A novel hydantoin synthesis and exploration of related reactions

PhD thesis

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A novel hydantoin synthesis and exploration of related reactions

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis/project is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

Matthew Johnathan Leonard

04-OCT-2015
Abstract

Chapter one gives a short history of the discovery of hydantoins, followed by their chemical properties and reactivity and concluding with the many ways to date that they have been synthesized.

In chapter two, a hydantoin compound RU58841, which is a popular anti-baldness agent is synthesized by an alternative pathway to those previously presented. The new synthesis gives 33% overall yield and avoids the hazardous reagent phosgene.

Chapter three explores the novel bromo–nitro substitution reaction. The reaction rate has been characterized by using a library of compounds and possible mechanisms for this reaction have been presented after consideration of the results of a Hammett plot.

In chapter four, another novel step from the alternative synthesis of RU58841 is explored. This reaction involves 2-nitropropane as a leaving group to create an isocyanate intermediate which gives a hydantoin upon ring closure. Attempts and progress towards preparing isocyanate compounds using this method are discussed.

Chapter five summarizes the key findings and describes the future directions that can be taken with the new chemistry presented in this thesis.
To my many good friends and colleagues

We are the music makers,
And we are the dreamers of dreams,
Wandering by lone sea-breakers,
And sitting by desolate streams.
World-losers and world-forsakers,
Upon whom the pale moon gleams;
Yet we are the movers and shakers,
Of the world forever, it seems.

With wonderful deathless ditties
We build up the world’s great cities,
And out of a fabulous story
We fashion an empire’s glory:
One man with a dream, at pleasure,
Shall go forth and conquer a crown;
And three with a new song’s measure
Can trample an empire down.

We, in the ages lying
In the buried past of the earth,
Built Nineveh with our sighing,
And Babel itself with our mirth;
And o’erthrew them with prophesying
To the old of the new world’s worth;
For each age is a dream that is dying,
Or one that is coming to birth.

Arthur William Edgar O’Shaughnessy
Acknowledgments

Despite many stressful and challenging changes in circumstance, I have managed to carry out the high quality work that you are about to read. I changed primary supervisor two times and second supervisor one time during my candidature.

I was married two times during my PhD, for the first time in the second month of my PhD candidature which lasted for 18 months and ended in September 2012. In November 2012 I began a new relationship and two years later I was married for a second time, only two months before the submission of this thesis.

I would like to thank both of my wives, Jennifer and Yvonne for their support throughout my candidature.

My Postdoctoral consultant Anthony Lingham shares many good ideas with me and I look forward to us going into business together.
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1. A general introduction to hydantoins, their properties & preparations

1.1 The hydantoin moiety

A hydantoin (IUPAC “imidazolidine-2,4-dione”) is a 5-membered ring with two nitrogens in the ring. There are two carbonyls in the ring, one of them between the two nitrogens. The five positions of the ring are numbered and, as such, there are four points of functionality, one at the 1 position, one at the 3 position and two at the 5 position.

While it is possible for the carbon at position 5 to act as a chiral centre when bound to two different functional groups, positions 1–4 are mostly rigid and planar. If the oxygen at the 2 or the 4 position is replaced by a sulphur, the structure is known as a 2-thiohydantoin or 4-thiohydantoin respectively. When all four points of functionality are hydrogen, the compound is known as ‘hydantoin’ (2): a white solid with m.p. 220 °C.

Hydantoins are sometimes mistakenly referred to as imidazoles; they are not, although the locations on the ring are numbered the same way and they can be formally formulated as dihydroxyimidazoles. Although imidazoles and hydantoin compounds have both been used as antibiotics, they each offer quite different chemistry and differ in their robustness and reactivity. This is mostly a function of the different properties of amides and amines. The hydantoin moiety can be more closely compared with the barbiturate moiety as its nitrogens behave in a similar way and it has two points of functionality at the 5 position. Like barbiturates, hydantoins can be substituted at one or both nitrogens, although the two nitrogens on a hydantoin are, unlike the barbiturate, not equivalent. Only one is an imide, the other being an amide and amides behave somewhat differently. The imide N at position 3 shows more nucleophilic activity and is more readily substituted than the amide N at position 1 [1].
1.1.1 Chemical properties

The hydantoin ring tends to be hard to break open and hydantoin compounds have been observed to resist several hours of heating in acids and bases [2], whereas the barbiturate moiety is known to readily hydrolyze when placed into basic solution [3]. Hydantoins have been observed to withstand the presence of hydrogen fluoride [4]. Nevertheless, the hydrolysis of hydantoins by strong alkali is an important preparation of α-amino acids [1].

Although the hydantoin ring is resilient to harsh chemical conditions, it can be hydrolyzed more easily in biological systems using metabolic hydantoinase enzymes [5]. This means that hydantoin compounds are highly suited for use as pharmaceuticals where a long shelf life but easy decomposition in the body is desirable. The hydantoin ring is planar and its inclusion in a compound imparts a good deal of rigidity to the structure. This rigidity is imparted by the two amides in the ring which give rise to a resonance form with double bond character at positions 1-2 and a 3-4.

Free movement of electrons in both amide groups impart planarity to hydantoins

It is not hard to imagine some double bond character also at the 2-3 position, whereupon
A novel hydantoin synthesis and exploration of related reactions

the hydantoin ring can be seen to have highly planar and rigid properties that make for a tough scaffold around which the rest of a compound may be constructed. For this reason, they have become popular start materials to synthesize compound libraries for drug design and discovery.

The N–H centre on an imide is capable of hydrogen bonding and the imide in a hydantoin ring is no exception. This means that compounds that contain the hydantoin moiety have a great solubility in hydrogen bonding solvents. This hydrogen bonding also enhances the capacity of the hydantoin compound to be retained in tissues of the body that contain a high aqueous proportion. The addition of the hydantoin moiety to a molecule tends to increase the overall polarity; many smaller hydantoins with minimal alkylation are highly soluble in methanol, ethanol or acetonitrile but poorly soluble in chlorinated solvents [6]. Hydantoin compounds are seen to have high melting points (> 200 °C) [7, 1] but their melting points decrease with an increase in alkyl functional groups.

1.1.2 Reactivity of the hydantoin ring

Reactions at the 2 and 4 positions (carbonyls) are rare; the only type known is the reduction of 5,5-disubstituted hydantoins with metal hydride reducing agents to give 2-imidazolidinones [1].

The acidity of hydantoins is well known by way of many example compounds. When substituted only at the 1 and 5 positions, a hydantoin ring contains an imide NH. This is more acidic than an amide NH as the carbonyls on either side of the nitrogen stabilize the anion by both electron withdrawal and resonance stabilization to delocalize the charge. If the nitrogen at position 1 is bonded to a hydrogen, this NH is less acidic than the NH at position 3 and its pK_a is more affected by substituents at C-5. However it still tends to be a removable proton and it can be readily converted to the sodium salt by treatment with NaH when position 3 is protected [2].
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Unlike the structurally-related acid anhydrides, imide bonds resist hydrolysis and some hydantoin compounds can be recrystallized from boiling water with practically no loss in yield. In fact, heating a dicarboxylic acid with ammonia is a common way to prepare an imide.

The 1 and 3 positions of the hydantoin ring can each readily be substituted with a chloro or bromo group to give a stable compound that is a useful reagent for chlorination or bromination. These halo-reagents are known to be easily prepared and handled. 1,3-Dichloro-5,5-dimethylhydantoin (4) is used as a chlorinating reagent in fine chemical synthesis but can also be used as a pool cleaning agent.

3-Acetyl hydantoins have also been prepared as reagents to selectively acylate phenols in the presence of alcohols [1].

1.1.3 Discovery of hydantoins

Historically, the first preparation of a hydantoin was done simply by cleaving urea from
the natural product ‘allantoin’ to give ‘hydantoin’.

Allantoin (6) is named from the allantois, which is an embryonic excretory organ present in all placental mammals, except for apes and humans whose embryos possess only a vestigial allantois. It is from the allantois that allantoin was first found in concentrated doses and for many years it continued to be extracted from there to be used in skin care products. It is today produced synthetically on a large scale and used in shampoos, cosmetics, toothpaste and other oral hygiene products. It is readily reduced (earlier chemists would use the word hydrogenated) to hydantoin and indeed the name hydantoin comes from hydrogenation of allantoin which was given by Adolf von Baeyer in 1861. During his studies on uric acid, Baeyer hydrogenated allantoin which to him was a compound to be isolated and characterized, but he was unable to elucidate its ring structure. Baeyer was however, confident of allantoin’s molecular formula from elemental analyses and knew that the transformation to hydantoin yielded urea [8].

In 1872 Urech [9] showed that Baeyer’s hydrogenated allantoin compound known as ‘hydantoin’ had chemical properties that were similar to a compound he produced by treating alanine sulphate with potassium cyanate and hydrochloric acid, a product which is now known to be 5-methylhydantoin. This method is known today as the ‘Urech hydantoin synthesis’ and is transferable to other amino acids to give hydantoins substituted at the 5 position.
Urech’s hydantoin synthesis

Urech not only carried out the first constructive synthesis of a hydantoin, he also put forward the correct five-membered ring structure for the hydantoin moiety [9].

In 1908 the work of Heinrich Biltz (section 1.4.2) brought hydantoins to the forefront of organic drug synthesis by preparing 5,5-diphenylhydantoins, including phenytoin (7) [2]. Despite the use of phenytoin to treat epilepsy going undiscovered until 1938, such was the anticipation of hydantoins as potentially useful compounds that Biltz apparently managed to sell this process shortly after publishing.

Phenytoin is not mentioned by name in Biltz’s 1908 paper and is likely to have received this trade name later. It did however, have a known molecular formula and properties but its structure had been hard to determine and was unsolved until Biltz showed that the five-membered amide ‘hydantoin’ ring best explained its properties and that these compounds behaved analogously to those prepared by Urech’s method [2]. Elemental analysis of phenytoin had confirmed its empirical formula, but a structure had been proposed with an epoxide and had the two nitrogens in the same environment.
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![Early proposed structure of phenytoin](image)

**Early proposed structure of phenytoin**

Biltz showed the hypothetical asymmetric hydantoin ring structure to be repeatable and verifiable by elemental analysis and solubility experiments on a library of 5,5-diarylhydantoins and in the same paper he deeply characterized the chemistry of hydantoin [2].

The 1911 Encyclopædia Britannica shows that quite a lot was known about hydantoin and allantoin and has an entry for each. Allantoin’s entry states that it is found in the allantoic liquid of the cow and the urine of suckling calves. It describes its synthesis using one part glyoxylic acid and two parts urea, as well as giving the crystal morphology as “glancing prisms of neutral reaction”, before going on to describe a number of ways to decompose the compound [10].

Hydantoin’s entry describes the molecule as “H₂N-CO-NH-CH₂CO₂H, which is readily soluble in hot water” and describes the many substituted hydantoin compounds that are known, although it uses an unusual numbering system for the ring based on Greek letters, for example “γ-Methyl hydantoin has been obtained as a splitting product of caffeine” [11].

These entries show that in spite of a loose grasp of the chemical structures, the work by Biltz in the preceding period had stimulated alternative strategies to synthesize hydantoin compounds as their medicinal properties and chemistry became of wide interest. In 1912 Lewis administered hydantoin to rabbits, cats, and dogs and came to the conclusion that the ring was not readily broken in the body [12]. In 1946 this conclusion was shown by Bernheim and Bernheim to be incorrect after they carried out studies on rat kidney and liver slices in vitro to show that the hydantoin ring was readily enzymatically broken down [5]. Bernheim and Bernheim concluded from their experiments that the responsible enzyme for hydantoin hydrolysis was “present in dog liver and kidney, cat kidney,
questionably in cat liver, and in frog liver. It is absent from dog and cat blood, mouse liver, rabbit and guinea pig liver, kidney, and blood, and frog kidney”.

By the 1920s, the structure of the hydantoin ring was widely accepted and in 1926, Biltz, in collaboration with Karl Slotta at the University of Breslau, wrote a review article summarizing the many existing hydantoin syntheses, many of which had been carried out on a 10 g to 100 g scale [13]. In 1934, naturally occurring allantoin was shown to have a chiral centre at the 5 position [14]. By the late 1940s hydantoin compounds had become widely known in the organic synthesis community [15] and their biological hydrolysis was being studied [5].

After something of a hiatus in the 1950s to 1980s, hydantoins and thiohydantoins became a popular component of molecules to be screened for their drug potential in the 1990s when their synthesis by rapid or multi-component techniques were widely carried out.

1.2 Natural products containing the hydantoin moiety

As well as synthetic compounds, there are notable examples of coveted hydantoin natural products with medicinal and anti-microbial properties such as hydantocidin [16] and the alysinopsins. Hydantocidin (8) is a potent herbicide against many types of weeds that would be used more often if it were cheaper to synthesize [16]. Isolated from the bacterium Streptomyces hygroscopicus, its mode of action is unknown, although considerable synthetic work has been invested on its preparation [17].

Hydantocidin (8) has a hydantoin moiety bound to the anomeric position of a pentose sugar to give a chiral centre at the 5 position of the hydantoin. Control of the configuration of this chiral centre has proven to be the main challenge in the synthesis of
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hydantocidin [17].

The aplysinopsins are a group of marine indole alkaloids with either a hydantoin or a 2-imino-hydantion moiety that have been isolated from sponges, corals, sea anemones and nudibranches [18]. Although reports on their testing as drug candidates are limited, several aplysinopsins have shown promise as anticancer, antiplasmodial and antimicrobial agents. Others, specifically methylaplysinopsin, have been observed to modulate serotonin receptors and have shown a potent antidepressant effect when given to mammals [18]. The aplysinopsins can be synthesized by the condensation of indole-3-carboxyaldehyde with 1,3-dimethylhydantoin where the substitution of nitrogen in position 1 of the hydantoin dictates formation of the E or Z aplysinopsin [18]. The natural compounds are said to contain the brominated indole ring, whereas the synthetic versions usually leave it off [18].

\((E)-\text{Axinohydantoin}\) (9) and mukanadin B (10) are hydantoin natural products which contain no chiral centres but, like the aplysinopsins, contain an exocyclic double bond at the 5 position [19].

\[
\begin{align*}
(9) & \quad \text{(E)-Axinohydantoin} \\
(10) & \quad \text{Mukanadin B}
\end{align*}
\]

Given the potential utility of the aplysinopsins it is of future interest to know of the effect and purpose of similar hydantoin natural products.

While not a natural product, the platelet aggregation inhibitor drug BW68C (11) contains a chiral centre at the 5 position. It was published by Barraclough et al. in 1996 as part of
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a series of hypotensive drug candidates that focused more on the results than the synthesis [20].

![BW68C](image)

### 1.3 Commercial compounds containing the hydantoin moiety

Many commercially important compounds contain a hydantoin ring. These include large scale bulk chemicals used in shampoos and hand wash formulations, as well as fine chemicals consumed as pharmaceuticals.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Substituents</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (7)</td>
<td>5,5-diphenyl</td>
<td>Anti-epileptic</td>
</tr>
<tr>
<td>Allantoin (6)</td>
<td>5-urea</td>
<td>Shampoo/hand wash</td>
</tr>
<tr>
<td>RU58841 (13)</td>
<td>1-alkyl-3-phenyl-5,5-dimethyl</td>
<td>Anti-baldness</td>
</tr>
<tr>
<td>Nilutamide (26)</td>
<td>3-aryl-5,5-dimethyl</td>
<td>Anti-prostate cancer</td>
</tr>
<tr>
<td>Nirvanol (18)</td>
<td>5-phenyl-5-ethyl</td>
<td>Sleep-inducer</td>
</tr>
<tr>
<td>Nitrofurantoin (16)</td>
<td>5-N-alkenylfuran</td>
<td>Anti-biotic</td>
</tr>
<tr>
<td>DMDM hydantoin (14)</td>
<td>1,3-dihydroxymethyl-5,5-dimethyl</td>
<td>Anti-microbial</td>
</tr>
<tr>
<td>1,3-Dichloro-5,5-dimethylhydan toins (4)</td>
<td>1,3-dichloro-5,5-dimethyl</td>
<td>Chlorination of swimming pools</td>
</tr>
<tr>
<td>Iprodione (15)</td>
<td>1-imidyl-3-aryl</td>
<td>Pesticide</td>
</tr>
<tr>
<td>1-[(5-Arylfurfurylidene)amino]hydantoins</td>
<td>1-(5-arylfurfurylidene)-5,5-dimethyl</td>
<td>Muscle relaxant</td>
</tr>
<tr>
<td>BW68C (11)</td>
<td>1-amino-5-alkyl</td>
<td>Platelet aggregation</td>
</tr>
</tbody>
</table>
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| 1,3-dichloro-5,5-bis(4-chlorophenyl)hydantoin (12) | 1,3-dichloro-5,5-bis(4-chlorophenyl)hydantoin | Anti-leukemia |

1,3-Dichloro-5,5-bis(4-chlorophenyl)hydantoin (12) is a hydantoin compound which has been observed to be active against leukemia strain P-388 [21].

