), 89.2 (s, 1 C, COH), 112.5 (s, 1 C, CH_{arom}), 122.3 (s, 1 C, CH_{arom}), 123.3 (s, 1 C, CH_{arom}), 126.6 (s, 1 C, CH_{arom}), 127.1 (s, 1 C, CH_{arom}), 129.1 (s, 1 C, CH_{arom}), 130.2 (s, 1 C, CH_{arom}), 130.8 (s, 1 C, Cq), 131.7 (s, 1 C, Cq), 132.7 (s, 1 C, Cq), 145.5 (s, 1 C, Cq), 154.9 (s, 1 C, Cq), 168.3 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 317 (M^+, <1), 299 (M^+-H_2O, <1), 265 (M^+-OH-Cl, 22), 162 (M^+-C_8H_8ClO, 100), 146 (M^+-$C_8H_9ClO_2^+$, 25), 77 (C_6H_5, 20).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 318.08915 g/mol for $C_{17}H_{16}ClNO_3 + H^+$.

Found [M + H]$^+$: 318.08929 g/mol for $C_{17}H_{16}ClNO_3 + H^+$.

Calc. [M + Na]$^+$: 340.07109 g/mol for $C_{17}H_{16}ClNO_3 + Na^+$.

Found [M + Na]$^+$: 340.07138 g/mol for $C_{17}H_{16}ClNO_3 + Na^+$.

Electronspray: (ESI, Positive ions)

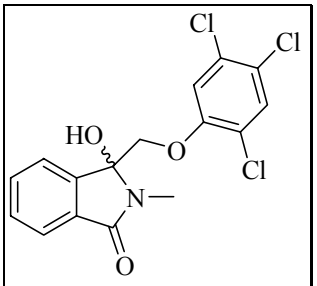
m/z (%) = 318 $(M + H)^+$, 637 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3261.76 (b, OH), 2925.38 (vi; CH_{aliph}), 2346.58 (w; CN), 1677.2 (s; C=O), 1618.51 (w; $C=C_{arom}$), 1054.81 (s, CO), 811.26 (s; CH_{arom}).

Experiment 40

6.3.8.10 Synthesis of 3-hydroxy-2-methyl-3-((2,4,5-trichloro phenoxy)methyl)isoindolin-1-one 14j (FH-62)



14j

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 1.15 g (4.50 mmol) of 2-(2,4,5-trichlorophenoxy) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 h. The photosolution was cloudy and colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.28 g (0.75 mmol; 51%) of **14j** as a yellow solid.

TLC: R_f = 0.45 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 150-155°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.84 (s, 3 H, NCH_3), 4.22 (d, ^2J = 9.5 Hz, 1 H, CH_2), 4.35 (d, ^2J = 9.5 Hz, 1 H, CH_2), 4.46 (s, 1 H, OH), 6.92 (s; 1 H; H_{arom}), 7.37 (s; 1 H; H_{arom}), 7.42 (dd, ^3J = 14.9, ^4J = 8.4 Hz, 1 H, H_{arom}), 7.55 (m, 2 H, H_{arom}), 7.69 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.4 (s, 1 C, NCH_3), 71.1 (s, 1 C, CH_2), 88.6 (s, 1 C, COH), 115.8 (s, 1 C, CH_{arom}), 122.7 (s, 1 C, Cq), 122.8 (s, 1 C, Cq), 123.6 (s, 1 C, CH_{arom}), 125.6 (s, 1 C, CH_{arom}), 130.5 (s, 1 C, CH_{arom}), 131.3 (s, 1 C, CH_{arom}), 131.5 (s, 1 C, Cq), 131.7 (s, 1

C, Cq), 132.7 (s, 1 C, CH_{arom}), 144.8 (s, 1 C, Cq), 152.9 (s, 1 C, Cq), 168.1 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 372 (M^+, <1), 357 (M^+-CH_3, <1), 355 (M^+-OH, <1), 353 (M^+-H_2O, <1), 174 (369-$C_6H_2Cl_3O$, 9), 162 (M^+-$C_7H_4Cl_3O^+$, 100), 133 (M^+-$C_8H_5Cl_3O_2$, 6), 77 (C_6H_5, 11).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 371.99555 g/mol for $C_{16}H_{12}Cl_3NO_3 + H^+$.

Found [M + H]$^+$: 371.99513 g/mol for $C_{16}H_{12}Cl_3NO_3 + H^+$.

Electronspray: (ESI, Positive ions)

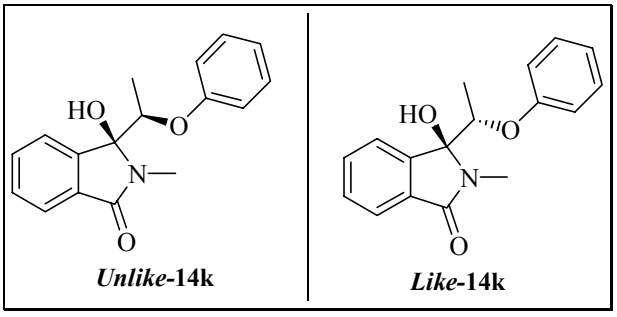
m/z (%) = 372 $(M)^+$, 744 $(M_2)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3289.57 (b, OH), 2925.96 (vi; CH_{aliph}), 2344.88 (w; CN), 1678.04 (s; C=O), 1619.26 (w; $C=C_{arom}$), 1082.88 (s, CO), 834.303 (s; CH_{arom}).

Experiment 41

6.3.8.11 Synthesis of 3-hydroxy-2-methyl-3-(1-phenoxyethyl) isoindolin-1-one 14k (FH-109)



***Unlike*-14k** **Like-14k**

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.75 g (4.51 mmol) of 2-phenoxypropionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction

was irradiated for 2 h. The photosolution was clear and yellow. The product obtained 0.37 g (1.30 mmol; 87%) of **14k** was yellow oily.

TLC: R_f = 0.44 (Ethyl Acetate/n-Hexane 1:1)

3-Hydroxy-2-methyl-3-(1-phenoxyethyl)isoindolin-1-one (14k)

Main Diastereoisomer: 53%

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 1.35 (d, ^3J = 6.3 Hz, 3 H, CH_3), 3.01 (s, 3 H, NCH_3), 5.04 (q, ^3J = 12.6, ^4J = 6.3 Hz, 1 H, CH), 5.73 (br. s, 1 H, OH), 6.99 (d, ^3J = 7.1 Hz, 2 H, H_{arom}), 7.28-7.37 (m, 3 H, H_{arom}), 7.60 (ddd, ^3J = 2.0, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.66 (ddd, ^3J = 2.0, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.73 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 7.80 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 15.5 (q, 1 C, CH_3), 24.9 (s, 1 C, NCH_3), 76.9 (d, 1 C, CH), 91.8 (q, 1 C, COH), 116.9 (d, 2 C, CH_{arom}), 122.1 (d, 1 C, CH_{arom}), 123.3 (d, 1 C, CH_{arom}), 124.0 (d, 1 C, CH_{arom}), 130.3 (d, 1 C, CH_{arom}), 130.4 (d, 2 C, CH_{arom}), 132.4 (d, 1 C, CH_{arom}), 133.6 (s, 1 C, Cq), 146.2 (s, 1 C, Cq), 159.1 (s, 1 C, Cq), 167.4 (s, 1 C, C=O).

Minor Diastereoisomer: 47%

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 0.95 (d, ^3J = 6.3 Hz, 3 H, CH_3), 3.08 (s, 3 H, NCH_3), 5.09 (q, ^3J = 6.3 Hz, 1 H, CH), 5.75 (br. s, 1 H, OH), 6.99 (d, ^3J = 7.1 Hz, 2 H, H_{arom}), 7.16 (d, ^3J = 7.1 Hz, 2 H, H_{arom}), 7.28-7.37 (m, 1 H, H_{arom}), 7.58 (ddd, ^3J = 2.0, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.69 (ddd, ^3J = 2.0, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.75 (d, ^3J = 7.3 Hz, 1 H, H_{arom}), 8.03 (d, ^3J = 7.3 Hz, 1 H, H_{arom}).

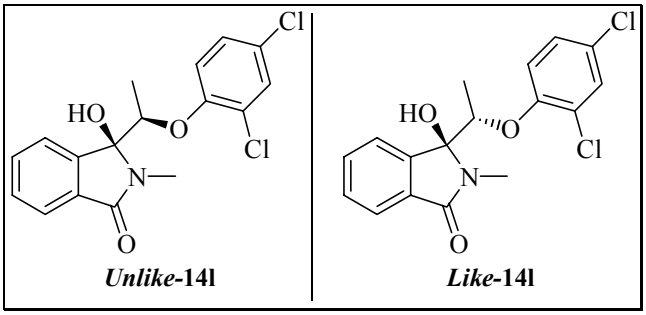
^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 14.9 (q, 1 C, CH_3), 24.1 (q, 1 C, NCH_3), 77.2 (d, 1 C, CH), 91.6 (q, 1 C, COH), 117.0 (d, 2 C, CH_{arom}), 121.8 (d, 1 C, CH_{arom}), 123.0 (d, 1 C, CH_{arom}), 125.8 (d, 1 C, CH_{arom}), 130.3 (d, 2 C, CH_{arom}), 130.4 (d, 1 C, CH_{arom}), 132.5 (d, 1 C,

CH_{arom}), 133.9 (s, 1 C, Cq), 146.0 (s, 1 C, Cq), 159.4 (s, 1 C, Cq), 167.6 (s, 1 C, C=O).

Experiment 42

6.3.8.12 Synthesis of 3-(1-(2,4-dichlorophenoxy)ethyl)-3-hydroxy-2-methylisoindolin-1-one 14l (FH-59)



The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.99 g (4.21 mmol) of 2-(2,4-dichlorophenoxy) propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 11 h. The photosolution was cloudy and yellow. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.32 g (0.91 mmol; 61%) of **14l** as a yellow solid.

TLC: R_f = 0.53 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 115-125°C.

3-(1-(2,4-Dichlorophenoxy)ethyl)-3-hydroxy-2-methylisoindolin-1-one (14l)
Main Diastereoisomer: 53%
^{1}H–NMR: (400 MHz, $CDCl_3$)
δ (ppm) = 0.99 (d, ^3J = 6.3 Hz, 3 H, CH_3), 3.06 (s, 3 H, NCH_3), 4.22 (s, 1 H, OH), 4.78 (q, ^3J = 12.6, ^4J = 6.3 Hz, 1 H, CH), 7.15 (dd, ^3J = 5.1, ^4J = 2.5 Hz, 1 H, H_{arom}),

7.34 (d, ^{3}J = 2.5 Hz, 1 H, H_{arom}), 7.42-7.58 (m, 1 H, H_{arom}), 7.67 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 7.68 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 14.8 (q, 1 C, CH_3), 25.8 (q, 1 C, NCH_3), 80.1 (d, 1 C, CH), 91.3 (s, 1 C, COH), 116.8 (d, 1 C, CH_{arom}), 123.4 (s, 1 C, Cq), 123.9 (d, 1 C, CH_{arom}), 125.1 (s, 1 C, Cq), 127.6 (s, 1 C, Cq), 128.2 (d, 1 C, CH_{arom}), 130.7 (s, 1 C, CH_{arom}), 130.8 (d, 1 C, CH_{arom}), 132.4 (s, 1 C, Cq), 132.6 (d, 1 C, CH_{arom}), 144.2 (s, 1 C, Cq), 152.4 (s, 1 C, Cq), 168.4 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 352 (M^+, <1), 333 (M^+-H_2O, <1), 188 (M^+-$C_9H_8NO_2^-$, 23), 162 (M^+-$C_8H_7Cl_2O^+$, 100), 146 (M^+-$C_{11}H_{12}NO_3$, 8), 77 (C_6H_5, 8).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 352.05018 g/mol for $C_{17}H_{15}Cl_2NO_3 + H^+$.

Found [M + H]$^+$: 352.05007 g/mol for $C_{17}H_{15}Cl_2NO_3 + H^+$.

Electronspray: (ESI, Positive ions)

m/z (%) = 352 $(M)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3304.14 (b, OH), 2982.82 (vi; CH_{aliph}), 2346.22 (w; CN), 1681.44 (s; C=O), 1618.01 (w; $C=C_{arom}$), 1063.55 (s, CO), 750.36 (s; CH_{arom}).

<u>Minor Diastereoisomer:</u> 47%

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 0.85 (d, ^{3}J = 6.3 Hz, 3 H, CH_3), 2.91 (s, 3 H, NCH_3), 3.69 (s, 1 H, OH), 4.73 (q, ^{3}J = 12.6, ^{4}J = 6.3 Hz, 1 H, CH), 7.16 (dd, ^{3}J = 5.1, ^{4}J = 2.5 Hz, 1 H, H_{arom}), 7.36 (d, ^{3}J = 2.5 Hz, 1 H, H_{arom}), 7.42-7.58 (m, 3 H, H_{arom}), 8.03 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}).

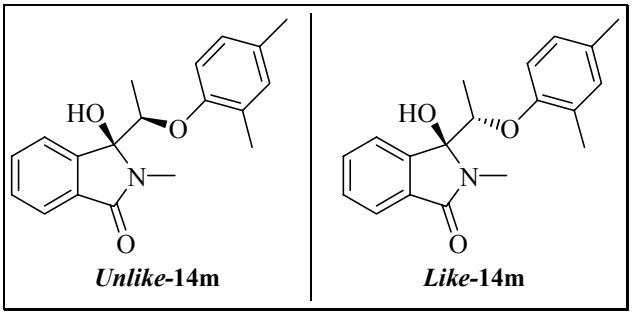
^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 14.9 (q, 1 C, CH_3), 24.4 (q, 1 C, NCH_3), 78.7 (d, 1 C, CH), 91.2 (s, 1 C, COH), 116.9 (d, 1 C, CH_{arom}), 122.4 (d, 1 C, CH_{arom}), 125.3 (s, 1 C, Cq), 125.5 (s, 1 C, Cq), 127.3 (s, 1 C, Cq), 128.1 (d, 1 C, CH_{arom}), 130.3 (d, 1 C, CH_{arom}), 130.6 (d, 1

C, CH_{arom}), 132.0 (s, 1 C, Cq), 132.8 (d, 1 C, CH_{arom}), 144.1 (s, 1 C, Cq), 152.8 (s, 1 C, Cq), 168.2 (s, 1 C, C=O).

Experiment 43

6.3.8.13 Synthesis of 3-(1-(2,4-dimethylphenoxy)ethyl)-3-hydroxy-2-methylisoindolin-1-one <u>14m</u> (FH-63)



***Unlike*-14m** ***Like*-14m**

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.88 g (4.53 mmol) of 2-(2,4-dimethylphenoxy) propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was cloudy and colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.37 g (1.19 mmol; 80%) of **14m** as a colourless solid.

TLC: R_f = 0.49 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 129-134°C.

3-(1-(2,4-Dimethylphenoxy)ethyl)-3-hydroxy-2-methylisoindolin-1-one (14m)
<u>Main Diastereoisomer:</u> 53%
^{1}H–NMR: (400 MHz, $CDCl_3$)
δ (ppm) = 0.81 (d, ^3J = 6.3 Hz, 3 H, CH_3), 2.21 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 2.96 (s, 3 H, NCH_3), 4.14 (br. s, 1 H, OH), 4.72 (q, ^3J = 12.6, ^4J = 6.3 Hz, 1 H, CH),

6.83 (d, ^{3}J = 8.6 Hz, 1 H, H_{arom}), 6.89-6.94 (m, 2 H, H_{arom}), 7.42-7.56 (m, 3 H, H_{arom}), 7.84 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 15.0 (q, 1 C, CH_3), 17.3 (q, 1 C, CH_3), 21.1 (q, 1 C, CH_3), 24.8 (q, 1 C, NCH_3), 78.6 (d, 1 C, CH), 91.6 (s, 1 C, COH), 113.4 (d, 1 C, CH_{arom}), 122.8 (d, 1 C, CH_{arom}), 124.6 (d, 1 C, CH_{arom}), 127.9 (d, 1 C, CH_{arom}), 128.4 (s, 1 C, Cq), 130.5 (d, 1 C, CH_{arom}), 131.8 (s, 1 C, Cq), 132.6 (s, 1 C, Cq), 132.7 (d, 1 C, CH_{arom}), 132.8 (d, 1 C, CH_{arom}), 144.5 (s, 1 C, Cq), 154.1 (s, 1 C, Cq), 168.5 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3286.6 (b, OH), 2917.86 (vi; CH_{aliph}), 2346.65 (w; CN), 1671.96 (s; C=O), 1615.35 (w; $C{=}C_{arom}$), 1079.11 (s, CO), 816.96 (s; CH_{arom}).

