An Investigation into the Smiles Rearrangement, and other studies

A dissertation submitted to The University of Manchester for the degree of Master of Science by Research in the faculty of Science and Engineering

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Tim P Evans

School of Chemistry

Supervisor: Professor M. F. Greaney

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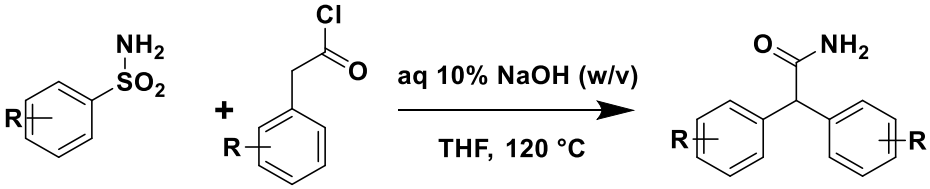
Abbreviations

APCI	Atmospheric Pressure Chemical Ionization
Aq	Aqueous
Ar	Aromatic
Bpy	Bipyridine
Br	Broad
d	Doublet (NMR)
ddd	Doublet of doublet of doublets
DMF	*N*,*N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
dt	Doublet of triplets
EAS	Electrophilic Aromatic Substitution
ESI	Electrospray Ionization
Eq	Equivalent(s)
Et al	Et alli (and others)
EWG	Electron Withdrawing Group
FT-IR	Fourier Transform Infrared Spectroscopy
h	Hour(s)
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IAd	Di(adamantyl)imidazol-2-ylidene
IR	Infrared
l	Liquid
LED	Light Emitting Diode
LRMS	Low Resolution Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
m	multiplet
Me	Methyl
mg	Milligram(s)
MHz	Mega Hertz
mL	Millilitres
M.P.	Melting Point

mmol	millimole
m/z	mass to charge ratio
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
ONSH	Oxidative Nucleophilic Substitution of Hydrogen
Pka	Acid dissociation constant
ppm	Parts per million
Pr	Propyl
q	Quartet
Quin	Quintet
rt	Room Temperature
s	Singlet
S_NAr	Nucleophilic Aromatic Substitution
t	Triplet
^tBu	Tertiary butyl
TLC	Thin Layer Chromatography
tt	Triplet of triplets
THF	Tetrahydrofuran
UV	Ultra Violet
VNS	Vicarious Nucleophilic Substitution
w/v	Weight per volume
°C	Degrees centigrade
µL	Micro litres

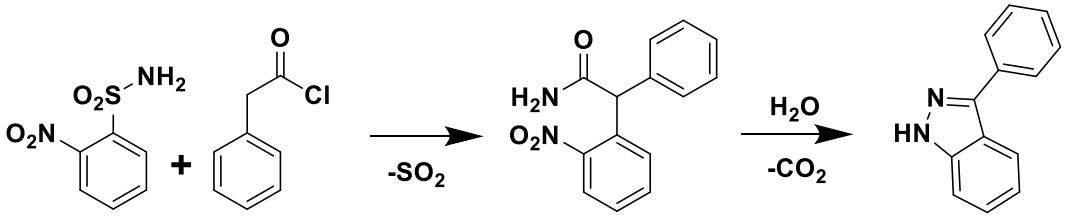
Abstract

Rearrangement reactions are useful tools in organic synthesis. The Smiles Rearrangement is a type of intramolecular nucleophilic aromatic substitution. Work has previously been completed by a member of the Greaney group to discover a set of optimised conditions for the rearrangement. Part one of this report investigated the scope of the rearrangement using the optimised reaction conditions. The set reaction conditions can be seen below.



The sulfonamide first attacks the carbonyl of the acyl chloride, displacing a chloride ion to get the addition product. The CH_2 next to the carbonyl group is then deprotonated by sodium hydroxide and subsequently attacks the carbon of the aromatic ring which is bonded to SO_2. SO_2 is then displaced and the negative charge is pushed onto the nitrogen. The nitrogen is then reprotonated to give the Smiles product.

The second reaction investigates the Smiles Rearrangement utilising an *ortho* nitro group which interestingly yields an indazole, which can be seen below.



Part two of this report investigated a potential novel Smiles Rearrangement, inspired by previous work completed by a member of the Greaney group that worked on aminoarylation of alkynes.

Part three of this report investigated *N*-Heterocyclic Carbenes (NHCs) as organocatalysts in a bid to perform a potential novel electrophilic substitution of electron-deficient aromatic rings.

Declaration

No portion of the work referred to in the dissertation has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright

Acknowledgements

I would like to thank Professor Michael Greaney for giving me the opportunity to work in his laboratory and for his supervision and guidance during the project. I would also like to thank Dr Alastair Durie for his support and encouragement during the project, as well as a thank you to all the members of the Greaney group that helped in any way during the day to day workings.

1. Introduction

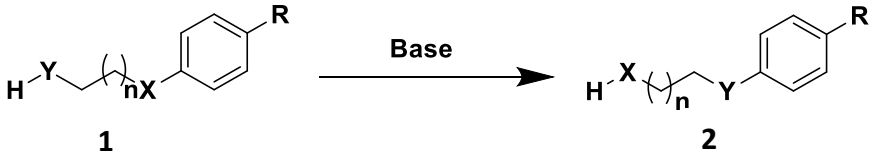
1.1. Smiles Rearrangement

Rearrangement reactions are considered a useful tool in synthesis as they can be used to synthesise challenging products from more accessible starting materials. The Smiles rearrangement is a type of intramolecular nucleophilic aromatic substitution reaction where a C–X single bond is broken, and a new C–Y or C–C bond is formed, usually through *ipso* substitution.

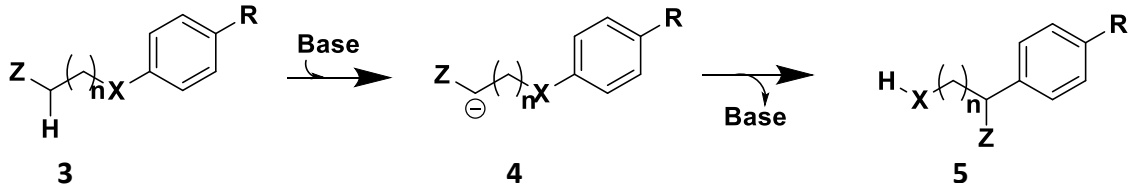
The rearrangement can be split into two types: a polar 2 electron rearrangement; or a radical single electron rearrangement. [1,2]

1.1.1. Polar Smiles Rearrangement

The polar 2-electron rearrangement can be further split into two categories; when a new C–Y bond is formed, the reaction is termed the traditional Smiles rearrangement incorporating a heteroatom as the nucleophilic component[1]. However when a new C-C bond is formed, this is termed the Truce-Smiles rearrangement, which utilises a carbon based nucleophile (a carbanion).[3]



Scheme 1 General Smiles Rearrangement, with Y as the nucleophile, X as a suitable leaving group, R as an activating group

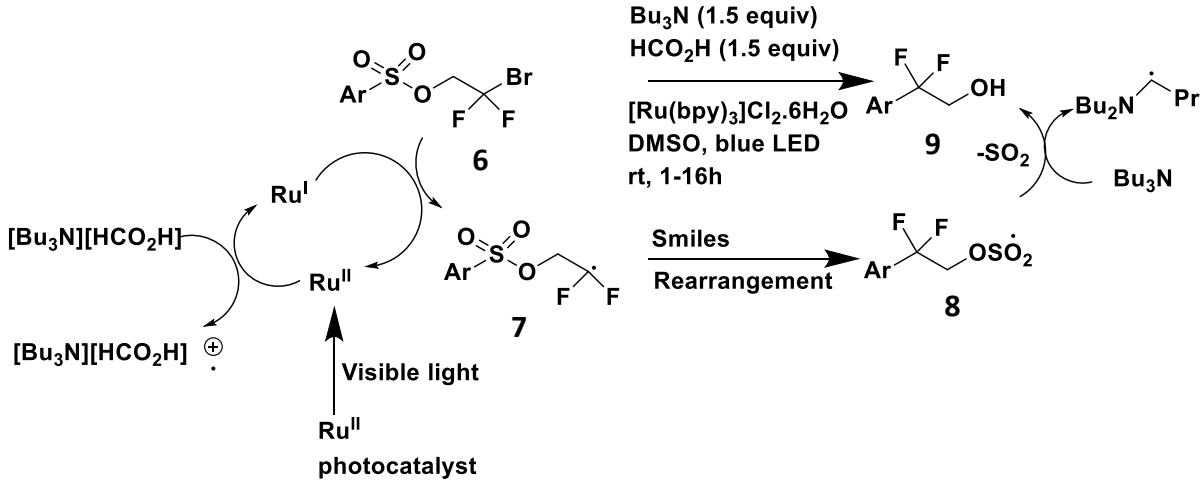


Scheme 2 General Truce-Smiles rearrangement depicting the carbanion nucleophile facilitated by a base

1.1.2. Radical Smiles Rearrangement

The single electron radical smiles rearrangement was first utilised by Speckamp, the initial reaction starts by attack by free radicals at the *ipso*-position of sulfonates or sulfonamides, followed by sulfur dioxide extrusion and hydrogen abstraction to end the process. [2,4] Benefits of the radical reaction are that the presence of an activating substituent on the migrating unit is not required.[5] In addition to this UV or visible light can be used as a

sustainable and inexpensive source of energy. This was demonstrated by Stephenson *et al.*[6] where the group utilised the radical Smiles rearrangement in their synthesis of a difluoro-substituted spirocyclic ORL-1 antagonist.



Scheme 3 Reaction mechanism deduced by Stephenson depicting a radical smiles rearrangement

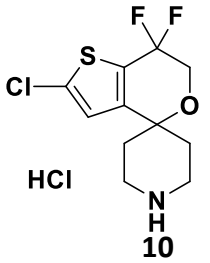
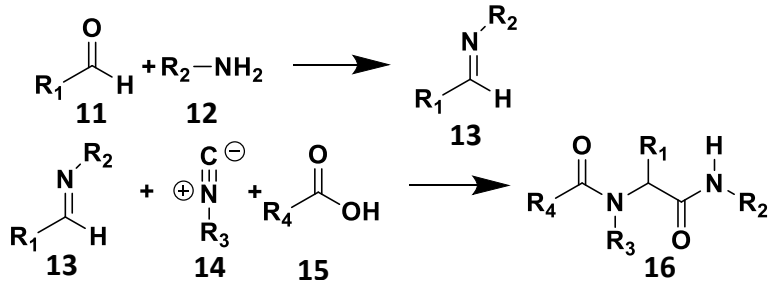


Figure 1 Difluoro-substituted spirocyclic ORL-1 antagonist

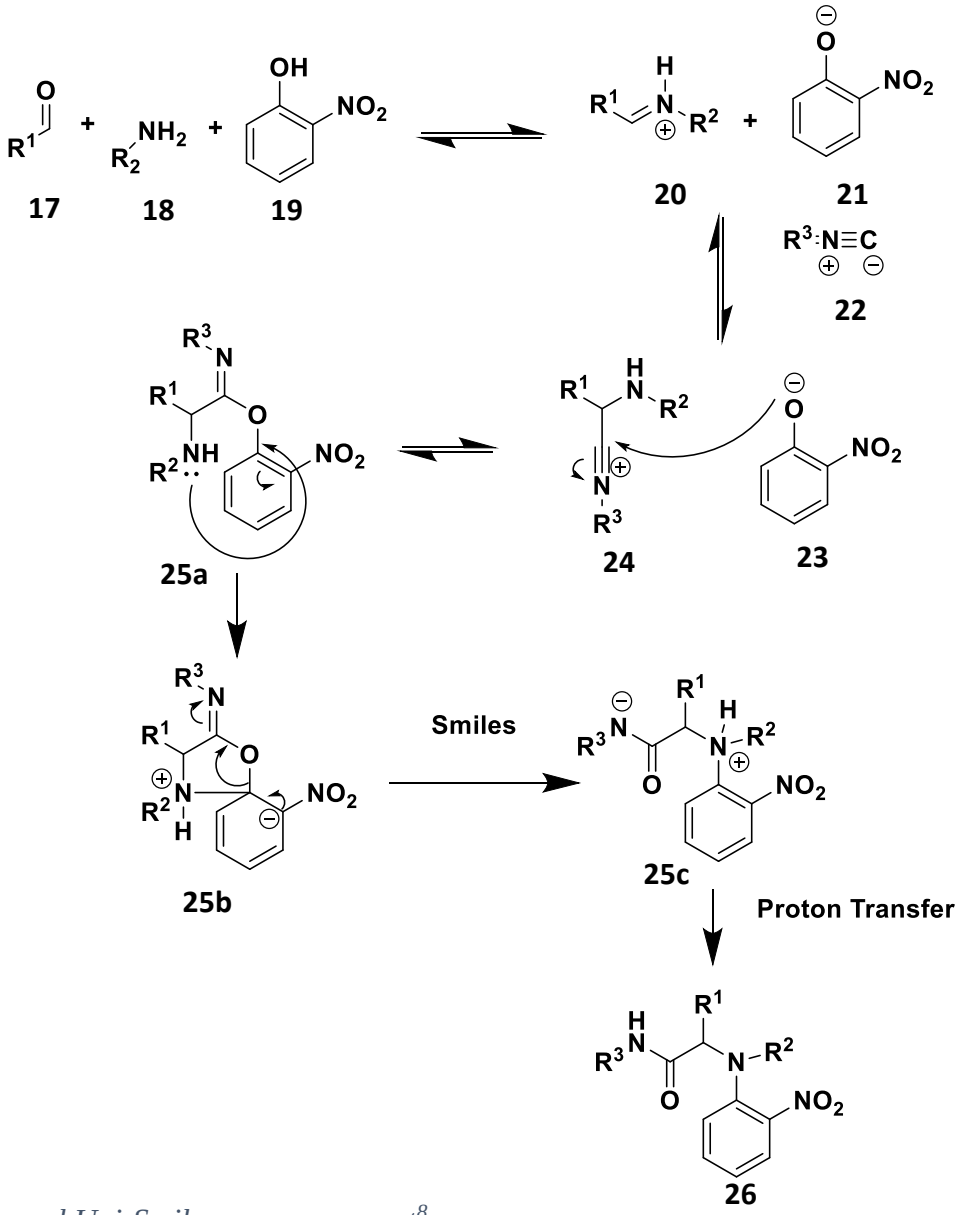
1.1.3.Ugi-Smiles Rearrangement

Another variant of the Smiles rearrangement is the Ugi-Smiles rearrangement. The original Ugi reaction is a four component condensation reaction between an aldehyde, an amine, a carboxylic acid and an isocyanide which forms α-aminoacyl amide derivatives.[7]



Scheme 4 General Ugi Reaction

The Ugi-Smiles rearrangement makes use of an electron deficient phenol such as nitro-phenol instead of the carboxylic acid which is typically used.[8]