![Chemical structure of hydantoin compounds](image)

**1,3-Dichloro-5,5-bis(4-chlorophenyl)hydantoin and phenytoin**

The previously mentioned phenytoin (7) is also known as Dilantin and is a well-known hydantoin compound that is used to treat epilepsy [2].

![Chemical structure of RU58841](image)

RU58841 (13) is a commercially available hydantoin used to treat baldness. Its mode of action as an anti-androgen will be discussed in section 1.3.3 and its synthesis will be the subject of chapter 2 of this thesis.

### 1.3.1 Anti-microbial hydantoins

The previously mentioned 1,3-dichloro-5,5-dimethylhydantoin (4) is a soft chlorinating reagent which can replace Cl₂ in many syntheses [22]. It is easily handled and can be added to swimming pool water.
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1,3-Dihydroxymethyl-5,5-dimethylhydantoin (14) is a compound added in small doses (0.1–0.6%) to handwash formulations, shampoos and skin care products for its antimicrobial properties which are derived from the slow release of formaldehyde. This compound is most commonly referred to as dimethylol dimethyl – (DMDM) hydantoin, although the hydroxymethyl groups can also be called carbinols. The preparation of DMDM hydantoin was described in a 1947 patent as reacting hydantoin with formaldehyde in an aqueous medium containing concentrated hydrochloric acid and a zinc or cadmium catalyst at 50–70 °C for 6 hours [15]. While pure DMDM hydantoin is a solid, it spontaneously forms a liquid as 5,5-dimethylhydantoin and formaldehyde are released and it is likely that airborne water takes part in this degradation.

Iprodione (15) is a hydantoin compound that is used for crop protection where it inhibits the DNA and RNA production in germinating fungal spores and is also active against nematodes [23].

Nitrofurantoin (16) is a potent antibiotic [24] which due to its pharmacokinetics, is used
mostly for urinary tract infections (hydantoins do tend to be highly polar and accumulate in the urine).

![Nitrofurantoin](image)

**Nitrofurantoin**

**1.3.2 Neuroactive hydantoins**

Phenytoin (7) is an anti-convulsant drug that is commonly used today to treat epilepsy. It has a more water-soluble prodrug form known as fosphenytoin (17) which is delivered intravenously and has improved bioavailability [25].

![Phenytoin and fosphenytoin](image)

**Phenytoin and fosphenytoin**

A similar hydantoin compound called ethotoxin (5-phenyl-3-ethylhydantoin) can also be used as an anti-convulsant in the same way as phenytoin, however as it is less potent, it is now rarely used.

Changing one of the phenyl groups in phenytoin to an ethyl group gives nirvanol (18) which has been used as an effective sleep-inducing drug since 1917 [26].
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Another anti-convulsant drug known as mephenytoin (19) differs from nirvanol only by an N-methylation at the 3 position [27]. It was however observed to have strong hypnotic properties, probably due to it being metabolized to nirvanol, therefore it is no longer used as an anti-convulsant [28].

In 1967 a new class of muscle relaxant hydantoins known as 1-[(5-arylfurfurylidene)amino]hydantoins were described [7]. These compounds are 1-aminohydantoins. Their preparation and activity was described by Snyder et al. who state that the compounds act by inhibiting the polysynaptic pathway [7].

As these 1-aminohydantoins were prepared by coupling 1-amino-5,5-dimethylhydantoin with 2-furfurylaldehydes, this did not present a new synthesis of the hydantoin moiety.

Many of the aplysinsopsins (mentioned in section 1.2) that have been isolated from marine sources have neuroactive properties [18]. These always contain the indole group, plus a five-membered N-heterocycle; some aplysinsopsins are true hydantoins while others are not.
Methylaplysinopsin is an aplysinopsin that contains the hydantoin moiety

Some of these, specifically methylaplysinopsin (20), have shown promise in the pursuit of anti-depression medications [18].

1.3.3 Androgen inhibitors

A number of hydantoin compounds act as androgen inhibitors. Androgen inhibitors or ‘anti-androgens’ are drugs that competitively inhibit ligand binding to the androgen receptor. The action of the androgen receptor, which is a protein that regulates gene expression, is required for male phenotype characteristics to be expressed in an individual. The suppression of the activity of the androgen receptor is therefore a potent trigger that can be used to regulate ailments that occur in the male phenotype such as baldness, acne and prostate cancer.
Testosterone bound to the androgen receptor protein

The activity of the androgen receptor can be altered by androgen receptor inhibitor drugs that block the binding action of the main androgen receptor hormones testosterone (21) and dihydrotestosterone (22). These two hormones are secreted by the testicles, but the adrenal glands also produce a small amount meaning that the compounds are found in the female body at lower levels. Unlike testosterone, dihydrotestosterone can’t be converted by the enzyme aromatase to estradiol [29].
Dihydrotestosterone is a more potent androgen hormone than testosterone and it dissociates from the androgen receptor five times more slowly than testosterone [30]. Dihydrotestosterone is produced from testosterone in the prostate, testes, hair follicles and adrenal glands by the action of the enzyme 5-α-reductase. Interference in 5-α-reductase activity lowers male phenotype expression, and as such, represents another mode of action of anti-androgen drugs.

A steroidal inhibitor compound such as megestrol acetate (23) (sold under the trade name Megace) can competitively occupy the same location within the androgen receptor protein.

As the presence of testosterone and dihydrotestosterone has been widely observed to stimulate the growth of prostate cancer cells, lowering their levels or lowering their interaction with the androgen receptor by the addition of a competitive compound that can ‘switch off’ the activity of the androgen receptor tends to slow the growth or even shrink the amount of prostate cancer tissue for a short time. Anti-androgen drugs alone do
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not cure prostate cancer and their effect gradually fades, however when androgen inhibitor drugs are used in tandem with chemotherapy or radiotherapy they greatly increase the survival chances of a patient. Unfortunately, therapies which lower testosterone levels or activity have significant side-effects such as hot flashes, loss of libido, muscle wasting, personality changes and loss of bone density. Given the advanced age of many men with prostate cancer, a mild anti-androgen therapy can often retain a reasonable quality of life.

As well as accelerating the growth of prostate cancers, the male androgen hormones also play a role in accelerating male pattern baldness. In an analogous way to that of prostate cancer treatment, anti-androgen drugs can be used to slow or even reverse the progress of male pattern baldness. Even though this effect may only last for 2–3 years and result in the above-mentioned side-effects, many men choose to use topical non-steroidal anti-androgens to impede the progress of their baldness.

Recent research, which remains ongoing, has investigated the modes of interaction of non-steroidal compounds with the androgen receptor [31], which have all been hydantoins or hydantoin-like compounds. The compounds flutamide (24) and bicalutamide (25) which are both used in prostate cancer treatment each contain moieties with a similar shape and electron donor atoms to that of a true hydantoin.

**Flutamide and bicalutamide**

Bicalutamide (25), which is sold under the brand name ‘Casodex’ by Astra-Zeneca, grossed US$210 million retail dollars in 2008 [32].

Nilutamide (26) (sold under the trade name Nilandron) is an N-aryl hydantoin compound which, like flutamide and bicalutamide, is used as a non-steroidal androgen receptor inhibitor for prostate cancer treatment.
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As well as nilutamide, the hydantoin RU58841 (13) (IUPAC name: 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile) has been found to act as a non-steroidal androgen inhibitor and is particularly active against male pattern baldness when applied topically. The more formal avenues such as peer reviewed journals, textbooks and pharmaceutical companies have ignored RU58841 for some reason. Despite this, the drug has developed a cult-like popularity among men who seek to reverse the progress of their baldness. RU58841 is reported to regrow hair and there are YouTube videos where it is dissolved into 70% vodka/30% propylene glycol and then rubbed into balding scalps [33]. The RU58841 is highly soluble in the vodka and the propylene glycol is added last merely as a thickening solvent – a recipe which illustrates the highly polar nature of the hydantoin group.

The recommended dose of RU58841 for baldness treatment is 100 mg per day. If this is exceeded, side-effects are observed with erectile dysfunction being the most commonly reported. RU58841 was originally developed in the 1970s at the French pharmaceutical company Roussel Uclaf where it was targeted as an anti-cancer drug. While it did achieve some measure of success against prostate cancers, it has become better known for its effect against baldness. The creators published its synthesis and biological activity in 1994 [34], which was followed up with further biological activity results in a dermatology journal in 1997 [35]. Although the compound is out of patent, it is still in demand. Its originally reported synthesis [34] uses phosgene to prepare the hydantoin
A novel hydantoin synthesis and exploration of related reactions

ring via an isocyanate intermediate. New chemistry that will be the subject of chapter 2 of this thesis provides an alternative synthesis for RU58841 (13) and avoids the highly toxic phosgene reagent.

A similar hydantoin, RU58642 (27), was also developed for screening by the Roussel Uclaf corporation. This compound, like RU58841, was investigated for its pharmacological properties as a topical baldness treatment [36]. This avenue was eventually abandoned for reasons that are unrecorded.

RU58642 is however, still used today as a model compound for anti-androgen receptors in biochemical research [37, 38].

1.4 Preparations of hydantoins

The many hydantoin syntheses developed over the years have each allowed access to hydantoin compounds with different substitution. Choice must be made from a number of pathways depending on which functionality is desired in the end-use hydantoin compound. Some of the best-used syntheses of hydantoin compounds include the Urech hydantoin synthesis, the Biltz synthesis, the Read synthesis and the Bucherer-Bergs synthesis, all of which will be discussed below.

1.4.1 Synthesis by Biltz et. al. via benzilic rearrangement

Heinrich Biltz, born in Berlin in 1865, studied chemistry at Humboldt University and then the University of Göttingen where he was awarded a doctorate in 1888 for research into vapour pressures of SnCl₂ and sulphur. From 1891 he was a professor of chemistry at the University of Greifswald and from 1897 he continued research into the determination of vapour densities at the University of Kiel where, despite holding the position of Chair of Inorganic Chemistry he also found time to carry out organic syntheses and he
Evidently, Biltz’s 1908 paper sealed his fate as an organic chemist and he was shortly thereafter offered a lectureship in organic chemistry at the newly formed Albert Ladenburg Institute of the University of Breslau in 1911 where he went on to research autoxidations and the reactions of acetylene and uric acid. Located in modern day Poland, the city of Breslau (Polish name Wrocław) was part of the German Empire in 1911 and remained so until 1945. Biltz’s younger brother Wilhelm was also a chemistry professor and the two often collaborated. Both Heinrich and Wilhelm Biltz participated in WWI as reserve officers; Wilhelm earned the claim to fame of commanding the German tank used in the first tank-on-tank battle. After WWI Biltz returned to his lectureship in Breslau where he remained for the rest of his life and retired in 1933 at the age of 68. The city of Breslau was a left-wing stronghold of intelligentsia when Biltz accepted his position and settled there in 1911, but by 1925 this situation had begun to change. There was an exodus of about half of the city’s 20 000 Jews between 1925 and 1933. In the 1932 German election the city voted 44% in favour of the Nazi party; the third highest Nazi vote in Germany. Biltz’s marriage remained childless and he died in 1943 at the age of 78, living just long enough to witness the Nazi occupation of Poland and the extermination of the 10 000 or so Jews who remained in Breslau. While it is unclear whether Biltz died of natural causes, he certainly found himself on the wrong side of
history as his retirement years must have been filled with turmoil.

Biltz’s 1908 paper was the first informed synthesis of a hydantoin compound, namely phenytoin (7). Here, benzil (28) is reacted with urea under basic conditions followed by what was later shown to be a benzilic acid rearrangement (1,2 phenyl migration) to give the desired hydantoin [2].

An examination of the original German text reveals that Biltz went to great effort to expose the compounds he made by fusion of substituted ureas and benzils to acids, heat, solvents and dilute NaOH until he was satisfied that only an asymmetrical ring system explained the structure he had achieved. An important clue in this process was that when his compounds were $N$-alkylated (for example if he had started with dimethylurea) they were not soluble in NaOH solution, but when starting with regular unsubstituted urea they went easily into NaOH solution to form a sodium salt. On this basis, Biltz had assigned a symmetrical structure to his hydantoin compounds, which we may remember from a few pages back, contained a carbonyl and an epoxide ring.
However, when Biltz alkylated his compounds that he’d made from regular urea by exposing them to methyl sulphate or ethyl sulphate, he found that one of the nitrogens was much easier to alkylate than the other, a fact confirmed by elemental analysis and also observation of the product’s solubility in NaOH solution. This fact allowed Biltz to dismiss his other possible structures for the ring system. In his seminal 1908 paper [2], he predicted that making a hydantoin that was N-substituted at the 1 position but not the 3 position would give a product that would dissolve in NaOH solution as the imide hydrogen on N-3 would more readily exchange to create the sodium salt [2]. This prediction was later confirmed to be correct [8].

Biltz’s 1908 solubility observations of hydantoin compounds

Biltz established that solubility of a hydantoin in NaOH solution is not due to hydrolysis and ring opening to hydantoinic acid, otherwise the N-substituted hydantoins would dissolve just as readily [2].

The mechanism for the 1,2-diphenyl migration occurring in the synthesis of phenytoin was, for many years, believed to occur by a pinacol type rearrangement of the phenyl groups [2, 39].
In 1956, Dunnavant and James suspected that as the pinacol rearrangement requires acidic conditions, the rearrangement in the Biltz synthesis could be occurring by a different pathway [39]. They carried out experiments in which they altered the urea concentration, the alkali concentration and also delayed the addition of urea to the reaction which allowed them to modify and monitor the yield of glycoluril side product (29) that forms when one molecule of benzil reacts with 2 molecules of urea. This species, which is referred to here as a glycoluril, has an inconsistent name. Poupaert et al. called it a “glycoluryl derivative” [40], Biltz called it “die acetylendiureine” [2] and later in 2003 workers, including Poupaert, called it a “glycolureide” [41].

They observed that the glycoluril yield decreased as alkali concentration increased. Their data allowed them to rule out the pinacol pathway and they instead put forward an asymmetrical benzilic acid intermediate, which undergoes a ring closure to a hydantoin either before or after the 1,2-diphenyl migration [39].
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Possible intermediates of the Biltz hydantoin synthesis

In 1974 Ivin and co-workers condensed ureas with a library of substituted oxaloacetates to achieve their desired 5-alpha-acetate hydantoins [42]. This targeted synthesis was an extension of Biltz’s hydantoin synthesis whereby the two nitrogens on urea sequentially attach to a carbonyl and its α-carbon, the difference being that here the α-carbon exists in the start material, unlike in Biltz’s synthesis where it is formed as an intermediate from reacted benzil [2].

In 1984, Poupaert and co-workers [40] reinvestigated the Biltz synthesis of phenytoin with the aim of preventing the glycoluril side product. They developed a biphasic system using a phase transfer catalyst to prevent the formation of the glycoluril by allowing urea to enter the organic phase only slowly and briefly. This was found to prevent urea from reacting with the diol intermediate (30). In toluene/water, no glycoluril was formed, but
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the reaction yield was lowered to 17–23%. A less polar alcohol than the lower alcohols used by Biltz was tried, namely n-butanol, which gave a 87–93% yield of phenytoin and no side product – a much improved result compared to the 50–55% yield when a homogenous ethanol/water solvent was used.

Biltz phenytoin synthesis and its side product which has multiple names

Several phase transfer catalysts were found to work equally well for this process [40]. It may be taken therefore, that the Biltz phenytoin synthesis relies upon being performed in a hydroxylic/alcohol (protic) solvent for appreciable yields.