<u>Minor Diastereoisomer:</u> 47%

^{1}H–NMR: (400 MHz, $CDCl_3$)

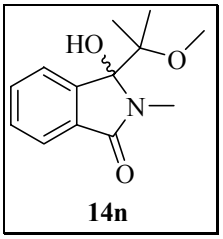
δ (ppm) = 0.99 (d, ^{3}J = 6.3 Hz, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 3.04 (s, 3 H, NCH_3), 3.59 (br. s, 1 H, OH), 4.78 (q, ^{3}J = 12.6, ^{4}J = 6.3 Hz, 1 H, CH), 6.76 (d, ^{3}J = 8.6 Hz, 1 H, H_{arom}), 6.89-6.94 (m, 2 H, H_{arom}), 7.42-7.56 (m, 2 H, H_{arom}), 7.71 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 14.8 (q, 1 C, CH_3), 17.7 (q, 1 C, CH_3), 21.2 (q, 1 C, CH_3), 26.0 (q, 1 C, NCH_3), 77.8 (d, 1 C, CH), 91.5 (s, 1 C, COH), 114.3 (d, 1 C, CH_{arom}), 123.9 (d, 1 C, CH_{arom}), 124.1 (d, 1 C, CH_{arom}), 127.8 (d, 1 C, CH_{arom}), 128.2 (s, 1 C, Cq), 130.8 (d, 1 C, CH_{arom}), 132.6 (s, 1 C, Cq), 132.7 (s, 1 C, CH_{arom}), 132.8 (d, 1 C, CH_{arom}), 133.1 (s, 1 C, Cq), 145.1 (s, 1 C, Cq), 153.7 (s, 1 C, Cq), 168.4 (s, 1 C, C=O).

Experiment 44

6.3.8.14 Synthesis of 3-hydroxy-3-(2-methoxypropan-2-yl)-2-methylisoindolin-1-one 14n (FH-16)



14n

The general procedure (GP-1) was followed and 0.17 g (1.05 mmol) of *N*-methyl-phthalimide **4a**, 0.36 g (3.05 mmol) of 2-methoxy-2-methylpropanoic acid and 0.21 g (1.52 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 ½ h. The photosolution was clear and colourless. Then, the product 0.23 g (0.98 mmol; 94%) of **14n** was yellow oily.

Melting point: 97-105°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 0.93 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 3.05 (s, 3 H, NCH_3), 3.34 (s, 3 H, OCH_3), 4.45 (s, 1 H, OH), 7.48 (m, 2 H, H_{arom}), 7.62 (dd, ^3J = 6.6, ^4J = 1.5 Hz, 1 H, H_{arom}), 7.76 (dd, ^3J = 6.6, ^4J = 1.5 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 19.5 (s, 1 C, CH_3), 20.6 (s, 1 C, CH_3), 26.8 (s, 1 C, NCH_3), 49.7 (s, 1 C, OCH_3), 81.2 (s, 1 C, Cq), 94.0 (s, 1 C, COH), 123.4 (s, 1 C, CH_{arom}), 124.5 (s, 1 C, CH_{arom}), 130.0 (s, 1 C, CH_{arom}), 131.6 (s, 1 C, CH_{arom}), 133.3 (s, 1 C, Cq), 144.7 (s, 1 C, Cq), 168.2 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 235 (M^+, 2), 220 (M^+-CH_3, 7), 217 (M^+-H_2O, 17), 204 (M^+-CH_3O, 55), 163 (M^{+1}-CH_2OCH_3, 75), 77 ($C_6H_5^+$, 9).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 236.12812 g/mol for $C_{13}H_{17}NO_3 + H^+$.

Found [M + H]$^+$: 236.12783 g/mol for $C_{13}H_{17}NO_3 + H^+$.

Calc. [M$_2$ + H]$^+$: 471.24896 g/mol for $(C_{13}H_{17}NO_3)_2 + H^+$.

Found [M$_2$ + H]$^+$: 471.24892 g/mol for $(C_{13}H_{17}NO_3)_2 + H^+$.

Calc. [M$_2$ + Na]$^+$: 493.23091 g/mol for $(C_{13}H_{17}NO_3)_2 + Na^+$.

Found [M$_2$ + Na]$^+$: 493.23083 g/mol for $(C_{13}H_{17}NO_3)_2 + Na^+$.

Electronspray: (ESI, Positive ions)

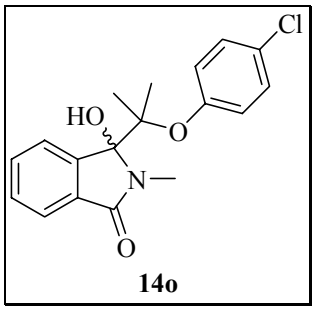
m/z (%) = 236 $(M + H)^+$, 471 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3293.82 (b, OH), 2942.45 (vi; CH_{aliph}), 2346.41 (w; CN), 1677.23 (s; C=O), 1618.12 (w; $C=C_{arom}$), 1067.33 (s, CO), 757.16 (s; CH_{arom}).

Experiment 45

6.3.8.15 Synthesis of 3-(2-(4-chlorophenoxy)propan-2-yl)-3-hydroxy -2-methylisoindolin-1-one 14o (FH-30)



14o

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.84 g (3.92 mmol) of 2-(4-chlorophenoxy)-2-methyl propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 2 h. The photosolution was clear and yellowish.

Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.25 g (0.76 mmol; 51%) of **14o** as a yellow brownish solid.

Melting point: 127-137°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.03 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 3.21 (s, 3 H, NCH_3), 4.63 (s, 1 H, OH), 6.82 (m, 2 H, H_{arom}), 6.88 (m, 2 H, H_{arom}), 7.52 (m, 2 H, H_{arom}), 7.69 (m, 1 H, H_{arom}), 7.81 (m, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.8 (s, 1 C, CH_3), 22.6 (s, 1 C, CH_3), 27.2 (s, 1 C, NCH_3), 86.0 (s, 1 C, Cq), 93.9 (s, 1 C, COH), 123.6 (s, 1 C, CH_{arom}), 124.5 (s, 1 C, CH_{arom}), 125.8 (s, 1 C, CH_{arom}), 126.1 (s, 2 C, CH_{arom}), 129.7 (s, 1 C, CH_{arom}), 130.3 (s, 2 C, CH_{arom}), 131.9 (s, 1 C, Cq), 144.7 (s, 1 C, Cq), 153.6 (s, 1 C, Cq), 168.6 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 331 (M^+, <1), 315 (M^{+1}-OH, <1), 298 (M^{+1}-Cl, <1), 279 (M^+-$C_4H_3^+$, <1), 254 (M^+-C_6H_5, <1), 204 (M^+-C_6H_4ClO, 17), 188 (M^+-$C_7H_7ClO^+$, 8), 169 (M^+-$C_9H_8NO_2$, 15), 162 (M^+-$C_9H_{10}ClO$, 100), 128 (M^+-$C_6H_4ClO^-$, 17), 105 (M^+-$C_{11}H_{14}ClNO_2^-$, 9), 77 (C_6H_5, 16), 56 ($C_2H_3NO^+$, 9), 51 (C_4H_3, 5).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 332.10480 g/mol for $C_{18}H_{18}ClNO_3 + H^+$.

Found [M + H]$^+$: 332.10495 g/mol for $C_{18}H_{18}ClNO_3 + H^+$.

Electronspray: (ESI, Positive ions)

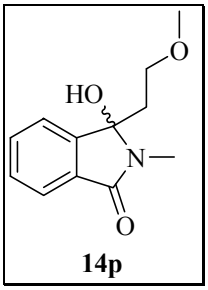
m/z (%) = 332 $(M + H)^+$, 663 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3256.98 (b, OH), 2991.2 (vi; CH_{aliph}), 2346.76 (w; CN), 1673.57 (s; C=O), 1613.95 (w; C=C_{arom}), 1073.53 (s, CO), 764.23 (s; CH_{arom}).

Experiment 46

6.3.8.16 Synthesis of 3-hydroxy-3-(methoxyethyl)-2-methyl isoindolin-1-one 14p (FH-22)



14p

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.47 g (4.51 mmol) of 3-methoxy propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 16 h. The photosolution was clear and yellowish. Then, the product 0.026 g (0.12 mmol; 8%) of **14p** which was yellow solid.

TLC: R_f = 0.27 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, $CDCl_3$)

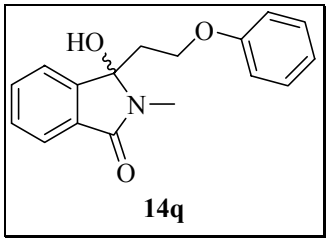
δ (ppm) = 2.18 (td, ^2J = 14.1, ^3J = 6.8 Hz, 1 H, CH_2), 2.36 (td, ^2J = 14.1, ^3J = 6.8 Hz, 1 H, CH_2), 2.76 (s, 3 H, NCH_3), 3.00 (t, ^3J = 6.8 Hz, 1 H, CH_2O), 3.07 (s, 3 H, OCH_3), 4.27 (br. s, 1 H, OH), 7.33 (m, 1 H, H_{arom}), 7.47 (br. m, 3 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.5 (q, 1 C, NCH_3), 35.6 (t, 1 C, CH_2), 58.7 (q, 1 C, OCH_3), 67.9 (t, 1 C, CH_2O), 89.4 (s, 1 C, COH), 122.0 (d, 1 C, CH_{arom}), 123.0 (d, 1 C, CH_{arom}), 129.4 (d, 1 C, CH_{arom}), 130.9 (s, 1 C, Cq), 132.1 (d, 1 C, CH_{arom}), 146.6 (s, 1 C, Cq), 167.0 (s, 1 C, C=O).

Experiment 47

6.3.8.17 Synthesis of 3-hydroxy-2-methyl-3-(2-phenoxyethyl) isoindolin-1-one 14q (FH-23)



14q

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.75 g (4.51 mmol) of phenoxy propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 16 h. The photosolution was clear and yellowish. Then, the product 0.11 g (0.38 mmol; 26%) of **14q** which was a yellow solid.

^{1}H–NMR: (400 MHz, $CDCl_3$)

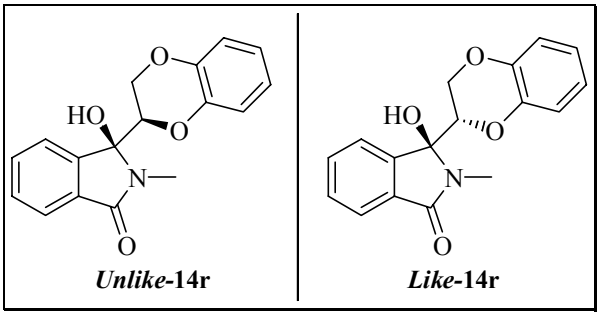
δ (ppm) = 2.54 (m, 1 H, CH_2), 2.66 (m, 1 H, CH_2), 2.88 (s, 3 H, NCH_3), 3.62 (m, 2 H, CH_2), 3.78 (s, 1 H, OH), 6.61 (d, ^2J = 7.84 Hz, 2 H, H_{arom}), 6.87 (m, 1 H, H_{arom}), 7.17 (m, 2 H, H_{arom}), 7.42 (m, 1 H, H_{arom}), 7.57 (m, 3 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 15.2 (s, 1 C, NCH_3), 23.9 (s, 1 C, CH_2), 63.2 (s, 1 C, CH_2), 89.7 (s, 1 C, COH), 114.5 (s, 2 C, CH_{arom}), 121.3 (s, 1 C, CH_{arom}), 122.4 (s, 1 C, CH_{arom}), 123.5 (s, 1 C, CH_{arom}), 129.7 (s, 2 C, CH_{arom}), 129.9 (s, 1 C, CH_{arom}), 131.3 (s, 1 C, CH_{arom}), 132.6 (s, 1 C, Cq), 146.6 (s, 1 C, Cq), 158.4 (s, 1 C, Cq), 167.5 (s, 1 C, C=O).

Experiment 48

6.3.8.18 Synthesis of 3-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)-3-hydroxy-2-methylisoindolin-1-one 14r (FH-66)



The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.82 g (4.55 mmol) of 2,3-dihydrobenzo*[b]*[1,4]dioxin-2-carboxylic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear and colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.37 g (1.24 mmol; 83%) of **14r** as a colourless solid.

TLC: R_f = 0.34 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 163-166°C.

3-(2,3-Dihydrobenzo*[b]*[1,4]dioxin-2-yl)-3-hydroxy-2-methylisoindolin-1-one (14r)

Main Diastereoisomer: 64%

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.80 (s, 3 H, NCH_3), 3.95 (dd, ^3J = 11.1, ^4J = 2.1 Hz, 1 H, CH_2), 4.36 (dd, ^3J = 11.1, ^4J = 2.1 Hz, 1 H, CH_2), 4.48 (s, 1 H, OH), 4.53 (dd, ^3J = 9.1, ^4J = 2.2 Hz, 1 H, CH), 6.70-6.79 (m, 3 H, H_{arom}), 6.82 (dd, ^3J = 7.4, ^4J = 1.8 Hz, 1 H, H_{arom}), 7.39-7.45 (m, 1 H, H_{arom}), 7.44-7.53 (m, 2 H, H_{arom}), 7.57 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.7 (s, 1 C, NCH_3), 65.0 (t, 1 C, CH_2), 74.4 (d, 1 C, CH), 89.4 (s, 1 C, COH), 117.5 (d, 1 C, CH_{arom}), 117.7 (d, 1 C, CH_{arom}), 122.1 (d, 1 C, CH_{arom}), 122.4 (d, 1 C, CH_{arom}), 123.0 (d, 1 C, CH_{arom}), 123.9 (d, 1 C, CH_{arom}), 130.8 (d, 1 C, CH_{arom}), 132.3 (s, 1 C, Cq), 132.6 (d, 1 C, CH_{arom}), 142.9 (s, 1 C, Cq), 143.3 (s, 1 C, Cq), 143.4 (s, 1 C, Cq), 168.2 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 297 (M^+, 2), 279 (M^+-H_2O, 55), 77 (C_6H_5, 14).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 298.10738 g/mol for $C_{17}H_{15}NO_4 + H^+$.

Found [M + H]$^+$: 298.10718 g/mol for $C_{17}H_{15}NO_4 + H^+$.

Calc. [M + Na]$^+$: 320.08933 g/mol for $C_{17}H_{15}NO_4 + Na^+$.

Found [M + Na]$^+$: 320.08911 g/mol for $C_{17}H_{15}NO_4 + Na^+$.

Electronspray: (ESI, Positive ions)

m/z (%) = 298 $(M + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3269.3 (b, OH), 2923.59 (vi; CH_{aliph}), 2345.41 (w; CN), 1682.71 (s; C=O), 1613.59 (w; $C=C_{arom}$), 1072.7 (s, CO), 862.30 (s; CH_{arom}).

<u>Minor Diastereoisomer:</u> 36%

^{1}H–NMR: (400 MHz, $CDCl_3$)

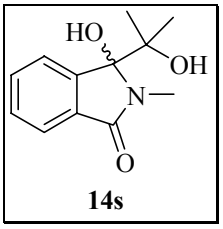
δ (ppm) = 2.89 (s, 3 H, NCH_3), 3.24 (dd, ^3J = 11.1, ^4J = 2.1 Hz, 1 H, CH_2), 3.99 (dd, ^3J = 11.1, ^4J = 2.1 Hz, 1 H, CH_2), 4.20 (s, 1 H, OH), 4.60 (dd, ^3J = 9.1, ^4J = 2.2 Hz, 1 H, CH), 6.70-6.79 (m, 2 H, H_{arom}), 6.85 (dd, ^3J = 7.4, ^4J = 1.8 Hz, 1 H, H_{arom}), 7.00 (dd, ^3J = 7.4, ^4J = 1.8 Hz, 1 H, H_{arom}), 7.39-7.45 (m, 1 H, H_{arom}), 7.44-7.53 (m, 1 H, H_{arom}), 7.59 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 7.73 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.7 (s, 1 C, NCH_3), 64.2 (t, 1 C, CH_2), 75.4 (d, 1 C, CH), 88.6 (s, 1 C, COH), 117.6 (d, 1 C, CH_{arom}), 117.7 (d, 1 C, CH_{arom}), 122.3 (d, 1 C, CH_{arom}), 122.5 (d, 1 C, CH_{arom}), 123.8 (d, 1 C, CH_{arom}), 124.2 (d, 1 C, CH_{arom}), 130.7 (d, 1 C, CH_{arom}), 131.3 (s, 1 C, Cq), 133.0 (d, 1 C, CH_{arom}), 143.2 (s, 1 C, Cq), 143.3 (s, 1 C, Cq), 144.0 (s, 1 C, Cq), 168.0 (s, 1 C, C=O).

Experiment 49

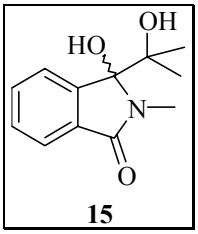
6.3.8.19 Attempted synthesis of 3-hydroxy-3-(2-hydroxypropan-2-yl)-2-methylisoindolin-1-one 14s (FH-27)



14s

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.47 g (4.51 mmol) of 2-hydroxy-2-methyl propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 4 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.21 g (0.95 mmol; 64%) of colourless solid. NMR analysis showed that a mixture of **15**, **16** and **17** was obtained instead of the desired product **14s**.

3–Hydroxy–3–(1–hydroxy–1–methylethyl)–2–methyl–2,3–dihydroisoindol–1–on 15



15

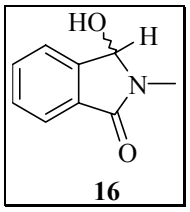
^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 0.98 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 2.92 (s, 3 H, NCH_3), 2.95 (s, 1 H, OH), 7.54 (m, 4 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.7 (q, 1 C, NCH_3), 25.9 (q, 1 C, CH_3), 26.3 (q, 1 C, CH_3), 75.7 (s, 1 C, COH), 92.9 (s, 1 C, COH), 122.4 (d, 1 C, CH_{arom}), 123.8 (d, 1 C, CH_{arom}), 128.9 (d, 1 C, CH_{arom}), 130.9 (d, 1 C, CH_{arom}), 132.4 (s, 1 C, Cq), 146.0 (s, 1 C, Cq), 167.6 (s, 1 C, C=O).