Scheme 5 General Ugi-Smiles rearrangement[8]

1.1.4.Key Aspects of the Smiles Rearrangement

There are three factors considered key in the Smiles rearrangement, these are: the nucleophilicity of the entering group; the nucleofugality of the leaving group; and the activation of the aromatic ring. For a Smiles rearrangement the aromatic ring is typically activated using a strong electron-withdrawing group such as an NO_2 in the *ortho* or *para* position. In addition, work by other groups has demonstrated that sulfonyl- and halo-substituted aromatic rings also work.[9] However, Truce stated that in a Truce-Smiles rearrangement the substrates do not require activating groups on the migrating ring which are normally required for nucleophilic aromatic substitution substrates.[6]

Work was carried out by Smiles *et al*. where the nucleophilicity of the entering group and nucleofugality of the leaving group were considered to be intertwined where a stronger nucleophile allowed for a weaker leaving group.[10] Expanding on this work, the desired rearrangement product is also facilitated by a nucleophile that is a poorer leaving group than the intended leaving group and the rate of the reverse reaction is suppressed in the same way when the leaving group is less nucleophilic than the intended nucleophile. This principal is of particular prominence in the Truce-Smiles rearrangement where the nucleophile is always a carbanion species that is a strong nucleophile and poor leaving group.[11]

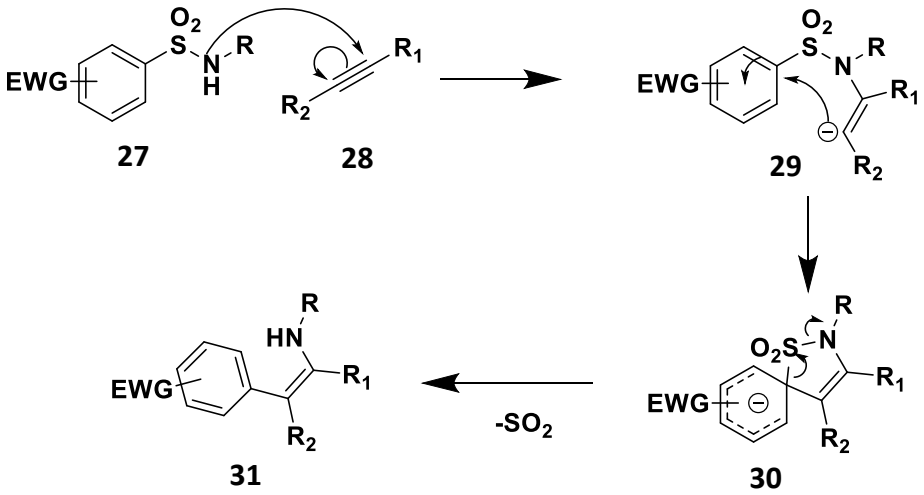
Furthermore, another variable to take into account is the tether length of the nucleophile, wherein the nucleophile can be located two, three, four and five atoms removed from the aromatic ring; therefore demonstrating the reaction could proceed through three, four, five and six membered transition states.[12] Work carried out by Fuss *et al*. investigated the effect of the tether length on a Truce-Smiles rearrangement where the substrate utilised a *para* nitro group on the aryl ring.[12] Their findings concluded that the highest yield of product was for a tether length of 3 atoms, which meant forming a 5 membered spirocyclic Meisenheimer intermediate. This was in agreement with past literature reports of successful rearrangement reactions.[11]

The mechanism of the Smiles rearrangement is thought to proceed *via* a Meisenheimer intermediate (**30**), an anionic spiro-cyclic complex. Stabilisation of the Meisenheimer intermediate is considered essential to promoting the nucleophilic aromatic substitution process, this is achieved by previously mentioned strong electron withdrawing substituents at the *ortho* and/or *para* position to the leaving group.[11] The rate of the rearrangement was found to depend upon the collapse of the intermediate.[13]

1.2. A potentially novel Smiles-type Rearrangement

1.2.1. Similar Work in the Area

Work has been carried out by another member of the Greaney group Pauline Rabet where she investigated the aminoarylation of alkynes.[14] The proposed mechanism scheme 6 draws similarities between the work trying to be achieved here, that being the initial addition of the sulfonamide to substrate, followed by *ipso* substitution and extrusion of SO_2 to complete the Smiles rearrangement. It was also agreed that there needs to be a strongly electron withdrawing group on the attacking sulfonamide to stabilise the Meisenheimer intermediate **30**. Another positive to take from her work is that the rearrangement was also demonstrated on secondary *N*-aryl sulfonamides, opening up new syntheses using more varied started materials.



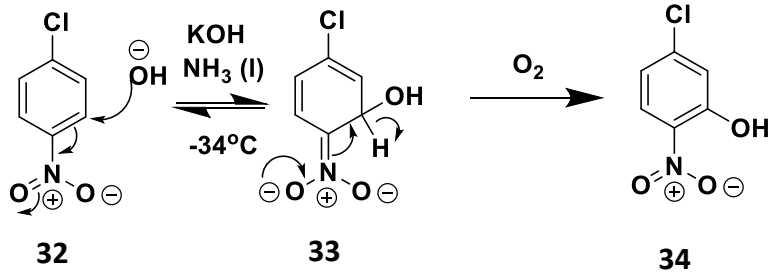
Scheme 6 Smiles Rearrangement deduced from Rabet [14]

Work has also been completed by Bowden where the group have researched rate coefficients for Smiles rearrangements.[15] Their work concludes that the reaction does proceed via a spirocyclic Meisenheimer intermediate with the formation of the intermediate being the rate determining step, influenced by solvent choice. The group has also demonstrated that the reaction is successful on substrates based around a 3-nitropyridine, which is what will be used in this experiment to activate the ring to nucleophilic attack.[15]

However a difficulty in this investigation that needs to be overcome is undesired side reactions namely oxidative nucleophilic substitution of hydrogen (ONSH) and vicarious nucleophilic substitution (VNS).

1.2.2. Oxidative Nucleophilic Substitution of Hydrogen

ONSH, as expected, results in replacement of a hydrogen by the attacking nucleophile therefore eliminating the chance for the Smiles-rearrangement to occur. This type of reaction was investigated heavily by Makosza *et al.*[16,17] In electrophilic arene systems, the typical reaction would be S_NAr in halogenated compounds, however Makosza believes this to be a secondary process which is preceded by a reversible addition of a nucleophile to a carbon atom on the ring bearing a hydrogen and therefore forming σ^H adducts.[16] This adduct can then become the product of ONSH upon removal of the hydride anion when oxidised by an external oxidant such as $KMnO_4$ in liquid ammonia. Makosza extended this work into halonitroarenes,[17] where it was deduced in the reaction between *p*-chloronitrobenzene and potassium hydroxide ONSH occurs almost exclusively at lower temperatures (−34 °C) in the presence of oxygen in liquid ammonia.

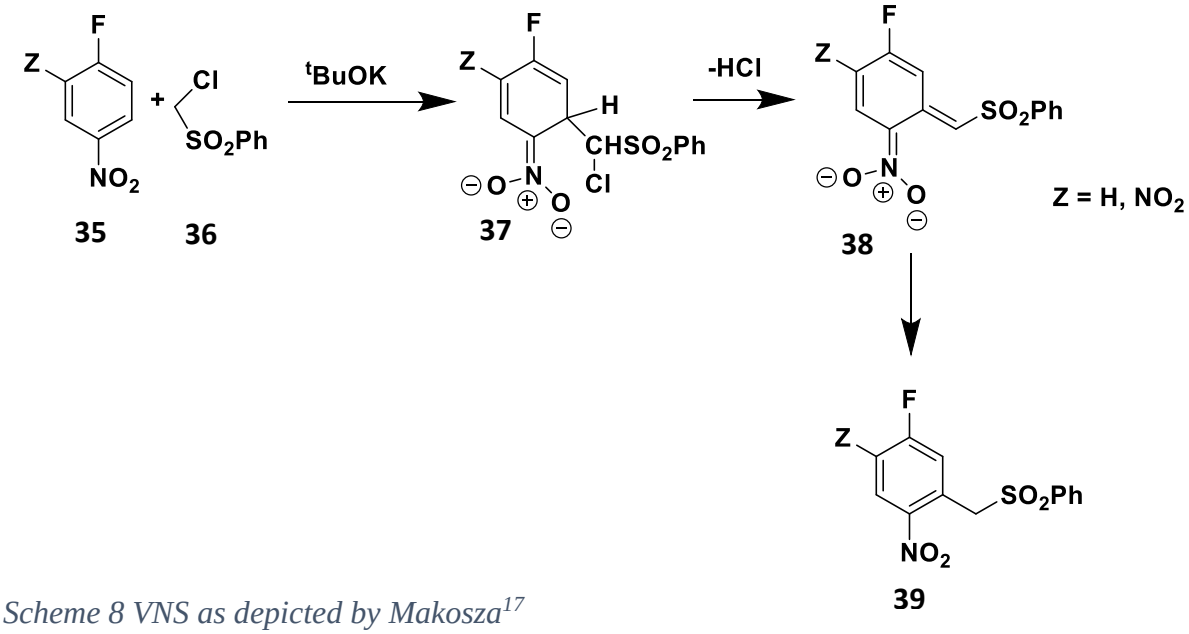


Scheme 7 ONSH as depicted by Makosza[17]

1.2.3. Vicarious Nucleophilic Substitution

VNS draws similarities to ONSH though the main difference is that the carbanion attacking also contains a leaving group itself such as a halocarbanion. Makosza states α-halocarbanions are usually unstable entities which means in some cases VNS proceeds more efficiently when carbanions that contain RO or RS as nucleofugal groups because they are able to undergo base induced β-elimination.[17]

VNS is an unlikely reaction to occur during this investigation because the nucleophile will be a secondary amine, and is unlikely to displace CH_4 (methyl group plus hydrogen from nitroarene). ONSH however, is a possible pathway that this investigation could follow which would result in just an addition product and no smiles rearrangement.



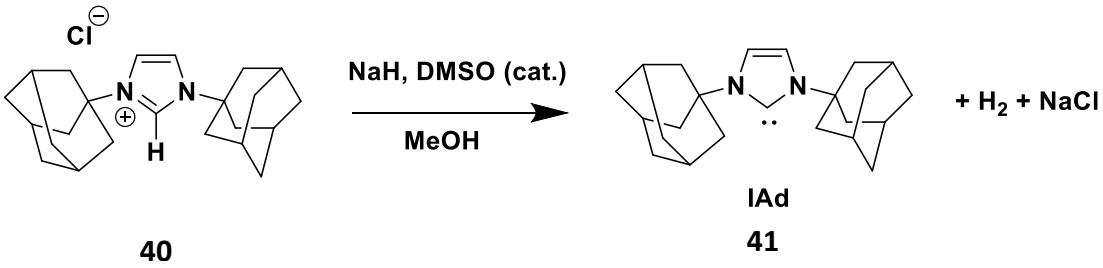
Scheme 8 VNS as depicted by Makosza[17]

1.3. *N*-Heterocylic Carbenes

A carbene is defined as a neutral compound containing a divalent carbon atom with a six-electron valence shell, an *N*-Heterocyclic Carbene (NHC) is defined as a heterocyclic species containing a carbene carbon atom and at least one nitrogen atom within the ring structure.[18]

1.3.1. Stability of *N*-Heterocyclic Carbenes

A trend in NHCs is that they generally feature bulky substituents adjacent to the carbene carbon atom which help to kinetically stabilise the species.[19] This is by sterically disfavouring dimerisation to the corresponding olefin, also known as the Wanzlick equilibrium.[18] However, a more important factor is the electronic stabilisation by the nitrogen atoms; when compared with standard carbenes, NHCs such as 1,3-di(adamantyl)imidazol-2-ylidene (IAd, the first synthesised NHC, **41**) display a singlet ground-state electronic configuration with the HOMO and the LUMO best described as a formally sp^2-hybridized lone pair and an unoccupied p-orbital at the C^2 carbon respectively.[18]



Scheme 9 Synthesis of the first observable NHC, IAd[18]

Furthermore, the adjacent nitrogen atoms are both σ-electron withdrawing and π-electron donating which stabilise the NHC structure both inductively by lowering the energy of the occupied σ-orbital and mesomerically by donating electron density in the empty p-orbital.[18]

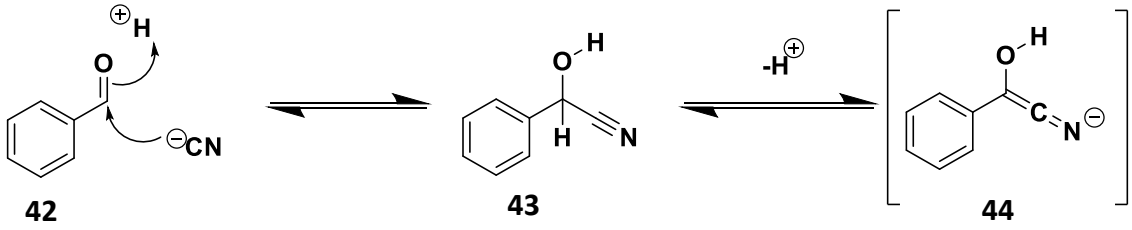
The groundstate electronic structure of NHCs provides a framework for understanding their reactivity; in comparison to the typical electrophilicity of most carbenes, the lone pair situated in the plane of the heterocyclic ring of an NHC makes these compounds nucleophilic. With the main consequence of this characteristic is the inclination of NHCs to act as σ-donors and bind to a wide range of metallic and non-metallic species.[18] Because NHCs can act as σ-donors often they can substitute classical $2e^-$ donors such as phosphanes or ethers in metal coordination chemistry. Building on this, in a review paper published in

2002, NHCs have also found use as catalysts in common processes such as Heck and Suzuki couplings as well as aryl aminations or olefin metathesis reactions. [20]

1.3.2. *N*-Heterocyclic Carbenes as Organocatalysts

Their inclination to coordinate to carbon electrophiles has lead NHCs to being used as organocatalysts. This is of particular importance in both the benzoin condensation and the Stetter reaction.[21, 22]