In 2002, work carried out by Muccioli and co-workers [41] (who included Jacques Poupaeart, the primary author of [40]*) extended the Biltz phenytoin synthesis further by showing yet another high yielding strategy which avoids ‘glycolureide’ formation. This was achieved by the use of thiourea to give a 92% yield of thiophenytoin (31) which totally avoids formation of the sulfur equivalent of the ‘glycolureide’ produced from two ureas. It is interesting that thiourea does not re-react with the thiodiol intermediate (32) formed in the same way that urea does in the Biltz synthesis to form the thio-equivalent of 29. Thiophenytoin was then oxidised with $\text{H}_2\text{O}_2$ in DMF/acetic acid at room temperature to furnish phenytoin (7) in 95% yield, making this two-step process a better scalable alternative for medicinal phenytoin synthesis compared with the low yields of

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50–55% in Biltz’s original ethanol/water phenytoin synthesis.

*Jacques Poupaert has therefore contributed two viable alternatives to increase the yield of phenytoin or other 5,5-diarylhydantoins (the other being the butanol/water biphasic reaction).

The thio equivalent of the Biltz phenytoin synthesis does not undergo diureation

A library of hydantoins and thiohydantoins was subsequently created this way. Muccioli et al. [41] also claimed that these hydantoin forming reactions were activated by microwaves. The reactions are certainly enhanced and optimized by microwaves to give better yields from less time and energy input. The belief that bond formations that can’t be achieved otherwise are activated by microwaves, as is alluded to in this paper, has
been brought into doubt by investigations into microwave-assisted reactions by Kappe and co-workers [43].

1.4.2 Preparation via the Read hydantoin synthesis

Biltz’s 1908 work had described thoroughly the method to prepare 5,5-diarylhydantoins by reacting urea with 1,2-diketoaryls (benzil and substituted benzils) but it did not report on the possibility of producing 5,5-dialkylhydantoins by exposing 1,2-diketoalkyls to urea [2]. While it is probably theoretically possible to use Biltz’s pathway to achieve 5,5-dialkylhydantoins, in his 1926 review article, Biltz instead recommended the synthesis developed by William T. Read in 1922 [26] as a higher yielding route.

Read’s reaction was actually described in his 1915 paper [44] where he made 1-amino-5,5-dimethylhydantoins by reacting potassium cyanate (KCNO) with hydrazoisobutyrate, which evidently inspired his PhD project that found a similar process to make regular hydantoins, reported in his 1922 paper. It uses a reagent with a cyano and an amino group on the same carbon which is reacted with urea to give a ‘cyano-urea’ intermediate (34) that undergoes an intramolecular 5-exo-dig ring closure to a hydantoin in the presence of HCl and KCNO [13].

![33](2-Amino-2-cyanopropane)

![34](Cyanoisopropyl-urea)

![35](5,5-Dimethylhydantoin)

Read’s synthesis of 5,5-dimethylhydantoin

Read’s synthesis is also applicable to 5,5-diarylhydantoins (described in his paper as 4,4-disubstituted) [26]. Read built upon a previously reported technique [45] for this pathway, which had been successful only in low yields, that prepared the cyanohydrin by exposing a ketone first to hydrogen cyanide and then to ammonia in the one pot. Read showed that the cyanohydrin intermediate could be isolated before treatment with ammonia by preparing it in an acidic medium. He also showed that the sequential use of hydrogen cyanide/ammonia could be replaced by a one-pot process using an ammonium
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cyanide solution, a change which tended to greatly increase the overall yield of the two steps [26].

Read described his synthesis as a new and more efficient way to prepare nirvanol (18), which was introduced in 1917 and had become popular as an effective sleeping pill [26]. He carried out experiments on the viability of using ammonium cyanide in different solutions and on different compounds and combined his own observations with those in previous literature [26]. His key contribution was to increase the yield of the 5,5-disubstituted hydantoin by reacting the cyanohydrin intermediate in the one pot before it had a chance to decompose.

1.4.3 Development of the Bucherer-Bergs reaction

An extension of the Read hydantoin synthesis for 5,5-dialkylhydantoins was simultaneously developed by two Germans to give what is now known as the Bucherer-Bergs reaction. It starts with a carbonyl compound and uses the same cyanohydrin intermediate as the Read synthesis, but replaces the ammonia and potassium cyanate steps with the more convenient ammonium carbonate (which gives ammonia and carbon dioxide when dissolved in water/ethanol). Bergs’ synthesis makes the
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cyanohydrin in the one pot, whereas the Bucherer synthesis prepares it discretely [46, 47]. Ammonium carbonate is far more handleable than the previously used ammonia and potassium cyanate which have the capability of releasing ammonia, or the even more toxic hydrogen cyanide into the gas phase.

[Diagram of hydantoin synthesis by Bucherer and Bergs]

This process was patented by Bergs in 1929 [46]. It was studied and published with more elaborate examples by Bucherer in 1934 [47] who showed that the cyanohydrin was in fact an isolatable intermediate with shelf life of a few days which could be separately prepared and used as start material. Biltz’s 1926 review article states that hydantoin synthesis using the cyanohydrin had been attempted but not successfully at that point [13].

The Bucherer-Bergs method prepares a hydantoin that is disubstituted at the 5 position from its ketone component. It is applicable to dialkylketones, diarylketones and aldehydes. Prior studies by Dr Anthony Lingham in our laboratory at RMIT have shown that esters are not applicable in the Bucherer-Bergs synthesis and both of the R groups which end up bound to the 5 position on the hydantoin must be carbons that are alpha to a carbonyl in the start material. Therefore the R groups that are wanted on the final hydantoin must be available as a ketone reactant in order utilize the Bucherer-Bergs reaction for a hydantoin synthesis.

In 1940 Henze applied the Bucherer-Bergs method of 5,5-diarylhydantoin synthesis with readily available benzophenone (36) as start material to achieve phenytoin. Benzophenone was heated in ethanol/water and 1 mol of potassium or sodium cyanide and 3 mol of ammonium carbonate were added to give a carboxyaminonitrile intermediate (37). This species quickly cyclizes 5-exo-dig to give a hydantoin-like ring with an imine in place of the carbonyl at position 4 and an oxygen in place of NH at position 3 (38). This species rearranged into the desired hydantoin. The reaction was quenched with acid and cooling, the solid filter residue was then treated with base to
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dissolve and remove the hydantoin from any unreacted benzophenone [48].

\[
\begin{align*}
\text{36} & \quad \text{NaCN/NH}_4\text{CO}_3 \\
\text{37} & \quad \text{38} \\
\text{Phenytoin} \\
\end{align*}
\]

Henze’s phenytoin synthesis

The Bucherer-Bergs synthesis was favoured over the Biltz synthesis for its first few decades since avoidance of the glycoluril side product increased yields; it also had the advantage of giving access to 5,5-dialkylhydantoins.

A 1955 *Organic Syntheses* entry [49] shows an example of how widely the Bucherer-Bergs synthesis had been tried and tested at that stage. This simple preparation uses gentle heating with acetone cyanohydrin as the solvent and ammonium carbonate in a 30% molar excess of the acetone cyanohydrin to achieve the hydantoin ring.

\[
\begin{align*}
\text{39} & \quad \text{NH}_4\text{CO}_3 \\
\text{Acetone cyanohydrin} & \quad \text{(ammonium carbonate)} \\
\text{50-80 °C} & \quad 3 \text{~h} \\
\text{35} & \quad \text{5,5-Dimethylhydantoin} \\
\end{align*}
\]

**Preparation of 5,5-dimethylhydantoin as described in Organic Syntheses**

While this synthesis can not be used to prepare *N*-substituted hydantoins, modification may be carried out once the hydantoin scaffold is made. For example, in 1977 Rodgers *et
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*al. N-chlorinated hydantoins using chlorine gas after they were prepared using the Bucherer-Bergs synthesis* [21]. A 2009 *Organic Syntheses* entry also uses Bucherer-Bergs followed by *N*-alkylation [50] and reminds the user to wash the hydantoin thoroughly with water to remove residual ammonia before the next reaction.

While it is unclear who first developed the reaction, using an amine equivalent of acetone cyanohydrin (2-amino-2-cyanopropane, 33) with an isocyanate compound is reported to produce a hydantoin-like ring similar to the intermediate postulated by Henze [48]; both have an imine in place of the carbonyl at position 4 but Henze’s intermediate has an oxygen in the 3 position of the ring. This imine species is isolatable but the imine hydrolyses readily to the carbonyl in aqueous HCl to form the hydantoin ring [34].

![Diagram showing preparation of 3-substituted-5,5-dimethylhydantoins](image)

**Preparation of 3-substituted-5,5-dimethylhydantoins**

This presents an alternative way to carry out the Bucherer synthesis and if a 5,5-dimethylhydantoin is required, either of the two similar reactants - acetone cyanohydrin (37) or 2-amino-2-cyanopropane (33) - may theoretically be used. Of these two complementary synthetic pathways, the first is unable to provide a 3-substituted 5,5-dimethylhydantoin whereas the latter is only able to provide a 3-substituted 5,5-dimethylhydantoin.

### 1.4.4 Solid phase hydantoin preparations

Solid phase synthesis of hydantoin libraries became popular in the 1990s and hydantoins were an early class of compound to be extensively studied by combinatorial synthesis [51] on solid state supports. The solid state synthesis of small heterocycles like hydantoins is popular and successful due to the prevention of intermolecular polymerization which would otherwise decrease yields. This is due to closer proximity of
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functional groups on adjacent molecules which are intended to react. However, the scale of this type of preparation is limited by the loading capacity of the resin used, which is the number of binding sites on the resin for the reactant compound; only so much compound can be bound to the resin which has a finite number of binding sites which, when full, have reached their loading capacity.

In 1993 De Witt and co-workers used solid phase resins to synthesize a library of 40 hydantoins for drug screening [52]. α-Amino acid esters that were resin bound by the oxygen (“C-terminal ester linkage” [53]) were exposed to isocyanates, then treated with acids to access hydantoins. The substituent on the isocyanate is incorporated into the 3 position (nitrogen), while the 5 position retains the original two substituents on the resin bound primary amine β-esters.

In 1996 Dressman and co-workers at Eli Lilly followed up on the work of De Witt et al. with solid phase synthesis of an 800 compound hydantoin library [53]. They showed that making De Witt’s hydantoins by reverse addition of the amino acid to the C-terminal ester linkage using carbodiimide initiated coupling gives a resin bound moiety that cyclizes to a hydantoin under base exposure. Unlike De Witt’s synthesis, Dressman’s synthesis enables N-substitution at position 1.
De Witt and Dressman solid phase hydantoin syntheses

Hanessian and Yang [54] followed up in 1996 with another solid phase synthesis of 5-alkoxyhydantoin libraries with control over substitution at the 3 and 5 positions. This method is similar to that of De Witt but with the later addition of an alcohol to a carbon nitrogen double bond between the 1 and 5 position in the ring to give the 5-alkoxyhydantoin. This method uses a caesium ester salt to bind to the solid phase at the point of a C-Cl bond, to give CsCl as a leaving group [54].

In 1998 Nefzi et al. prepared a library of fifteen 3,5-disubstituted hydantoin using what they refer to as the “tea-bag” method [4]. Although the paper is brief, they claim to have obtained all “15 individual compounds in good yield and high purity” after having cleaved the hydantoins from the resin using hydrogen fluoride.

The work of De Witt and Dressman continued to inspire the solid phase syntheses of 1,3,5-trisubstituted hydantoin as developed by Heine et al. in 2001 [51], Lamothe et al. in 2002 [25], Lebreton et al. in 2003 [55] and Lee et al. in 2004 [27]. It also apparently inspired Lu et al. who in 2005 reported the preparation of a library of 1,3,5-trisubstituted hydantoin and thiohydantoin using a fluorous-phase technique [56].

1.4.5 Other synthetic routes to hydantoin derivatives

In a largely forgotten synthesis, Read’s 1922 paper briefly describes an early preparation of hydantoin (2) in which malonamide (40) is exposed to sodium hypobromite. Read’s language suggests that the malonamide synthesis fell out of favour due to its low yields [26].

![Synthesis of hydantoin from malonamide](image)

In 1972 Marquez and co-workers showed that hydantoins can be converted to 2-imidazolidinones by reduction with lithium aluminium hydride [57]. This work was extended in 2011 by Kieseritzky et al. [58] who found that the milder commercially
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Available hydridic reagent Red-Al (3.5 M bis(2-methoxyethoxy) aluminium hydride in toluene) converts hydantoins to 2-imidazolidinones, followed by a ring-contraction to aziridines.

![Diagram of hydantoin to aziridine conversion](image)

**Aziridines from hydantoins**

This makes it possible to access aziridines by first synthesizing the corresponding hydantoin.

Many alterations of the hydantoin ring itself are also known. For example a hydantoin with a carboxylic acid in the 5 position (41) will rearrange to the corresponding 6-membered orotic acid when subjected to aqueous alkali solutions [56].

![Diagram of 5-acetic acid hydantoin to orotic acid](image)

**Orotic acid from 5-acetic acid hydantoin**

In 1974 Ivin and co-workers showed that this reaction proceeds with a number of different substitutions on the 5 position of the pyrimidine ring as well as with the corresponding esters [42].

The previously mentioned synthesis of BW68C (11) by Barraclough *et al.* in 1996 was carried out as an elaborate and poorly explained series of alterations to a group of hypotensive drug candidate compounds whereby the chiral centres were kept intact [20]. It would not add scope to the history of hydantoin syntheses to fully describe the
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synthetic steps here, except to say that the route is one that is not readily upscaled or applicable to the synthesis of other hydantoins.

A 1999 journal article by Beller et al. [59] described a one-pot synthesis using aldehydes, various ureas and carbon monoxide with acidic palladium as a catalyst and N-methylpyrrolidinone (NMP) as a solvent. The aldehyde substituent is incorporated into the 5 position of the resultant hydantoin.

A 1999 journal article by Beller et al. [59] described a one-pot synthesis using aldehydes, various ureas and carbon monoxide with acidic palladium as a catalyst and N-methylpyrrolidinone (NMP) as a solvent. The aldehyde substituent is incorporated into the 5 position of the resultant hydantoin.

\[
\begin{align*}
\text{R}_1\text{H} & + \text{R}_2\text{NH} - \text{R}_3\text{H} \xrightarrow{\text{CO}} \text{N}_2\text{O}
\end{align*}
\]

\([\text{Pd}, \text{LiBr}, \text{H}^+]\)

**Hydantoin synthesis by Beller et al.**

In 2003, Iván Bélai described the synthesis of 1-aminohydantoins by reacting an isocyanate with an \textit{N}-acyl-\textit{N'}-(1-cyanoalkyl)hydrazine that cyclizes 5-\textit{exo-dig} to give a 5-membered imine ring that is easily quenched to the hydantoin [60]. Several 1-aminohydantoins were already known to be valuable compounds, such as the previously mentioned antibiotic nitrofurantoin (16), the class of muscle relaxants known as 1-[(5-arylfurfurylidene)amino]hydantoins and the platelet aggregation inhibitor BW68C (11).
Bélaï’s synthesis of 1-aminohydantoins

Mechanistically, Bélaï’s synthesis is similar to the Bucherer-Bergs in that it occurs by attack on a digonal carbon. This is a robust reaction and the N-acyl-N’-(1-cyanoalkyl)hydrazine start material is not as difficult to prepare as one might imagine; several methods are described for its preparation from affordable, commercially available compounds.

In 2004, Charton et al. prepared a library of fused ring hydantoins by reacting an α-aminoamide with 1,1’-carbonyldiimidazole.

Hydantoin synthesis by Charton et al.

This 1,1’-carbonyldiimidazole (42) is a carbonylation reagent. This is a similar strategy to that of Beller et al. [59], mentioned on the previous page, who used carbon monoxide as a carbonyl source to achieve the hydantoin.
A novel hydantoin synthesis and exploration of related reactions

In 2006, Aksinenko and co-workers reported the preparation of 5-amino-5-trifluoromethylhydantoins by reacting N-substituted imines of methyl trifluoropyruvate with monosubstituted ureas [61]. The prepared intermediates were boiled for 3–4 h in benzene with a catalytic amount of triethylamine, whereupon they cyclized by a 5-exo-trig mechanism to give the hydantoin in 82–96% yield with the loss of methanol as a leaving group.