3–Hydroxy–2–methyl–2,3–dihydroisoindol–1–on <u>16</u>



16

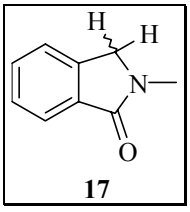
^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 3.00 (s, 3 H, NCH_3), 3.99 (br. s., 1 H, OH), 5.63 (s, 1 H, CH), 7.54 (m, 4 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 26.0 (q, 1 C, NCH_3), 83.5 (d, 1 C, CH), 122.8 (d, 1 C, CH_{arom}), 123.1 (d, 1 C, CH_{arom}), 131.2 (s, 1 C, Cq), 132.0 (d, 1 C, CH_{arom}), 133.8 (d, 1 C, CH_{arom}), 143.8 (s, 1 C, Cq), 167.6 (s, 1 C, C=O).

2–Methyl–2,3–dihydroisoindol–1–on <u>17</u>



17

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 3.17 (s, 3 H, NCH_3), 4.34 (s, 2 H, CH_2), 7.60 (m, 4 H, H_{arom}).

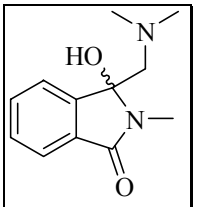
^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 29.4 (q, 1 C, NCH_3), 51.9 (t, 1 C, CH_2), 122.5 (d, 1 C, CH_{arom}), 123.6 (d, 1 C, CH_{arom}), 128.0 (d, 2 C, CH_{arom}), 131.1 (d, 1 C, Cq), 140.9 (s, 1 C, Cq), 168.6 (s, 1 C, C=O).

6.3.9 Photoreactions of *N*-methylphthalimide with nitrogen-containing carboxylates

Experiment 50

6.3.9.1 Attempted synthesis of 3-((dimethylamino)methyl)-3-hydroxy-2-methylisoindolin-1-one 18a (FH-67)



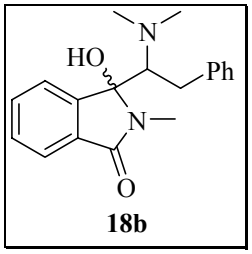
18a

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.47 g (4.55 mmol) of 2-(dimethylamino) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.097 g (0.66 mmol; 44%) of colourless solid. NMR analysis showed that a mixture of **15**, **16** and **17** was obtained instead of the desired product **18a**.

Analytical data identical to that of previous reaction (experiment 49).

Experiment 51

6.3.9.2 Attempted synthesis of 3-(1-(dimethylamino)-2-phenyl ethyl)-3-hydroxy-2-methylisoindolin-1-one 18b (FH-29)



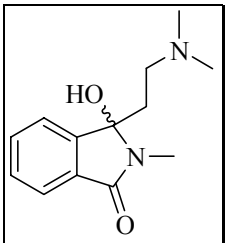
18b

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.87 g (4.50 mmol) of 2-(dimethylamino)-3-phenyl propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 h. The photosolution was clear, yellow greenish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.086 g (0.28 mmol; 19%) of colourless solid. NMR analysis showed that a mixture of **15**, **16** and **17** was obtained instead of the desired product **18b**.

Analytical data identical to that of previous reaction (experiment 49).

Experiment 52

6.3.9.3 Attempted synthesis of 3-(2-(dimethylamino)ethyl)-3-hydroxy-2-methylisoindolin-1-one 18c (FH-68)



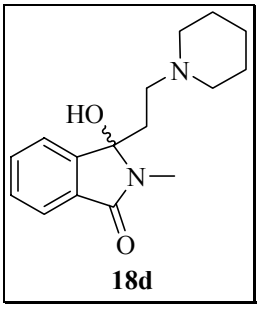
18c

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.53 g (4.52 mmol) of 3-(dimethylamino) propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear, yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.056 g (0.24 mmol; 16%) of colourless solid. NMR analysis showed that a mixture of **15**, **16** and **17** was obtained instead of the desired product **18c**.

Analytical data identical to that of previous reaction (experiment 49).

Experiment 53

6.3.9.4 Attempted synthesis of 3-hydroxy-2-methyl-3-(2-piperidin-1-yl)ethyl)isoindolin-1-one <u>18d</u> (FH-28)



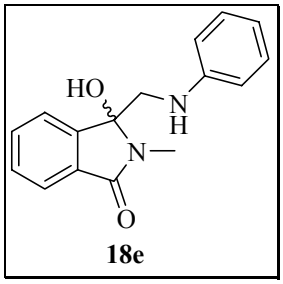
18d

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.71 g (4.51 mmol) of 3-(piperidin-1-yl) propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear, yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.032 g (0.12 mmol; 8%) of colourless solid. NMR analysis showed that a mixture of **15**, **16** and **17** was obtained instead of the desired product **18d**.

<u>Analytical data identical to that of previous reaction (experiment 49).</u>

Experiment 54

6.3.9.5 Synthesis of 3-hydroxy-2-methyl-3-(phenylamino)methyl) isoindolin-1-one 18e (JF-16)



18e

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.68 g (4.50 mmol) of 2-(phenylamino)acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 4 h. The photosolution was clear, yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.12 g (0.45 mmol; 30%) of **18e** as a light yellow solid.

TLC: R_f = 0.42 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 3.02 (s, 3 H, NCH_3), 3.67 (d, ^2J = 12.8, ^3J = 6.2 Hz, 1 H, CH_2), 3.90 (d, ^2J = 12.8, ^3J = 6.2 Hz, 1 H, CH_2), 4.60 (t, ^3J = 12.0, ^4J = 6.0 Hz, 1 H, NH), 5.54 (s, 1 H, OH), 6.58 (m, 1 H, H_{arom}), 6.68 (d, ^2J = 7.6 Hz, 2 H, H_{arom}), 7.06 (m, 2 H, H_{arom}), 7.51 (ddd, ^2J = 14.8, ^3J = 7.2, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.59 (ddd, ^2J = 14.8, ^3J = 7.2, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.66 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 7.79 (d, ^2J = 7.6 Hz, 1 H, H_{arom}).

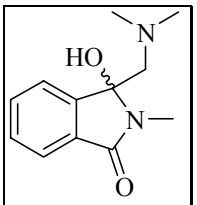
^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.9 (s, 1 C, NCH_3), 49.0 (s, 1 C, CH_2), 90.2 (s, 1 C, COH), 113.9 (s, 2 C, CH_{arom}), 117.8 (s, 1 C, CH_{arom}), 123.3 (s, 1 C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 129.8

(s, 2 C, CH_{arom}), 130.4 (s, 1 C, CH_{arom}), 130.7 (s, 1 C, CH_{arom}), 133.4 (s, 1 C, Cq), 147.7 (s, 1 C, Cq), 149.6 (s, 1 C, Cq), 167.5 (s, 1 C, C=O).

Experiment 55

6.3.9.6 Attempted synthesis of 3-((dimethylamino)methyl)-3-hydroxy-2-methylisoindolin-1-one <u>18f</u> (FH-146)



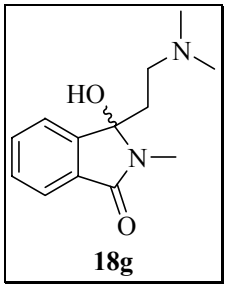
18f

0.24 g (1.49 mmol) of *N*-methylphthalimide **4a** and 0.47 g (4.56 mmol) of 2-(dimethylamino) acetic acid were dissolved in 150 ml of acetonitrile (MeCN) [50:50] and the reaction was irradiated for 2 h. The photosolution was clear, yellowish. The product obtained was 0.15 g (0.68 mmol; 46%) of yellow solid. NMR analysis showed that a mixture of **15**, **16** and **17** was obtained instead of the desired product **18f**.

<u>Analytical data identical to that of previous reaction (experiment 49).</u>

Experiment 56

6.3.9.7 Attempted synthesis of 3-(2-(dimethylamino)ethyl)-3-hydroxy-2-methylisoindolin-1-one 18g (FH-178)



18g

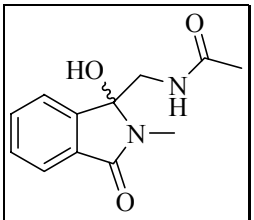
0.24 g (1.49 mmol) of *N*-methylphthalimide **4a** and 0.53 g (4.52 mmol) of 3-(dimethylamino) propanoic acid were dissolved in 150 ml of acetonitrile (MeCN) [50:50] and the reaction was irradiated for 2 h. The photosolution was clear, yellowish. The product obtained was 0.13 g (0.55 mmol; 37%) of yellow solid. NMR analysis showed that a mixture of **15**, **16** and **17** was obtained instead of the desired product **18g**.

Analytical data identical to that of previous reaction (experiment 49).

6.3.10 Photoreactions of *N*-methylphthalimide with amide-containing carboxylates

Experiment 57

6.3.10.1 Synthesis of N-((1-hydroxy-2-methyl-3-oxoisoindolin-1-yl) methyl) acetamide 19a (FH-41)



19a

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methylphthalimide **4a**, 0.53 g (4.53 mmol) of *N*-acetylglycine and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 2 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; MeOH:$CHCl_3$ = 1:9) gave 0.25 g (1.06 mmol; 71%) of **19a** as a brown viscous oil.

^{1}H–NMR: (400 MHz, $CDCl_3$)

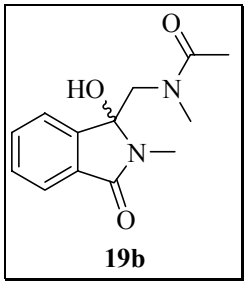
δ (ppm) = 1.88 (s, 3 H, CH_3), 2.92 (s, 3 H, NCH_3), 3.73 (dd, ^3J = 14.1, ^4J = 6.2 Hz, 1 H, CH_2), 3.86 (dd, ^3J = 14.1, ^4J = 6.2 Hz, 1 H, CH_2), 4.84 (s, 1 H, OH), 5.71 (s, 1 H, NH), 7.43 (m, 1 H, H_{arom}), 7.56 (m, 3 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.3 (s, 1 C, CH_3), 24.1 (s, 1 C, NCH_3), 44.4 (s, 1 C, CH_2), 89.6 (s, 1 C, COH), 122.5 (s, 1 C, CH_{arom}), 123.4 (s, 1 C, CH_{arom}), 130.3 (s, 1 C, CH_{arom}), 131.5 (s, 1 C, CH_{arom}), 132.7 (s, 1 C, Cq), 145.4 (s, 1 C, Cq), 171.0 (s, 1 C, C=O), 171.5 (s, 1 C, C=O).

Experiment 58

6.3.10.2 Synthesis of N-((1-hydroxy-2-methyl-3-oxoisoindolin-1-yl) methyl)-N-methylacetamide 19b (FH-73)



19b

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.59 g (4.50 mmol) of 2-(*N*-methylacetamido) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear and colourless. Then, the product 0.27 g (1.09 mmol; 73%) of **19b** was light brown solid. The melting point was recorded 100-105°C.

Melting point: 100-105°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

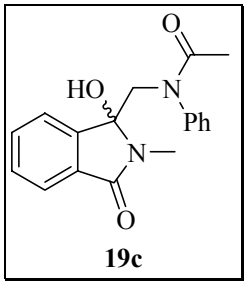
δ (ppm) = 2.14 (s, 3 H, CH_3), 2.87 (s, 3 H, NCH_3), 3.02 (s, 3 H, NCH_3), 3.49 (d, ^2J = 14.3 Hz, 1 H, CH_2), 4.13 (d, ^2J = 14.3 Hz, 1 H, CH_2), 7.46 (m, 1 H, H_{arom}), 7.53 (m, 2 H, H_{arom}), 7.73 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 22.1 (s, 1 C, CH_3), 24.5 (s, 1 C, NCH_3), 39.7 (s, 1 C, NCH_3), 56.8 (s, 1 C, CH_2), 90.0 (s, 1 C, COH), 122.7 (s, 1 C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 130.1 (s, 1 C, CH_{arom}), 131.6 (s, 1 C, CH_{arom}), 132.2 (s, 1 C, Cq), 146.3 (s, 1 C, Cq), 167.4 (s, 1 C, C=O), 174.9 (s, 1 C, C=O).

Experiment 59

6.3.10.3 Synthesis of N-((1-hydroxy-2-methyl-3-oxoisoindolin-1-yl) methyl)-N-phenylacetamide 19c (FH-74)



19c

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.87 g (4.50 mmol) of 2-(*N*-phenylacetamido) acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear and yellowish. Then, the product 0.45 g (1.45 mmol; 97%) of **19c** was yellow solid.

Melting point: 158-165°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.63 (s, 3 H, CH_3), 2.57 (s, 3 H, NCH_3), 4.18 (d, ^2J = 14.5 Hz, 1 H, CH_2), 4.51 (s; 1 H, OH), 4.66 (d, ^2J = 14.5 Hz, 1 H, CH_2), 6.69 (dd, ^3J = 7.8, ^4J = 2.3 Hz, 2 H, H_{arom}), 7.19 (m, 3 H, H_{arom}), 7.36 (m, 2 H, H_{arom}), 7.44 (m, 1 H, H_{arom}), 7.56 (m, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 22.9 (s, 1 C, CH_3), 23.9 (s, 1 C, NCH_3), 52.5 (s, 1 C, CH_2), 90.0 (s, 1 C, COH), 122.9 (s, 1 C, CH_{arom}), 123.6 (s, 1 C, CH_{arom}), 127.6 (s, 2 C, CH_{arom}), 128.1 (s, 1 C, CH_{arom}), 129.8 (s, 2 C, CH_{arom}), 130.0 (s, 1 C, CH_{arom}), 131.7 (s, 1 C, CH_{arom}), 132.0 (s, 1 C, Cq), 143.1 (s, 1 C, Cq), 145.5 (s, 1 C, Cq), 167.7 (s, 1 C, C=O), 172.2 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 310 (M^+, 4), 292 (M^+-H_2O, 35), 77 (C_6H_5, 51).

HR-MS: (ESI, Positive ions)

Calc. [M + H]$^+$: 311.13902 g/mol for $C_{18}H_{18}N_2O_3 + H^+$.

Found [M + H]$^+$: 311.13944 g/mol for $C_{18}H_{18}N_2O_3 + H^+$.

Calc. [M + Na]$^+$: 333.12096 g/mol for $C_{18}H_{18}N_2O_3 + Na^+$.

Found [M + Na]$^+$: 333.12141 g/mol for $C_{18}H_{18}N_2O_3 + Na^+$.

Electronspray: (ESI, Positive ions)

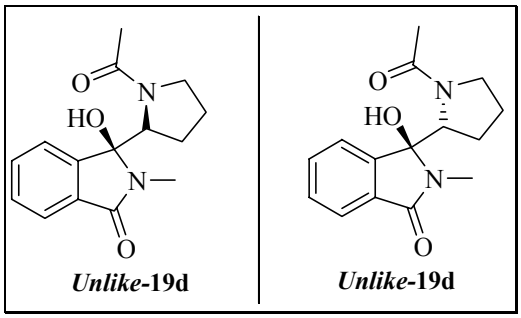
m/z (%) = 311 $(M + H)^+$, 621 $(M_2 + H)^+$.

IR: (KBr, disk)

ν (Cm^{-1}) = 3249.52 (b, OH), 2934.91 (vi; CH_{aliph}), 2345.48 (w; CN), 1656.09 (s, C=O), 1690.56 (s; C=O), 1630.85 (w; $C=C_{arom}$), 702.55 (s; CH_{arom}).

Experiment 60

6.3.10.4 Synthesis of 3-(1-acetylpyrrolidin-2-yl)-3-hydroxy-2-methyl isoindolin-1-one 19d (FH-78)



The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.71 g (4.51 mmol) of 1-acetylpyrrolidine-2-carboxylic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 1 h. The photosolution was clear and colourless.

Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.31 g (1.13 mmol; 76%) of **19d** as a light brown viscous oil.

3-(1-Acetylpyrrolidin-2-yl)-3-hydroxy-2-methylisoindolin-1-one (19d)

Main Diastereoisomer:

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.18 (m, 2 H, CH_2), 1.72 (m, 2 H, CH_2), 2.28 (s, 3 H, CH_3), 3.04 (s, 3 H, NCH_3), 3.29 (m, 1 H, CH_2), 3.54 (m, 1 H, CH_2), 4.78 (m, 1 H, CH), 7.36 (m, 1 H, H_{arom}), 7.47 (m, 2 H, H_{arom}), 8.06 (s, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.2 (s, 1 C, CH_2), 24.0 (s, 1 C, CH_3), 24.5 (s, 1 C, CH_2), 27.2 (s, 1 C, NCH_3), 50.2 (s, 1 C, CH_2), 64.0 (s, 1 C, CH), 92.2 (s, 1 C, COH), 122.8 (s, 1 C, CH_{arom}), 123.5 (s, 1 C, CH_{arom}), 129.9 (s, 1 C, CH_{arom}), 132.2 (s, 1 C, CH_{arom}), 132.9 (s, 1 C, Cq), 145.4 (s, 1 C, Cq), 167.3 (s, 1 C, C=O), 174.6 (s, 1 C, C=O).