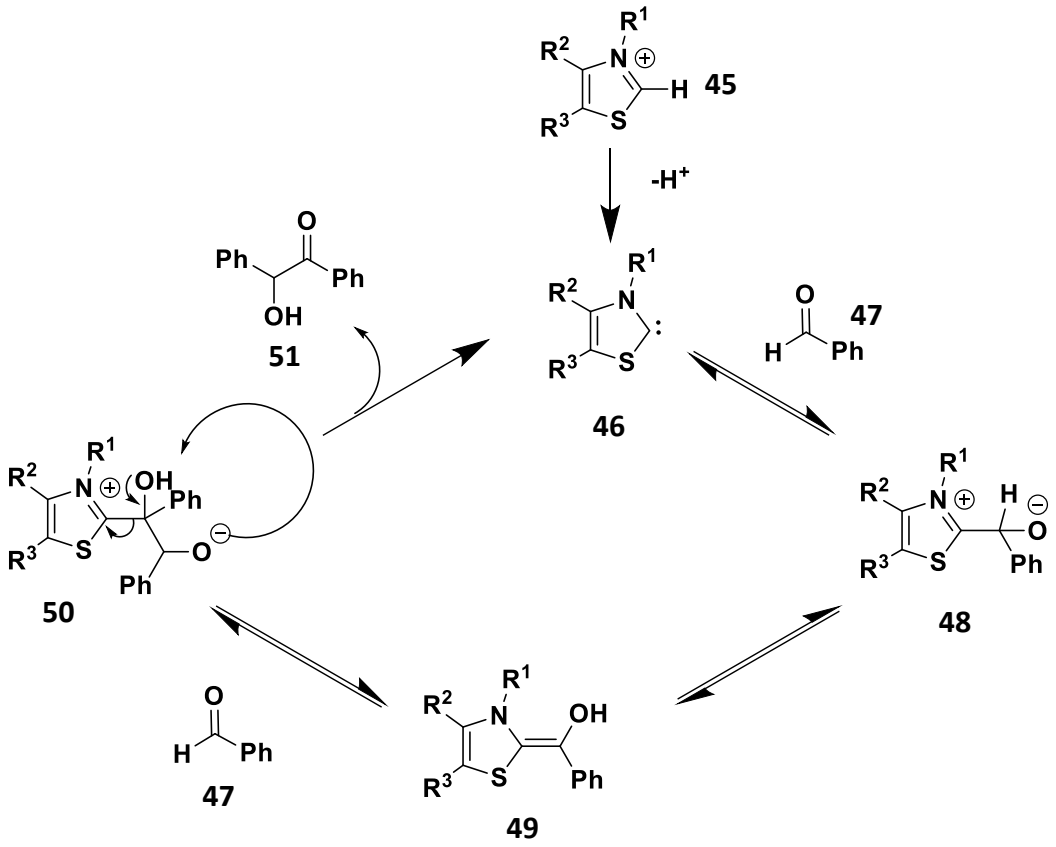
The benzoin condensation catalysed by NHCs was first investigated back in 1832 by Wöhler and Liebig when they discovered the cyanide-catalysed coupling of benzaldehyde to form benzoin.[21] Later in 1903, Lapworth postulated a mechanism for this reaction in which an intermediate carbanion is formed by hydrogen cyanide addition to benzaldehyde followed by deprotonation. It is here that the former carbonyl carbon features an inverted nucleophilic reactivity; this intermediate 'active aldehyde' exemplifies the 'Umpolung' concept (the reversal of polarity).[23]



Scheme 10 Mechanism postulated by Lapworth

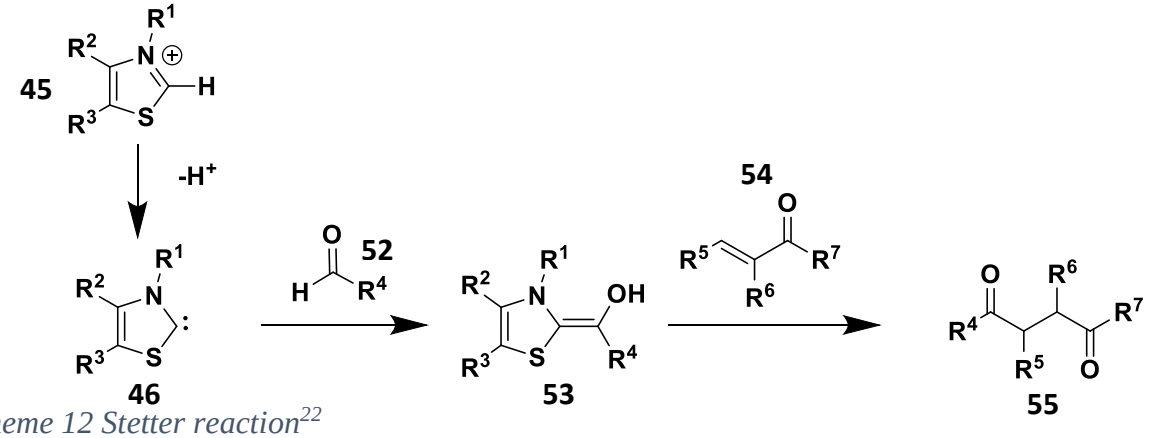
In 1943 Ugai *et al*, found that thiazolium salts could be used as catalysts in the benzoin condensation. Later in 1958, based on the work by Lapworth, Breslow proposed a mechanistic model for the thiazolium salt-catalysed benzoin condensation which utilises thiazolin-2-ylidene as the catalytically active species.[24]

The mechanism can be seen in scheme 10, it begins with Breslow assuming that the thiazolium salt **45** was deprotonated at its most acidic position to form the thiazolin-2-ylidene **46**. Nucleophilic attack of the carbonyl functional group of an aldehyde **47** then generates the thiazolium salt adduct **48**; deprotonation/reprotonation leads to the active aldehyde in the form of the resonance-stabilised enaminol-type Breslow intermediate **49** this intermediate then reacts again with an electrophilic substrate such as the carbonyl group of a second aldehyde molecule **47** the final intermediate **50** then eliminates benzoin **51** and the original carbene catalyst **46** is regenerated.[25]



Scheme 11 Benzoin condensation mechanism as deduced by Breslow[25]

The Stetter reaction transfers the concept of a thiazolium-catalysed nucleophilic acylation to the substrate class of Michael acceptors. Any reaction that makes use of a 1,4-addition of aldehydes **54** to an acceptor bearing an activated double bond **53** carries his name.[26] The mechanism can be seen in scheme 11, which again proceeds via the Breslow intermediate **50**.

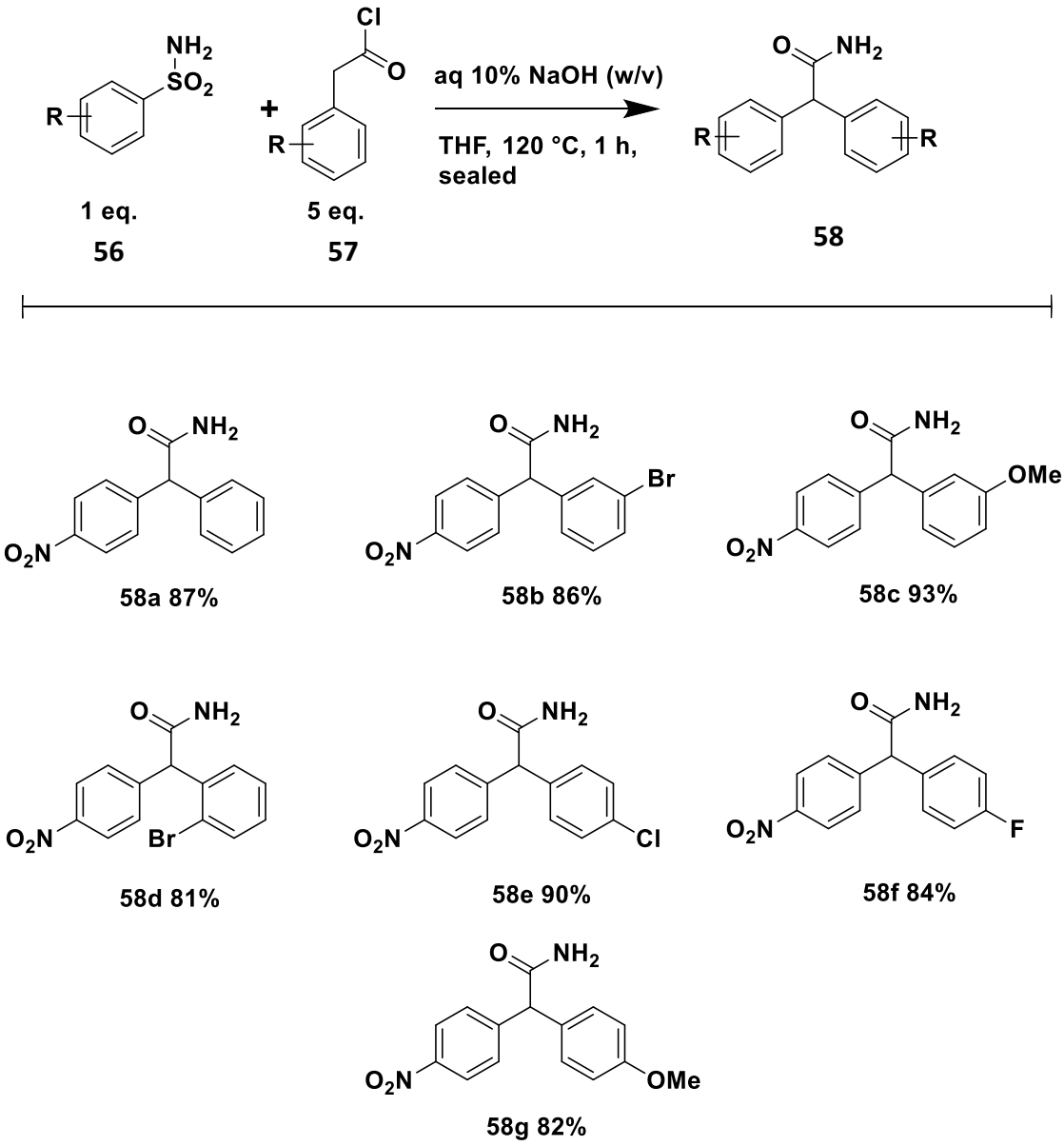


Scheme 12 Stetter reaction[22]

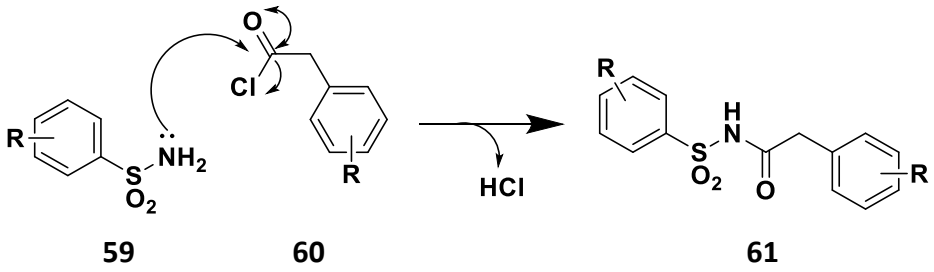
2. Results and Discussion

2.1. Smiles Rearrangement

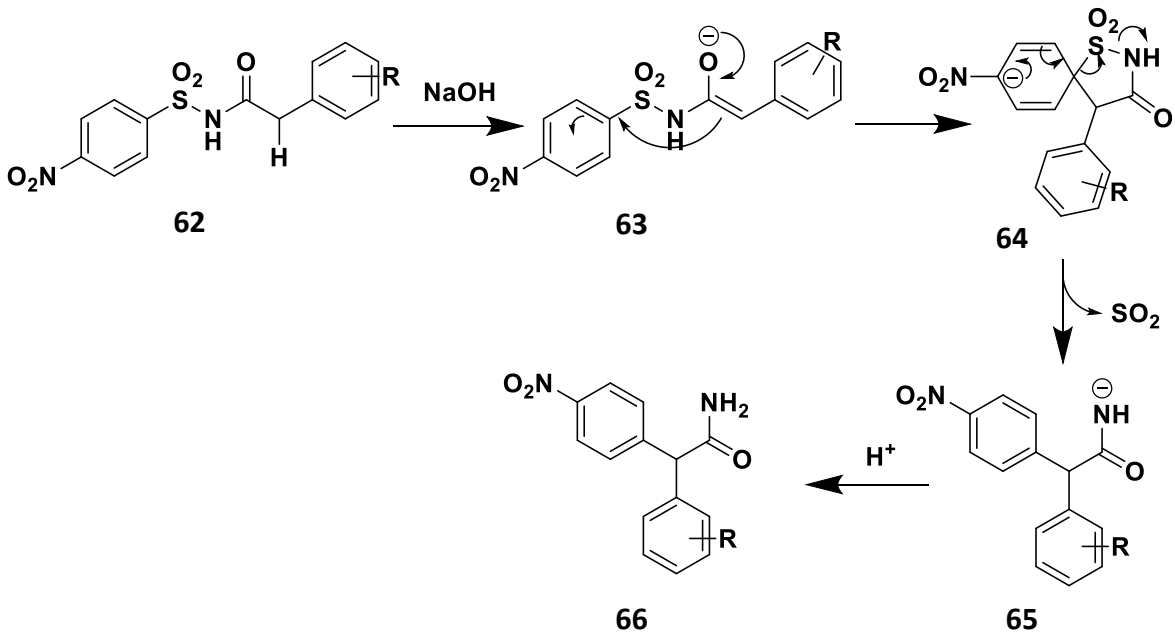
Previous work was carried out by Pauline Rabet of the Greaney group; this included optimising the reaction conditions for the Smiles rearrangement as seen in scheme 12, as well as some of her early preliminary results.



Scheme 13 Optimised reaction conditions to be investigated as well as preliminary results obtained by Pauline Rabet



Scheme 14 Sulfonamide addition, R is an electron-withdrawing group

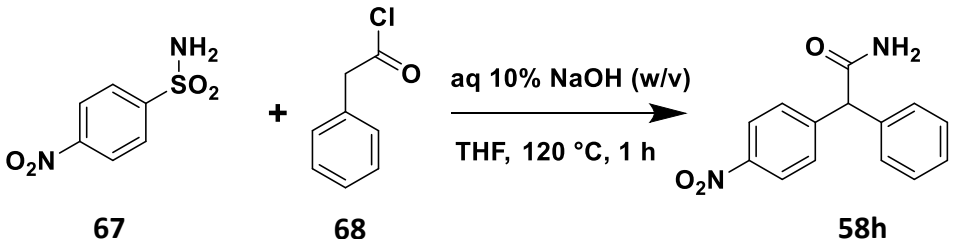


Scheme 15 Truce-Smiles Rearrangement displaying the Meisenheimer Intermediate, with R as an electron withdrawing group

The aim of this investigation was to build on work previously completed by the Greaney group and investigate the scope of a pre-determined set of optimised reaction conditions for the polar Smiles rearrangement between a sulfonamide and an acetyl chloride.