5-Amino-5-trifluoromethylhydantoin synthesis by Aksinenko et al.

When refluxed in DMF in the presence of 1 M KOH, both Aksinenko’s prepared intermediates and the hydantoins were found to hydrolytically decarboxylate to disubstituted ureas [61].

Decomposition of 5-amino-5-trifluoromethylhydantoins

Therefore it seems that these 5-amino-5-trifluoromethylhydantoins had a greater affinity than other hydantoins for ring cleavage. This is perhaps due to the proximity of the electronegative CF$_3$ group to the carbonyl.
A novel hydantoin synthesis and exploration of related reactions

Also in 2006, Shipman and Montagne expanded upon the four points of chemical diversity that are possible for the hydantoin ring itself by synthesizing hydantoin libraries that have functional groups pre-installed one carbon away from the 5 position of the hydantoin ring [62]. These syntheses were conducted both in solution and on solid phase supports and proceed from a methyleneaziridine ring expansion which, combined with the Bucherer-Bergs synthesis and a Grignard reaction provides a multi component reaction to produce a hydantoin with points of diversity that are alpha rather than ipso to the 5 position [62].

![Methyleneaziridine Reaction Scheme](image)

**5,5-Multisubstituted hydantoin synthesis by Shipman et al.**

While Shipman et al.’s synthesis is excellent for the rapid preparation of large hydantoin compound libraries for drug screening, one has to suspect that the methyleneaziridine would not be a cheaply available start material and its preparation may prohibit the practicability of the upscale of this synthesis. The Shipman group at at the University of Warwick continued with the theme of hydantoins in 2008 by reporting a preparation of 2-thio-3-alkyl-5,5-diaryl hydantoins, which used the Bucher-Bergs synthesis to prepare the 5,5-diarylhydantoin, followed by N-alkylation using halogen coupling, but added the novel step of selectively thiating the more nucleophilic 2 position of the hydantoin using Lawesson’s reagent (43) [63].
Lawesson’s reagent used to selectively thiate the 2 position of a hydantoin

In 2007, Keiko and co-workers described a synthesis of hydantoins with a vinyloxy group on the 5 positon, where a C=C double bond has a methyl and an ether group on the 5-alpha carbon [6]. This was carried out by in situ condensation of an α-alkoxyaminocyanohydrid to form an α-alkoxyaminocyanooalkene species which then follows a Bucherer-Bergs synthesis to react with ammonium carbonate.

Keiko et al’s synthesis of 5-vinyloxyhydantoins

No mention is made of the stereochemistry about the C=C double bond. While these 5-vinyloxyhydantoins were stable compounds, they were found to convert to 5-acetylhydantoin (44) upon vigorous heating with carbonic acid, or gentle heating with hydrochloric acid. The 5-acetylhydantoins underwent keto-enol tautomerism and were seen to present with a majority ratio of the enol form (45) when in polar solvents [6].
Preparation and keto-enol tautomerization of 5-acetylhydantoin

Although this conversion of 5-vinylxyhydantoin to 5-acetylhydantoin (44) removes the installed R group, the keto-enol functionality at the 5 position will surely allow many further reactions to access a broad range of 5-substituted hydantoins.

In 2008 Olimpieri, Volonterio and Zanda [64] demonstrated a method to achieve 1,3-disubstituted-5-arylhydantoins by clicking together substituted carbodiimides (prepared from azides and isocyanates and left in the solvent) with the appropriate α-halo-arylacetic acid. This reaction was run in DCM at room temperature using 1 molar equivalent of 2,2,6,6-tetramethylpiperidine (46) (TMP) as a base to initiate the ring closure. The small amount of acyclic product was easily converted to the desired hydantoin by treatment with NaOH solution [64]. This synthesis gives a hydantoin substituted not only at the 1 and 3 positions, but also at the 5 position with an aryl group.

Hydantoin synthesis by Olimpieri et al.

However, this synthesis is limited in situations where R\(^1\) and R\(^2\) are different; in this case, a mixture of products with R\(^1\) and R\(^2\) at alternating positions is produced. The authors
claim that the more sterically hindered R group on the carbodiimide will end up mostly or even exclusively on the 3 position of the hydantoin [64]. This method built upon an earlier reported synthesis by Volonterio [65], which used α,β-unsaturated ethyl ester carboxylic acids (fumarates) and carbodiimides to prepare 1,3,5-trisubstituted hydantoins in which the substituent at the 5 position incorporates an ethyl ester on the alpha carbon.

This synthesis is an example of a ring rearrangement to the more stable hydantoin moiety and it produced an impressive library of hydantoins. However it is unlikely to be widely used as the α,β-unsaturated carboxylic acid start material was rather tedious to prepare [65]. The mechanism of ring closure is however of interest and it is 5-exo-trig.

In a very recent hydantoin synthesis, Baccolini et al. reported in 2011 the synthesis of hydantoins and thiohydantoins by reacting ureas or thioureas with aldehydes such as glyoxal using water as the solvent and catalyzed by either phosphoric anhydride (P₄O₁₀) or phosphoric acid [66].
A novel hydantoin synthesis and exploration of related reactions

The group report a reaction time of only 10 min, which must surely represent the cheapest and easiest hydantoin synthesis yet discovered. However, it has the limitation of giving a mixture of 1- and 3-methylhydantoin products when methylurea is used as start material [66].

1.4.6 Summary of hydantoin preparations

The Baldwin rules for a five-membered ring allow an exo ring-closure regardless of the geometry of the attacked carbon, whereas an endo ring-closure is only allowed if the attacked carbon has a digonal geometry. While all types of the 5-exo ring closures have been observed in hydantoin preparations, 5-endo-dig hydantoin formations have, to the best of our knowledge, not been reported. The preparation of a hydantoin ring has been achieved multiple times using C–C bond forming reactions and also by ring closure and rearrangements. Some of the best methods summarized here are still restricted to start materials with certain pre-installed functional groups.
A novel hydantoin synthesis and exploration of related reactions

For example, the Urech synthesis can preinstall at the 5 position, whereas the Biltz synthesis can preinstall at the 1, 3 or 5 positions but it requires the use of a more exotic diketo (‘Benzil’) reagent which must be prepared freshly before the reaction as it has a short shelf life. De Witt and Dressman’s syntheses give a great deal of control at the 1 and 3 positions but not at the 5 position. Heine’s synthesis provides 5,5-unsubstituted hydantoins with pre-installed functionality at the 3 position but uses a solid phase technique which limits its scale. Thus Heine’s synthesis is good for making libraries of hydantoin compounds but poor for large scale hydantoin syntheses.

Table of various hydantoin syntheses

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<th>5-C=C</th>
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<th>1-aryl</th>
<th>3-alkyl</th>
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1.4.7 Installment of substituents to the hydantoin ring

Once formed, the hydantoin ring can have substituents attached to it; this is often quite easily done even in the presence of functional groups. One of the simpler ways to functionalize is by N-halogenation at the 1 and/or 3 position. Many methods have been developed to prepare $N$-chlorohydantoins in order to use them as gentle chlorinating reagents.

In 1963, Corral and co-workers [67] passed Cl$_2$ gas through an aqueous alkaline solution of hydantoin to achieve 1,3-dichlorohydantoin. This method was used by Rodgers et al. in 1977 to prepare $N$-chlorohydantoins as antitumour agents, but by this time the process had been optimized to a 0.1 M NaOH solution [21].

In 1984, Klimavichyus and co-workers [68] found that when the 3 position was already substituted, it was possible to nitrosate at the 1 position using sodium nitrite, glacial acetic acid and acetic anhydride.

![Diagram of 1-nitrosohydantoins]

**Preparation of 1-nitrosohydantoins**

In 1990, Lipinski and co-workers [69] used aqueous sodium hypochlorite solution to $N$-chlorinate hydantoins. This method, while using an easy reagent to handle, met problems upon solvent extraction when a less substituted, more water-soluble hydantoin is used.
In 2009, Whitehead and co-workers used one mole equivalent of trichloroisocyanuric acid (47) (TCCA) to N-chlorinate hydantoin at room temperature for 30 min with acetonitrile as solvent [22]. This procedure was found not to chlorinate the 5 position even when this carbon was unsubstituted, which gives this method excellent selectivity by only chlorinating the nitrogens on the hydantoin. If the nitrogen at position 1 is alkylated, chlorination proceeds on position 3 only. No mention was made of monochlorination on position 1. Whitehead’s method N,N-dichlorinated a number of natural product hydantoin without disturbing their chiral centre at the 5 position, with the aim to use these reagents for asymmetric halogenations [22].

Non N-protected hydantoin, as has been mentioned, will condense with formaldehyde to give an N-carbinol hydantoin (DMDM hydantoin (14)). It may therefore be, in some cases, desirable to N-protect a hydantoin compound to prevent it from reacting with formaldehyde. N-Alkylation to prepare certain target compounds has been carried out using an excess of bromo-, chloro- or even iodoalkanes in dry DMF in the presence of K₂CO₃ at room temperature overnight to give near quantitative yields but tends to give better yields at the 3 position than the 1 position [41, 63, 70].

Hydantoin can also be N-arylated. Approaches to pre-install the N-aryl, or to N-arylate the hydantoin once formed, have both been researched and are described in the next section.

1.5 Preparation of N-Aryl hydantoin

N-Arylhydantoin compounds, as has been mentioned, have been found to act as testosterone inhibitor compounds [31]. They have traditionally been prepared from N-aryl
isocyanates [34] or by catalytic coupling using aryl halides [71]. Several new approaches have also been recently explored and will be described.

1.5.1 Formation via N-Aryl isocyanates

While Read’s synthesis, as described in his 1922 paper, reacted 2-amino-2-cyanopropane (33) with KOCN to achieve hydantoins substituted at the 5 position [26], it has long been known that N-aryl hydantoins can be made by reacting 2-amino-2-cyanopropane or similar compounds with aryl isocyanates followed by quenching in HCl to give a 3-aryl hydantoin. Biltz refers to the use of this method in his 1926 review but does not say who developed it [13].

![Chemical Structure](image)

**Preparation of N-aryl hydantoins using aryl-isocyanates**

This synthesis of N-arylhydantoins is high yielding and generally robust. Its drawback is not so much the presence of the isocyanate intermediate, but rather the use of the phosgene reagent required to create it. Phosgene is a poisonous gas that was used as a weapon in WWI. Even when used in solution, small amounts of phosgene can often escape and be breathed in, so its use requires the close monitoring of workers’ health. This type of hydantoin synthesis using phosgene was used by Battmann et al. to prepare RU58841 as reported in 1994 [34].

1.5.2 Aryl hydantoins by catalytic organometallic coupling and by halo nucleophilic aromatic substitution

In 2006 Hügel et al. prepared RU58841 by an N-arylation of 5,5-dimethylhydantoin (35) [72]. This achieved the RU58841 hydantoin synthon (48) in 55% yield by S_NAr coupling of an active aryl halide with hydantoin/NaH, but their yield was lowered to 30% when the synthesis was carried out on a 10 g scale [72].
A novel hydantoin synthesis and exploration of related reactions

*N-Arylation of 5,5-dimethylhydantoin using NaH/hydantoin S_NAr by Hügel et al.*

The 55% yield was obtained from doing the reaction on a 1 g scale [Helmut Hügel, personal communication]. Replacement of the NaH coupling with copper acetate-promoted boronic acid coupling gave a 79% yield of the same synthon [72].

*N-arylation of 5,5-dimethylhydantoin using boronic acid coupling by Hügel et al.*

When this type of boronic acid N-aryl coupling was applied to aryl compounds with other functional groups the yields were mostly limited to 30–50%; yields above 60% could only be achieved when the aniline was being attached to the hydantoin had either o-nitrile or p-methoxy substituents [73].

### 1.5.3 Carbamate cyclization

Other (unpublished) work by Dr. Anthony Lingham in the synthesis lab at RMIT explored preparation of the RU58841 N-aryl hydantoin synthon (48) by using pre-installed aryl groups on a carbamate intermediate (50). As shown below, the N-aryl carbamate was formed from the α-amino anilide (49) using ethyl chloroformate (51) (methyl chloroformate could be used but yields of carbamate and cyclized product were...
A novel hydantoin synthesis and exploration of related reactions

found to be lowered).

![Chemical Structure](image)

**Preparation of N-arylhydantoin using ethyl chloroformate**

Cyclization of the carbamate was achieved by deprotonation of the amide using potassium t-butoxide in THF/t-butyl alcohol, followed by 5-*exo-trig* cyclization with an ethoxide leaving group. This synthesis uses fewer steps to reach the hydantoin than our recently published RU58841 synthesis [74] but demands high purity of reagents and anhydrous conditions, and its yields decrease from near quantitative to ~ 70% upon scaleup to 10 g. This approach towards synthesizing N-aryl hydantoins with other aromatic substituents has not been pursued and may prove to retain high yields on scaleup.

### 1.5.4 A new pathway for the synthesis of N-aryl hydantoins

Other procedures were trialled by Dr Lingham to prepare the α-amido anilide precursor (49) to RU58841.
One was the substitution of the α-bromo anilide (52) using azide, nitrite and amine nucleophiles. Reaction of aqueous or liquid ammonia gave 2-amino-2-methylpropanamide (53) and aromatic amine (54) quantitatively. Reaction of 52 with NaNO₂ in DMF gave clean conversion to the α-nitro compound (55) in 70% yield, although Dr. Lingham observed the compound 55 to be unstable on a GC-MS and did not pursue this pathway. We later together revisited this pathway and found that the compound 55 is only unstable when heated, but is actually produced in quantitative yield and can be hydrogenated to prepare the desired α-amido anilide precursor (49) used for the next step of the reaction.

Reaction of 52 with NaN₃ in ethanol/water at reflux for 8 h gave 97% conversion to the azide (56) which could be reduced by Parr hydrogenation using Pd/C in ethanol (but not ethyl acetate).
A novel hydantoin synthesis and exploration of related reactions

The above preliminary research had indicated that the lability of the α-isobutyryl-nitro group could be exploited as a leaving group later in the synthesis. We therefore felt that Dr Lingham’s 5-exo-trig N-arylhydantoin synthesis using ethyl chloroformate (51) that gave ethanol as a leaving group could be expanded upon by the use 2-nitropropane as a more novel leaving group.

This has been pursued and studies of the ring closure mechanism will be discussed in greater detail in the following chapters of this thesis.
2. **A new synthesis of N-aryl hydantoins**

With the chemistry of the hydantoin moiety now established, as well as the knowledge that many useful hydantoin drugs have their functional groups installed on the nitrogen, it is clear that any discovery of a new way to synthesize N-substituted hydantoins represents potentially valuable options for drug making that can be assessed for their yield, expense and practicality. Using the example of the anti-baldness compound RU58841 (13), the following chapter presents such a discovery as an example of a new synthesis of N-aryl hydantoins.

### 2.1 The target compound RU58841

RU58841 (13) is commonly used today as a topical baldness treatment. It can be mail ordered over the internet and users are instructed to dissolve the powder into vodka and propylene glycol before rubbing into the scalp. Based on internet blogs, its efficiency appears limited and highly varied between individuals. No controlled studies of its effectiveness have been found and it has no Wikipedia page. Despite its popularity as a consumer drug, it seems to be an ‘underground’ phenomenon and is largely absent from synthesis journals and is not marketed by reputable consumer goods companies as a topical baldness treatment.

The blog comments suggest that RU58841’s absence from off the shelf products is due to the compound being unstable when in solution. It does not seem to be a high margin product: the price appears to be ~US$30 [75] per gram and at a recommended dose of 20 mg per day, a year’s worth of treatment might come to a little over US$200.

RU58841 was discovered in the 1970s by researchers at the French pharmaceutical company Roussel-Uclaf who explored hydantoin compounds to treat a number of ailments. They developed RU58841 (13) which had been targeted as a prostate cancer treatment but when given to rats it was observed that they grew more and thicker hair.
A novel hydantoin synthesis and exploration of related reactions

than usual. RU58841 was then subsequently pursued for its hair regrowth properties. Researchers from this same group eventually published their original preparation method as well as biological results in 1994 in the Journal of Steroid Biochemistry and Molecular Biology (Battmann et al.) [34]. The preparation starts by treating a substituted aniline (54) with phosgene to give an isocyanate followed by reaction with 2-amino-2-cyanopropane (33). As mentioned in 1.5.1, this is a classic method to prepare an N-arylhydantoin. The paper goes on to show that RU58841 is an effective topical anti-androgen stating that it produces hair growth at a third of the dose that causes other, unwanted effects of androgen inhibition. Later in 1994 Battmann and co-workers [76] furthered their work by outlining the pharmacokinetics and metabolites of RU58841 and a number of its analogues.