Minor Diastereoisomer:

^{1}H–NMR: (400 MHz, $CDCl_3$)

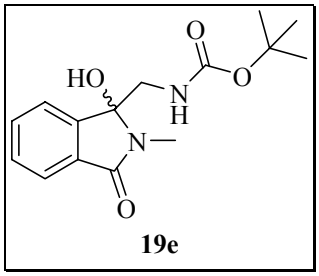
δ (ppm) = 1.06 (m, 2 H, CH_2), 1.57 (m, 2 H, CH_2), 1.88 (m, 1 H, CH_2), 2.22 (s, 3 H, CH_3), 2.97 (s, 3 H, NCH_3), 3.43 (m, 1 H, CH), 3.62 (m, 1 H, CH_2), 7.55 (m, 1 H, H_{arom}), 7.77 (m, 2 H, H_{arom}), 8.59 (s, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 23.3 (s, 1 C, CH_2), 24.1 (s, 1 C, CH_3), 25.5 (s, 1 C, CH_2), 28.6 (s, 1 C, NCH_3), 50.3 (s, 1 C, CH_2), 65.2 (s, 1 C, CH), 92.6 (s, 1 C, COH), 121.8 (s, 1 C, CH_{arom}), 129.8 (s, 1 C, CH_{arom}), 131.7 (s, 1 C, CH_{arom}), 132.8 (s, 1 C, CH_{arom}), 132.9 (s, 1 C, Cq), 147.3 (s, 1 C, Cq), 169.1 (s, 1 C, C=O), 174.7 (s, 1 C, C=O).

Experiment 61

6.3.10.5 Synthesis of tert-butyl(1-hydroxy-2-methyl-3-oxoisoindolin -1-yl)methyl carbamate 19e (FH-44)



19e

The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.79 g (4.51 mmol) of *N*-(*tert*-butoxycarbonyl) glycine and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.32 g (1.10 mmol; 74%) of **19e** as a colourless solid.

TLC: R_f = 0.22 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 105-109°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.32 (s, 9 H, CH_3), 2.90 (s, 3 H, NCH_3), 3.58 (dd, ^3J = 14.5, ^4J = 6.6 Hz, 1 H, CH_2), 3.78 (dd, ^3J = 14.5, ^4J = 6.6 Hz, 1 H, CH_2), 4.50 (s, 1 H, NH), 4.67 (s, 1 H, OH), 7.43 (ddd, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.54 (ddd, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.60 (m, 2 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 24.1 (s, 1 C, NCH_3), 28.5 (s, 3 C, CH_3), 45.0 (s, 1 C, CH_2), 80.6 (s, 1 C, Cq), 89.9 (s, 1 C, COH), 122.7 (s, 1 C, CH_{arom}), 123.5 (s, 1 C, CH_{arom}), 130.2 (s, 1 C, CH_{arom}), 131.7 (s, 1 C, Cq), 132.5 (s, 1 C, CH_{arom}), 145.4 (s, 1 C, Cq), 156.5 (s, 1 C, C=O), 167.8 (s, 1 C, C=O).

MS: (EI, 70 eV)

m/z (%) = 274 (M^+-H_2O, <1), 236 (M^+-C_4H_8, <1), 218 (236-H_2O, 29), 162 (M^+-$C_6H_{12}NO_2$, 100), 117 (M^+-$C_{10}H_{10}NO_2^-$, 16), 76 (M^+-$C_9H_{16}N_2O_4$, 17), 57 (M^+-$C_{11}H_{11}N_2O_4^-$, 76).

HR-MS: (ESI, Positive ions)

Calc. [M + Na]$^+$: 315.13153 g/mol for $C_{15}H_{19}N_2O_4 + Na^+$.

Found [M + Na]$^+$: 315.13149 g/mol for $C_{15}H_{19}N_2O_4 + Na^+$.

Calc. [M$_2$ + H]$^+$: 585.29189 g/mol for $(C_{15}H_{19}N_2O_4)_2 + H^+$.

Found [M$_2$ + H]$^+$: 585.29183 g/mol for $(C_{15}H_{19}N_2O_4)_2 + H^+$.

Calc. [M$_2$ + Na]$^+$: 607.27384 g/mol for $(C_{15}H_{19}N_2O_4)_2 + Na^+$.

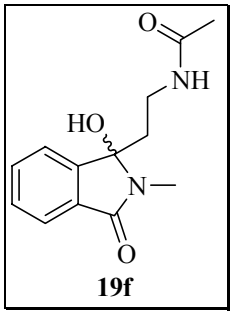
Found [M$_2$ + Na]$^+$: 607.27381 g/mol for $(C_{15}H_{19}N_2O_4)_2 + Na^+$.

Electronspray: (ESI, Positive ions)

m/z (%) = 293 $(M + H)^+$, 585 $(M_2 + H)^+$.

Experiment 62

6.3.10.6 Attempted synthesis of N-(2-(1-hydroxy-2-methyl-3-oxo isoindolin-1-yl)ethyl) acetamide 19f (FH-80)



19f

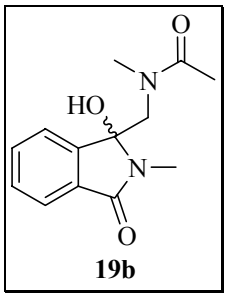
The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.59 g (4.50 mmol) of 3-acetamido propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 11 h. The photosolution was clear, yellowish. Then, 0.22 g (0.88

mmol; 59%) of S.M. which was colourless solid, as the proposed product **19f** have not been obtained.

*No product was observed therefore the original S.M. **4a** was reisolated.*

Experiment 63

6.3.10.7 Attempted synthesis of N-((1-hydroxy-2-methyl-3-oxo isoindolin-1-yl)methyl)-N-methylacetamide 19b (FH-179)



19b

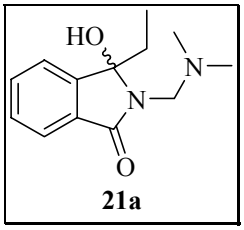
The general procedure (GP-1) was followed and 0.24 g (1.49 mmol) of *N*-methyl-phthalimide **4a**, 0.39 g (4.48 mmol) of *N,N*-dimethylacetamide and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 5 h. The photosolution was clear, yellowish. Then, 0.30 g (1.21 mmol; 81%) of S.M. which was colourless solid, as the proposed product **19b** have not been obtained.

*No product was observed therefore the original S.M. **4a** was reisolated.*

6.3.11 Photoreactions of donor-substituted phthalimides with carboxylates

Experiment 64

6.3.11.1 Attempted synthesis of 2-((dimethylamino)methyl)-3-ethyl-3-hydroxyisoindolin-1-one 21a (FH-50)



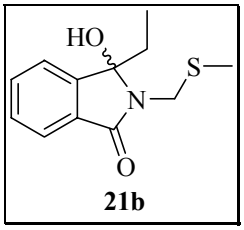
21a

The general procedure (GP-1) was followed and 0.31 g (1.51 mmol) of 2-((dimethylamino)methyl)isoindoline-1,3-dione, 0.34 g (4.58 mmol) of propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 4 h. The photosolution was clear, yellowish. Column chromatography (SiO_2; MeOH:$CHCl_3$ = 1:9) gave 0.083 g (0.35 mmol; 23%) of S.M. as yellow solid, as the proposed product **21a** have not been obtained.

*No product was observed therefore the original S.M. **20a** was reisolated.*

Experiment 65

6.3.11.2 Attempted synthesis of 3-ethyl-3-hydroxy-2-(methylthio methyl)isoindolin-1-one 21b (FH-49)



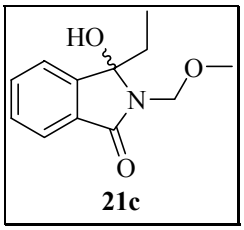
21b

The general procedure (GP-1) was followed and 0.31 g (1.51 mmol) of 2-(methyl-thiomethyl)isoindoline-1,3-dione, 0.35 g (4.73 mmol) of propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 10 h. The photosolution was clear, colourless. Then, 0.301 g (1.45 mmol; 96%) of S.M. was obtained as colourless solid, as the proposed product **21b** have not been identified.

*No product was observed therefore the original S.M. **20b** was reisolated.*

Experiment 66

6.3.11.3 Synthesis of 3-ethyl-3-hydroxy-2-(methoxymethyl) isoindolin-1-one 21c (FH-35)



21c

The general procedure (GP-1) was followed and 0.12 g (0.63 mmol) of 2-(methoxy-methyl)isoindolin-1,3-dione, 0.15 g (2.02 mmol) of propionic acid and 0.13 g (0.94 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 2 h. The photosolution was clear, colourless. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.07 g (0.32 mmol; 51%) of **21c** as a reddish solid.

TLC: R_f = 0.32 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, $CDCl_3$)

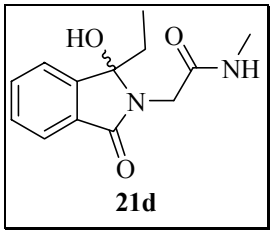
δ (ppm) = 0.59 (t, ^3J = 14.8, ^4J = 7.6 Hz, 3 H, CH_3), 2.24 (m, 2 H, CH_2), 3.40 (s, 3 H, OCH_3), 4.93 (q, ^3J = 22.4, ^4J = 10.8 Hz, 2 H, CH_2), 5.30 (s, 1 H, OH), 7.58 (ddd, ^3J = 7.6, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.65 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 7.71 (ddd, ^3J = 7.6, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.75 (d, ^3J = 7.2 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 8.3 (s, 1 C, CH_3), 31.2 (s, 1 C, CH_2), 57.0 (s, 1 C, OCH_3), 70.5 (s, 1 C, CH_2), 91.9 (s, 1 C, COH), 123.1 (s, 1 C, CH_{arom}), 123.8 (s, 1 C, CH_{arom}), 130.1 (s, 1 C, CH_{arom}), 133.5 (s, 1 C, CH_{arom}), 144.0 (s, 1 C, Cq), 149.0 (s, 1 C, Cq), 166.0 (s, 1 C, C=O).

Experiment 67

6.3.11.4 Synthesis of 2-(1-ethyl-1-hydroxy-3-oxoisoindolin-2-yl)-N-methylacetamide 21d (FH-56)



21d

The general procedure (GP-1) was followed and 0.33 g (1.51 mmol) of 2-(1,3-dioxoisoindolin-2-yl)-*N*-methylacetamide, 0.34 g (4.59 mmol) of propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 4 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 8:1) gave 0.16 g (0.65 mmol; 43%) of **21d** as a yellow solid.

TLC: R_f = 0.18 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 95-103°C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 0.46 (t, ^3J = 14.9, ^4J = 7.3 Hz, 3 H, CH_3), 2.15 (m, 2 H, CH_2), 2.72 (s, 3 H, NCH_3), 3.81 (d, ^2J = 16.4 Hz, 1 H, CH_2), 4.35 (d, ^2J = 16.4 Hz, 1 H, CH_2), 5.67 (s, 1 H, OH), 7.02 (s, 1 H, NH), 7.46 (ddd, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.53 (d, ^3J = 7.3 Hz, 1 H, H_{arom}), 7.57 (ddd, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.70 (d, ^3J = 7.3 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

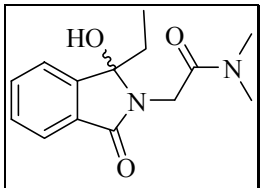
δ (ppm) = 8.1 (s, 1 C, CH_3), 26.7 (s, 1 C, NCH_3), 29.6 (s, 1 C, CH_2), 42.7 (s, 1 C, CH_2), 92.1 (s, 1 C, COH), 122.3 (s, 1 C, CH_{arom}), 123.5 (s, 1 C, CH_{arom}), 129.7 (s, 1 C, CH_{arom}), 130.7 (s, 1 C, Cq), 133.2 (s, 1 C, CH_{arom}), 147.5 (s, 1 C, Cq), 169.0 (s, 1 C, C=O), 170.6 (s, 1 C, C=O).

IR: (KBr, disk)

ν (Cm^{-1}) = 3291.48 (b, OH), 2928.61 (vi; CH_{aliph}), 2346.43 (w; CN), 1690.49 (s; C=O), 1663.46 (s; C=O), 1616.98 (w; $C{=}C_{arom}$), 1260.38 (s; CO), 760.29 (s; CH_{arom}).

Experiment 68

6.3.11.5 Synthesis of 2-(1-ethyl-1-hydroxy-3-oxoisoindolin-2-yl)-N,N-dimethylacetamide 21e (FH-36)



21e

The general procedure (GP-1) was followed and 0.35 g (1.50 mmol) of 2-(1,3-dioxoisoindolin-2-yl)-*N,N*-dimethyl acetamide, 0.34 ml (4.55 mmol) of propionic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 21 h. The photosolution was clear and yellowish. Then, the product 0.20 g (0.76 mmol; 51%) of **21e** was brown solid.

TLC: R_f = 0.10 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 0.53 (t, 3 H, CH_3), 2.22 (q, 2 H, CH_2), 2.98 (s, 3 H, NCH_3), 3.04 (s, 1 H, OH), 3.16 (s, 3 H, NCH_3), 3.77 (d, ^2J = 16.7 Hz, 2 H, CH_2), 4.86 (d, ^2J = 16.7 Hz, 2 H, CH_2), 7.46 (m, 1 H, H_{arom}), 7.56 (m, 2 H, H_{arom}), 7.77 (d, ^3J = 7.3 Hz, 1 H, H_{arom}).

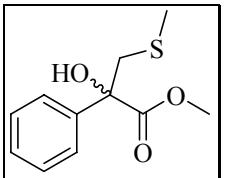
^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 8.1 (s, 1 C, CH_3), 29.3 (s, 1 C, CH_2), 36.6 (s, 1 C, NCH_3), 37.2 (s, 1 C, NCH_3), 40.5 (s, 1 C, CH_2), 91.6 (s, 1 C, COH), 122.1 (s, 1 C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 129.5 (s, 1 C, CH_{arom}), 130.9 (s, 1 C, Cq), 132.9 (s, 1 C, CH_{arom}), 148.1 (s, 1 C, Cq), 166.5 (s, 1 C, C=O), 168.8 (s, 1 C, C=O).

6.3.12 Photoaddition of sulphur-containing carboxylates to phenylglyoxolates

Experiment 69

6.3.12.1 Synthesis of methyl-2-hydroxy-3-(methylthio)-2-phenyl propanoate 22a (JF-12)



22a

The general procedure (GP-1) was followed and 0.26 g (1.58 mmol) of methyl 2-oxo-2-phenylacetate, 0.48 g (4.52 mmol) of 2-(methylthio)acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 10 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:3) gave 0.08 g (0.35 mmol; 31%) of **22a** as a yellow oil.

^{1}H-NMR: (400 MHz, acetone-d_6)

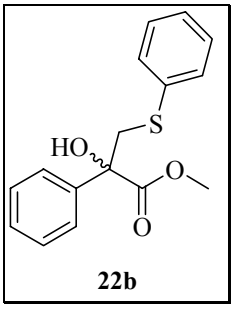
δ (ppm) = 2.21 (s, 3 H, SCH_3), 3.00 (d, ^2J= 14.0 Hz, 1 H, CH_2), 3.40 (dd, ^2J= 14.0, ^3J= 1.2 Hz, 1 H, H_{arom}), 3.79 (s, 3 H, OCH_3), 5.03 (s, 1 H, OH), 7.37 (m, 3 H, H_{arom}), 7.67 (m, 2 H, H_{arom}).

^{13}C-NMR: (100 MHz, acetone-d_6)

δ (ppm) = 17.9 (s, 1 C, SCH_3), 45.4 (s, 1 C, CH_2), 53.2 (s, 1 C, OCH_3), 81.4 (s, 1 C, COH), 126.5 (s, 2 C, CH_{arom}), 128.8 (s, 1 C, CH_{arom}), 129.2 (s, 2 C, CH_{arom}), 142.9 (s, 1 C, Cq), 174.8 (s, 1 C, C=O).

Experiment 70

6.3.12.2 Synthesis of methyl-2-hydroxy-2-phenyl-3-(phenylthio) propanoate 22b (JF-13)



22b

The general procedure (GP-1) was followed and 0.25 g (1.52 mmol) of methyl 2-oxo-2-phenylacetate, 0.76 g (4.52 mmol) of 2-(phenylthio)acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 9 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:3) gave 0.11 g (0.38 mmol; 44%) of **22b** as a yellow oil.

^{1}H-NMR: (400 MHz, acetone-d_6)

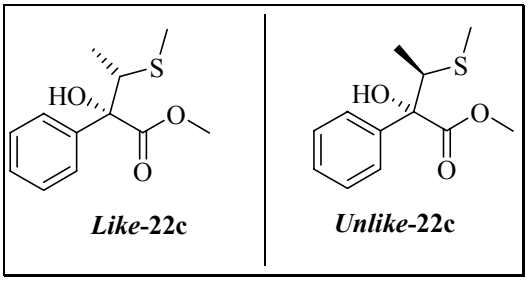
δ (ppm) = 3.54 (d, ^2J= 13.6 Hz, 1 H, CH_2), 3.67 (s, 3 H, OCH_3), 3.91 (dd, ^2J= 13.2, ^3J= 0.8 Hz, 1 H, CH_2), 5.19 (s, 1 H, OH), 7.24 (m, 1 H, H_{arom}), 7.38 (m, 5 H, H_{arom}), 7.49 (m, 2 H, H_{arom}), 7.70 (m, 2 H, H_{arom}).