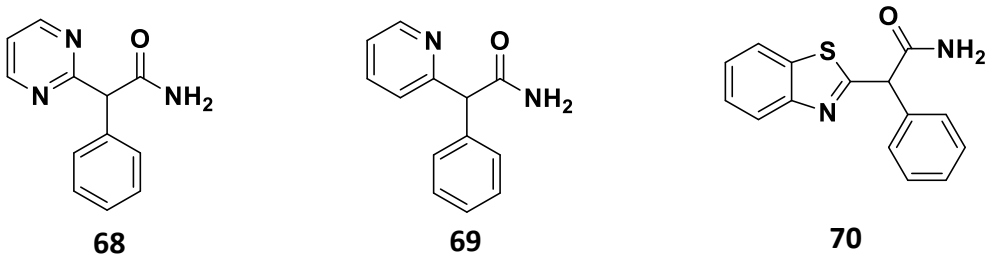
There are two variables that are going to be investigated; variation of the nucleophilic sulfonamide and variation of the electrophilic acetyl chloride. Historically, it has been an *ortho* or *meta* substituted NO_2 group that activates the ring towards nucleophilic aromatic substitution, however it will be interesting to explore other groups which could prove viable such as a cyano group.

The first stage of this study was to reproduce the work carried out by a previous member of the Greaney group. This was the Smiles rearrangement under optimised conditions as seen in scheme 15, where the product **58h** was obtained in 86% yield which is comparable with results from other members of the group for this reaction.

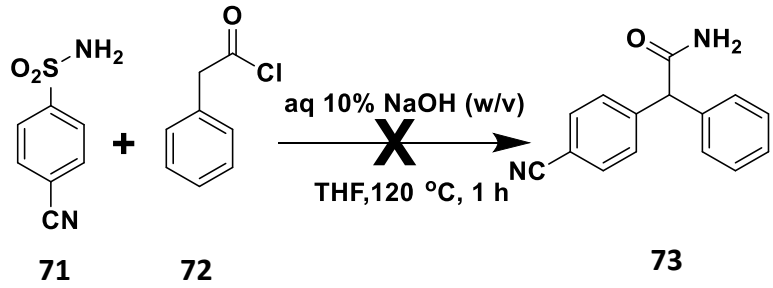


Scheme 16 Initial optimised reaction conditions, repeating an example already completed by Pauline Rabet

The next step in the study was attempting the Smiles rearrangement with a different electron withdrawing group on the sulfonamide aryl ring. A cyano group was chosen for this task **67**; however once subject to the reaction conditions it was found that there was no Smiles reaction, only addition to the acyl chloride. This is likely to be caused by the cyano group being less electronegative and therefore less activating than the nitro group. Despite this, work in the group found pyrimidine **68**, pyridine **69** and benzothiazole **70** to be suitably activating and gave moderate to good yields when subjected to the reaction conditions.

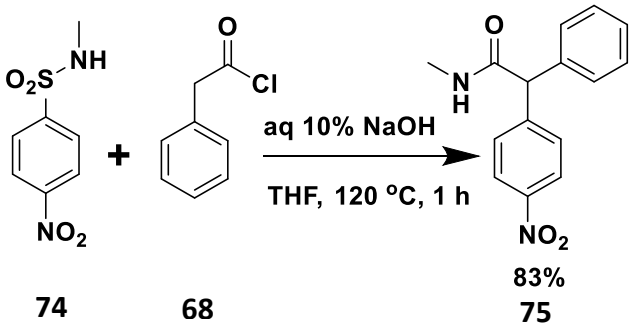


Scheme 17 Successful Smiles rearrangements completed by the group



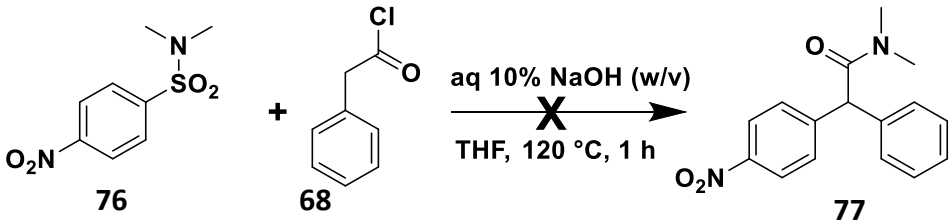
Scheme 18 An unsuccessful reaction using a different electron withdrawing group

Varying the sulfonamide nucleophile was then investigated. Work had already been completed by a previous member of the Greaney group, where instead of an amino nucleophile a methyl substituted amine *N*-methyl-4-nitrobenzenesulfonamide **74** was used and obtained in 83% yield.



Scheme 19 Methyl substituted sulfonamide performing a Smiles rearrangement (carried out by Pauline Rabet)

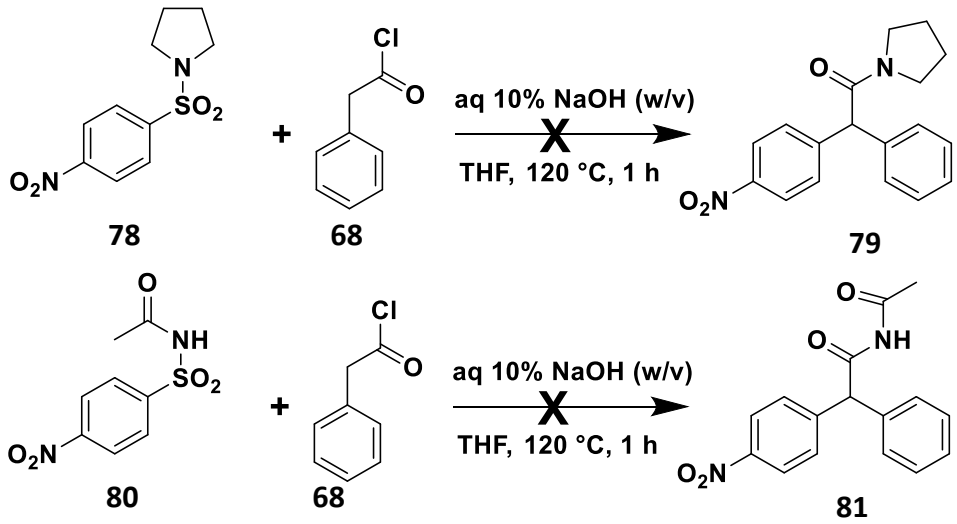
Building on this, work already completed by the Greaney group included the tertiary dimethyl substituted *N*,*N*-dimethyl-4-nitrobenzenesulfonamide **76** however the reaction was unsuccessful, which was expected since amide linkage is required to effect the intramolecular Smiles rearrangement.



Scheme 20 Unsuccessful Smiles rearrangement carried out by Pauline Rabet

Another tertiary example was elected to be investigated this was 1-((4-nitrophenyl)sulfonyl)pyrrolidine **78**, however after being subject to the reaction conditions the reaction was not successful. Therefore, we hypothesise that tertiary sulphonamides are too sterically hindered to form the amide linkage required for the intramolecular Smiles rearrangement.

The final variation of the sulfonamide nucleophile was the secondary acetamide group **80**. This reaction was also unsuccessful; this could be because of resonance effects where the carbonyl group is making the lone pair on the nitrogen less nucleophilic.

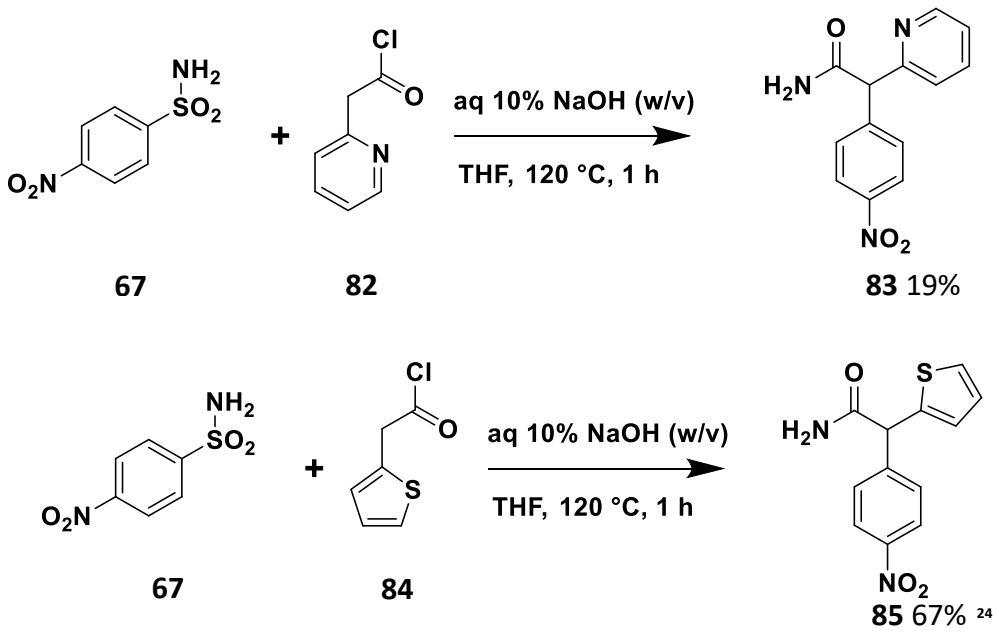


Scheme 21 Unsuccessful Smiles rearrangements

In the next stage of the project, variation in the acetyl chloride was investigated. As previously stated, the standard reaction conditions utilised an unsubstituted benzene ring scheme 12. There were two methods of investigation, 4-nitrobenzenesulfonamide with a varying acetyl chloride and 2-nitrobenzenesulfonamide with a varying acetyl chloride.

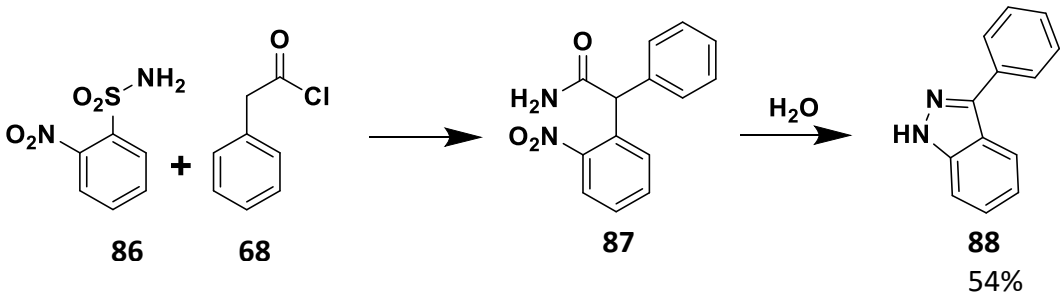
Work initially started by a member of the research group first investigated a *para* methoxy-phenyl acetyl chloride and a *meta* substituted methoxy-phenyl acetyl chloride with 4-nitrobenzenesulfonamide. These were encouraging results and obtained the smiles products **55g**, **55c** in 82% and 93% yield respectively.

Building on this work, a thiophen-2-yl acetyl chloride was used as well as 2-(pyridine-2-yl)acetyl chloride, this was to try and broaden the scope of the reaction. The 2-(pyridine-2-yl)acetyl chloride smiles product **83** yielded a disappointing 19% yield. The thiophen-2-yl acetyl chloride obtained the Smiles product **85** in 67% yield. Although lower yield products, these reactions demonstrated that a heteroatom can be incorporated into the system.



Scheme 22 Smiles rearrangement incorporating a heteroatom

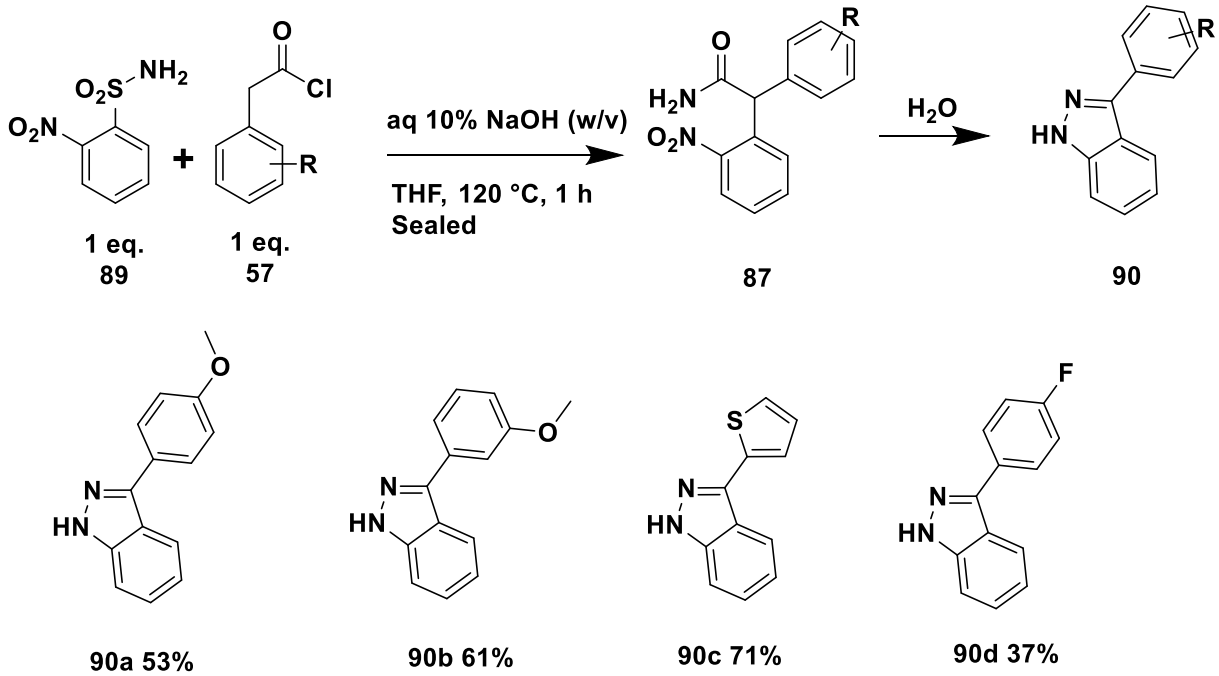
Next Investigated was varying the phenylacetyl chloride with 2-nitrobenzenesulfonamide. Initial experiments had already been investigated by Pauline Rabet where the base reaction (phenylacetyl chloride with 2-nitrobenzenesulfonamide) yielded an indazole (**88** in scheme 23) in 54% yield rather than the anticipated smiles product. This was a running theme whilst investigating the 2-nitrobenzene sulfonamide.