RU58841 was the subject of a 1997 study [35] that involved grafting balding human scalp segments onto mice and then treating those skin grafts topically with RU58841. The results of this study confirmed the effect of RU58841 as an anti-androgen [35]. A 2008 study assessed RU58841 for its performance as an androgen receptor inhibitor and labelled the compound as “efficacious in vivo for hair growth” [77].

The alternative synthesis of RU58841 described in this chapter represents an addition to the options for synthesizing a hydantoin scaffold. In this case the desired trifluoromethyl and cyano substituents for RU58841 are pre-installed on the aniline. The aniline amino group becomes the 3 nitrogen of the hydantoin which is subsequently built around the aniline nitrogen in a number of steps ending with a ring closure that yields 2-nitropropane as a by-product. As a final step in this synthesis, N-alkylation is carried out on the nitrogen in position 1. This novel N-arylhydantoin preparation adds to the field of hydantoin syntheses by providing an alternative to the isocyanate pathway to N-arylhydantoins. In addition, two of the steps in this synthesis demonstrate new synthetic methodology which can be transferred to other organic syntheses: a halo–nitro substitution at a tertiary carbon and the formation of an isocyanate from 2-nitropropane as a leaving group; both of these steps are characterized and discussed in chapters 3 and 4 respectively.

2.1.1 Existing syntheses of RU58841

Analysis of Battmann’s RU58841 synthesis (below) shows four discrete steps, the least desirable being the use of phosgene to prepare the isocyanate intermediate 57. Purity is

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not likely to be an issue with the Battmann preparation. The second last hydantoin compound in this pathway (48) has an unsubstituted nitrogen and as Biltz showed in his classic 1908 paper [2], hydantoins with unsubstituted nitrogens are readily soluble in NaOH solution which make them easy to purify from other organics.

RU58841 synthesis by Battmann et al.

Recognizing the merit of avoiding phosgene, in 2005 the Hügel group at RMIT began exploring alternative hydantoin preparations to achieve RU58841 without compromising yields. They carried out direct attachment to the 3 position of 5,5-dimethylhydantoin rather than synthesizing a hydantoin ring. They did this both by a NaH/halogen N-aryl nucleophilic aromatic substitution approach and by a boronic acid coupling approach. As noted earlier, the NaH/halogen was successful on a 1 g scale where it gave a 55% yield of 48, but the yield was reduced to 30% or below when performed on a 10 g scale [72]. Even so, as it reduces the number of steps in the synthesis and makes use of materials that are cheaply available and easy to handle, the 30% yield represents a viable option for preparing RU58841. However, this mode of N-aryl coupling was found to have much lower yields for the attachment of most other anilines to 5,5-dimethylhydantoin; for example m-methoxy gave a 39% yield, p-methyl a 47% yield [72].
A novel hydantoin synthesis and exploration of related reactions

Preparation of N-aryl compound by NaH/hydantoin S_NAr

The yield of 48 was stated to be 79% when the coupling was carried out by copper acetate promoted boronic acid coupling [72], although it is unclear whether this yield was also lowered significantly when increased from a 1 g to a 10 g scale.

Preparation of N-aryl compound by boronic acid coupling

This boronic acid coupling method gives an acceptably high yield and allows an RU58841 synthesis with fewer steps than the one described by Battmann.

An alternative to Battmann and Hügel’s RU58841 synthesis will now be presented that instead of using aryl-coupling, builds the hydantoin moiety around an aniline (54) and may give higher yields when used to synthesize other N-arylhydantoins from anilines with different functional groups.

2.2 Retrosynthetic analysis of RU58841

From a retrosynthetic point of view, the first and most obvious bond to break is the C–N bond of the alkyl chain to the 1 N position of the hydantoin ring.
As NaH-halogen substitution can readily carry out this step in good yield, there is not much improvement to be made.

The next retrosynthetic step has far more viable options. Battmann et al. have already shown that this hydantoin can be prepared by bond formations at the 2-3 and 5-1 positions. Hügel et al. have then characterized the making of this hydantoin by bond formation from the 3 nitrogen to the aryl group.
Retrosynthetic steps by Battmann and Hügel

Our new approach involves breaking the bond between the 1 and 2 position of the hydantoin ring, which can be done if R is a good leaving group.

Previous work by Dr Anthony Lingham towards synthesizing RU58841 (as outlined in 1.5.4) showed that if R possessed an adequate leaving group the double amide chain could undergo a 5-exo-trig ring closure that produces the C-N bond between position 2 and 3 of the hydantoin ring. As we had seen compound 55 decompose on the GC-MS injector port to achieve the isocyanate synthon (57) from Battmann’s synthesis, it occurred to us that this may be a pyrolysis that only occurs upon heating and gives 2-nitropropane as a leaving group. We therefore planned our synthesis to exploit the possible but hitherto unreported properties of 2-nitropropane as a leaving group.
It is well known that a bromo group can be substituted for a nitro group by using the conditions known as the Kornblum reaction. It is generally accepted however, that only a primary or secondary bromo group will substitute for a nitro by using nitrite ions \[78,79\]. Tertiary bromo compounds are known to instead undergo a HBr elimination and so they are normally ruled out of the Kornblum reaction. However, in this case the neighbouring carbonyl makes a HBr elimination pathway very difficult as the newly formed double bond would have to be a disfavoured terminal $\alpha$-$\beta$ double bond. There are in fact precedents of the Kornblum’s reaction proceeding on a tertiary halo compound that is alpha to a carbonyl \[80,81\]. This reaction will be further discussed in chapter 3.
A novel hydantoin synthesis and exploration of related reactions

**Retrosynthesis step four**

The following retrosynthetic steps then become easy. An acylation using $\alpha$-bromoisobutyryl bromide (60) takes us back to compound 49. This is followed by hydrogenation of 49 that takes us back to the previous nitro compound (55) that had been prepared by Dr. Lingham from 52.

![Chemical structures](image)

**Retrosynthesis steps five and six**

### 2.3 New synthetic route to RU58841

Building upon Dr. Lingham’s previous observations of a 5-*exo-trig* ring closure to give an *N*-aryl hydantoin, we devised the synthesis below.
A novel hydantoin synthesis and exploration of related reactions

Alternative synthesis of the anti-baldness compound RU58841 [75]

This pathway prepares RU58841 (13) from the same 3-trifluoromethyl-4-cyanoaniline start material (54) as Battmann et al. [34] but creates the N-aryl hydantoin (48) without the use of phosgene. This adds to the repertoire of hydantoin syntheses and may be transferable to the preparation of other N-aryl hydantoin end-products. The second step, substitution of a bromo group for a nitro group occurring on a tertiary carbon, was an unexpected result and became the subject of chapter 3 of this thesis. This synthesis of RU58841 offers the up-scaling process chemist an alternative pathway that avoids phosgene and should be applicable to the preparation of other N-aryl hydantoin compounds.

The synthesis itself and the mechanism for the serendipitous ring closure are discussed in the remainder of this chapter. The unexpected Br–NO₂ substitution used in step two and the implications of its possible mechanism will be discussed in chapter 3 and the implications of 2-nitropropane as a leaving group seen in step five will be discussed in chapter 4.

Future experiments to make analogues of RU58841 for testing as anti-baldness agents involve adding a methyl to the N-alkyl chain and making a six-membered double-amided ring in place of the hydantoin. Tactics for the synthesis of both of these sets of analogues will be discussed in chapter 5 of this thesis.

New RU58841 synthesis.

Step one was an acylation of 54 to give the α-bromoisobutyranilide 52.
The acylation of 3-trifluoromethyl-4-cyanoaniline (54) using α-bromoisobutyryl bromide (60) to yield 52 is not particularly difficult chemistry but a few observations are noteworthy. The use of K$_2$CO$_3$ was partly to take up any water so as to minimize the quenching of the acid bromide reagent (60), but had two added advantages: neutralizing any HBr formed by converting it to KBr which improved the handleability of the workup by minimizing the HBr vapours in the lab; and the carbonate acts as a base which, prevents the protonation of some of the amine to the non-nucleophilic ammonium salt. The solvent used was 1,2-dichloroethane (1,2-DCE). As emulsions were commonly encountered when worked up in this solvent it was removed by evaporation and the solids worked up in EtOAc/water. This preparation and workup method was performed on other substituted anilines to prepare a variety of α-bromoisobutyranilides, all of which recrystallized from hot methanol to give yields of 75–99%. The preparation of this compound library was part of a further study into the Br–NO$_2$ substitution and will be described in chapter 3.

**Step two** was a bromo–nitro substitution of 52 to give the α-nitroisobutyranilide 55.

This reaction is carried out in DMF at room temperature with a 4–10 molar excess of NaNO$_2$ and with no effort made to keep anhydrous conditions. The reaction was inspired by the finding that when the α-bromoisobutyranilide (52) was exposed to nitrite ions in DMF, GC-MS showed a consumption of 52 and formation of a product that had apparently lost a 2-nitropropane group, with $m/z$ equal that of the isocyanate (57). This appeared to be a promising alternative synthesis of isocyanates, along with 2-nitropropane, which is also valuable. However IR showed that the reaction product lacked the characteristic isocyanate C=N stretch at 2250–2300 cm$^{-1}$ and electrospray ionization mass spectrometry (which is carried out at room temperature) showed by a
clear M−1 negative ion that the nitro group had in fact replaced the bromine to form a discrete α-nitroisobutyranilide. This was confirmed by hydrogenating the nitro compound to the amine and acylating the amine, and finally by a crystal structure of the α-nitroisobutyranilide product (55). Experiments showed that α-nitroisobutyranilides pyrolize under the conditions of a GC-MS injector port at 170 °C to give isocyanates.

Current knowledge does not predict that a bromine would be replaced by a nitro group on a tertiary carbon [80] and it is of great potential use to synthetic chemists generally to know how to access an α-nitro group on a tertiary centre. We viewed the serendipitous access to the nitro compound 55 as worthy of exploitation in pursuit of an alternative synthesis of RU58841 and this goal was achieved with the rest of the synthetic steps presented here. This reaction is an extension of what is known as the Kornblum reaction and its synthetic utility will be explored in chapter 3 by applying it to a library of compounds.

**Step three** was a Béchamp reduction of 55 using alcohol, HCl and Fe⁰ to give the amine 49.

While there are multiple approaches to convert a nitro (NO₂) to a primary amine (NH₂), on a small scale a Béchamp reduction was chosen as although the workup of this method uses 1–2 L of solvent per 1–5 g of compound prepared, the procedure uses only solvents/reagents that are widely available so it can be readily repeated by other workers [82]. Usually −NO₂ is easy to reduce [83], but there can be problems with −NH₂ reacting with intermediates such as −NO, or with the amine poisoning the catalyst; results that can usually be minimised by conducting the hydrogenation in acidic solution [84]. In the case of step three (above) a Béchamp type reduction was highly effective but had a messy
workup. H₂ with Pd-C in a Parr hydrogenator proceeded quantitatively in ethanol but not at all in EtOAc. Reduction by hydrazine hydrate with Pd-C in ethanol at reflux also proceeded at high yield.

**Step four** was treatment of the amine 49 with α-bromoisobutyryl bromide (60).

Inspired by the observation of 2-nitropropane as a leaving group from the α-nitroisobutyranilide (55) on the GC-MS, this step to prepare a long chain moiety was carried out with the idea of performing a second Br–NO₂ substitution as we felt that the nitro species may undergo a ring-closure to give the five-membered hydantoin ring with the loss of 2-nitropropane. Compound 59 was prepared by acylation of 49 in exactly the same manner as the preparation of 52. With a molecular weight of 420 it was the heaviest molecule in this synthesis. This, as well as its long chain, made it hard to simply recrystallize out of solution. In most efforts, the compound went into solution but resolidified only as an amorphous mass.

At the end of the workup when the EtOAc phase was evaporated off, compound 59 was obtained as an oil, but resolidified as an off-white foam after several hours on a high vacuum pump. This foam was dissolved in DCM and passed through a silica gel column. Each fraction was then evaporated to give a solid, or sometimes a light brown viscous liquid. It was then boiled in n-heptane at 98 °C; when cooled the solvent was immiscible with the compound but had turned cloudy and the compound separated to the bottom of the flask as an amorphous and highly viscous mass. This seemed to take some impurities away as after it was decanted off the solid was whiter and more readily dissolved in m-xylene at RT. n-Pentane was then added to the m-xylene/59 mixture until the solution
A novel hydantoin synthesis and exploration of related reactions

turned cloudy or refractive. It was placed in a crystal-growing fridge overnight at 8 °C. The resultant crystals, which contained *m*-xylene of crystallization, were pure enough to use in the next reaction. Compound 59 is highly soluble in methanol but poorly soluble in DCM, TBME, diisobutyl ether and diethyl ether.

If one desires to obtain a pure crystal of 59 with no solvent of crystallization, *m*-xylene may be removed by placing in a flask at high vacuum at 60 °C for ~6 h. The crystal lattice collapses to give an opaque white solid. It is then easily recrystallized in toluene by slow evaporation in a screw-cap vial left slightly ajar. Crystallography on a crystal prepared this way confirmed the structure of 59 (lodged with the CCDC as number 892388).

**Step five** was a two-part, one-pot process.

![Step five](image)

Compound 59 was treated with NaNO₂ in DMF in an analogous manner to step two to undergo bromo–nitro substitution. The same flask was then heated to induce a ring closure of 58 to the hydantoin 48 and yield 2-nitropropane as a side product. A number of room temperature methods with catalysts were tried; however the best conditions for ring closure to 48 proved to be heating 58 at an optimized time/temperature while still in the DMF from the previous step. Compound 58 was therefore heated in DMF at 110 °C for 7 h, at which point GC-MS showed a major peak that integrated as 89%. Heating for more than 7 h or above 110 °C produced 48 in lower yield and that was harder to purify. DMF was removed by a high performance rotary evaporator with the flask in a water bath.
bath at 70 °C. The excess NaNO₂ was removed by EtOAc/water extraction. The organic portion was then dried to leave 48 as a white solid in 92% yield that was perfectly ready for the next reaction.

ESI-MS and GC-MS indicated that 48 had been formed. However, after two reaction steps in the one flask and especially if too much heat had been applied, it could be hard to isolate. When the reaction was first run it was ‘overheated’ and TLC indicated (correctly) that purification could be achieved by passing the crude product through a short column of silica. Compound 48 travels poorly in chlorinated solvents (low Rᵢ in DCM, lower in CHCl₃, lowest in CCl₄ where it remained on baseline) but very well in ethyl acetate and THF. Tertiary butyl methyl ether (TBME) gave an Rᵢ of 0.64 for 48 and left impurities at Rᵢ = 0.10–0.30. After 48 was passed through a silica gel column with TBME as eluent, evaporation of the solvent yielded a crystalline solid imbued with a slight redness. Trituration with DCM removed the red colouration, yielding a white solid (as noted in chapter 1, most hydantoins are poorly soluble in DCM). As suggested by Battmann et al. [34], 48 can be recrystallized from hot 2-propanol. It should be emphasized that if the ring closure is carried out according to the optimized temperature/time of 110 °C for 7 h, 48 is obtained as a clean-looking white solid without the need for such purification efforts.

**Step six** was an N-alkylation of the hydantoin 48.

![Chemical structure of step six](image)

Although it is possible to alkylate this nitrogen using K₂CO₃ in dry DMF before exposure to the alkylhalo compound, experiments by Dr Anthony Lingham in our laboratory a few years earlier showed extremely poor yields and presumably, so did Battman as he reported using NaH in his 1994 publication of the synthesis of RU58841. We therefore
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adopted this well-established process [71] of treating the hydantoin with NaH under anhydrous conditions to then react with 4-bromobutyl acetate (61) in DMF. The product was then de-acylated by exposure to NaOH to yield the free alcohol, RU58841.