^{13}C-NMR: (100 MHz, acetone-d_6)

δ (ppm) = 46.4 (s, 1 C, SPh), 53.8 (s, 1 C, OCH_3), 80.5 (s, 1 C, COH), 127.7 (s, 1 C, Cq), 129.6 (s, 1 C, CH_{arom}), 129.8 (s, 2 C, CH_{arom}), 130.4 (s, 2 C, CH_{arom}), 131.4 (s, 2 C, CH_{arom}), 138.8 (s, 1 C, Cq), 139.4 (s, 1 C, CH_{arom}), 140.0 (s, 1 C, Cq), 143.1 (s, 1 C, CH_{arom}), 175.0 (s, 1 C, C=O).

Experiment 71

6.3.12.3 Synthesis of methyl-2-hydroxy-3-(methylthio)-2-phenyl butanoate 22c (JF-08)



The general procedure (GP-1) was followed and 0.26 g (1.58 mmol) of methyl 2-oxo-2-phenylacetate, 0.55 g (4.57 mmol) of 2-(methylthio)propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 4 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:3) gave 0.32 g (1.33 mmol; 84%) of **22c** as a yellow oil.

Methyl 2-hydroxy-3-(methylthio)-2-phenylbutanoate (22c)

Main Diastereoisomer:

^{1}H-NMR: (400 MHz, acetone-d_6)

δ (ppm) = 1.05 (d, ^2J= 7.2 Hz, 3 H, CH_3), 1.84 (s, 3 H, SCH_3), 3.49 (q, ^2J= 7.6, ^3J= 7.2, ^4J= 0.8 Hz, 1 H, CH), 3.76 (s, 3 H, OCH_3), 4.77 (s, 1 H, OH), 7.33 (m, 3 H, H_{arom}), 7.69 (m, 2 H, H_{arom}).

^{13}C-NMR: (100 MHz, acetone-d_6)

δ (ppm) = 15.4 (s, 1 C, CH_3), 16.3 (s, 1 C, SCH_3), 50.7 (s, 1 C, CH), 53.9 (s, 1 C, OCH_3), 83.7 (s, 1 C, COH), 127.4 (s, 2 C, CH_{arom}), 127.6 (s, 2 C, CH_{arom}), 129.1 (s, 1 C, CH_{arom}), 143.2 (s, 1 C, Cq), 175.6 (s, 1 C, C=O).

Minor Diastereoisomer:

^{1}H-NMR: (400 MHz, acetone-d_6)

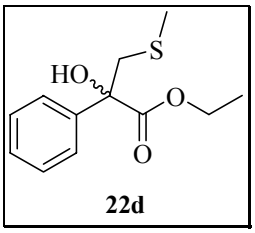
δ (ppm) = 1.38 (d, ^{2}J= 6.8 Hz, 3 H, CH_3), 2.19 (s, 3 H, SCH_3), 3.53 (q, ^{2}J= 6.8, ^{3}J= 4.0, ^{4}J= 0.8 Hz, 1 H, CH), 3.76 (s, 3 H, OCH_3), 4.83 (s, 1 H, OH), 7.33 (m, 3 H, H_{arom}), 7.69 (m, 2 H, H_{arom}).

^{13}C-NMR: (100 MHz, acetone-d_6)

δ (ppm) = 15.5 (s, 1 C, CH_3), 18.2 (s, 1 C, SCH_3), 51.5 (s, 1 C, CH), 54.0 (s, 1 C, OCH_3), 84.1 (s, 1 C, COH), 128.9 (s, 1 C, Cq), 129.3 (s, 2 C, CH_{arom}), 129.7 (s, 2 C, CH_{arom}), 142.3 (s, 1 C, Cq), 175.8 (s, 1 C, C=O).

Experiment 72

6.3.12.4 Synthesis of ethyl-2-hydroxy-3-(methylthio)-2-phenyl propanoate 22d (FH-133)



22d

The general procedure (GP-1) was followed and 0.27 g (1.52 mmol) of ethyl 2-oxo-2-phenylacetate, 0.49 g (4.62 mmol) of 2-(methylthio)acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were dissolved in 150 ml water/acetone [50:50] and the reaction was irradiated for 3 h. The photosolution was clear and yellowish. Column chromatography (SiO_2; EA:Hex = 1:3) gave 0.10 g (0.42 mmol; 28%) of **22d** as a white solid.

TLC: R_f = 0.34 (Ethyl Acetate/n-Hexane 1:1)

^{1}H-NMR: (400 MHz, acetone-d_6)

δ (ppm) = 1.29 (s, 3 H, CH_3), 2.22 (s, 3 H, SCH_3), 3.00 (d, ^{2}J= 14.0 Hz, 1 H, SCH_2), 3.41 (d, ^{2}J= 14.0 Hz, 1 H, SCH_2), 4.22 (q, ^{2}J= 10.8, ^{3}J= 6.8, ^{4}J= 3.6 Hz, 2 H, CH_2), 4.95 (s, 1 H, OH), 7.39 (m, 2 H, H_{arom}), 7.52 (m, 1 H, H_{arom}), 7.69 (m, 2 H, H_{arom}).

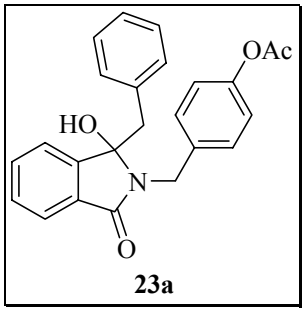
^{13}C-NMR: (100 MHz, acetone-d_6)

δ (ppm) = 14.4 (s, 1 C, CH_3), 17.8 (s, 1 C, SCH_3), 45.3 (s, 1 C, SCH_2), 62.5 (s, 1 C, CH_2), 81.1 (s, 1 C, COH), 127.1 (s, 2 C, CH_{arom}), 129.1 (s, 1 C, CH_{arom}), 129.4 (s, 2 C, CH_{arom}), 142.9 (s, 1 C, Cq), 174.1 (s, 1 C, C=O).

6.3.13 Photoreactions of 2-(4-acetoxybenzyl)isoindoline-1,3-dione 9 with carboxylates

Experiment 73

6.3.13.1 Synthesis of 4-((1-benzyl-1-hydroxy-3-oxoisoindolin-2-yl) methyl)phenyl acetate 23a (JF-02)



23a

Following the general procedure (GP-4), 0.44 g (1.49 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.61 g (4.48 mmol) of 2-phenylacetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 5 h in 150 ml of water/acetone [50:50]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.25 g (0.65 mmol; 44%) of **23a** as a colourless powder-like solid.

TLC: R_f = 0.44 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 115-118 °C.

^{1}H-NMR: (400 MHz, acetone-d_6)

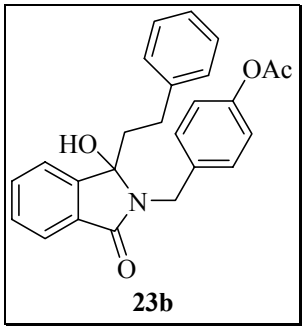
δ (ppm) = 2.28 (s, 3 H, CH_3), 2.87 (s, 1 H, OH), 3.34 (d, ^2J= 14.0 Hz, 1 H, CH_2), 3.56 (d, ^2J= 13.6 Hz, 1 H, CH_2), 4.84 (s, 1 H, CH_2), 6.89 (m, 2 H, H_{arom}), 7.08 (m, 5 H, H_{arom}), 7.45 (m, 2 H, H_{arom}), 7.55 (m, 4 H, H_{arom}).

^{13}C-NMR: (100 MHz, acetone-d_6)

δ (ppm) = 21.0 (s, 1 C, CH_3), 42.7 (s, 1 C, CH_2), 44.3 (s, 1 C, CH_2), 92.2 (s, 1 C, COH), 122.2 (s, 2 C, CH_{arom}), 123.1 (s, 1 C, CH_{arom}), 124.0 (s, 1 C, CH_{arom}), 127.3 (s, 1 C, CH_{arom}), 128.4 (s, 2 C, CH_{arom}), 130.0 (s, 1 C, CH_{arom}), 130.4 (s, 2 C, CH_{arom}), 131.1 (s, 2 C, C_{arom}), 132.3 (s, 1 C, C_{arom}), 132.7 (s, 1 C, Cq), 136.2 (s, 1 C, Cq), 137.7 (s, 1 C, Cq), 148.0 (s, 1 C, Cq), 150.8 (s, 1 C, Cq), 167.3 (s, 1 C, C=O), 169.7 (s, 1 C, C=O).

Experiment 74

6.3.13.2 Synthesis of 4-((1-hydroxy-3-oxo-1-phenylisoindolin-2-yl) methyl)phenyl acetate <u>23b</u> (FH-86)



23b

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.68 g (4.53 mmol) of hydrocinnamic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 2 h in 150 ml of water/acetone [50:50].

Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.27 g (0.67 mmol; 44%) of **23b** as a white solid; with 79% conversion yield.

TLC: R_f = 0.44 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 121-123 °C.

^{1}H-NMR: (400 MHz, acetone-d_6)

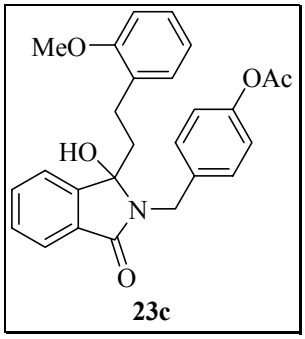
δ (ppm) = 1.79 (ddd, ^2J = 25.5, ^3J = 12.7, ^4J = 4.8 Hz, 1 H, CH_2), 1.94 (ddd, ^2J = 25.5, ^3J = 12.7, ^4J = 4.8 Hz, 1 H, CH_2), 2.30 (s, 3 H, CH_3), 2.33 (ddd, ^2J = 26.3, ^3J = 13.2, ^4J = 4.9 Hz, 1 H, CH_2), 2.43 (ddd, ^2J = 26.3, ^3J = 13.2, ^4J = 4.9 Hz, 1 H, CH_2), 4.57 (d, ^2J = 15.3 Hz, 2 H, CH_2), 4.92 (d, ^2J = 15.3 Hz, 2 H, CH_2), 5.50 (s, 1 H, OH), 6.72 (d, ^3J= 7.1 Hz, 2 H, H_{arom}), 7.13 (m, 5 H, H_{arom}), 7.61 (ddd, ^2J = 14.4, ^3J = 7.2, ^4J = 1.4 Hz, 1 H, CH_2), 7.66 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 7.72 (ddd, ^2J = 14.4, ^3J = 7.2, ^4J = 1.4 Hz, 1 H, H_{arom}), 7.75 (m, 1 H, H_{arom}), 7.80 (d, ^3J= 7.6 Hz, 1 H, H_{arom}).

^{13}C-NMR: (100 MHz, acetone-d_6)

δ (ppm) = 21.7 (s, 1 C, CH_3), 31.6 (s, 1 C, CH_2), 40.7 (s, 1 C, CH_2), 42.6 (s, 1 C, CH_2), 92.5 (s, 1 C, COH), 123.3 (s, 2 C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 124.3 (s, 1 C, CH_{arom}), 127.3 (s, 1 C, CH_{arom}), 129.7 (s, 2 C, CH_{arom}), 129.8 (s, 2 C, CH_{arom}), 131.0 (s, 1 C, CH_{arom}), 131.4 (s, 2 C, CH_{arom}), 133.4 (s, 1 C, Cq), 134.0 (s, 1 C, CH_{arom}), 138.5 (s, 1 C, Cq), 142.5 (s, 1 C, Cq), 149.1 (s, 1 C, Cq), 151.9 (s, 1 C, Cq), 168.8 (s, 1 C, C=O), 170.4 (s, 1 C, C=O).

Experiment 75

6.3.13.3 Synthesis of 4-((1-(2-methoxyphenethyl)-1-hydroxy-3-oxo isoindolin-2-yl)methyl)phenyl acetate 23c (FH-150)



23c

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.82 g (4.55 mmol) of 3-(2-methoxy-phenyl)propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 3 h in 150 ml of water/acetone [75:25]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.14 g (0.32 mmol; 21%) of **23c** as a white solid.

TLC: R_f = 0.36 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 179-182 °C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.84 (t, ^3J = 16.4, ^4J = 8.0 Hz, 2 H, CH_2), 2.22 (m, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.38 (m, 1 H, CH_2), 3.75 (s, 3 H, OCH_3), 4.57 (d, ^2J = 15.0 Hz, 1 H, CH_2), 4.65 (s, 1 H, OH), 4.76 (d, ^2J = 15.0 Hz, 1 H, CH_2), 6.50 (dd, ^3J = 7.6, ^4J = 1.6 Hz, 1 H, H_{arom}), 6.75 (m, 2 H, H_{arom}), 6.09 (m, 3 H, H_{arom}), 6.58 (m, 4 H, H_{arom}), 7.68 (ddd, ^2J = 16.0, ^3J = 7.6, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.79 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

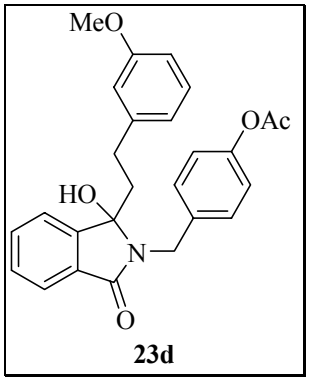
^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.9 (s, 1 C, CH_2), 25.5 (s, 1 C, CH_3), 37.6 (s, 1 C, CH_2), 42.2 (s, 1 C, CH_2), 55.9 (s, 1 C, OCH_3), 92.0 (s, 1 C, COH), 110.9 (s, 1 C, CH_{arom}), 121.2 (s, 1 C, CH_{arom}), 122.4 (s, 2 C, CH_{arom}), 123.1 (s, 1 C, CH_{arom}), 123.5 (s, 1 C, CH_{arom}), 128.1

(s, 1 C, CH_{arom}), 129.7 (s, 1 C, CH_{arom}), 130.1 (s, 1 C, CH_{arom}), 130.4 (s, 1 C, CH_{arom}), 130.6 (s, 2 C, CH_{arom}), 132.2 (s, 1 C, CH_{arom}), 133.0 (s, 1 C, Cq), 137.3 (s, 1 C, Cq), 148.4 (s, 1 C, Cq), 157.8 (s, 1 C, Cq), 168.5 (s, 1 C, C=O), 170.0 (s, 1 C, C=O).

Experiment 76

6.3.13.4 Synthesis of 4-((1-(3-methoxyphenethyl)-1-hydroxy-3-oxo isoindolin-2-yl)methyl)phenyl acetate 23d (FH-151)



23d

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.81 g (4.50 mmol) of 3-(3-methoxy-phenyl)propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 2 h in 150 ml of water/acetone [75:25]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.50 g (1.16 mmol; 76%) of **23d** as a white solid.

TLC: R_f = 0.46 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 153-154 °C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 1.79 (ddd, ^2J = 25.2, ^3J = 12.6, ^4J = 4.8 Hz, 1 H, CH), 1.94 (ddd, ^2J = 25.2, ^3J = 12.6, ^4J = 4.8 Hz, 1 H, CH), 2.29 (s, 3 H, CH_3), 2.40 (m, 2 H, CH_2), 3.73 (s, 3 H, OCH_3), 4.58 (d, ^2J = 15.6 Hz, 1 H, CH_2), 4.89 (d, ^2J = 15.6 Hz, 1 H, CH_2), 6.30 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 6.36 (m, 1 H, H_{arom}), 6.67 (dd, ^3J = 8.4, ^4J = 2.0 Hz, 1 H,

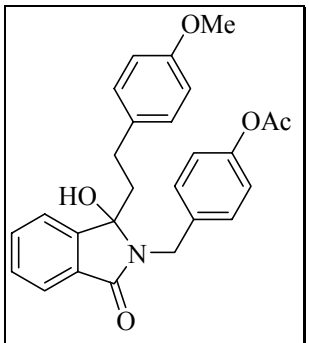
H_{arom}), 7.07 (t, ^{3}J = 15.6, ^{4}J = 7.6 Hz, 1 H, H_{arom}), 7.14 (d, ^{3}J = 8.4 Hz, 2 H, H_{arom}), 7.60 (ddd, ^{2}J = 14.4, ^{3}J = 7.0, ^{4}J = 1.0 Hz, 1 H, H_{arom}), 7.65 (d, ^{3}J = 8.8 Hz, 2 H, H_{arom}), 7.71 (ddd, ^{2}J = 14.4, ^{3}J = 7.0, ^{4}J = 1.0 Hz, 2 H, H_{arom}), 7.74 (d, ^{3}J = 1.2 Hz, 2 H, H_{arom}), 7.75 (d, ^{3}J = 5.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.0 (s, 1 C, CH_2), 38.3 (s, 1 C, CH_3), 39.7 (s, 1 C, CH_2), 41.9 (s, 1 C, CH_2), 55.3 (s, 1 C, OCH_3), 91.8 (s, 1 C, COH), 112.3 (s, 1 C, CH_{arom}), 114.2 (s, 1 C, CH_{arom}), 121.3 (s, 1 C, CH_{arom}), 122.5 (s, 2 C, CH_{arom}), 123.0 (s, 1 C, CH_{arom}), 123.6 (s, 1 C, CH_{arom}), 130.1 (s, 1 C, CH_{arom}), 130.2 (s, 1 C, CH_{arom}), 130.6 (s, 2 C, CH_{arom}), 132.7 (s, 1 C, CH_{arom}), 133.2 (s, 1 C, Cq), 137.7 (s, 1 C, Cq), 143.4 (s, 1 C, Cq), 148.3 (s, 1 C, Cq), 151.1 (s, 1 C, Cq), 160.6 (s, 1 C, Cq), 168.1 (s, 1 C, C=O), 169.6 (s, 1 C, C=O).