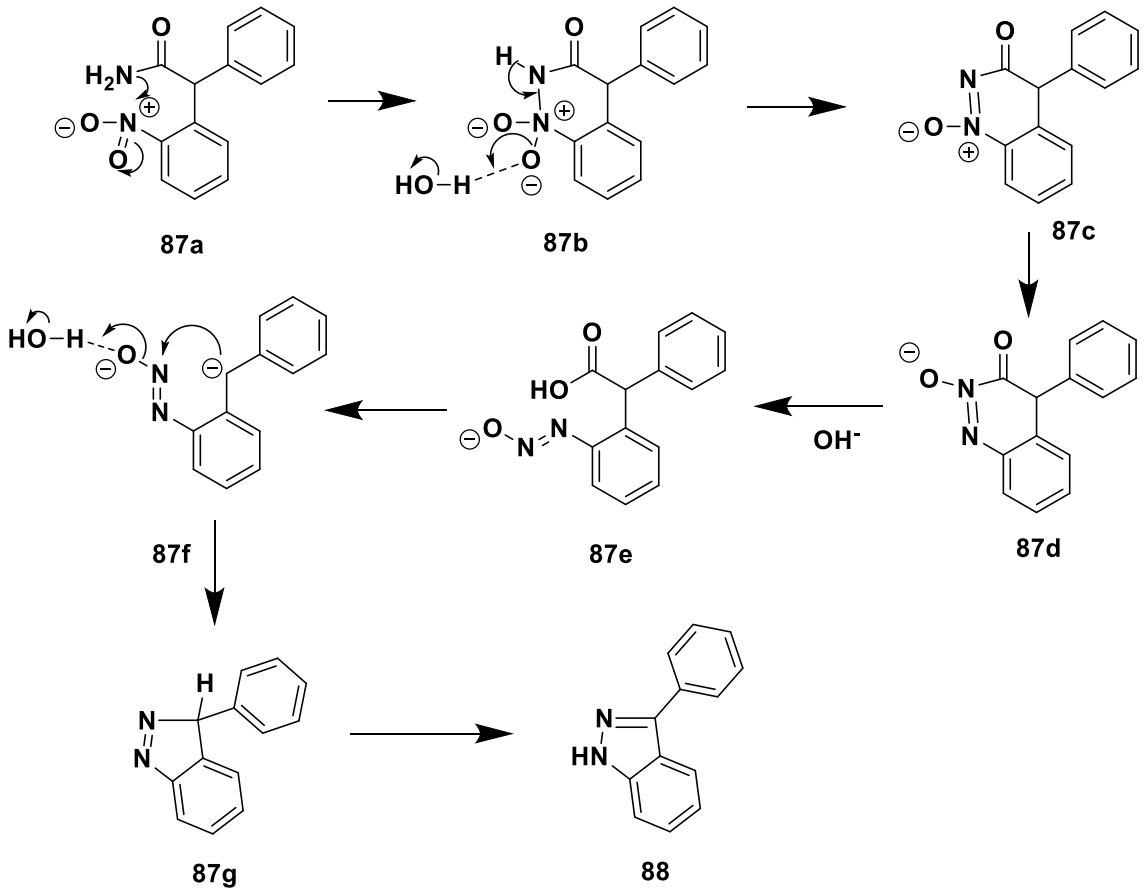
Scheme 23 Smiles rearrangement followed by a further rearrangement to yield an Indazole, performed by Pauline Rabet

The first substrates to be tested were the *para*-methoxyphenyl acetyl chloride and *meta*-methoxyphenyl acetyl chloride which gave indazoles **90a**, **90b** in comparable yields that were 53% and 61% respectively. Next the thiophen-2-yl acetyl chloride was subjected to the optimised reaction conditions to yield an indazole **90c** in 71% yield. This result demonstrates the broad scope of this reaction where we have successfully incorporated a heterocycle in to the structure. The final substrate analysed was *para*-fluorophenyl acetyl chloride, which yielded the indazole **90d** in 37% yield. This is an interesting result because

when compared with the methoxy substituted substrates, the reaction demonstrates its broad scope by working with both activating and deactivating groups.



Scheme 24 Successful Smiles rearrangements followed by indazole formation

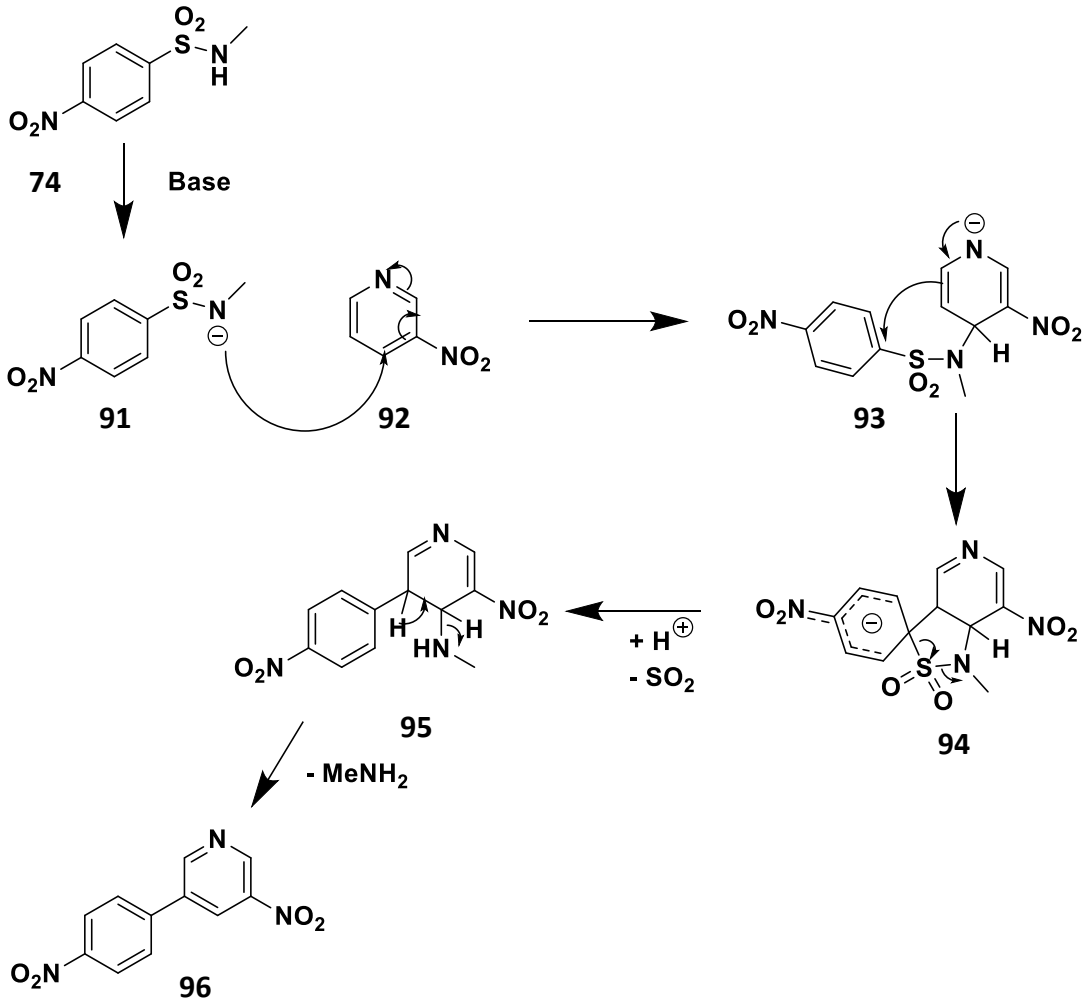


Scheme 25 Indazole formation mechanism, proposed by Rabet

The reaction mechanism depicted in Scheme 25 is the proposed mechanism for the formation of the indazole base on work by Blackburn and co workers.[27] According to their mechanism, the amide nitrogen attacks the nitro group to form the heterocycle **87b** which is subsequently reduced by water to form **87c**. This intermediate then rearranges to form **8**7d and is then ring opened by hydroxide to form **87e**, this intermediate then decarboxylates with the resulting anion attacking the nitroso group as seen in **87f** causing a ring closure as seen in **87g** and a final tautomerization to yield the indazole **88**.

2.2. A potential novel Smiles-Type Rearrangement

Building on the work previously completed in Smiles Rearrangement chemistry, the aim of this investigation is to apply the concept to new substrates that can perform the rearrangement. The proposed reaction can be seen in Scheme 26, there are some similarities for the mechanism as the reaction still proceeds via a Meisenheimer intermediate **94**. However, the attacking nucleophile is electrons being pushed from the nitrogen atom through the conjugated π system, compared with the original Truce-Smiles which is a carbanion species generated using a base; but still producing the spirocyclic five membered transition state as depicted in **94**. Furthermore, 3-nitropyridine was elected as the substrate due to it being more electron deficient and welcoming the nucleophile through stabilisation of the negative charge on the nitrogen as seen in structure **93**. Another subtle difference between the two Meisenheimer intermediates is that **94** makes use of a fused ring system in theory.

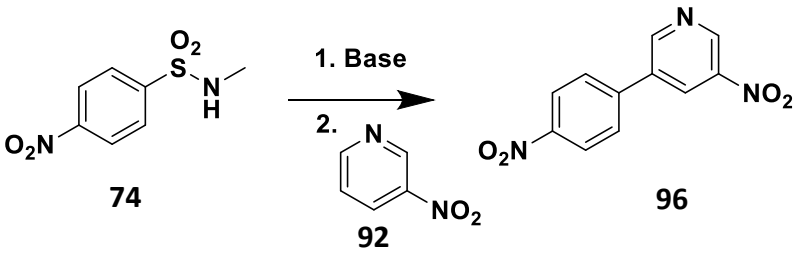


Scheme 26 Proposed reaction mechanism for the novel Smiles type rearrangement

The Smiles-type rearrangement to be investigated used *N*-Methyl-4-nitrobenzenesulfonamide. This was used because the amine has only one proton that can be

deprotonated, and when the elimination stage of the smiles rearrangement occurs, there would not be a second proton to interfere with the reaction. Furthermore, if 4-nitrobenzenesulfonamide was used, the Meisenheimer intermediate could be deprotonated further perhaps and cause other undesired reactions.

The first reaction set up used *N*-methyl-4-nitrobenzenesulfonamide in dry THF and under a nitrogen atmosphere; with potassium *tert*-butoxide as the base and 3-nitropyridine as the substrate. 3-nitropyridine was used because it is a good electrophile, as the nitrogen atom can bear the negative charge which accumulates upon addition of the sulfonamide before going on to undergo the Smiles-type rearrangement as well as the nitro group causing the ring to be electron deficient and welcoming the nucleophile.



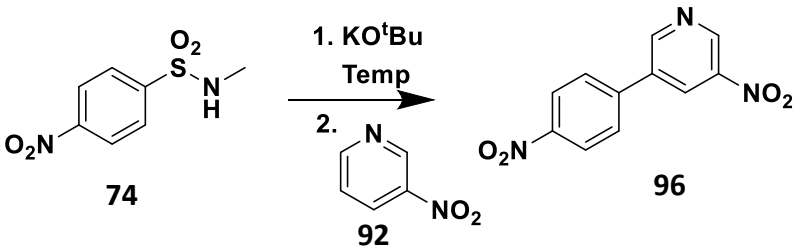
Scheme 27 Investigating base to be used

Table 1 Investigating base to be used in the novel Smiles-type rearrangement

Entry	Base, pKa_H	Substrate	Solvent	Result
1	KO^tBu, 19	3-nitropyridine	Dry THF	Trace addition
2	NaH, 33	3-nitropyridine	Dry THF	No reaction

The initial reaction did not give the desired product, only a trace amount of the addition product which was confirmed by proton NMR. The first variable to be investigated was the base used; NaH was the base of choice as it has a considerably higher pKa_H.

This result was surprising as a stronger base should promote a higher concentration of deprotonated sulfonamide to go on to react further, though the actual result yielded no reaction. The next variable to be investigated was the temperature at which the reaction was being carried out, initially this was room temperature however it was concluded that higher temperatures should be employed to provide the reaction with more energy, a lower temperature was also investigated to see if this would hinder the reaction at all.

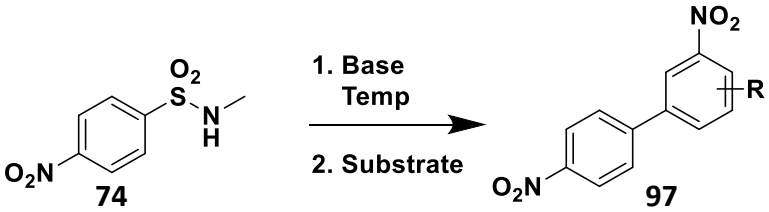


Scheme 28 Investigating temperature changes

Table 2 Investigating temperature changes in the novel Smiles-type rearrangement

Entry	Base	Temperature /°C	Substrate	Result
1	KO^{t}Bu	80	3-nitropyridine	Trace addition
2	KO^{t}Bu	120	3-nitropyridine	Trace addition
3	KO^{t}Bu	-78	3-nitropyridine	Trace addition

Altering the temperature did not help facilitate the desired reaction. This suggested that the starting materials may not be suited to undergoing the Smiles-type rearrangement, meaning a change in substrates should be investigated.



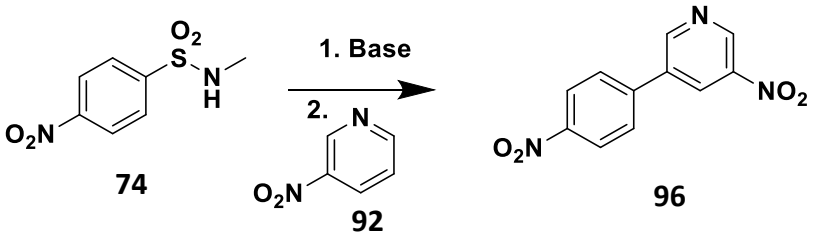
Scheme 29 Investigating use of different base and substrate combinations

Table 3 Investigating base, temperature and substrate combinations in the novel smiles type rearrangement

Entry	Base	Temperature /°C	Substrate	Result
1	KO^{t}Bu	120	1,3-dinitrobenzene	No reaction
2	NaH	RT	1.3-dinitrobenzene	No reaction
3	KO^{t}Bu	RT	nitrobenzene	Trace addition
4*	NaH	RT	3-nitropyridine	No reaction

*Solution of starting material and base left to stir for 30 mins before adding substrate.

The next variable to be investigated was the substrate in which the Smiles rearrangement should take place on. 1,3-dinitrobenzene was first used as it is believed to be a more electron deficient substrate which should in theory aid the addition process before the Smiles rearrangement. However this was not the case, there was no reaction as the result. The next substrate tested was nitrobenzene, believed to be the least electron deficient system of the three substrates being investigated; trace addition product was achieved which was a surprising result (confirmed by proton NMR), but still no Smiles rearrangement had occurred.



Scheme 30 Investigating counter ion to be used in the base

Table 4 Solvent and counter ion changes in novel Smiles-type rearrangement

Entry	Base	Solvent	Temp. /°C	Substrate	Result
1	KO^{t}Bu	DMF	RT	3-nitropyridine	Trace addition
2	NaO^{t}Bu	DMF	RT	3-nitropyridine	No reaction

Using DMF with potassium *tert*-butoxide yielded no significant changes in result, again producing only trace amounts of the addition product.