Battmann gave the only literature report of the spectra of RU58841 [34] until we reported them in 2014 [74]. Compound 48 and RU58841 (13) had identical UV and IR properties to those reported by Battmann et al. The \(^{1}\)H NMR chemical shifts measured for each compound differed slightly from those reported by Battmann et al.; this may be due to a difference in solvent as Battmann et al. did not report their solvent or compound concentration. The melting point for 48 matched that reported, but in this work a melting point for RU58841 of 71–72 °C was repeatedly obtained from highly crystalline samples that are pure by \(^{1}\)H and \(^{13}\)C NMR, while Battmann et al. report 103–104 °C.

2.4 Novel ring closure

The observation of the isocyanate species 57 on the GC-MS may lead one to suspect that mechanism for the ring closure to the hydantoin featured in this synthesis contains an isocyanate intermediate. However, an analysis of the mechanistic possibilities of the ring closure should be considered. The electron density associated with the anilide nitrogen lone pair is very limited; this nitrogen atom is unlikely to be able to attack the other amide carbon. It may, however, be just nucleophilic enough to attack an isocyanate carbon at high temperature.

Two alternative ring-closure mechanisms can therefore be envisaged for this cyclisation, both of which are favoured under the Baldwin rules. The anilide nitrogen could perform an acyl substitution at the other carbonyl in a 5-exo-trig attack, with loss of 2-nitropropane anion. However the high degree of steric hindrance makes this amide carbonyl less susceptible to attack by the amine.
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Proposed mechanisms for ring closure of 58 to hydantoin

The steric hindrance of nucleophilic attack at a carbonyl with a dimethyl α-carbon has been shown to be highly influential and is often exploited in peptide synthesis by the use of pivaloyl chloride to prepare mixed anhydrides which have a protected carbonyl that divert attack by the amine exclusively to the unhindered carbonyl [86].
The alternative mechanism therefore seems more likely, in which the 2-nitropropane anion is lost first to create a much more electrophilic, much less hindered isocyanate, which is then attacked in a 5-exo-dig geometry. This mechanism is supported by our observation that 55 as well as the other α-nitroisobutyranilides appears to be converted into the corresponding isocyanates with the loss of 2-nitropropane upon injection into a conventional mass spectrometer. Here the compounds are subjected to temperatures of 170–190 °C, high vacuum and silica gel.

From the above considerations this ring closure to hydantoin therefore appears to be via the base-induced isocyanate mechanism. This mechanism is in contrast to that described recently by Hutchby and associates who have reported using masked isocyanates to reach substituted urea compounds [87] which proceed via the addition of a proton to a urea.

Hutchby’s preparation of substituted urea compounds with isocyanate intermediate

The formation of an isocyanate group that gives 2-nitropropane as a leaving group is previously unreported and will be further investigated in chapter 4.

2.5 Experimental procedures and compound characterization

IR spectra were measured on a Varian 1000 FTIR spectrophotometer as KBr disks (4000–400 cm⁻¹). Accurate mass spectra were measured using a Waters GCT Premier HR-TOFMS equipped with an Agilent 7890 GC column. NMR spectra were obtained using a Bruker 300 MHz Avance spectrometer. Chemical shifts in ¹H NMR spectra were reported in parts per million (ppm δ) relative to the TMS signal, measured by the residual
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chloroform signal (δ = 7.24 ppm) in the CDCl₃ solvent. Chemical shifts in ¹³C NMR spectra are reported relative to TMS and measured by the central peak of the deuterochloroform signal (δ = 77.5 ppm). Crystallography was carried out on a Bruker APEX II DUO diffractometer. While the data for the IR and NMR spectra are listed here, the images of each spectrum are listed in appendix V.

2-Bromo-N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methylpropanamide (52).

![Chemical structure of 2-Bromo-N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methylpropanamide (52)]

3-Trifluoromethyl-4-cyanoaniline (54) (3.00 g, 16.1 mmol), dissolved in 1,2-dichloroethane (35 mL), was stirred with oven-dried K₂CO₃ (2.0 g). α-Bromoisobutyryl bromide (60) (4.10 g, 17.8 mmol) was added and stirring continued at room temperature for 14 h. The solvent was removed by rotary evaporator right after the reaction and the solids worked up in EtOAc/water to yield 5.30 g (99%) of 52, which recrystallized from methanol to give 4.85 g (14.5 mmol, 99% yield) as amber cubes or on some occasions rhombohedra, m.p. 127–129 °C; Rᵢ = 0.50 in 4:1 hexanes/EtOAc; IR(cm⁻¹): 3293, 3099, 3057, 2987, 2935, 2234 (CN), 1666 (C=O), 1586, 1520, 1427, 1325, 1185 & 1139 (C-F), 1052, 847, 672; ¹H NMR (300 MHz, 16 mg: 0.4 mL, CDCl₃): δ 2.06 (6H, s, CH₃), δ 7.82 (d, ArH₅, J 8), δ 7.92 (dd, ArH⁶, J 2, J 8), δ 8.05 (d, ArH⁷, J 2), δ 8.73 (br, s, NH); ¹³C NMR (75 MHz, 16 mg: 0.4 mL, CDCl₃): δ 31.3 (s, C-3ₐₐB), δ 60.6 (s, C-2), δ 103.3 (s, C-4'), δ 116.7 (s, C-N), δ 118.5 (q, C-2', J 5), δ 123.4 (q, CF₃, J 136), δ 123.7 (s, C-6'), δ 132.6 (q, C-3', J 32), δ 137.1 (s, C-5'), δ 144.4 (s, C-1'), δ 171.3 (s, C-1); Neg ESI HRMS: calc’d m/z for C₁₂H₁₀N₂O₃F₃Br (M-H): 332.9850, observed: 332.9858; CCDC 894556.
N-[4-Cyano-3-(trifluoromethyl)phenyl]-2-methyl-2-nitropropanamide (55).

Compound 52 (5.00 g, 15.0 mmol) was dissolved in DMF (130 mL) and NaNO₂ (10.0 g, 145 mmol) was added. The contents were stirred at room temperature for 14 h then transferred to a larger flask where deionized water (130 mL) was added which gave heat and produced clean white needles that were filtered and washed with water to give 4.84 g of 55. These needles were shown to actually be 55 co-crystallized in a 1:1 ratio with DMF and therefore contained 12.9 mmol of 55 for a corrected yield of 86%, m.p. 129–131 °C (co-crystallized with DMF); Rᵋ = 0.79 in 1:1 hexanes/EtOAc or 0.17 in 4:1 hexanes/EtOAc; IR(cm⁻¹): 3337, 3191, 3119, 3062, 3003, 2948, 2237 (CN), 1706 (C=O), 1603, 1562, 1536, 1504, 1323, 1180 & 1134 (C-F), 1050, 895, 857, 640, 558; ¹H NMR (300 MHz, 20 mg: 0.4 mL, CDCl₃): δ 2.02 (6H, s, CH₃), δ 3.53 (br, s, NH), δ 8.18 (d, ArH⁴, J₈), δ 8.26 (dd, ArH⁶, J₂, J₈), δ 8.40 (d, ArH₂, J 2), δ 10.80 (s, NH); ¹³C NMR (75 MHz, 40 mg : 0.4 mL CDCl₃): δ 23.7 (s, C-3ₐ/B), δ 92.1 (s, C-2), δ 103.8 (s, C-4'), δ 115.9 (s, CN), δ 118.1 (q, C-2', J 5), δ 123.0 (q, CF₃, J 136), δ 123.5 (s, C-6'), δ 132.5 (q, C-3', J 17), δ 136.7 (s, C-5'), δ 143.5 (s, C-1'), δ 167.4 (s, C-1); Neg ESI HRMS: calc’d m/z for C₁₂H₁₀N₃O₃F₃ (M-H): 300.0596, observed: 300.0602; CCDC 904089.
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\[ \text{2-Amino-N-[4-cyano-3-(trifluoromethyl)phenyl]-2-methylpropanamide (49).} \]

Parr hydrogenation: 55 (500 mg, 1.34 mmol) in ethanol (25 mL) with 10% palladium on charcoal (100 mg) was hydrogenated in a Parr apparatus at 35 psi. The flask was agitated mechanically for 4 h at a temperature of 28 °C, after which time TLC showed that the nitro compound (55) had been replaced with the amine 49.

Transfer hydrogenation using hydrazine: 55 (500 mg, 1.34 mmol) was placed in ethanol (10 mL) was stirred with 10% palladium on charcoal (60 mg) and heated to 80 °C. Hydrazine hydrate (0.2 mL) was added dropwise. The contents were allowed to reflux for 1 h, after which time TLC showed that the nitro compound (55) had been replaced with the amino compound (49).

Béchamp reduction: The addition of 2-propanol improved miscibility but is not strictly necessary. For this workup it should be noted that 49 is highly soluble in EtOAc. Fe readily chelates to the free amine, needing repeated adjustment of pH and addition of solvent to dislodge as a suspension that is removed by filtration. This may not be the optimal reduction method on a large scale. Instructions for this messy workup are as follows:

- Vacuum filter through celite to remove iron solids.
- Extract the filter residue with hot ethanol.
- Remove water/ethanol/2-propanol using rotary evaporator.
- Dissolve solids in ethyl acetate/water. The aqueous phase should be ~ pH2 (this
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may be due to the presence of FeCl₃ which acts as a buffer). At a pH of less than 7 compound 49 will reside in the aqueous portion.

- Remove and discard ethyl acetate portion. If the starting aniline 54 was orange from a small amount of dimerized compound, the ethyl acetate discarded here will be orange, thus purifying the product to a white solid.
- Add conc. NaOH to the aqueous portion. This precipitates iron zero as a dark green or black substance. 49 precipitates at > pH7 as a white solid. Bring to a pH of ~10.
- Add plenty of ethyl acetate and shake. Compound 49 dissolves into EtOAc while a further precipitate of Fe⁰ is yielded which sits itself at the bottom of the aqueous layer.
- Remove the bottom fraction along with Fe precipitate. Add another volume of pure water. Be sure to add enough water to dissolve Fe.
- Dry the organic layer with MgSO₄, filter through celite, wash filtrate with hot EtOAc.
- Evaporate off EtOAc to get 49 as a clean white solid.

Compound 55 (5.00 g, 13.4 mmol) was placed in a flask and solvents were added in the following order: ethanol (32 mL), water (18 mL), 2-propanol (9.0 mL). Iron powder (Fe⁰) (1.50 g, 35.8 mmol) was added and the reaction taken to reflux (90 °C) at which time ~1 mL of [32%] hydrochloric acid was added through the top of the condenser. After 1 h the reaction was allowed to cool and TLC showed start material gone, replaced by a stickier (lower Rf) tailing spot that looked characteristic of an amine compound.

The reaction contents were filtered through celite and the solvents (the last of which was most likely water) removed by evaporation. The solids were extracted into EtOAc/water and the organic fraction gave 2.72 g (10.0 mmol, 75% yield) of 49 as clean white fluffy crystals which did not need to be stored away from air or light, m.p. 113–115 °C; Rf = 0.11 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3388, 3362, 3277 & 3233 (N-H), 2993, 2972, 2934, 2231 (CN), 1699 (C=O), 1613 (C=O), 1514, 1490, 1422, 1326, 1178 & 1138 (C-F), 1050, 909, 888, 858, 749, 734, 673, 558; ¹H NMR (300 MHz, 75 mg: 0.5 mL, d₆-DMSO): δ 1.34 (6H, s, CH₃), δ 3.53 (br, s, NH), δ 5.05 (br, s, NH), δ 8.04 (d, ArH⁵, J 8), δ 8.18 (dd, ArH⁶, J 2, J 8), δ 8.43 (d,
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ArH₂, J 2); ¹³C NMR (75 MHz, 75 mg: 0.5 mL, d₆-DMSO): δ 29.2 (s, C-3ₐ/ₜ), δ 56.3 (s, C-2), δ 102.4 (s, C-4'), δ 116.8 (s, CN), δ 117.8 (q, C-2', J 5), δ 123.1 (s, C-6'), δ 123.4 (q, CF₃, J 136), δ 132.6 (q, C-3', J 17), δ 137.2 (s, C-5'), δ 144.6 (s, C-1'), δ 179.1 (s, C-1); Neg ESI HRMS: calc’d m/z for C₁₂H₁₂N₃O₃ (M-H): 270.0854, observed: 270.0864; CCDC 893326.

2-Bromo-N-(1-[[4-cyano-3-(trifluoromethyl)phenyl]carbamoyl]-1-methylethyl)-2-methylpropanamide (59).

Compound 49 (1.03 g, 3.80 mmol) was dissolved in 1,2-dichloroethane (20 mL) in a flask that contained oven-dried K₂CO₃ (1 g) and then stirred with α-bromoisobutyryl bromide (60) (1.06 g, 4.06 mmol) for 14 h. The solvent was removed by evaporation and the product partitioned between ethyl acetate and water. The EtOAc phase was evaporated and placed under high vacuum for 3 h to yield 1.36 g (3.23 mmol) of 59 (85% yield) as an amorphous solid foam. This was dissolved in dichloromethane and passed through silica. Some of 59 stuck to the silica, but this was recovered by passing EtOAc through into a separate flask (59 is highly soluble in EtOAc). Each fraction was then removed in vacuo to solid, or sometimes a light brown viscous liquid. It was then boiled in n-heptane at 98 °C which sat on top when cooled and went cloudy. The decanted solid was dissolved in m-xylene at RT and n-pentane was added to m-xylene/59 until the solution turned cloudy, or in some cases refractive. The mixture was placed in a fridge overnight at 8 °C to give colourless crystals containing m-xylene of co-
crystallization, m.p. 121–123 °C. Xylene free crystals were obtained by heating in high vacuum at 60 °C for ~6 h, giving a white powder, which formed crystals by very slow evaporation from toluene, m.p. 107–109 °C; Rf = 0.78 in 1:1 hexanes/EtOAc or 0.07 in 4:1 hexanes/EtOAc; IR(cm⁻¹): 3401, 3312 (N-H), 2992, 2932, 2229 (CN), 1722 (C=O), 1664 (C=O), 1611, 1512, 1427, 1328, 1174 & 1132 (C-F), 1049, 882, 850, 555; ¹H NMR (300 MHz, 32 mg: 0.4 mL, d₆-DMSO): δ 1.51 (6H, s, C-3/CH₃), δ 1.94 (6H, s, C-6/CH₃), δ 3.38 (NH-2), δ 8.09 (d, ArH⁵, J 8), δ 8.15 (dd, ArH⁶, J 2, J 8), δ 8.34 (d, ArH², J 2), δ 10.03 (NH-1); ¹³C NMR (75 MHz, 32 mg: 0.4 mL, d₆-DMSO): δ 24.8 (s, C-3A/B), δ 31.7 (s, C-6A/B), δ 58.2 (s, C-5), δ 61.7 (s, C-2), δ 102.3 (s, C-4'), δ 116.8 (s, CN), δ 117.8 (q, C-2', J 5), δ 123.2 (s, C-6'), δ 123.5 (q, CF₃, J 136), δ 132.4 (q, C-3', J 17), δ 137.3 (s, C-5'), δ 146.0 (s, C-1'), δ 171.1 (s, C-4), δ 174.7 (s, C-1); Neg ESI HRMS: calc’d m/z for C₁₆H₁₇N₃O₃F₃Br (M-): 420.0359, observed: 420.0362; CCDC 892388.

_N-(1-{[4-Cyano-3-trifluoromethyl]phenyl}carbamoyl)-1-methylethyl)-2-methyl-2-nitropropanamide (58)._  

1.00 g (2.38 mmol) of 59 was dissolved in DMF (15 mL) and NaN₃ 1.30 g (18.8 mmol) added. The contents were stirred at RT for 14 h. The reaction was monitored by TLC and electrospray mass spectrometry. A TLC showed that all 59 had reacted and a single, different, Rf of the newly formed compound. High resolution mass spectrometry confirmed that the bromine had been replaced by a nitro group. The product (58) was not isolated but used _in situ_ for the next step. 

Rf = 0.50 in 1:1 hexanes/EtOAc; Neg ESI HRMS: calc’d m/z for C₁₆H₁₇N₄O₄F₃ (M-H): 385.1124, observed: 385.1133.