Experiment 77

6.3.13.5 Synthesis of 4-((1-(4-methoxyphenethyl)-1-hydroxy-3-oxo isoindolin-2-yl)methyl)phenyl acetate 23e (FH-152)



23e

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.81 g (4.50 mmol) of 3-(4-methoxy-phenyl)propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 2 h in

150 ml of water/acetone [75:25]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.36 g (0.83 mmol; 55%) of **23e** as a white solid.

TLC: R_f = 0.38 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 155-157 °C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

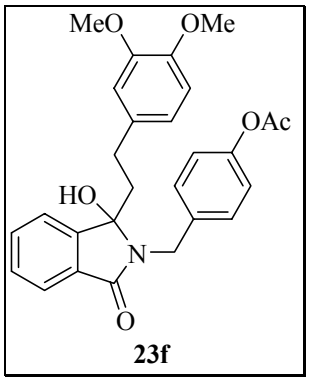
δ (ppm) = 1.73 (ddd, ^2J = 25.8, ^3J = 12.9, ^4J = 4.8 Hz, 1 H, CH), 1.87 (ddd, ^2J = 25.8, ^3J = 12.9, ^4J = 4.8 Hz, 1 H, CH), 2.27 (m, 1 H, CH), 2.31 (s, 3 H, CH_3), 2.40 (ddd, ^2J = 26.2, ^3J = 13.9, ^4J = 4.8 Hz, 1 H, CH), 3.73 (s, 3 H, OCH_3), 4.56 (d, ^2J = 15.2 Hz, 1 H, CH_2), 4.91 (d, ^2J = 15.2 Hz, 1 H, CH_2), 6.62 (d, ^3J = 8.8 Hz, 2 H, H_{arom}), 6.72 (d, ^3J = 8.8 Hz, 2 H, H_{arom}), 7.14 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 7.60 (ddd, ^2J = 14.1, ^3J = 7.6, ^4J = 2.0 Hz, 1 H, H_{arom}), 7.65 (d, ^3J = 8.3 Hz, 2 H, H_{arom}), 7.72 (m, 2 H, H_{arom}), 7.79 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.0 (s, 1 C, CH_3), 40.2 (s, 1 C, CH_2), 41.8 (s, 1 C, CH_2), 55.3 (s, 1 C, OCH_3), 61.0 (s, 1 C, CH_2), 91.8 (s, 1 C, COH), 114.5 (s, 2 C, CH_{arom}), 122.6 (s, 2 C, CH_{arom}), 123.0 (s, 1 C, CH_{arom}), 123.6 (s, 1 C, CH_{arom}), 129.9 (s, 2 C, CH_{arom}), 130.2 (s, 1 C, CH_{arom}), 130.6 (s, 2 C, CH_{arom}), 132.7 (s, 1 C, Cq), 133.2 (s, 1 C, CH_{arom}), 133.6 (s, 1 C, Cq), 137.8 (s, 1 C, Cq), 148.4 (s, 1 C, Cq), 151.2 (s, 1 C, Cq), 158.8 (s, 1 C, Cq), 168.1 (s, 1 C, C=O), 169.7 (s, 1 C, C=O).

Experiment 78

6.3.13.6 Attempted synthesis of 4-((1-(3,4-dimethoxyphenethyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)phenyl acetate 23f (FH-153)



23f

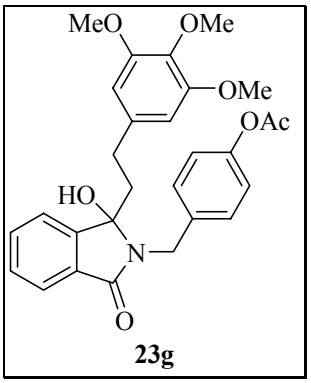
Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.95 g (4.52 mmol) of 3-(3,4-dimethoxy-phenyl)propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 20 h in 150 ml of water/acetone [75:25]. Only reisolation of S.M. of 0.31 g (1.05 mmol; 69%) as a yellow solid could be observed but not the desired product **23f**.

TLC: R_f = 0.45 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 125-128 ^{o}C.

*No product was observed therefore the original S.M. **9** was reisolated.*

Experiment 79

6.3.13.7 Attempted synthesis of 4-((1-(3,4,5-trimethoxyphenethyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)phenyl acetate 23g (FH-154)



23g

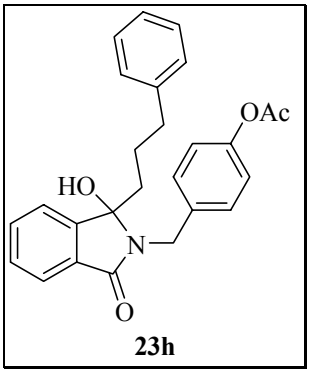
Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 1.08 g (4.50 mmol) of 3-(3,4,5-trimeth-oxyphenyl)propanoic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 20 h in 150 ml of water/acetone [75:25]. Only reisolation of S.M. of 0.40 g (1.35 mmol; 89%) as a yellow solid could be observed but not the desired product **23g**.

TLC: R_f = 0.31 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 134-138 °C.

*No product was observed therefore the original S.M. **9** was reisolated.*

Experiment 80

6.3.13.8 Synthesis of 4-((1-hydroxy-3-oxo-1-(3-phenylpropyl) isoindolin-2-yl)methyl)phenyl acetate 23h (FH-143)



23h

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.74 g (4.51 mmol) of 4-phenylbutyric acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 10 h in 150 ml of water/acetone [75:25]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.06 g (0.15 mmol; 10%) of **23h** as a white solid.

TLC: R_f = 0.58 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 0.82 (m, 1 H, CH_2), 0.95 (m, 1 H, CH_2), 2.20 (m, 4 H, 2 * CH_2), 2.98 (s, 3 H, CH_3), 4.53 (d, ^2J = 15.2 Hz, 1 H, CH_2), 4.80 (d, ^2J = 15.2 Hz, 1 H, CH_2), 6.92 (d, ^2J = 6.8 Hz, 2 H, H_{arom}), 7.12 (m, 4 H, H_{arom}), 7.20 (m, 2 H, H_{arom}), 7.52 (ddd, ^2J = 15.7, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.58 (m, 3 H, H_{arom}), 7.64 (ddd, ^2J = 15.7, ^3J = 7.3, ^4J = 1.0 Hz, 1 H, H_{arom}),7.71 (d, ^3J = 7.6 Hz, 1 H, H_{arom}).

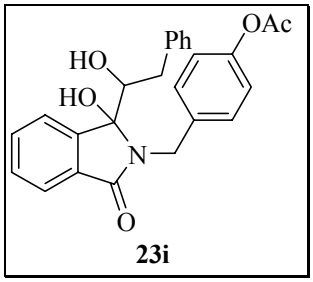
^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 21.7 (s, 1 C, CH_3), 27.4 (s, 1 C, CH_2), 36.6 (s, 1 C, CH_2), 37.9 (s, 1 C, CH_2), 42.5 (s, 1 C, CH_2), 92.7 (s, 1 C, COH), 123.2 (s, 2 C, CH_{arom}), 123.6 (s, 1 C, CH_{arom}), 124.2 (s, 1 C, CH_{arom}), 127.2 (s, 1 C, CH_{arom}), 129.7 (s, 2 C, CH_{arom}), 129.8 (s, 2 C, CH_{arom}), 130.8 (s, 1 C, CH_{arom}), 131.3 (s, 2 C, CH_{arom}), 133.2 (s, 1 C, Cq),

133.8 (s, 1 C, CH_{arom}), 138.3 (s, 1 C, Cq), 143.4 (s, 1 C, Cq), 149.1 (s, 1 C, Cq), 151.8 (s, 1 C, Cq), 168.7 (s, 1 C, C=O), 170.4 (s, 1 C, C=O).

Experiment 81

6.3.13.9 Attempted synthesis of 4-((1-hydroxy-1-(1-hydroxy-2-phenethyl)-3-oxoisoindolin-2-yl)methyl)phenyl acetate <u>23i</u> (FH-123)



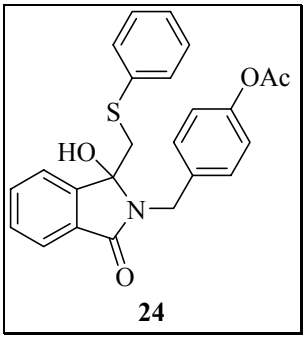
23i

Following the general procedure (GP-4), 0.44 g (1.49 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.75 g (4.51 mmol) of *L*-3-phenyllactic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 2 h in 150 ml of water/acetone [50:50]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.03 g (0.07 mmol; 5%) of yellow solid. NMR analysis showed that the compound **23a** was formed instead of the desired product **23i**.

*<u>Analytical data identical to that of previous **23a**.</u>*

Experiment 82

6.3.13.10 Synthesis of 4-((1-hydroxy-3-oxo-1-(phenylthio)isoindolin -2-yl)methyl)phenyl acetate 24 (FH-92)



24

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.76 g (4.52 mmol) of 2-(phenylthio)acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 9 h in 150 ml of water/acetone [75:25]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.28 g (0.67 mmol; 44%) of **24** as a yellow solid.

TLC: R_f = 0.39 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 92-95 °C.

^{1}H–NMR: (400 MHz, acetone-d_6+DMSO)

δ (ppm) = 2.27 (s, 3 H, CH_3CO), 3.62 (d, ^2J = 16.0 Hz, 1 H, CH_2S), 3.74 (d, ^2J = 16.0 Hz, 1 H, CH_2S), 4.54 (d, ^2J = 16.0 Hz, 1 H, CH_2N), 4.62 (d, ^2J = 16.0 Hz, 1 H, CH_2N), 5.85 (s, 1 H, OH), 7.05 (d, ^3J = 16.0 Hz, 2 H, H_{arom}), 7.10 (dd, ^3J = 8.0; ^4J = 4.0 Hz, 2 H, H_{arom}), 7.19 (m, 3 H, H_{arom}), 7.51 (m, 3 H, H_{arom}), 7.55 (d, ^3J = 8.0 Hz, 2 H, H_{arom}), 7.74 (d, ^3J = 8.0 Hz, 1 H, H_{arom}).

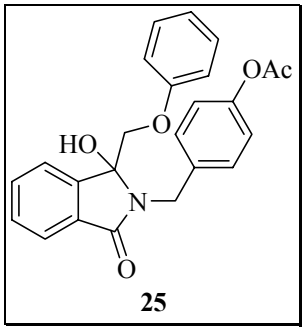
^{13}C–NMR: (100 MHz, acetone-d_6+DMSO)

δ (ppm) = 21.7 (s, 1 C, CH_3), 42.8 (s, 1 C, CH_2), 43.2 (s, 1 C, CH_2), 91.9 (s, 1 C, COH), 122.8 (s, 2 C, CH_{arom}), 123.7 (s, 1 C, CH_{arom}), 124.2 (s, 1 C, CH_{arom}), 127.8 (s, 2 C, CH_{arom}), 130.2 (s, 2 C, CH_{arom}), 130.8 (s, 1 C, CH_{arom}), 130.9 (s, 2 C, CH_{arom}),

131.6 (s, 1 C, CH_{arom}), 133.2 (s, 1 C, CH_{arom}), 133.6 (s, 1 C, Cq), 137.7 (s, 1 C, Cq), 137.8 (s, 1 C, Cq), 148.2 (s, 1 C, Cq), 151.4 (s, 1 C, Cq), 168.5 (s, 1 C, C=O), 170.4 (s, 1 C, C=O).

Experiment 83

6.3.13.11 Synthesis of 4-((1-hydroxy-3-oxo-1-(phenoxymethyl) isoindolin-2-yl)methyl)phenyl acetate 25 (FH-87)



25

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.69 g (4.53 mmol) of phenoxy acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 4 h in 150 ml of water/acetone [50:50]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.21 g (0.52 mmol; 34%) of **25** as a white solid; with 52% conversion yield.

TLC: R_f = 0.46 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 120-122 °C.

^{1}H–NMR: (400 MHz, $CDCl_3$)

δ (ppm) = 2.24 (s, 3 H, CH_3CO), 3.67 (br. s, 1 H, OH), 3.99 (d, ^2J = 9.6 Hz, 1 H, CH_2N), 4.21 (d, ^2J = 9.6 Hz, 1 H, CH_2N), 4.61 (d, ^2J = 15.4 Hz, 1 H, CH_2O), 4.70 (d, ^2J = 15.4 Hz, 1 H, CH_2O), 6.63 (dd, ^3J = 7.6; ^4J = 0.8 Hz, 2 H, H_{arom}), 6.91 (m, 3 H, H_{arom}), 7.19 (dd, ^3J = 8.4; ^4J = 7.2 Hz, 2 H, H_{arom}), 7.38 (d, ^3J = 8.8 Hz, 2 H, H_{arom}), 7.52 (ddd, ^2J = 14.8; ^3J = 7.2; ^4J = 1.4 Hz, 1 H, H_{arom}), 7.57 (ddd, ^2J = 14.8; ^3J = 7.2;

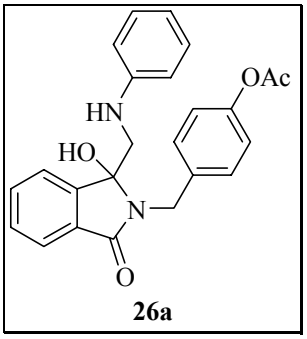
^{4}J = 1.4 Hz, 1 H, H_{arom}), 7.67 (d, ^{3}J = 7.2 Hz, 1 H, H_{arom}), 7.81 (d, ^{3}J = 6.8 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, $CDCl_3$)

δ (ppm) = 21.5 (s, 1 C, CH_3), 42.2 (s, 1 C, CH_2), 70.2 (s, 1 C, CH_2), 89.5 (s, 1 C, COH), 114.8 (s, 2 C, CH_{arom}), 121.9 (s, 2 C, CH_{arom}), 123.0 (s, 1 C, CH_{arom}), 123.9 (s, 1 C, CH_{arom}), 129.5 (s, 2 C, CH_{arom}), 129.8 (s, 2 C, CH_{arom}), 130.5 (s, 1 C, CH_{arom}), 131.4 (s, 1 C, Cq), 132.8 (s, 1 C, CH_{arom}), 132.9 (s, 1 C, CH_{arom}), 136.1 (s, 1 C, Cq), 145.5 (s, 1 C, Cq), 150.1 (s, 1 C, Cq), 157.9 (s, 1 C, Cq), 168.3 (s, 1 C, C=O), 169.8 (s, 1 C, C=O).

Experiment 84

6.3.13.12 Synthesis of 4-((1-hydroxy-3-oxo-1-((phenylamino) methyl)isoindolin-2-yl)methyl)phenyl acetate <u>26a</u> (FH-158)



26a

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.68 g (4.50 mmol) of *N*-phenylglycine and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 5 h in 150 ml of water/acetone [75:25]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.54 g (1.34 mmol; 88%) of **26a** as a brown oil.

TLC: R_f = 0.56 (Ethyl Acetate/n-Hexane 1:1)

^{1}H–NMR: (400 MHz, acetone-d_6)

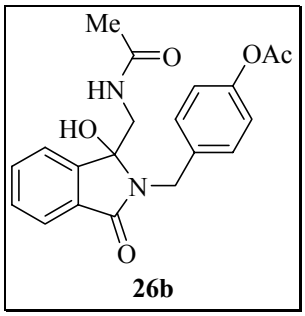
δ (ppm) = 2.26 (s, 3 H, CH_3), 3.53 (dd, ^{2}J = 13.2, ^{3}J = 6.8 Hz, 1 H, CH_2N), 3.85 (dd, ^{2}J = 13.2, ^{3}J = 6.8 Hz, 1 H, CH_2N), 4.14 (t, ^{2}J = 12.8, ^{3}J = 6.4 Hz, 1 H, NH), 4.69 (d, ^{2}J = 15.4 Hz, 1 H, CH_2), 4.86 (d, ^{2}J = 15.4 Hz, 1 H, CH_2), 5.85 (s, 1 H, OH), 6.55 (m, 3 H, H_{arom}), 7.01 (m, 2 H, H_{arom}), 7.07 (d, ^{2}J = 8.8 Hz, 2 H, H_{arom}), 7.07 (ddd, ^{2}J = 14.8, ^{3}J = 7.2, ^{4}J = 0.8 Hz, 1 H, H_{arom}), 7.58 (d, ^{2}J = 8.8 Hz, 2 H, H_{arom}), 7.59 (m, 1 H, H_{arom}), 7.71 (m, 1 H, H_{arom}), 7.73 (d, ^{3}J = 1.2 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 21.0 (s, 1 C, CH_3), 42.1 (s, 1 C, CH_2), 50.0 (s, 1 C, NCH_2), 90.9 (s, 1 C, COH), 114.0 (s, 2 C, CH_{arom}), 117.9 (s, 1 C, CH_{arom}), 123.4 (s, 2 C, CH_{arom}), 123.8 (s, 1 C, CH_{arom}), 124.6 (s, 1 C, CH_{arom}), 130.1 (s, 2 C, CH_{arom}), 130.3 (s, 2 C, CH_{arom}), 131.0 (s, 1 C, CH_{arom}), 133.3 (s, 1 C, CH_{arom}), 133.4 (s, 1 C, Cq), 137.5 (s, 1 C, Cq), 148.0 (s, 1 C, Cq), 150.0 (s, 1 C, Cq), 151.1 (s, 1 C, Cq), 168.1 (s, 1 C, C=O), 170.0 (s, 1 C, C=O).