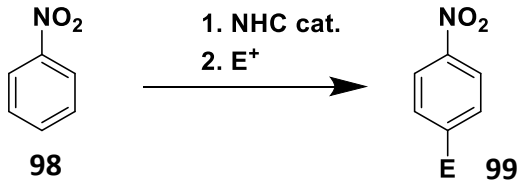
Another variation included changing the counter-ion of the base being used. This was to see whether changing the nature of the deprotonated nucleophile would result in an improved reaction. Sodium *tert*-butoxide was used as sodium is smaller than potassium but similar in reactivity; however this base yielded no reaction.

In conclusion, I have tried various base combinations, along with varied solvents and substrates on which to perform the Smiles-type rearrangement. Thus far, the best result has been minor addition products (confirmed by proton NMR), more work needs to be completed to try and push the reaction to completion.

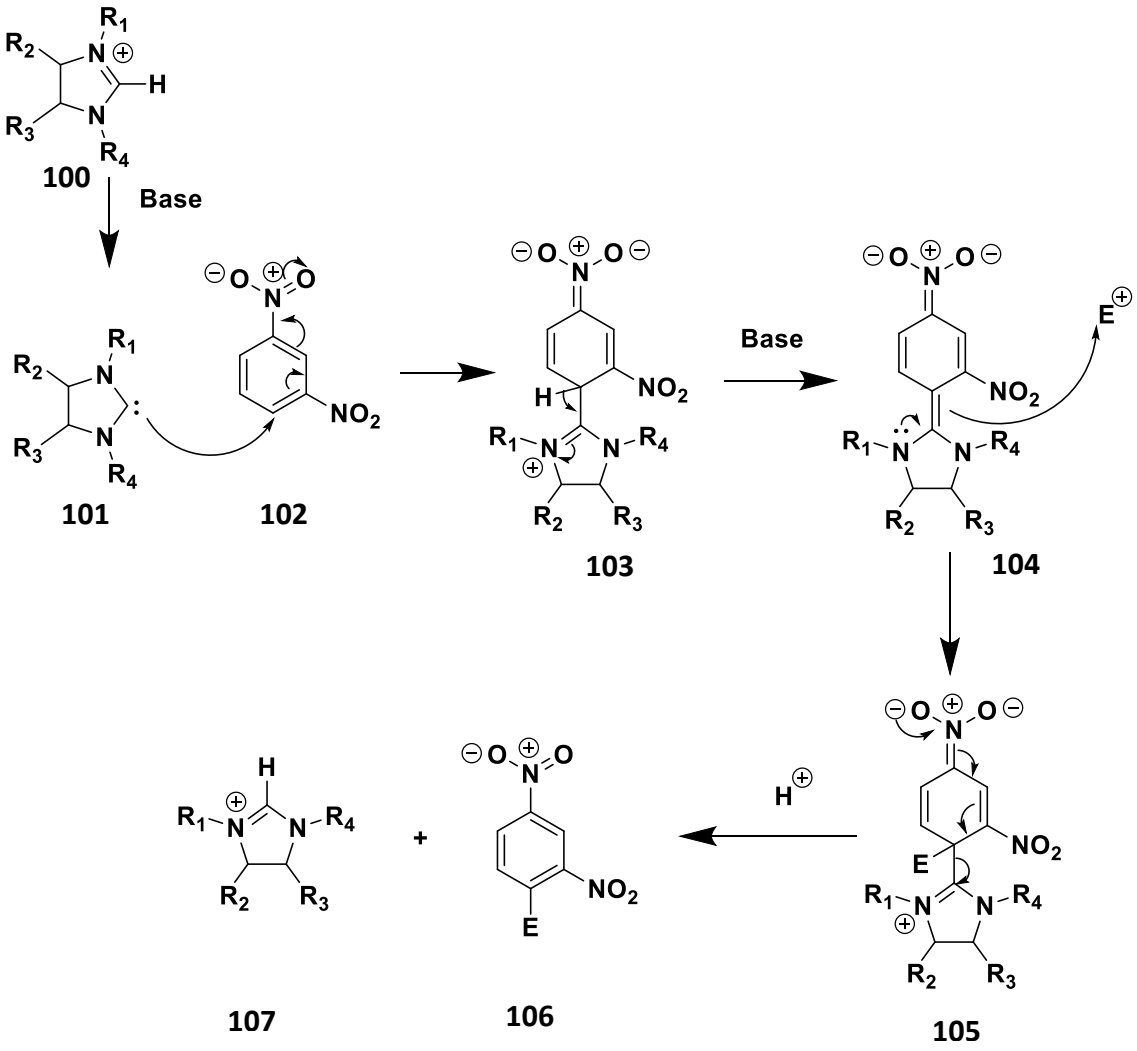
2.3. Using *N*-Heterocyclic Carbenes to Perform a Potential Novel Electrophilic Substitution of Electron-deficient Aromatic Rings

As previously discussed in the introduction, vicarious nucleophilic substitution (VNS) is a useful tool for adding substituents to electron deficient aromatics.[17] A similar reaction has been proposed and the aim of this investigation is to use an NHC to permit an analogous electrophilic aromatic substitution on a substrate that is too electron deficient to perform the reaction without the use of an NHC. This will be completed by using stoichiometric amounts of the NHC, and by staggering the reaction to avoid the NHC from reacting with the electrophile first rather than with the substrate. The proposed theoretical reaction can be seen in schemes 31 and 32. The intermediate formed between the NHC and substrate forms a deoxy-Breslow intermediate **104**.[26] Work has been completed by Susuki *et al*. where he investigated transfer hydrogenation using NHCs and water.[28] He also used deuterium labelling experiments to elucidate the reaction mechanism which confirmed the involvement of deoxy-Breslow intermediates. However he deduced that it depends on the substrate as to whether the deoxy-Breslow intermediate is formed and claims this is the first reaction using deoxy-Breslow intermediates.

The reaction will be investigated using varied NHCs, different electrophiles and different bases in a bid to find the optimised conditions for the proposed reaction.



Scheme 31 Simplified Scheme for NHC catalysed reaction to be carried out



Scheme 32 General proposed reaction to be investigated using E^+ as an electrophile

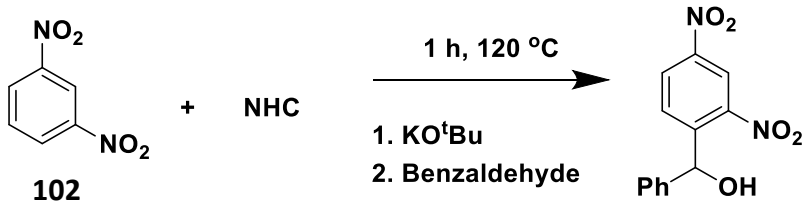
Initially, it was decided that 1,3-dinitrobenzene would be used as the substrate in which electrophilic aromatic substitution (EAS) would be performed on, using 1,3-dimethylimidazolium iodide as the NHC precursor in a 1:1 ratio. Finding a suitable base (2 equivalents, to deprotonate the NHC precursor into the NHC) was first investigated with benzaldehyde (2 equivalents) as the electrophile. All reactions were completed under a nitrogen atmosphere and left overnight to react before an acidic work up.

Scheme 33 Initial reaction conditions

Table 5 Investigating base and solvent combinations for the N-heterocyclic carbene reaction

Entry	Base	Solvent	Result
1	NaH	MeTHF	No reaction
2	K_2CO_3	Dry THF	No reaction
3	KO^tBu	Dry THF	Trace unknown

These very early results as depicted in table 5 suggested that potassium *tert*-butoxide should be used as the base in further reactions. The trace unknown was deduced using proton NMR. The next investigation was on what NHC to be used, this is an important factor as some NHCs are more nucleophilic than others to aid in the initial addition to the substrate before forming the deoxy-Breslow intermediate.[29]



Scheme 34 Investigating suitable NHC to be used

Table 6 Varying NHC

Entry	NHC	Solvent	Temp /°C	Time /h	Result
1	**110**	Dry THF	120	1	Trace Unknown
2	**111**	Dry THF	120	1	Trace Unknown
3	**112**	Dry THF	120	1	Trace Unknown

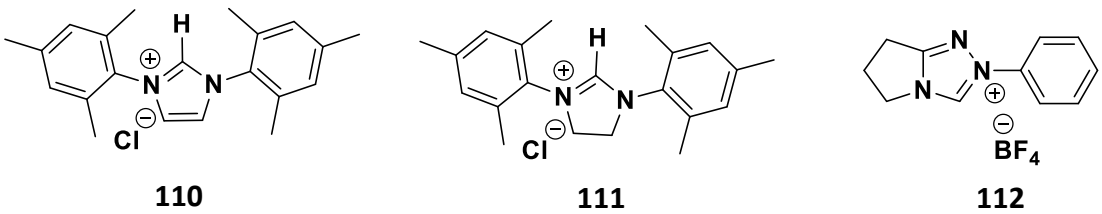
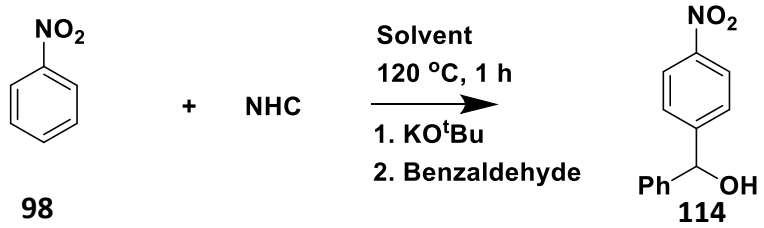


Figure 2 NHCs screened as seen in table 6

There was no clear product formed in any of the reactions completed with variation of the NHC. All of the NHCs showed trace quantities of an unknown product formed; not the desired product. One reason for this could be that the 1,3-dinitrobenzene could be too electrophilic; therefore the next variable investigated was the use of nitrobenzene as the substrate.

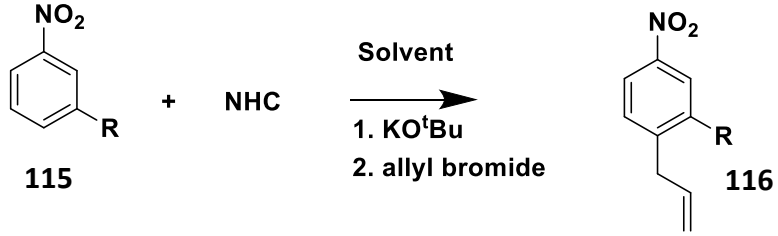


Scheme 35 Investigating solvent and NHC with nitrobenzene, as seen in table 7

Table 7 Investigating solvent and NHC on a nitrobenzene substrate

Entry	NHC	Solvent	Result
1	**110**	Dry THF	No reaction
2	**111**	Dry THF	No reaction
3	**110**	DMF	No reaction

All three reactions using nitrobenzene were unsuccessful, no reaction was found however another potential reason for unsuccessful (or undesired) reactions could be that the benzaldehyde electrophile was not reactive enough, therefore further experiments were conducted using allyl bromide as the electrophile and 1,3-dinitrobenzene as the substrate.

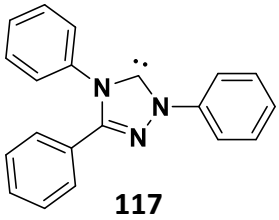


Scheme 36 Investigating use of allyl bromide as electrophile, as seen in table 8

Table 8 Investigation using Allyl Bromide as the electrophile

Entry	Substrate	NHC	Solvent	Result
1	1,3-dinitrobenzene	**111**	Dry THF	Trace **118***
2	1,3-dinitrobenzene	**112**	Dry THF	Trace **118***
3	1,3-dinitrobenzene	**111**	DMF	No reaction
4	Nitrobenzene	**112**	DMF	No reaction
5	1,3-dinitrobenzene	**110**	Dry THF	No reaction
6	1,3-dinitrobenzene	**111**	Dry THF	Trace **118***

*see figure 4 for proposed structure

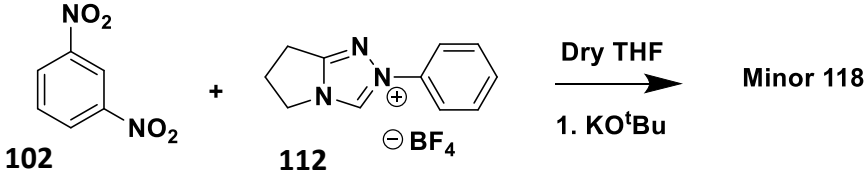


117

Figure 3 Commercially available NHC, no base required

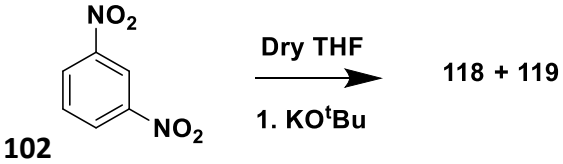
The trace unknowns found under these experiments were comparable to the trace unknowns found when benzaldehyde was used, suggesting that the electrophile was not participating in the reaction which means that the desired reaction mechanism as set out in scheme 28 is not occurring. The next step in the process was to determine if the NHC was influencing the reaction, or if that too was not involved in the reaction. This was completed with NHC **106** and dinitrobenzene with no electrophile.

This reaction yielded the same trace unknown that has previously been observed, the next step in this investigation was to try and repeat the reaction with no electrophile and no NHC to determine whether the NHC was influencing the reaction at all. Dinitrobenzene was again used as the substrate.



102 **112**

Scheme 37 Reaction with no electrophile, as seen in table 9, see figure 4 for proposed structure of 112



Scheme 38 Reaction with no electrophile and no NHC, as seen in table 9, see figure 4 for proposed structures of 112 and 113

Table 9

Entry	Solvent	NHC	Electrophile	Result
1	Dry THF	**112**	-	Trace **118**
2	Dry THF	-	-	Trace amount of **118** and **119**
3	DMF	-	-	No reaction

An interesting result here is that when completing the reaction with no electrophile and no NHC there were 2 unknowns formed; the compound that was being observed throughout the investigation, compound **118** and one new compound, **119**.

Further analysis of the unknowns lead to the hypothesis that **113** could be 2,4-dinitrophenol. This hypothesis is based on a crude ^{1}H NMR sample where peak shapes correspond with that of the literature, as well as low and high resolution mass spec results which show an m/z value that corresponds with a deprotonated 2,4-dinitrophenolate.

Compound **112** is tentatively thought to be addition of the *tert*-butoxide group to the 4 position of 1,3-dinitrobenzene; again this hypothesis is based on a crude ^{1}H NMR sample and a low resolution mass spec which shows an m/z value that corresponds with addition of a *tert*-butoxide group.