_4-(4,4-Dimethyl-2,5-dioxoimidazolin-1-yl)-2-(trifluoromethyl)benzonitrile (48)._
The reaction vessel from the preparation of 58 was fitted with an air condenser left open at the top and heated at 110 °C for 7 h and no longer. Removal of the solvent by evaporation gave 48 (587 mg, 1.98 mmol, 83% yield) which was suitable for the next reaction. For the purposes of obtaining m.p., IR and NMR data the compound was recrystallized from hot 2-propanol which sacrificed the yield down to 40%.

m.p. 210–212 °C; UV max = 256 nm (ε = 16200); Rf = 0.25 in 1:1 hexanes/EtOAc; IR(cm−1): 3337, 3121, 2983, 2936, 2242 (CN), 1789, 1725 (C=O), 1612 (C=O), 1504, 1440, 1398, 1282, 1182 & 1135 (C-F), 1049, 899, 855, 808, 762, 733, 658, 559, 441; ¹H NMR (300 MHz, 20 mg: 0.4 mL, CD₃CN): δ 2.88 (6H, s, CH₃), δ 6.85 (s, NH), δ 8.62 (dd, ArH₆, J₂, J₈), δ 8.70 (d, ArH₅, J₈), δ 8.75 (d, ArH², J₂); ¹³C NMR (75 MHz, 20 mg: 0.4 mL, CD₃CN): δ 25.3 (s, CH₃ x 2), δ 59.7 (s, hyd-C-5), δ 108.8 (s, C-4'), δ 116.5 (s, CN), δ 123.7 (q, CF₃, J 136), δ 124.9 (q, C-2', J 5), δ 130.4 (s, C-6'), δ 133.4 (q, C-3', J 17), δ 137.0 (s, C-5'), δ 138.2 (s, C-1'), δ 154.4 (s, hyd-C-2), δ 177.1 (s, hyd-C-4); GC-(EI) TOF-HRMS: calc'd m/z for C₁₃H₁₀N₅O₂F₃ (M): 297.0725, observed: 297.0713.

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile (RU58841).
Anhydrous conditions were kept by using oven-dried glassware and by flame drying a Schlenk line before the reaction using the vac/purge method. Compound 48 (1.00 g, 3.37 mmol) was dissolved in dry DMF (25 mL). Sodium hydride 60% suspension in mineral oil (280 mg, 7.00 mmol) was twice washed in a sealed flask with dry n-hexane (5.0 mL) using a syringe to transfer the n-hexane. The solution of 48 in DMF was transferred to the flask containing the NaH using a pressure-equalizing addition funnel. The resulting mixture was stirred for 15 min until the evolution of bubbles of H₂ gas ceased. 4-Bromobutyl acetate (61) (680 mg, 3.49 mmol) was added by syringe through the addition funnel and washed in with a second portion of dry DMF (25 mL). The mixture was stirred and heated at 50 °C for 2 h. After this time the reaction was considered to be complete; a pellet of NaOH (~200 mg) was added, followed by deionized water (45 mL). The mixture was cooled overnight at 0 °C and the filtrate collected to give 996 mg (2.70 mmol) of RU58841.

The crude yield was close to quantitative (92–98%) after the residual DMF and water were removed by evaporation but a subsequent recrystallization from diisopropyl ether/n-heptane gave a purer product as sheaves of blades with a reduced yield of 80%. RU58841 was very difficult to dissolve in diisopropyl ether, the solvent used by Battmann et al. [34], and a large volume was needed. Crystallization was also difficult, and required use of n-heptane to the point of cloudiness and standing overnight at 8 °C, and even then was not always successful. The crystals dried in vacuo for several days to remove residual solvent prior to m.p., IR and NMR measurements. After several months in the vacuum desiccator, the crystals were sent to the Campbell Microanalytical laboratory in New Zealand for C,H,N analysis.

m.p. 71–72 °C; UV max = 261 nm (ε = 15100); Rₐ = 0.07 in 1:1 hexanes/EtOAc, 0.18 in 1:3 hexanes/EtOAc and 0.42 in EtOAc; IR(cm⁻¹): 3392 (OH), 3133, 2944, 2876, 2234 (CN), 1774, 1719 (C=O), 1612, 1573, 1505, 1438, 1413, 1377, 1312, 1179 & 1133 (C-F), 1051, 894, 837, 763, 675, 555; ¹H NMR (300 MHz, 20 mg: 0.4 mL, CDCl₃): δ 1.52 (6H, s, CH₃), δ 1.64 (2H, m,
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CH$_2$-3), δ 1.82 (2H, m, CH$_2$-2), δ 2.12 (1H, s, OH), δ 3.39 (2H, t, CH$_2$-1, $J$ 6), δ 3.68 (2H, t, CH$_2$-4, $J$ 6), δ 7.89 (d, ArH$^5$, $J$ 8), δ 7.98 (dd, ArH$^6$, $J$ 2, J 8), δ 8.13 (d, ArH$^2$, $J$ 2); $^{13}$C NMR (75 MHz, 20 mg: 0.4 mL, CDCl$_3$): δ 23.7 (s, CH$_3$ x 2), δ 26.4 (s, al-C-2), δ 30.0 (s, al-C-3), δ 40.4 (s, al-C-1), δ 62.2 (s, hyd-C-5), δ 62.3 (s, al-C-4), δ 108.4 (s, C-4'), δ 115.3 (s, CN), δ 122.3 (q, CF$_3$, $J$ 136), δ 123.3 (q, C-2', $J$ 5), δ 128.2 (s, C-6'), δ 133.8 (q, C-3', $J$ 17), δ 135.6 (s, C-5'), δ 136.8 (s, C-1'), δ 153.2 (s, hyd-C-2), δ 174.9 (s, hyd-C-4); GC-(EI) TOF-HRMS: calc’d $m/z$ for C$_{17}$H$_{18}$N$_3$O$_3$F$_3$ (M): 369.1300, observed: 369.1294; C, H, N: calc’d for C$_{17}$H$_{18}$N$_3$O$_3$F$_3$: 55.28, 4.91, 11.38. Found: 55.19, 4.84, 11.28.

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3. **Investigation into the mechanism of Br–NO₂ substitution on tertiary α-carbons**

One of the key steps in the RU58841 synthesis from chapter 2 was a bromo–nitro substitution of 52 to give 55. When the PhD candidate carried out this reaction, we in our group did not expect it to proceed as a substitution. The reaction had originally been an attempt at a novel method to prepare an isocyanate. This reaction will here be further investigated.

**3.1 Introduction**

This substitution reaction has confounded the synthetic organic chemists whom I’ve spoken with at conferences, all of whom have viewed it as bafflingly simple.

![Step two](image)

This bromo–nitro substitution is highly unexpected because the steric hindrance on a tertiary carbon usually impedes an S_N2 pathway and encourages S_N1. The nitrite ion is usually seen to attack with the oxygen under S_N1 to give an alkyl nitrite product (R–O–N=O) instead of an alkyl nitro (R–NO₂) [78]. Hence an axiom has developed ‘bromo–nitro substitutions using NaNO₂ proceed on primary or secondary but not tertiary carbons’ [78]. In this case we see that the substitution does proceed on tertiary bromides that are α to a carbonyl. The most obvious conclusion is that the neighbouring carbonyl is playing a role. There are two examples of precedents for this (1957 and 1977), both of which are largely unknown.
As aliphatic nitro compounds are known to be highly versatile building blocks in organic synthesis [88], the recognition of this exception to the general principle of bromo–nitro substitutions will encourage better ways to prepare alpha-nitro ketones, esters and amides. Previous summaries on the preparation of aliphatic nitro compounds have struggled to provide more than a limited repertoire of reactions and new ways to prepare them are of great utility.

### 3.2 Halo–nitro substitutions: the Kornblum reaction

As we will see throughout this chapter, Nathan Kornblum at Purdue University in Indiana and his various co-workers took a great deal of interest in halo–nitro substitutions throughout the 1950s and 60s.
The reaction was eventually named the Kornblum reaction and was widely known to occur only on primary or secondary halo-carbons. When applied to tertiary halo-carbons, the result is an alkene elimination product [89].

March's Advanced Organic Chemistry (2007 edition) describes something known as Kornblum's rule [90]. To paraphrase, Kornblum’s rule refers to the principle that hard acids prefer hard bases and soft acids prefer soft bases; as an $S_N1$ carbocation is a hard acid, an ambident nucleophile attacks its carbon with its more electronegative atom, whereas the reverse is true for $S_N2$. Kornblum’s rule dictates that for bromo–nitro substitutions, $S_N1$ gives alkyl nitrite ($\text{R–O–N}=\text{O}$) and $S_N2$ gives alkyl nitro ($\text{R–NO}_2$).

March's Advanced Organic Chemistry (2007 edition) makes reference to one of Kornblum’s papers [91] for Kornblum’s rule and in this paper he states that the production of a nitro compound using nitrite ions is more $S_N2$ than $S_N1$ in nature, but that it has some properties of both [91].

Kornblum also investigated in what way an ambident nucleophile will react in various solvents and showed that both hydrogen bonding capacity and dielectric constant of the solvent chosen greatly influenced control over the product [92]. However, he did not observe the reaction of nitrite ions in this study, but instead used alkali phenoxides, probably because the phenoxides were capable of being dissolved by a wider range of solvents than are nitrite ions.

### 3.3 Kornblum and the $S_{N1}/S_{N2}$ dichotomy

Many researchers, especially earlier ones, have discussed substitution mechanisms as a comparison between $S_{N1}$ and $S_{N2}$, implying that these are the only two possibilities [78, 93, 94] and Kornblum consistently wrote as though these were the only two options [79,
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95, 96, 91]. However, it is a false dichotomy that the bromo–nitro substitution considered in this chapter must be $S_N1$ or $S_N2$. This reaction has other possible rate determining steps, and in fact, as will be discussed in 3.4.1, the Hammett plots prepared herein indicate a transition state with a negative charge, meaning that the bromo–nitro substitution on a tertiary halo carbon alpha to a carbonyl is definitely neither $S_N1$ nor $S_N2$. Having said that, the $S_N1/S_N2$ dichotomy is a useful starting point for a discussion as these two substitution mechanisms are commonly observed and widely understood, making it easier to compare. A number of possible experiments exist that could provide simple evidence of $S_N1$ versus $S_N2$ character of this bromo–nitro substitution. Many of these potential experiments will be discussed in this section and the results of those that have been carried out will be reported.

It is commonly thought by synthetic organic chemists that while halo–nitro substitutions proceed with primary and secondary carbons (Kornblum reaction), they will not proceed on tertiary carbons as steric hindrance impedes an $S_N2$ pathway [79]. It is also understood that an $S_N2$ pathway is required to achieve a nitro product as the nitrite ion, being an ambident nucleophile, will attack a carbocation with the oxygen during an $S_N1$ reaction to give the nitrite ester product (R–O–N=O) which is usually undesired. When, during the course of this project, this unexpected substitution reaction occurred on a tertiary $\alpha$-haloamide (52), a subsequent literature search found that Kornblum et al.’s reported and characterized nitro substitutions on primary and secondary halides had included one where the halide was alpha to a carbonyl, namely ethyl 2-bromopropionate [89]. The content of this article was discussed in a 1955 PhD thesis by Blackwood [97] and again by Blackwood, Kornblum and co-workers who co-authored a 1955 paper in Chemistry and Industry [98]. In a later JACS paper [99], the authors of [89] on this same topic claimed that $\alpha$-nitroesters can be prepared in generous yields by the action of sodium nitrite on $\alpha$-bromoesters. They do not mention whether the esters need be primary, secondary or tertiary. Kornblum seems to have been well aware of the substitution proceeding readily on carbons next to a carbonyl and even placed a patent in December 1957 on the preparation of $\alpha$-nitroesters from $\alpha$-haloesters [100]. One example preparation given in this patent is that of ethyl $\alpha$-nitroisobutyrate (65). The authors indeed state that $\alpha$-nitroisobutyrate and other homologues that also lack an alpha proton do not need nitrite ester scavengers for the reaction to proceed in good yield [100].
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The preparation of ethyl α-nitroisobutyrate as reported in a 1957 patent [100]

Despite the information conveyed in this patent, the concept that halide−nitro substitutions do indeed proceed on tertiary centres next to a carbonyl was not absorbed by the organic synthesis community. Years later, chemists still chose longer methods to achieve tertiary α-nitro compounds; in one example (to be discussed later in this chapter), Sayo et al. use four steps to achieve an α-nitroisobutyranilide [101].

Kornblum and co-workers reported that the addition of a “nitrite ester scavenger” (read: alkyl nitrite scavenger) considerably improved the yield of nitro substitution on secondary halo carbons [99]. These are any of the phenolic compounds phloroglucinol (66), catechol (67) or resorcinol (68), with phloroglucinol reported as the most effective [89]. These compounds remove alkyl nitrites and nitrous acid by rapidly irreversibly nitrosating to nitrosophenols, which exist in the tautomeric quinone oxime forms [102].

Nitroalkanes are easily separated from their equivalent alkyl nitrites by fractional distillation as the nitro alkane boils at a much higher temperature [103]. However even when the proportion of nitro to nitrite product is highly in favour of the desired nitro compound, the use of an alkyl nitrite scavenger is important as the degradation pathway as described by Kornblum requires only a catalytic amount of the alkyl nitrite side product [99] to decompose the desired nitro compound via a nitroso intermediate that significantly lowers the yield of the preparation. This pathway, which begins with the
loss of a highly acidic α-nitro proton, is not applicable to tertiary α nitro products such as 55 which lack an α proton. This means that they do not need the addition of an alkyl nitrite scavenger to be prepared in good yield.

While the authors of [99] observed nitration on a tertiary carbon alpha to a carbonyl, they did not discuss this phenomenon, and in a previous paper [89] used language that suggested that all tertiary halide substitutions do not proceed, but instead degrade to alkenes (Kornblum was an author on both of these papers). In [89] they declare the halo–nitro substitution to be S_N2, although the mechanism appears to have been incidental to the reported findings, which focus much more greatly on the merit of the newly discovered preparation. In Kornblum’s later 1966 work [96] he further discusses the characteristics of the substitution reaction that by then bore his name. He stated that the halo–nitro substitution exhibits some S_N1 and some S_N2 character and that performing the substitution using silver nitrite gave reaction kinetics with carbonium ion character but the a product that indicates an S_N2 process. He therefore claimed that it proceeds through a transition state with both S_N1 and S_N2 character [96]. Kornblum seems to rely on his own authority for this viewpoint as he does not show new data as evidence for this claim. He instead gives two references to his own earlier works, which on close inspection are actually both referring to the same 1955 publication [91].

The general method of halo–nitro substitution published by Kornblum and associates was robust from its inception: it proceeds at room temperature, uses DMF as a solvent, NaNO_{2} as a reagent and does not require anhydrous conditions. Kornblum et al. claimed that the reaction was faster and higher yielding in DMF than it was in ethanol due to the excellent solubility of NaNO_{2}. They offered the explanation that the faster reaction in DMF allows the nitro compound to form and be isolated before the usual degradation to nitrite esters that is observed with haloparaffins [89]. Kornblum used the term nitrite ester (R–O–N=O) to describe the undesired side product but the more modern term, alkyl
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nitrite, will hereafter be used. The reaction was also reported to proceed in ethylene glycol, but as this was slower and the solvent harder to remove than DMF, Kornblum advised against this [89].

It is of course now known that DMF is an excellent dipolar aprotic solvent and dissolves salts by solvating their cations, while leaving the anions in a highly reactive ‘naked’ (unsolvated) state [104].

Kornblum and co-workers reported in the same paper [89] that the addition of 8% urea to the DMF dissolved far more NaNO₂ which further increased the reaction rate. However when the PhD candidate tried this a slight reduction in rate was observed. Further, the use of urea in these conditions is odd as urea actually reacts with nitrous acid to give nitrogen, carbon dioxide and water: H₂NCONH₂ + 2HNO₂ → 2N₂ + CO₂ + 3H₂O [105].