Experiment 85

6.3.13.13 Synthesis of 4-((1-hydroxy-3-oxo-1-((acetylamino)methyl) isoindolin-2-yl)methyl)phenyl acetate <u>26b</u> (FH-159)



26b

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.53 g (4.53 mmol) of *N*-acetylglycine and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 2 h in 150 ml of water/acetone [75:25].

Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.50 g (1.36 mmol; 89%) of **26b** as a white solid.

TLC: R_f = 0.46 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 130-133 °C.

^{1}H–NMR: (400 MHz, acetone-d_6)

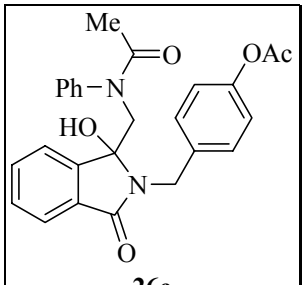
δ (ppm) = 1.72 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 2.88 (s, 1 H, OH), 3.72 (dd, ^2J = 14.0, ^3J = 6.0 Hz, 1 H, CH_2), 3.91 (dd, ^2J = 14.0, ^3J = 6.0 Hz, 1 H, CH_2), 4.73 (dd, ^2J = 27.8, ^3J = 15.6 Hz, 2 H, CH_2), 6.77 (s, 1 H, NH), 7.07 (d, ^3J = 8.7 Hz, 2 H, H_{arom}), 7.53 (d, ^3J = 8.7 Hz, 2 H, H_{arom}), 7.55 (ddd, ^2J = 14.7, ^3J = 7.3, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.62 (ddd, ^2J = 14.7, ^3J = 7.3, ^4J = 1.2 Hz, 1 H, H_{arom}), 7.67 (d, ^3J = 7.5 Hz, 1 H, H_{arom}), 7.71 (d, ^3J = 7.5 Hz, 1 H, H_{arom}).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 21.7 (s, 1 C, CH_3), 23.3 (s, 1 C, CH_3), 43.0 (s, 1 C, CH_2), 45.7 (s, 1 C, CH_2), 91.6 (s, 1 C, COH), 123.1 (s, 2 C, CH_{arom}), 124.0 (s, 1 C, CH_{arom}), 124.5 (s, 1 C, CH_{arom}), 130.8 (s, 2 C, CH_{arom}), 131.0 (s, 1 C, CH_{arom}), 133.4 (s, 1 C, Cq), 133.5 (s, 1 C, CH_{arom}), 138.4 (s, 1 C, Cq), 147.9 (s, 1 C, Cq), 151.5 (s, 1 C, Cq), 168.8 (s, 1 C, C=O), 170.4 (s, 1 C, C=O), 171.5 (s, 1 C, C=O).

Experiment 86

6.3.13.14 Synthesis of 4-((1-hydroxy-3-oxo-1-((N-phenylacetamido) methyl)isoindolin-2-yl)methyl)phenyl acetate 26c (FH-164)



26c

Following the general procedure (GP-4), 0.45 g (1.52 mmol) of 2-(4-acetoxy-benzyl)isoindoline-1,3-dione **9**, 0.87 g (4.50 mmol) of 2-(*N*-phenylacetamido)acetic acid and 0.31 g (2.24 mmol) of K_2CO_3 were irradiated for 5 h in 150 ml of water/acetone [75:25]. Column chromatography (SiO_2; EA:Hex = 1:1) gave 0.37 g (0.83 mmol; 55%) of **26c** as a Brown solid.

TLC: R_f = 0.14 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 167-170 °C.

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 1.62 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 4.39 (s, 2 H, CH_2), 4.64 (dd, ^2J = 32.8; ^3J = 14.4 Hz, 1 H, CH_2), 5.81 (s, 1 H, OH), 4.68 (d, 1 H, ^2J = 14.6 Hz, CH_2), 6.88 (m, 2 H, H_{arom}), 6.98 (d, ^3J = 8.4 Hz, 2 H, H_{arom}), 7.25 (m, 3 H, H_{arom}), 7.41 (m, 5 H, H_{arom}), 7.64 (d, ^3J = 7.3 Hz, 1 H, H_{arom}).

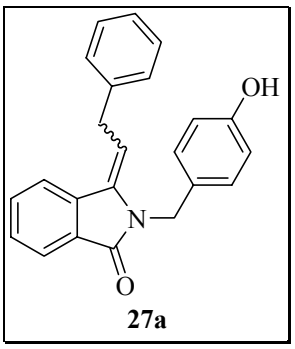
^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 21.7 (s, 1 C, CH_3), 23.3 (s, 1 C, CH_3), 43.5 (s, 1 C, CH_2), 53.1 (s, 1 C, CH_2), 91.8 (s, 1 C, COH), 122.7 (s, 2 C, CH_{arom}), 123.6 (s, 1 C, CH_{arom}), 125.1 (s, 1 C, CH_{arom}), 128.7 (s, 1 C, CH_{arom}), 129.3 (s, 2 C, CH_{arom}), 130.7 (s, 2 C, CH_{arom}), 130.8 (s, 1 C, CH_{arom}), 131.0 (s, 2 C, CH_{arom}), 133.0 (s, 1 C, CH_{arom}), 133.6 (s, 1 C, Cq), 138.2 (s, 1 C, Cq), 144.9 (s, 1 C, Cq), 147.7 (s, 1 C, Cq), 151.4 (s, 1 C, Cq), 168.3 (s, 1 C, C=O), 170.5 (s, 1 C, C=O), 171.8 (s, 1 C, C=O).

6.3.14 Dehydration/deprotection

Experiment 87

6.3.14.1 Synthesis of (E)-2-(4-hydroxybenzyl)-3-(2-phenethylidene) isoindolin-1-one 27a (FH-147)



27a

Following the general procedure (GP-5), 0.12 g (0.30 mmol) of 4-((1-hydroxy-3-oxo-1-((phenethylisoindolin-2-yl)methyl)phenyl acetate **23b**, was dehydrated to give 0.07 g (0.21 mmol; 70%) of **27a** as a white solid.

TLC: R_f = 0.64 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 187-190 °C.

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 4.05 (d, ^3J = 7.8 Hz, 2 H, CH_2), 5.00 (s, 2 H, CH_2), 5.80 (t, ^3J = 15.9, ^4J = 8.1 Hz, 1 H, CH), 6.81 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 7.17 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 7.23 (m, 3 H, H_{arom}), 7.30 (m, 2 H, H_{arom}), 7.63 (ddd, ^2J = 15.0, ^3J = 7.5, ^4J = 1.1 Hz, 1 H, H_{arom}), 7.71 (ddd, ^2J = 15.0, ^3J = 7.5, ^4J = 1.1 Hz, 1 H, H_{arom}), 7.91 (d, ^3J = 7.5 Hz, 1 H, H_{arom}), 8.08 (d, ^3J = 7.5 Hz, 1 H, H_{arom}), 8.32 (s, 1 H, OH).

^{13}C–NMR: (100 MHz, acetone-d_6)

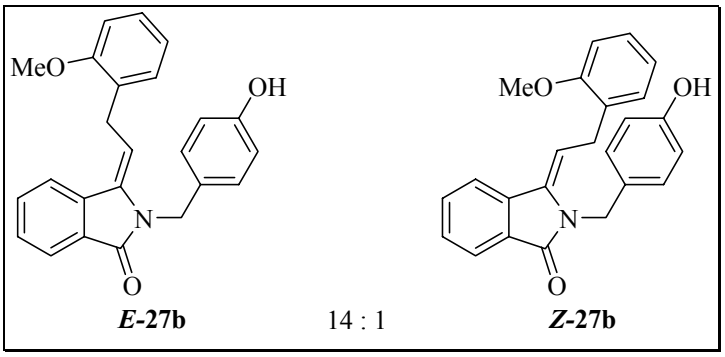
δ (ppm) = 34.2 (s, 1 C, CH_2), 43.4 (s, 1 C, CH_2), 96.0 (s, 1 C, COH), 112.7 (s, 1 C, CH_{arom}), 116.9 (s, 1 C, CH_{arom}), 124.7 (s, 1 C, CH_{arom}), 125.3 (s, 1 C, CH_{arom}), 127.8 (s, 1 C, CH_{arom}), 129.8 (s, 2 C, CH_{arom}), 130.0 (s, 2 C, CH_{arom}), 130.1 (s, 2 C, CH_{arom}),

130.6 (s, 1 C, CH_{arom}), 133.8 (s, 1 C, CH_{arom}), 136.6 (s, 1 C, Cq), 137.2 (s, 1 C, Cq), 141.7 (s, 1 C, Cq), 156.0 (s, 1 C, Cq), 167.1 (s, 1 C, Cq), 171.6 (s, 1 C, C=O).

***Z**-isomer could not be detected in the NMR.*

Experiment 88

6.3.14.2 Synthesis of 2-(4-hydroxybenzyl)-3-(2-(2-methoxyphenyl) ethylidene)isoindolin-1-one 27b (FH-155)



***E*-27b** 14 : 1 ***Z*-27b**

Following the general procedure (GP-5), 0.10 g (0.23 mmol) of 4-((1-(2-methoxy-phenethyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)phenyl acetate **23c**, was dehydrated to give 0.08 g (0.22 mmol; 96%) of **27b** as a light yellow solid.

TLC: R_f = 0.71 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 205-208 °C.

***E*-2-(4-hydroxybenzyl)-3-(2-(2-methoxyphenyl)ethylidene)isoindolin-1-one (*E*-27b)**

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 3.84 (s, 3 H, CH_3), 3.95 (d, ^2J = 8.0 Hz, 2 H, CH_2), 5.25 (s, 1 H, CH_2), 5.90 (t, ^2J = 16.0, ^3J = 8.0 Hz, 1 H, CH), 6.34 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 6.41 (m, 1

H, H_{arom}), 6.52 (d, ^{3}J = 7.3 Hz, 1 H, H_{arom}), 6.63 (m, 1 H, H_{arom}), 6.71 (d, ^{3}J = 9.4 Hz, 2 H, H_{arom}), 6.78 (ddd, ^{2}J = 15.7; ^{3}J = 8.1; ^{4}J = 1.8 Hz, 1 H, H_{arom}), 7.14 (ddd, ^{2}J = 15.2; ^{3}J = 7.6; ^{4}J = 1.0 Hz, 1 H, H_{arom}), 7.23 (ddd, ^{2}J = 15.1; ^{3}J = 7.3; ^{4}J = 1.2 Hz, 1 H, H_{arom}), 7.40 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 7.62 (d, ^{3}J = 7.8 Hz, 1 H, H_{arom}), 8.55 (s, 1 H, OH).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 29.0 (s, 1 C, CH_2), 39.0 (s, 1 C, CH_2), 61.0 (s, 1 C, CH_3), 110.8 (s, 1 C, CH), 112.8 (s, 1 C, CH_{arom}), 116.8 (s, 2 C, CH_{arom}), 122.0 (s, 1 C, CH_{arom}), 124.6 (s, 1 C, CH_{arom}), 125.4 (s, 1 C, CH_{arom}), 129.3 (s, 1 C, CH_{arom}), 129.8 (s, 2 C, CH_{arom}), 130.3 (s, 1 C, CH_{arom}), 130.5 (s, 1 C, CH_{arom}), 133.7 (s, 1 C, CH_{arom}), 134.7 (s, 1 C, Cq), 136.9 (s, 1 C, Cq), 149.4 (s, 1 C, Cq), 158.5 (s, 1 C, Cq), 167.0 (s, 1 C, Cq), 170.8 (s, 1 C, C=O).

_Z_-2-(4-hydroxybenzyl)-3-(2-(2-methoxyphenyl)ethylidene)isoindolin-1-one (_Z_-27b)

^{1}H–NMR: (400 MHz, acetone-d_6)

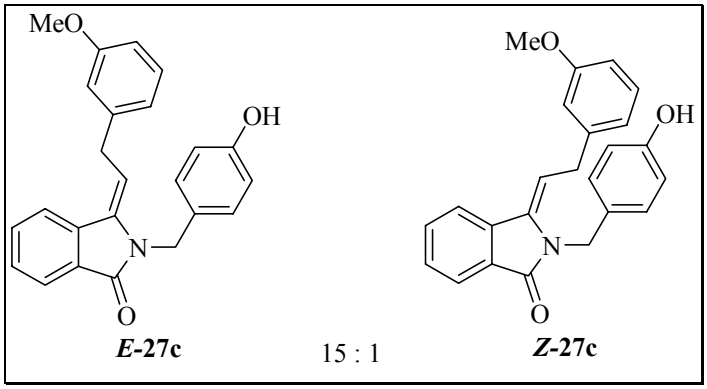
δ (ppm) = 3.84 (s, 3 H, CH_3), 3.95 (d, ^{2}J = 8.0 Hz, 2 H, CH_2), 4.96 (s, 1 H, CH_2), 5.77 (t, ^{2}J = 16.0, ^{3}J = 8.0 Hz, 1 H, CH), 6.35 (d, ^{3}J = 8.6 Hz, 2 H, H_{arom}), 6.40 (m, 1 H, H_{arom}), 6.56 (d, ^{3}J = 8.0 Hz, 1 H, H_{arom}), 6.64 (m, 1 H, H_{arom}), 6.70 (d, ^{3}J = 8.6 Hz, 2 H, H_{arom}), 6.79 (ddd, ^{2}J = 15.7; ^{3}J = 8.1; ^{4}J = 1.8 Hz, 1 H, H_{arom}), 7.18 (ddd, ^{2}J = 15.2; ^{3}J = 7.6; ^{4}J = 1.0 Hz, 1 H, H_{arom}), 7.28 (ddd, ^{2}J = 15.1; ^{3}J = 7.3; ^{4}J = 1.2 Hz, 1 H, H_{arom}), 7.45 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 7.62 (d, ^{3}J = 7.8 Hz, 1 H, H_{arom}), 8.55 (s, 1 H, OH).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 28.9 (s, 1 C, CH_2), 43.3 (s, 1 C, CH_2), 56.4 (s, 1 C, CH_3), 111.3 (s, 1 C, CH), 112.9 (s, 1 C, CH_{arom}), 116.9 (s, 2 C, CH_{arom}), 121.9 (s, 1 C, CH_{arom}), 124.5 (s, 1 C, CH_{arom}), 125.3 (s, 1 C, CH_{arom}), 129.2 (s, 1 C, CH_{arom}), 129.9 (s, 2 C, CH_{arom}), 130.4 (s, 1 C, CH_{arom}), 130.6 (s, 1 C, CH_{arom}), 133.6 (s, 1 C, CH_{arom}), 134.6 (s, 1 C, Cq), 137.0 (s, 1 C, Cq), 149.3 (s, 1 C, Cq), 158.6 (s, 1 C, Cq), 167.1 (s, 1 C, Cq), 171.5 (s, 1 C, C=O).

Experiment 89

6.3.14.3 Synthesis of 2-(4-hydroxybenzyl)-3-(2-(3-methoxyphenyl) ethylidene)isoindolin-1-one 27c (FH-156)



***E*-27c** 15 : 1 ***Z*-27c**

Following the general procedure (GP-5), 0.11 g (0.25 mmol) of 4-((1-(3-methoxyphenethyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)phenyl acetate **23d**, was dehydrated to give 0.07 g (0.19 mmol; 76%) of **27c** as a yellow solid.

TLC: R_f = 0.57 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 160-164 °C.

***E*-(2-(4-hydroxybenzyl)-3-(2-(3-methoxyphenyl)ethylidene)isoindolin-1-one (*E*-27c)**

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 3.74 (s, 3 H, OCH_3), 4.03 (d, ^2J = 7.8 Hz, 2 H, CH_2), 5.00 (s, 2 H, NCH_2), 5.80 (t, ^3J = 16.2, ^4J = 8.1 Hz, 1 H, CH), 6.80 (m, 5 H, H_{arom}), 7.20 (m, 3 H, H_{arom}), 7.63 (ddd, ^2J = 15.1, ^3J = 7.5, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.72 (ddd, ^2J = 15.1, ^3J = 7.5, ^4J = 1.0 Hz, 1 H, H_{arom}), 7.91 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 8.07 (d, ^3J = 7.6 Hz, 1 H, H_{arom}), 8.35 (s, 1 H, OH).