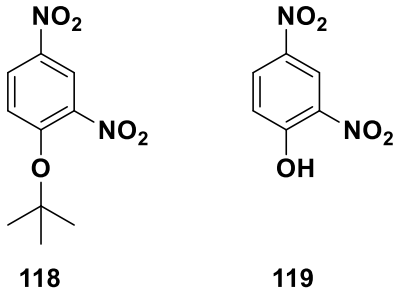
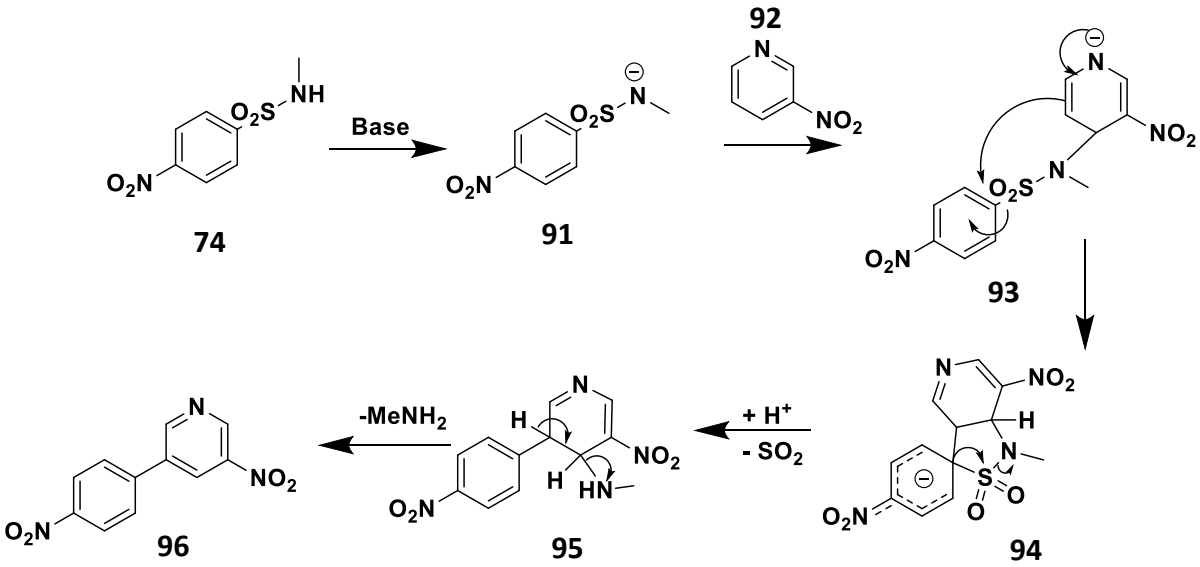


Figure 4 tentatively proposed structures for unknown compounds being seen in the reaction

3. Conclusions

Part one of this report regarded the Smiles rearrangement, the optimised reaction conditions as set out by a previous member of the Greaney group were investigated and successfully demonstrated the broad scope, utilizing both activating and deactivating substituents on the aryl ring.

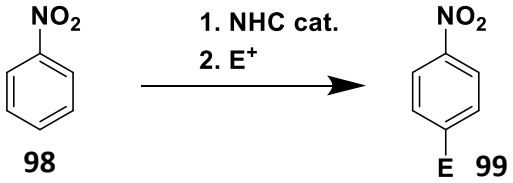
Part 2 of this report investigated the novel Smiles-type reaction, which can be seen in Scheme 39.



Scheme 39 Simplified mechanism for the attempted novel Smiles-type reaction

After preliminary studies work has been inconclusive, with the best results being only trace amounts of the addition product as confirmed by proton NMR. Various base, temperature and substrate combinations have been investigated. The substrate initially investigated was 3-nitropyridine though it was hypothesised that this substrate is not electron deficient enough to undergo the Smiles-type rearrangement, other substrates were then investigated with the most hopeful substrate being 1,3-dinitrobenzene as well as nitrobenzene. 1,3-dinitrobenzene did not even form the addition product which was a surprising result whereas nitrobenzene did form the addition product. Work is still ongoing in this area where another member of the Greaney group is undertaking the work.

Part 3 of this report investigated the use of an NHC to perform a potential novel electrophilic substitution of electron-deficient aromatic rings, the simplified reaction can be seen in Scheme 40.



Scheme 40 Simplified reaction using an NHC to perform a novel electrophilic substitution

The work that has been completed thus far has been unsuccessful in performing the desired the reaction. Various NHCs have been investigated to pursue the reaction as well as several different base and solvent combinations and using different electrophiles. The best results came in the form of two undesired reactions, structures of which can be seen in figure 4 and are tentatively proposed as 1-(*tert*-butoxy)-2,4-dinitrobenzene and 2,4-dinitrophenol. Future work in this area could be to purposely make the proposed undesired structures or if possible, buy from a reliable vendor in order to compare data in a bid to get closure on the products made.

4. Experimental

General remarks

^{1}H NMR, ^{13}C {^{1}H} NMR and ^{19}F NMR were recorded at 500/400 MHz, 125/100 MHz and 470/376 MHz on Bruker Avance 500/400 spectrometers. All spectra are referenced to $(CD_3)_2CO$ residual solvent peaks (^{1}H NMR δ = 2.05 ppm; ^{13}C {^{1}H} NMR δ = 29.84 ppm) and $CDCl_3$ (^{13}C {^{1}H} NMR δ = 77.16 ppm). All chemical shifts are quoted in parts per million (ppm), measured from the centre of the signal except in the case of multiplets which are quoted as a range. Coupling constants are quoted to the nearest 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q) quintet (quin) multiplet (m) and combinations thereof.

Infrared (IR) spectra were recorded on a spectrometer as neat using a Perkin-Elmer FT-IR spectrum RX1 or BX spectrometers.

Low resolution mass spectrometry was performed on an Agilent 6100 mass spectrometer using electrospray ionisation (ESI). High resolution mass spectrometry was performed on a Waters QTOF with ESI and Atmospheric Pressure Chemical Ionisation (APCI).

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected.

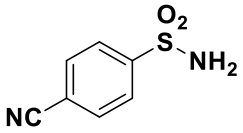
Thin layer chromatography (TLC) was performed using pre-coated Merck60F254 silica plates, visualisation was performed using UV light. Flash chromatography was performed using Merck Kieselgel (mesh size 220-240) silica or Biotage Snap Ultra cartridges on a Biotage Isolera automated columning machine.

All reagents and solvents were used as obtained from commercial source, unless otherwise stated.

4.1. Smiles Rearrangement

Starting material synthesis

*Synthesis of 4-cyanobenzenesulfonamide **71***

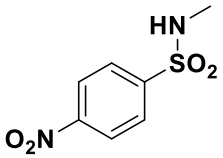


To a 25 ml round bottom flask, 4-cyanobenzenesulfonyl chloride (252 mg, 1.25 mmol, 1 eq.) was added. Ammonium hydroxide (0.5 mL, 33%) was then added and the reaction was refluxed for 1 hour. Ethyl acetate (60 mL) and water (60 mL) were then added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3× 20 mL), the combined organic layers were then washed with brine (1× 20 mL) The combined organic layers were then dried over magnesium sulfate, filtered and concentrated. The crude product was then purified by column chromatography (eluent 0-100% ethyl acetate in hexane) to give the title compound as a brown solid (93.3 mg, 0.51 mmol, 41%)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.09 (m, 2H), 8.01 (m, 2H), 6.9 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 148.9, 133.9, 127.8, 118.3, 116.2

Data in accordance with that of the literature.[30]

*Synthesis of N-Methyl-4-nitrobenzenesulfonamide **74***

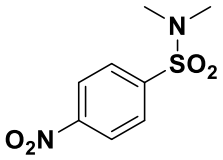


A solution of 4-nitrobenzenesulfonyl chloride (256 mg, 1.156 mmol, 1 eq.) and dichloromethane (3 mL) was cooled to 0 °C. Methyl amine (245 mg, 2.543 mmol, 2.2 eq.) was added slowly and then the reaction was stirred for 3 hours. Water (40 mL) then added and the aqueous layer was extracted with dichloromethane (3× 20 mL). The combined organic layers were then washed with brine (1× 20mL) and then dried with sodium sulfate, filtered and concentrated. Agreed sample pure, no purification, to yield the product as an off-white solid (221.1 mg, 1.02 mmol, 86 %)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.46 (m, 2H), 8.13 (m, 2H), 6.72 (br s, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $(CDCl_3)$, ppm): δ 150.3, 145.0, 128.6, 124.6, 29.5.

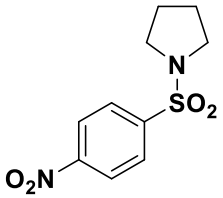
Data in accordance with that of the literature.[31]

*Synthesis of N,N-dimethyl-4-nitrobenzenesulfonamide **76***



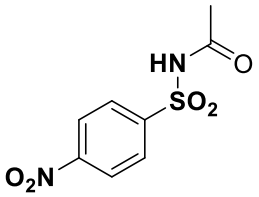
4-Nitrobenzenesulfonamide (201 mg, 0.909 mmol, 1 eq.) was added to dimethyl amine (1 mL, 2.0 mmol, 2.2 eq.) in THF (1 mL) at 0 °C. The reaction was stirred at 0 °C for one hour, then stirred at room temperature for 1 hour. THF was removed under vacuum, then water was added to induce the formation of a white solid precipitate, which was collected by filtration.
^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.49 (m, 2H), 8.09 (m. 2H), 2.79 (s, 6H) ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 150.4, 142.3, 130.0, 125.3, 38.1
Data in accordance with that of the literature.[32]

*Synthesis of 1-((4-nitrophenyl)sulfonyl)pyrrolidine **78***



4-Nitrobenzenesulfonyl chloride (221.6 mg, 1 mmol, 1 eq.) was added to dichloromethane (5 mL) and cooled to 0 °C. Pyrrolidine (156 mg, 2.2 mmol, 2.2 eq.) added slowly and stirred for 3 hours. Water (20 mL) then added and the aqueous layer was extracted with dichloromethane (3× 20 mL). The combined organic layers were then washed with brine (1× 20mL) and then dried with sodium sulfate, filtered and concentrated. Agreed sample pure, no purification, to yield the product as an off white solid (246.2 mg, 0.96 mmol, 96%)
^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.47 (m, 2H), 8.13 (m, 2H), 3.32-3.25 (m, 4H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 150.6, 143.8, 129.7, 125.3, 48.8, 25.9
Data in accordance with that of the literature.[33]

*Synthesis of N-((4-nitrophenyl)sulfonyl)acetamide **80***



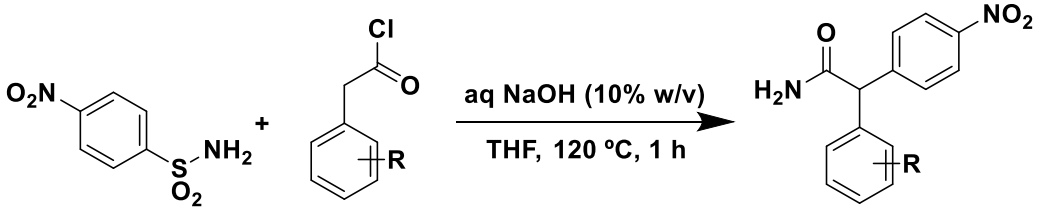
Under a nitrogen atmosphere, 4-nitrobenzenesulfonamide (202 mg, 1 mmol, 1 eq.) was added to a solution of acetic anhydride (154 mg, 1.5 mmol. 1.5 eq.) and acetonitrile (2 mL) and stirred at 60 °C for 30 minutes. Sulfuric acid (3.1 mg, 0.03 mmol, 0.03 eq) was then added and the resulting solution was stirred at 60 °C for a further 40 minutes. The solvent then removed under vacuum, then water was added to form a precipitate which was collected by filtration, to yield the product as a white solid (199.6 mg, 0.82 mmol, 82%)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 10.90 (br s, 1H), 8.47 (m, 2H), 8.29 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 169.1, 151.7, 145.8, 130.6, 125.0, 23.5

Data in accordance with that of the literature.[34]

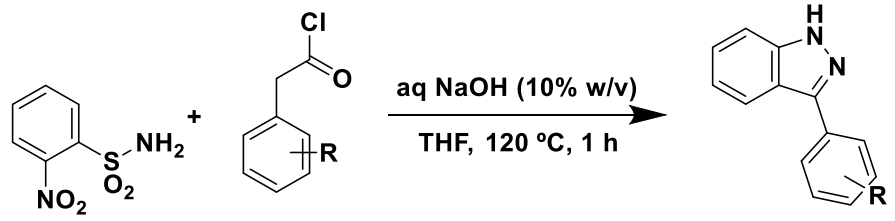
General Procedures

General procedure A for the Smile Rearrangement with variation of the acyl chloride



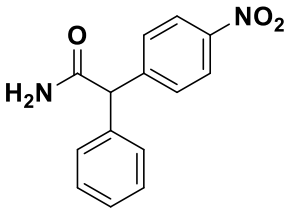
To a 5 mL microwave vial 4-nitrobenzene sulfonamide (40.4 mg, 0.2 mmol, 1 eq.) was added, THF (1 mL) was then added and cooled to 0 °C in an ice bath. Sodium hydroxide (1 mL 10% w/v) was then added and phenyl acyl chloride (1 mmol, 5 eq.) was added dropwise. The vial was then sealed and heated to 120 °C for 1 hour. After this time, the reaction was allowed to cool to room temperature. Ethyl acetate (60 mL) and water (60 mL) was then added and the aqueous layer was then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then dried over magnesium sulfate, filtered and concentrated. The crude product was then purified by column chromatography (eluent 0-100% ethyl acetate in hexane)

General procedure B for the Smile Rearrangement with variation of the acyl chloride



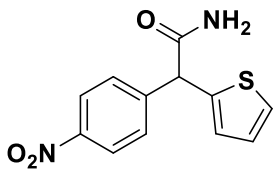
To a 5 mL microwave vial 2-nitrobenzene sulfonamide (40.4 mg, 0.2 mmol, 1 eq.) was added, THF (1 mL) was then added and cooled to 0 °C in an ice bath. Sodium hydroxide (1 mL 10% w/v) was then added, Phenyl acyl chloride (1 mmol, 5 eq.) was added dropwise. The mixture was then sealed and heated to 120 °C for 1 hour. After this time, the mixture was allowed to cool to room temperature. Ethyl acetate (60 mL) and water (60 mL) was then added and the aqueous layer was then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then dried over magnesium sulfate, filtered and concentrated. The crude product was then purified by column chromatography (eluent 0-100% ethyl acetate in hexane).

2-(4-nitrophenyl)-2-phenylacetamide ***58h***



Prepared following general procedure A using phenyl acetyl chloride (132 µL, 1.0 mmol, 5.0 eq.) to give the title compound as a yellow solid (42.5 mg, 0.166 mmol, 83%).
^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.18 (d, *J* = 8.9 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 2 H), 7.43-7.25 (m, 5 H), 6.71 (br. s, 1 H), 5.24, (s, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 172.9, 149.1, 147.7, 140.4, 130.9, 129.5, 129.4, 128.0, 124.0, 115.9, 57.7, 57.6 LRMS (ESI): 279 ($[M+K]^+$); m.p. 125-126 °C.

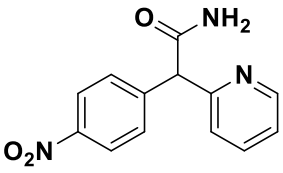
2-4-nitrophenyl)-2-(thiophen-2-yl)acetamide ***85***



Prepared following General Procedure A using 2-thiophenyl acetyl chloride (123 µL, 1 mmol, 5 eq.). The title compound was obtained as a brown solid (35.1 mg, 0.134 mmol, 67% yield).

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.20 (dt, *J* = 8.9, 1.9 Hz, 2 H), 7.73 (dt, *J* = 8.8, 2 Hz, 2 H), 7.38 (dd, *J* = 5.3, 1.0 Hz, 2 H), 7.09 (dt, *J* = 3.5, 1.0 Hz, 1 H), 6.98 (dd, *J* = 5.2, 3.5 Hz, 1 H), 6.72 (br. s 1 H), 5.50 (s, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 172.3, 148.8, 148.0, 142.2, 130.3, 127.3, 127.2, 126.5, 124.2, 52.95, 52.91; ν_{max} (neat) /cm^{-1}: 3367, 3194, 1670 (C=O), 1605, 1516, 1390, 1344, 701 LRMS (ESI): 261 ([M-H]$^-$); HRMS (ESI): $C_{12}H_9O_3N_2S$ ([M-H]$^-$) requires 261.0339; found 261.0343; m.p. 138-140 °C.

2-(4-nitrophenyl)-2-(pyridine-2-yl)acetamide ***83***



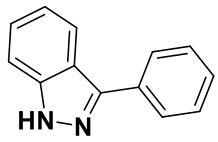
Under N_2, oxalyl chloride (0.1 mL, 1.2 mmol, 6 eq.) was added to a solution of 2-pyridine acetic acid (208.3 mg, 1.2 mmol, 6 eq.) and dichloromethane (2 mL), 1 drop of dimethylformamide. Solution was stirred for one hour.

4-nitrobenzenesulfonamide (40.4 mg, 0.2 mmol, 1 eq.) and tetrahydrofuran (1 mL) added to a 5 mL microwave vial and cooled to 0 °C in an ice bath. Sodium hydroxide (1 mL, 10% w/v) was added to the solution.

The previously prepared acid chloride was added to solution dropwise, the microwave vial was then sealed and heated for 1 hour at 120 °C. After this time, the mixture was allowed to cool to room temperature. Ethyl acetate (60 mL) and water (60 mL) was then added where the aqueous layer was then extracted with ethyl acetate (3× 20 mL). The combined organic layers were then dried over magnesium sulfate, filtered and concentrated. The crude product was then purified by column chromatography (first column 0-50% ethyl acetate in hexane, second column 10% methanol in dichloromethane) to give the title compound as a yellow oil (10.0 mg, 0.039 mmol, 19% yield)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.57 (m, 1 H), 8.19 (dt, J = 8.8, 2.0 Hz, 2 H), 7.81 – 7.74 (m, 3 H), 7.6-7.5 (m, 2 H), 7.32 – 7.27 (m, 1 H), 6.68 (br. s, 1 H), 5.33 (s, 1 H) ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 171.9, 171.8, 159.4, 150.1, 147.9, 147.87, 137.9, 130.9, 124.4, 124.1, 123.3, 60.6; LRMS (ESI): 256 ([M-H]$^-$).

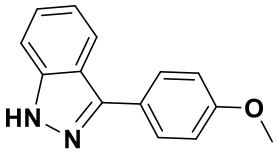
3-Phenyl-1H-Indazole ***88***



Prepared following General Procedure B using phenyl acetyl chloride (132 µL, 1 mmol, 5 eq.). The title compound was obtained as a colourless solid (17.6 mg, 0.0906 mmol, 45% yield)

^{1}H NMR (500 MHz, $(CD_3)_2CO$, ppm): δ 12.38 (br. s, 1 H), 8.11 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.56 Hz, 2H), 7.41 (q, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$, ppm): δ 145.0, 143.0, 135.2, 129.6, 128.5, 128.0, 127.0, 121.9, 121.60, 121.58, 111.3; LRMS (ESI): 193.1 ($[M-H]^-$).

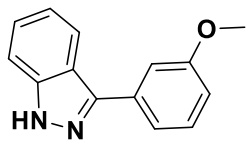
3-(4-methoxyphenyl)-1H-indazole ***90a***



Prepared following General Procedure B using 4-methoxyphenyl acetyl chloride (152 µL, 1 mmol, 5 eq.). The title compound was obtained as a yellow oil (23.9 mg, 0.106 mmol, 53% yield)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 12.26 (br. s, 1 H), 8.08 (dt, *J* = 8.2, 0.8 Hz, 1 H), 8.00 (dt, *J* = 8.9, 2.1 Hz, 2 H), 7.61 (dt, *J* = 9.4, 0.8 Hz, 1 H), 7.40 (ddd, *J* = 8.4, 6.9, 1 Hz, 1 H), 7.21 (ddd, *J* = 8.1, 6.9 0.9 Hz, 1 H), 7.09 (dt, *J* = 8.9, 6.7 Hz, 2 H), 3.86 (s, 3 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 160.4, 144.9, 142.9, 129.2, 127.8, 126.9, 121.64, 121.62, 121.5, 115.0, 111.2, 55.6; LRMS (ESI): 225 ($[M+H]^+$), 247 ($[M+Na]^+$), 263 ($[M+K]^+$), 487 ($[2M+K]^+$).

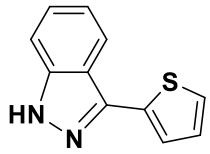
3-(3-methoxyphenyl)-1H-Indazole ***90b***



Prepared following General Procedure B using 3-methoxyphenyl acetyl chloride (155 µL, 1mmol, 5 eq.). The title compound was obtained as a yellow oil (27.3 mg, 0.122 mmol, 61% yield)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 12.40 (br. s, 1 H), 8.10 (dt, *J* = 8.3, 0.9 Hz, 1 H), 7.66-7.59 (m, 3 H), 7.46-7.39 (m, 2 H), 7.24 (ddd, *J* = 8.9, 6.9 0.9 Hz, 1 H), 6.98 (dd, *J* = 8.3, 2.6 Hz, 1 H), 3.89 (s, 3 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 161.0, 144.9, 143.0, 136.5, 130.6, 127.0, 122.0, 121.6, 120.3, 114.3, 113.1, 111.3, 55.5; LRMS (ESI): 225 ($[M+H]^+$), 247 ($[M+Na]^+$) 263 ($[M+K]^+$).

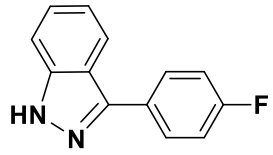
3-(thiophen-2-yl)-1H-Indazole ***90c***



Prepared following General Procedure B using 2-thiophenyl acetyl chloride (74 µL, 0.6 mmol, 3 eq.). The title compound was obtained as a yellow micro crystalline solid (34.3 mg, 0.171 mmol, 71% yield)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 12.32 (br. s, 1 H), 8.14-8.10 (m, 1 H), 7.75 (dd, *J* = 3.6, 1Hz, 1 H), 7.64-7.60 (m, 1 H), 7.49 (dd, *J* = 5.1, 1 Hz, 1 H) 7.45 – 7.40 (m, 1 H) 7.28 – 7.23 (m, 1 H), 7.20 (dd, *J* = 5.1, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 142.8, 140.5, 137.6, 128.5, 127.4, 125.6, 125.1, 122.1, 121.3, 121.0, 111.3; LRMS (ESI): 199 ($[M-H]^-$); m.p. 139-141 °C.

3-(4-fluorophenyl)-1H-Indazole ***90d***



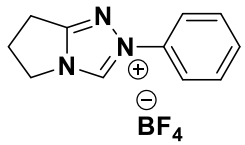
Prepared following General Procedure B using 4-fluorophenyl acetyl chloride (137 µL, 1 mmol, 5 eq.). The title compound was obtained as an off yellow solid (15.7 mg, 0.074 mmol, 37 % yield).

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 12.37 (br. s, 1 H), 8.15 – 8.05 (m, 3 H), 7.64 (dt, *J* = 8.4, 0.9 Hz, 1 H), 7.42 (ddd, *J* = 8.4, 6.9, 0.9 Hz, 1 H), 7.33-7.26 (m, 2 H), 7.26-7.21 (m, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 163.3 (d, *J* = 244.3 Hz) 131.7, 131.6, 129.84, 129.76, 127.1, 122.0, 121.44, 121.37, 116.4 (d, *J* = 21.5 Hz), 111.3; ^{19}F NMR (470 MHz, $(CD_3)_2CO$, ppm): −116.1 (tt, *J* = 8.8, 5.4 Hz); LRMS (ESI): 211 ($[M-H]^-$); m.p. 122-124 °C.

4.2. Using an N-Heterocyclic Carbene to perform Electrophilic Aromatic Substitution

Starting Material synthesis

2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium ***112***



Using oven dried glassware that was dried under vacuum, trimethyloxonium tetrafluoroborate (990 mg, 6.7 mmol) was added to a solution of pyrollidin-2-one (0.45 mL, 5.97 mmol) and dry dichloromethane (40 mL) and stirred at room temperature overnight for 18 hours. Phenyl hydrazine (0.59 mL, 5.97 mmol) was then added and the reaction was stirred for 48 hours at room temperature before being concentrated under vacuum. The residue was then dissolved in methanol (12 mL) and triethylorthoformate (12 mL) and refluxed overnight for 18 hours at 100 °C. The resultant solid was then filtered and recrystallized from methanol to give the title compound as a tan solid (402 mg, 1.472 mmol, 25 % yield)

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 10.1 (s, 1 H), 7.81 (dd, *J* = 8.03 Hz, 2 H), 7.56-7.53 (m, 3 H), 4.66 (t, 2 H), 3.25 (t, 2 H), 2.88 (q, 2 H); ^{13}C NMR (125 MHz, ($CDCl_3$), ppm): δ 162.74, 137.64, 135.6, 131.06, 130.45, 121.0, 47.96, 26.87, 22.02; LRMS (ESI): 186.1($[M]^+$).

5. References

1. W. J. Evans, S. Smiles*, J. Chem. Soc.,* 1935, 181
2. R. Loven, W.N. Speckamp, *Tetrahedron Lett.,* 1972, **13**, 1567
3. W. E. Truce, E. M. Kreider, W. W. Brand, *Org. React.,* 1970, **18**, 99
4. J.J. Koehler, W.N. Speckamp, *Tetrahedron Lett.,* 1977, **18**, 631
5. I. Allart-Simon, S. Gerard, J. Sapi, *Mol.,* 2016, **21** (7) 878
6. J.J. Douglas, H. Albright, M.J. Sevrin, K. Cole, C.R.J. Stephenson, *Angew. Chem., Int. Ed.,* 2015, **54** (49) 14898
7. L. El Kaim, L. Grimaud, J. Oble, *Angew. Chem. Int. Ed.,* 2005, **44** (48), 7961
8. L. El Kaim, M. Gizolme, L. Grimaud, J. Oble, *J. Org. Chem.,* 2007, **72** (11), 4169
9. K. Plesniak, A. Zarecki, J. Wicha, *Top. Curr. Chem.,* 2006, **275**, 163
10. A. Levi, L.A. Warren, S. Smiles, 1933, *J. Chem. Soc.,* **0**, 1490
11. A.R.P. Henderson, J.R. Kosowan, T.E. Wood, *Can. J. Chem.,* 2017, **95**, 483
12. D. Fuss, Q.Y. Wu, M.R. Grossi, J.W. Hollett, T.E. Wood, *J. Phys. Org. Chem.,* 2017, **31** (1) 3742
13. C.M. Holden, M.F. Greaney, *Chem. – Eur. J.,* 2017, **23** (38), 8992
14. P. Rabet. M.F. Greaney, *Angew. Chem. Int. Ed.,* 2017, **56** (15), 4183
15. K. Bowden, P.R. Williams, *J. Chem. Soc., Perkin Trans. 2,* 1991, **2**, 215
16. M. Makosza, K. Stalinski, *Chem. – Eur. J.,* 2006, **3** (12), 2025
17. M. Makosza, *Synth. Stutt.* 2017, **49** (15), 3247
18. M. N. Hopkinson, C. Richter, M. Schedler F. Glorius, *Nat. Chem.,* 2014, **510** (7506), 485
19. F. Glorius, *Top. Organomet. Chem.*, 2007, **21**, 1
20. W.A. Herrmann, *Angew. Chem. Int. Ed.,* 2002, **41** (8), 1290
21. F. Wöhler, J. Liebig, *Ann. Pharm.,* 1932, **3**, 249
22. H. Stetter, *Angew. Chem.* 1976, **88**, 695
23. A. Lapworth, *J. Chem. Soc.,* 1903, **83**, 995
24. R. Breslow, *J. Am. Chem. Soc.,* 1958, **90**, 3719
25. H. Stetter, *Angew. Chem.*, 1976, **88**, 695
26. B. Maji, M. Horn, H. Mayr, *Angew. Chem. Int. Ed.,* 2012, **51** (25), 6231
27. R. Sundberg, D. Blackburn, *J. Org. Chem.,* **34** (9), 2799
28. T. Kato, S. Matsuoka, M. Suzuki, *Chem. Commun.* 2015, **51**, 13906

29. A. Levens, F. An, M. Breugst, H. Mayr, D. W. Lupton, *Org. Lett.*, 2016, **16** (15), 3566

30. A. Angeli, E. Trallori, M. Ferraroni, L. Di Cesare Manelli, C. Ghelardini, C. T. Supuran, *Eur. J. Med. Chem.*, 2018, **157**, 1214

31. C. M. Holden, S. Sohel, M. Greaney, *Angew. Chem. Int. Ed.*, 2016, **55** (7), 2450

32. X. Bao, X. Rong, L. Zhiguo, Y. Gu, G. Liang, Q. Xia, *Tetrahedron. Lett.,* 2018, **59** (29), 2853

33. S. Myers, R. Bawn, L. Bisset, T. Blackburn, B. Cottyn, L. Molyneux, A. Wong, C. Cano, W. Clegg, R. Harrington, H. Leung, L. Rigoreau, S. Vidot, B. Golding, R. Griffin, T. Hammonds, D. Newell, I. Hardcastle, *ACS Comb. Sci.,* 2016, **18**, (8), 444

34. M. V. Pham, B. Ye, N. Cramer, *Angew. Chem. Int. Ed.,* 2012, **51** (42), 10610