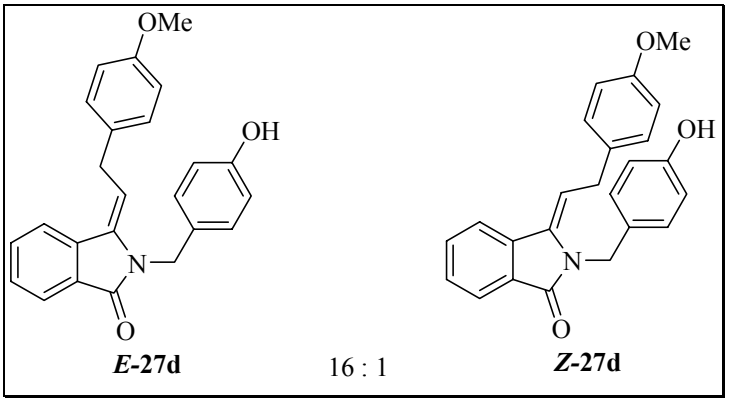
^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 34.2 (s, 1 C, CH_2), 43.4 (s, 1 C, CH_2), 56.1 (s, 1 C, OCH_3), 94.3 (s, 1 C, CH), 112.5 (s, 1 C, CH_{arom}), 113.4 (s, 1 C, CH_{arom}), 115.2 (s, 1 C, CH_{arom}), 116.9 (s, 2 C, CH_{arom}), 122.0 (s, 1 C, CH_{arom}), 124.7 (s, 1 C, CH_{arom}), 125.3 (s, 1 C, CH_{arom}), 130.0 (s, 2 C, CH_{arom}), 130.6 (s, 1 C, CH_{arom}), 131.1 (s, 1 C, CH_{arom}), 132.2 (s, 1 C, Cq), 133.8 (s, 1 C, Cq), 137.1 (s, 1 C, Cq), 143.3 (s, 1 C, Cq), 149.5 (s, 1 C, Cq), 161.7 (s, 1 C, Cq), 171.6 (s, 1 C, C=O).

***Z**-isomer could not be assigned because of the low intensity of the signals.*

Experiment 90

6.3.14.4 Synthesis of 2-(4-hydroxybenzyl)-3-(2-(4-methoxyphenyl) ethylidene)isoindolin-1-one <u>27d</u> (FH-157)



***E*-27d** 16 : 1 ***Z*-27d**

Following the general procedure (GP-5), 0.11 g (0.25 mmol) of 4-((1-(4-methoxy-phenethyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)phenyl acetate **23e**, was dehydrated to give 0.08 g (0.22 mmol; 88%) of **27d** as a yellow solid.

TLC: R_f = 0.56 (Ethyl Acetate/n-Hexane 1:1)

Melting point: 182-185 °C.

***E*-(2-(4-hydroxybenzyl)-3-(2-(4-methoxyphenyl)ethylidene)isoindolin-1-one (*E*-27d)**

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 3.78 (s, 3 H, OCH_3), 3.98 (d, ^{2}J = 8.1 Hz, 2 H, CH_2), 4.99 (s, 2 H, NCH_2), 5.77 (t, ^{3}J = 16.2, ^{4}J = 8.1 Hz, 1 H, CH), 6.81 (d, ^{3}J = 8.6 Hz, 2 H, H_{arom}), 6.86 (d, ^{3}J = 8.6 Hz, 2 H, H_{arom}), 7.13 (d, ^{3}J = 8.7 Hz, 2 H, H_{arom}), 7.17 (d, ^{3}J = 8.7 Hz, 2 H, H_{arom}), 7.63 (ddd, ^{2}J = 15.2, ^{3}J = 7.5, ^{4}J = 1.1 Hz, 1 H, H_{arom}), 7.71 (ddd, ^{2}J = 15.2, ^{3}J = 7.5, ^{4}J = 1.1 Hz, 1 H, H_{arom}), 7.91 (d, ^{3}J = 7.6 Hz, 2 H, H_{arom}), 8.06 (d, ^{3}J = 7.6 Hz, 2 H, H_{arom}), 8.36 (s, 1 H, OH).

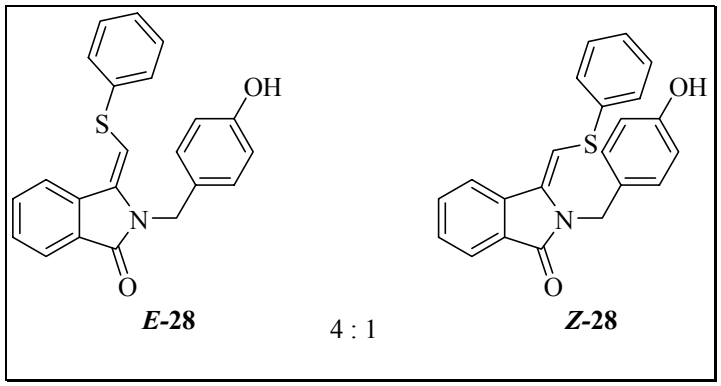
^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 33.4 (s, 1 C, CH_2), 43.4 (s, 1 C, CH_2), 56.2 (s, 1 C, OCH_3), 113.3 (s, 1 C, CH), 115.5 (s, 2 C, CH_{arom}), 116.9 (s, 2 C, CH_{arom}), 124.7 (s, 1 C, CH_{arom}), 125.3 (s, 1 C, CH_{arom}), 130.0 (s, 2 C, CH_{arom}), 130.6 (s, 1 C, CH_{arom}), 130.7 (s, 2 C, CH_{arom}), 132.2 (s, 1 C, Cq), 133.8 (s, 1 C, CH_{arom}), 136.5 (s, 1 C, Cq), 137.2 (s, 1 C, Cq), 140.3 (s, 1 C, Cq), 158.2 (s, 1 C, Cq), 159.9 (s, 1 C, Cq), 167.3 (s, 1 C, C=O).

***Z*-isomer could not be assigned because of the low intensity of the signals.**

Experiment 91

6.3.14.5 Synthesis of 2-(4-hydroxybenzyl)-3-((phenylthio) methyl ene)isoindolin-1-one <u>28</u> (FH-145)



***E*-28** 4 : 1 ***Z*-28**

Following the general procedure (GP-5), 0.11 g (0.26 mmol) of 4-((1-hydroxy-3-oxo-1-((phenylthio)methyl)isoindolin-2-yl)methyl)phenyl acetate **24**, was dehydrated to give 0.08 g (0.23 mmol; 88%) of **28** as a yellow solid.

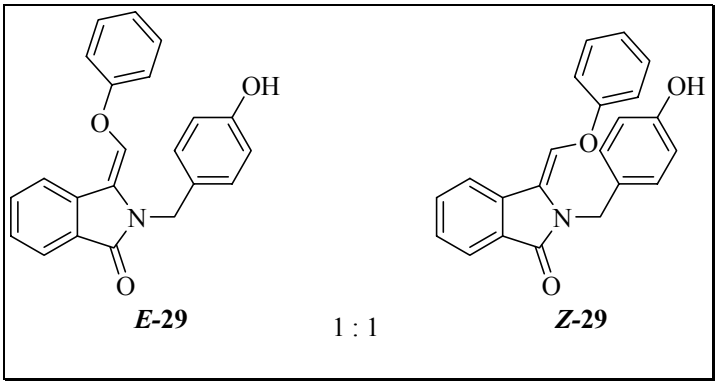
TLC: R_f = 0.59 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 170-173 °C.

***E*-(2-(4-hydroxybenzyl)-3-((phenylthio)methylene)isoindolin-1-one (*E*-28)**
^{1}H–NMR: (400 MHz, acetone-d_6)
δ (ppm) = 5.11 (s, 2 H, CH_2), 6.35 (s, 1 H, CH), 6.88 (d, ^2J = 8.6 Hz, 2 H, CH_2), 7.17 (m, 2 H, H_{arom}), 7.22 (d, ^3J = 8.6 Hz, 2 H, H_{arom}), 7.28 (m, 1 H, H_{arom}), 7.34 (m, 2 H, H_{arom}), 7.68 (ddd, ^2J = 15.1, ^3J = 7.6, ^4J = 1.1 Hz, 1 H, H_{arom}), 7.78 (ddd, ^2J = 15.1, ^3J = 7.6, ^4J = 1.1 Hz, 1 H, H_{arom}), 7.94 (ddd, ^2J = 8.6, ^3J = 2.0, ^4J = 1.0 Hz, 1 H, H_{arom}), 8.41 (ddd, ^2J = 8.6, ^3J = 2.0, ^4J = 1.0 Hz, 1 H, H_{arom}), 8.47 (s, 1 H, OH).
^{13}C–NMR: (100 MHz, acetone-d_6)
δ (ppm) = 43.7 (s, 1 C, CH_2), 105.6 (s, 1 C, CH), 116.1 (s, 1 C, Cq), 117.2 (s, 2 C, CH_{arom}), 124.9 (s, 1 C, CH_{arom}), 126.1 (s, 1 C, CH_{arom}), 128.1 (s, 1 C, CH_{arom}), 129.1 (s, 2 C, CH_{arom}), 129.7 (s, 1 C, CH_{arom}), 130.2 (s, 2 C, CH_{arom}), 130.6 (s, 1 C, CH_{arom}), 130.9 (s, 2 C, CH_{arom}), 131.1 (s, 1 C, Cq), 134.0 (s, 1 C, Cq), 137.9 (s, 1 C, Cq), 158.5 (s, 1 C, Cq), 158.2 (s, 1 C, Cq), 167.0 (s, 1 C, C=O).

Z*-*isomer could not be assigned because of the low intensity of the signals.

Experiment 92

6.3.14.6 Synthesis of 2-(4-hydroxybenzyl)-3-(phenoxymethylene) isoindolin-1-one 29 (FH-144)



Following the general procedure (GP-5), 0.11 g (0.27 mmol) of 4-((1-hydroxy-3-oxo-1-(phenoxymethyl)isoindolin-2-yl)methyl)phenyl acetate **25**, was dehydrated to give 0.08 g (0.24 mmol; 89%) of **29** as a white solid.

TLC: R_f = 0.60 (Ethyl Acetate/n-Hexane 1:1)
Melting point: 175-177 °C.

***E*-(2-(4-hydroxybenzyl)-3-(phenoxymethylene)isoindolin-1-one (*E*-29)**
^{1}H–NMR: (400 MHz, acetone-d_6)
δ (ppm) = 5.06 (s, 2 H, CH_2), 6.73 (d, ^2J = 8.6 Hz, 1 H, H_{arom}), 7.11 (s, 1 H, CH), 7.12 (m, 1 H, H_{arom}), 7.20 (m, 5 H, H_{arom}), 7.27 (d, ^2J = 8.6 Hz, 2 H, H_{arom}), 7.55 (ddd, ^2J = 14.9, ^3J = 7.5, ^4J = 0.8 Hz, 1 H, H_{arom}), 7.61 (ddd, ^2J = 14.9, ^3J = 7.5, ^4J = 0.8 Hz, 1 H, H_{arom}), 7.66 (ddd, ^2J = 15.2, ^3J = 7.6, ^4J = 1.3 Hz, 1 H, H_{arom}), 7.71 (ddd, ^2J = 15.2, ^3J = 7.6, ^4J = 1.3 Hz, 1 H, H_{arom}), 8.21 (s, 1 H, OH).
^{13}C–NMR: (100 MHz, acetone-d_6)
δ (ppm) = 43.9 (s, 1 C, CH_2), 116.6 (s, 2 C, CH_{arom}), 117.1 (s, 2 C, CH_{arom}), 120.6 (s, 1 C, CH), 125.0 (s, 1 C, Cq), 125.7 (s, 1 C, CH_{arom}), 129.6 (s, 1 C, Cq), 130.1 (s, 2 C, CH_{arom}), 130.4 (s, 1 C, Cq), 131.5 (s, 2 C, CH_{arom}), 133.3 (s, 1 C, Cq), 135.9 (s, 1 C,

CH_{arom}), 142.1 (s, 1 C, CH_{arom}), 148.5 (s, 1 C, CH_{arom}), 155.0 (s, 1 C, CH_{arom}), 158.5 (s, 1 C, Cq), 162.8 (s, 1 C, Cq), 167.9 (s, 1 C, C=O).

***Z*-(2-(4-hydroxybenzyl)-3-(phenoxymethylene)isoindolin-1-one (*Z*-29)**

^{1}H–NMR: (400 MHz, acetone-d_6)

δ (ppm) = 5.27 (s, 2 H, CH_2), 6.87 (d, ^{2}J = 8.6 Hz, 1 H, H_{arom}), 7.14 (m, 2 H, H_{arom}), 7.20 (m, 2 H, H_{arom}), 7.42 (s, 1 H, CH), 7.43 (m, 4 H, H_{arom}), 7.85 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 7.90 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 7.99 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 8.15 (d, ^{3}J = 7.6 Hz, 1 H, H_{arom}), 8.40 (s, 1 H, OH).

^{13}C–NMR: (100 MHz, acetone-d_6)

δ (ppm) = 46.0 (s, 1 C, CH_2), 117.4 (s, 2 C, CH_{arom}), 118.1 (s, 2 C, CH_{arom}), 124.6 (s, 1 C, CH), 125.3 (s, 1 C, Cq), 126.3 (s, 1 C, CH_{arom}), 130.2 (s, 2 C, CH_{arom}), 130.3 (s, 1 C, Cq), 131.0 (s, 1 C, Cq), 131.6 (s, 2 C, CH_{arom}), 133.8 (s, 1 C, Cq), 138.6 (s, 1 C, CH_{arom}), 142.2 (s, 1 C, CH_{arom}), 149.4 (s, 1 C, CH_{arom}), 155.1 (s, 1 C, CH_{arom}), 158.8 (s, 1 C, Cq), 166.7 (s, 1 C, Cq), 171.7 (s, 1 C, C=O).

7 Appendices

7.1 X-Ray Data

	11e	***unlike*-11h**	***like*-11h**	**23b**
Formula	$C_{17}H_{17}NO_2$	$C_{17}H_{17}NO_2$	$C_{17}H_{17}NO_2$	$C_{25}H_{23}NO_4$
FW [g/mol]	267.32	267.32	267.32	401.44
Colour	colourless	colourless	colourless	colourless
Shape	prism	platelet	prism	prism
Crystal dimensions [mm]	0.4×0.36×0.34	0.45×0.38×0.23	0.45×0.4×0.38	0.58×0.56×0.5
Crystal system	monoclinic	triclinic	monoclinic	monoclinic
Space group[159]	$P2_1$	P-1	$P2_1/c$	$P2_1/n$
***a* [Å]**	14.4399(3)	7.9053(4)	10.2136(4)	10.0460(3)
***b* [Å]**	28.1060(5)	8.6707(4)	10.8771(5)	14.2639(4)
***c* [Å]**	13.4152(2)	10.7456(5)	13.3876(6)	15.2060(4)
α [°]	90	73.026(2)	90	90
β [°]	90.1030(10)	74.305(2)	111.297(2)	104.634(2)
γ [°]	90	88.757(2)	90	90
V [Å^3]	5444.52(17)	676.89(6)	1385.72(10)	2108.26(10)
Z	16	2	4	4
ρ (calc.) [g/cm^3]	1.304	1.312	1.281	1.265
No. reflexes	11434	2922	3009	4594
Reflexes with $F > 2\sigma(F)$	8287	1945	2253	3037
R	0.0554	0.0425	0.0386	0.0395
***R*$_w$**	0.1222	0.0842	0.0849	0.0796

7.2 List of Publications and Presentations

1. A. R. Kim, K.-S. Lee, C.-W. Lee, D. J. Yoo, F. Hatoum, M. Oelgemöller "Photodecarboxylative Cyclizations of ω-Phthalimido-*ortho*-phenoxy Carboxylates", Communication, *Tetrahedron Lett.*, **2005**, *46*, 3395-3398.
2. F. Hatoum, M. Oelgemöller, A. G. Griesbeck "Photochemical Modifications of Amino Acids – En Route to Novel Fungicides", Poster, *RSC / Welcome Trust / CSCB Chemical Biology Interface Meeting*, Dublin (Ireland), 13. May 2005.
3. F. Hatoum, M. Oelgemöller, A. G. Griesbeck "Photochemical Modifications of Amino Acids – En Route to Novel Fungicides", Poster, *57th Irish Universities Chemistry Research Colloquium*, Maynooth (Ireland), 22. - 24. June 2005.
4. F. Hatoum, S. Gallagher, M. Ingargiola, M. Oelgemöller, A. G. Griesbeck "Photochemical Modifications of Amino Acids", Poster, *58th Irish Universities Chemistry Research Colloquium*, Galway (Ireland), 14. - 15. June 2006.
5. S. Gallagher, F. Hatoum, M. Oelgemöller, A. G. Griesbeck "Green Photochemistry - Photodecarboxylative Additions of Carboxylates to Phthalimides", Poster, *The 9th International 21st Century COE Symposium on Integrated EcoChemistry (COEIEC 9)*, Hyogo, Awaji Island (Japan), 16. - 18. January 2007.
6. F. Hatoum, S. Gallagher, P. Nœureuil, J. Fiedler, M. Oelgemöller, A. G. Griesbeck "Synthesis of bioactive compounds through photodecarboxylative additions of carboxylates to phthalimides", Poster, *XXIII International Conference on Photochemistry*, Cologne (Germany), 29. July - 3. August 2007.
7. S. Gallagher, F. Hatoum, M. Oelgemöller, A. G. Griesbeck "Synthesis of bioactive compounds through photodecarboxylative additions of carboxylates to phthalimides", Poster, *Central European Conference on Photochemistry – CECP 2008*, Bad Hofgastein (Austria), 10. - 14. February 2008.
8. K. Joyce, E. Coyle, S. Gallagher, F. Hatoum, S. Byrne, I. Woog, M. Oelgemöller "From large-scale solar Synthesis to Micro-Photochemistry", Poster, *60th Irish Universities Chemistry Research Colloquium*, Cork (Ireland), 11. - 13. June 2008.

8 References

[1] G. Ciamician, "The Photochemistry of the Future", *Science*, **1912**, *36*, 385-394.

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