The nitration was observed by Kornblum to proceed just as readily with an iodo group as with a bromo group and was reported to proceed with alkyl chlorides but at a much slower rate – for these it was advised that silver nitrite be used for their nitration [89]. In a follow up paper, Kornblum et al. [95] explained that silver nitrite could be used to synthesize α-nitroesters from α-bromoesters but since this was so much slower than using sodium nitrite, it was completely impractical for the nitration of α-bromoesters which should be carried out with the cheaper sodium nitrite. Kornblum et al. [95] pointed to this reduced substitution rate of silver nitrite compared with sodium nitrite as evidence of a bimolecular displacement mechanism (S₈2 process) which they had suggested in an earlier paper [89].

The Kornblum reaction is known to proceed on primary and secondary halo compounds

When Kornblum et al. applied the same conditions to a tertiary bromo-compound which did not have a carbonyl, namely t-butyl bromide, its substitution was unsuccessful and
isobutylene was formed as the elimination product [89, 104].

It is useful to design experiments to elucidate the mechanism by which the Kornblum reaction proceeds with tertiary α-halo-carbon compounds, which may well be a different mechanism from that which operates in primary and secondary halo-alkane substitutions.

Nitrite ions [NO$_2^-$] react with organo-halo compounds to form alkyl nitrites (R–O–N=O) under S$_N$1 conditions (O is the atom of higher electron density) and nitroalkanes (R–NO$_2$) under S$_N$2 conditions (N is the more readily polarisable atom) [78, 106]. This outcome is consistent with molecular orbital theory which states that the cationic intermediate of S$_N$1 is a hard electrophile (high-energy LUMO) and operates under charge control, therefore favouring the O of nitrite because it has more negative charge [107]. It requires stabilization by three neighbouring carbons which each donate some electron density to give a cation which in reality has only a partial charge. Conversely, the unaltered alkyl halide is a soft electrophile (low-energy LUMO) and operates under orbital control, which favours the N of nitrite because it has the higher atomic orbital coefficient in its HOMO than the O [107]. The substitution of a halogen by an S$_N$1 process is therefore expected to give an alkyl nitrite product. The formation of a nitro product through S$_N$1 would be at odds with previous knowledge on the topic [78].
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![Chemical reactions]

**$S_N1$ and $S_N2$ reaction pathways for nitrite substitution on tertiary and primary halocarbons**

In addition, primary halo-carbons have less steric hindrance than secondary or tertiary which encourages the approach of a nucleophile in a pull-push manner. This all holds true until the introduction of a carbonyl group, which imparts local planarity and increases the likelihood of an $S_N2$ substitution (which requires a low steric hindrance) over an $S_N1$.

A widely known halo–nitro substitution can be carried out by boiling the sodium salts of $\alpha$-halo-carboxylic acids in aqueous sodium nitrite to yield the nitroalkane by releasing $\text{HCO}_3^-$ [103].

**Action of NaNO₂ on the sodium salts of $\alpha$-halo-carboxylic acids**

This method works well to prepare terminal nitroalkanes, but it is unclear whether it has been tried with tertiary $\alpha$-halo carboxyls.

**3.3.1 Mechanistic evidence from ambident nucleophiles**

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Much of the existing knowledge of halo–nitro substitutions is derived from the fact that nitrite is an ambident nucleophile. A great deal is understood about which site on an ambident nucleophile will be likely to donate its electron pair and form a new bond and it has largely to do with the promotion of either nucleophilicity or basicity. Much of this is covered in Sykes, 1981, A guidebook to mechanism in organic chemistry, 5th ed. [78].

An ambident nucleophile is one that has its negative charge resonance delocalized over two non-equivalent atoms and so can attack from either of these two sites, each site resulting in a different product. It has been widely understood that with ambident nucleophiles \( S_N1 \) promotes attack by the more electronegative atom in the nucleophile, whereas \( S_N2 \) allows preferential attack by the more polarizable atom [78].

A commonly encountered ambident nucleophile is cyanide, which may be introduced using sodium, potassium or silver cations. In this case, the C is the more polarizable and the N is the more electronegative.

\[
\begin{align*}
\text{more polarisable} & \quad \text{more electronegative} \\
\text{CN} & \\
\end{align*}
\]

The nitrite ion is also an ambident nucleophile which can react at either the N or the O. In most targeted reactions in organic synthesis it is desired that the nitrite will react at the N to furnish a nitro compound as the product.

\[
\begin{align*}
\text{Resonance canonical forms of the nitrite ion} \\
\end{align*}
\]

This \( S_N1/S_N2 \) dichotomy has long been exploited for preparative halo–cyano substitutions which use cyanide as a nucleophile [78]. The use of AgCN as the cyanide source promotes \( S_N1 \) as the formation of the stable halo-silver salt drives the formation of the cationic \( S_N1 \) intermediate which is then readily attacked by the atom on the nucleophile.
with the higher electron density (N) to give an isonitrile product (R-NC). When NaCN is used as the cyanide source, the substitution proceeds as SN2 and reacts with the more polarizable atom on the ambident nucleophile (C) to produce a nitrile compound (R-CN) [78]. Similarly, the nitrite ion [NO2]- is found to result in the formation of alkyl nitrites (R-O-N=O) under SN1 conditions as O is the atom of higher electron density, so it reacts with hard electrophiles (such as an SN1 intermediate). Under SN2 conditions nitrite instead forms nitroalkanes (R–NO2) as N is the more readily polarizable atom – it has a higher HOMO atomic orbital coefficient, so it reacts with soft electrophiles (as in the SN2 process).

SN1 seems unlikely at a terminal bromo group on an n-alkane and it would be expected to undergo a Wagner-Meerwein rearrangement under SN1 conditions. For example, 1-bromooctane’s hypothetical carbocation could rearrange by H-migration to give the positive charge on the number 2 carbon, allowing the nitro to attach here and the reaction would be expected to yield 2-nitrooctane. Not only is H-migration more unusual than alkyl-migration in Wagner-Meerwein rearrangements, it is observed in [89] that treatment of 1-bromoheptane (71) and 1-bromooctane with NaNO2 in DMF give high yields of 1-nitroheptane (72) and 1-nitrooctane respectively; no rearrangement takes place.

For this reason alone, an SN1 mechanism can be ruled out for Br–NO2 substitutions on primary α-bromo-carbonyl compounds. However, this does not rule out SN1 substitution on the tertiary bromo-compounds and, given that it would be such a simple experiment, the substitution rate of our model reaction ought to be monitored while using a different concentration of nitrite, OR, a different nucleophile.

3.3.2 Stereochemical evidence
In 1962, Kornblum reported the inversion of configuration of halo–nitro substitutions in some but not all cases when reacting chiral halo-alkanes \([108]\). In a later discussion \([96]\) on the inversion of configuration of 1-chloroethylbenzene (\(\text{73, referred to by Kornblum as } \alpha\text{-phenylethyl chloride}\)), \([96]\) Kornblum reported retention of configuration in acetonitrile and petroleum ether. By contrast, an inversion of configuration was reported when the reaction was carried out in cyclohexane. Kornblum postulated that the substitution mechanism follows a spectrum of \(S_N1\)–\(S_N2\) character and he also asserted that in both diethyl ether and benzene the reaction proceeded via the \(\alpha\text{-phenylethyl carbonium ion}\).

![1-Chloro-ethylbenzene](image)

Furthermore, Kornblum proposed that the choice of metal cation with the nitrite was important in determining the mechanism and its balance between \(S_N1\) and \(S_N2\). This indicates that the reaction has properties of both \(S_N1\) and \(S_N2\) and could potentially proceed by both pathways depending on the solvent and the cation involved, but it should be remembered that Kornblum referred to the substitution on primary and secondary halo-carbons, as he had stated elsewhere that \(\text{Br}–\text{NO}_2\) substitution doesn’t occur on tertiary carbons (despite once carrying it out on a tertiary example \([100]\)).

In \([96]\) Kornblum also reported that a rapid silver-halide bond formation is required to lower the amount of carbocation formed to avoid the alkyl nitrite product, which is the result of the \(S_N1\) mechanism, and he advised the reader to choose silver nitrite in order to steer the reaction towards the nitro compound by encouraging \(S_N2\). However, he also admitted that the observed retention of configuration during halo–nitro substitution of 1-chloroethylbenzene (\(\text{73} \)) in diethyl ether and benzene but an inversion in cyclohexane showed that both mechanistic pathways can result in the desired nitro compounds. To explain this he infers that some carbonium ion intermediates (namely \(\alpha\text{-phenylethyl carbonium}) do allow nucleophilic attack by the nitrite N to produce nitroalkanes rather than at the nitrite O.
Kornblum implied in [96] that $S_N1$ does not give all nitrite, nor $S_N2$ all nitro. A nitro product with retention of configuration does not imply $S_N1$ (which usually gives racemisation). Retention can and often does come from a double $S_N2$ [109], although on such a simple molecule it is hard to see how a double $S_N2$ could take place.

The reason for the substitution following one mechanism in cyclohexane and another in benzene or diethyl ether is not clear. Cyclohexane ought to have a lot of trouble dissolving the sodium nitrite reagent. Diethyl ether and benzene might be polar enough to support carbocation formation, whereas in cyclohexane, with zero polarity, the carbocation has too high an energy form. Kornblum’s chirality experiments on 1-chloroethylbenzene (73) were observed using silver nitrite. It would be interesting to try the same reactions but instead use sodium nitrite to see whether the two competing substitution mechanisms would be capable of occurring the same way when the substitution is carried out. One would think that the reaction would not proceed at all since sodium nitrite is not soluble in benzene or diethyl ether and certainly not cyclohexane.

Kornblum stated in an earlier paper [89] that DMF does not participate in the reaction mechanism, but merely dissolves the NaNO$_2$ much better than other solvents, allowing it to enter solution and react quickly. Therefore it is unusual that he was able to monitor the retention of the chiral carbon in other solvents as the reaction should not have been expected to succeed. Kornblum only partially described his method to determine chirality where he referred to an earlier one of his own papers that showed the 2-octyl series the iodide, nitrite and nitro compound to all have the same sign of rotation when of the same configuration [110]. This is a weak point to rely on considering that Kornblum’s key model compound for optical observations was 1-chloroethylbenzene (73), which has both a different R group and a different halogen. If an alkyl nitrite was instead produced, it should be a different compound with an undefined optical rotation and therefore could not have its chirality determined from comparing its optical rotation to Kornblum’s 2-octyl series. Other nitrite sources such as tetrabutylammonium nitrite or caesium nitrite are known to have a cation that is more soluble in DMF than sodium. It would be pertinent to carry out the halo–nitro substitution of 1-chloroethylbenzene in an alternative solvent with and without a catalytic amount of DMF to see if the reaction proceeds, thereby confirming Kornblum’s statement that DMF does not participate in the mechanism but merely serves to deliver the nitrite in solution in high enough levels.
3.3.3 Other evidence

Kornblum reports [89] that the bromo–nitro substitution rate for the synthesis of aliphatic nitro compounds is first order although this paper does not present any kinetic data. Gelbard [81] seems to have followed this view and also describes the reaction as a bimolecular displacement process (S_N2); the discussions in these papers imply that an S_N2 process explains why the substitution fails for tertiary halides. It is well established that the nucleophilic reagent (the entering group) of an S_N1 displacement reaction does not take part in the rate-limiting step and changing to a different nucleophile will not alter the rate of substitution [78]. It follows that the concentration of the entering group does not affect the reaction rate of an S_N1 process and an experiment to disprove an S_N1 process is to monitor the rate of substitution on the same halo compound using a different concentration or entering group. Nitrite may be substituted with cyanide or azide and be expected to give the same rate if an S_N1 process were operative, as the formation of a cationic intermediate (which they do not take part in) would be the rate-limiting step. Conversely, in an S_N2 displacement the more strongly nucleophilic the reagent, the more the reaction will be promoted [78]. In this scenario the change of nucleophile could have a subtle effect on the reaction medium and alter the reaction rate, but this effect is likely to be so subtle that it won’t interfere with the experiment and many rate studies have been carried out this way [78].

3.4 Tertiary halo–nitro substitution α to a carbonyl

While the Kornblum reaction’s only proceeding on primary and secondary halo-carbons is an established principle, when the halogen is bound to a tertiary carbon that is alpha to a carbonyl, the reaction will proceed in high yield. This exception seems to have been overlooked by Kornblum and others. Step two of our alternative synthesis of RU58841 (13) (chapter 2) can therefore be described as a rare example of the Kornblum reaction occurring on a tertiary carbon when alpha to a carbonyl. A close look at the literature reveals that this has been done twice before: once in 1957 and again in 1977.

In the first example, after Kornblum’s 1956 paper in Chemistry and Industry [98] had reported the procedure to prepare the secondary nitro compound ethyl 2-nitropropionate from ethyl 2-bromopropionate, it was referred to by Ungnade et al. in 1957 [80] who followed the same method on ethyl α-bromoisobutyrate (the tertiary equivalent of ethyl 2-bromopropionate) to synthesize ethyl α-nitroisobutyrate (65) in 68% yield. This
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compound is also reported as the example of an alpha-nitro-carbon preparation in Kornblum’s 1957 patent on halo–nitro substitutions [100].

![Chemical structure](image)

The preparation of ethyl α-nitroisobutyrate as reported in a 1957 patent [100]

Ungnade et al. did not consider the bromo–nitro substitution on this carbon to be novel; their procedure was slipped into the experimental section without discussion.

To the best of our knowledge after extensive literature searching, tertiary halo–nitro substitution occurring alpha to a carbonyl group was not touched upon again until twenty years later in 1977, when Gelbard and Colonna [81] carried out halo–nitro substitutions on tertiary bromo and chloro esters to test the nitrite-loaded solid phase resin ‘Amberlite IRA 900’, which acts as a nitrite source using benzene as a solvent. In this method, the reaction occurs at the surface of the solid support which is the NO$_2^-$ source and this paper focused on the performance of the Amberlite IRA 900. The authors did not acknowledge the novelty of the substitution occurring on a tertiary carbon; however they stated that the near quantitative yields for both the tertiary bromo and chloro compounds when NaNO$_2$ was used as the nitrite source were reduced to 60% for the bromo and 10% for the chloro compound when the Amberlite resin was used [81]. This implies that they also carried out the reaction using NaNO$_2$, although they did not provide their procedure. It is hard to imagine that they could have obtained near quantitative yields by substituting using NaNO$_2$ in benzene as this reagent is not soluble in this solvent. They suggest that steric effects associated with the Amberlite resin were responsible for the yield reduction [51].
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Gelbard and Colonna’s preparation of tertiary α-nitro compounds

Gelbard and Colonna reported that the reaction could be sped up by heating at 50 °C with Amberlite, but they did not characterize the reaction any further than this, as the essence of their paper was to assess the effectiveness of the Amberlite resin as a nitrite source on a well known reaction. Despite Gelbard and Colonna’s 1977 paper, it appears that halo-nitro substitution on a tertiary carbon remained unnoticed into the 1990s and 2000s [111, 103, 112].

As the PhD candidate thought it was unusual that such a simple synthetic step had gone largely uncharacterized, a further literature search was carried out for α-nitroesters from α-bromoesters using molecular structures on SciFinder. This gave only an Organic Syntheses procedure (again by Kornblum) [110], but as this was for the preparation of secondary α-bromoesters, not tertiary, Kornblum’s Br–nitro substitution on a tertiary carbon still appears to have remained largely unnoticed by the organic synthesis community. A literature search using the keyword “alpha-nitroester” led to a 1957 publication by Kornblum et al. on the synthesis of α-nitroesters using sodium nitrite in DMF or DMSO [113]. This publication used the same ethyl ester example compounds as in the patent [100] (discussed above) namely ethyl α-nitroisobutyrate (65) (the only tertiary halo-compound), ethyl α-nitropropionate, ethyl α-nitrobutyrate, ethyl α-nitrovalerate, ethyl α-nitroisovalerate, ethyl α-nitrocaproate and ethyl α-phenyl-α-nitroacetate. This paper noted, as did the 1957 patent [100], that the substitution when it occurs on the tertiary carbon, can proceed preparatively without the addition of a nitrite ester scavenger [113]. It also stated that the reaction can proceed in
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reasonable yield using DMSO as the solvent as long as phloroglucinol is added as a scavenger [113]. Although this article contained an example of the bromo–nitro substitution occurring on a tertiary α carbon, it did not comment on its unusual nature and potential utility in preparative reactions.

The compounds produced when the halogen is substituted on a dimethyl alpha anilide carbon are called α-nitroisobutyranilides.

![Illustration of α-Nitroisobutyranilides from α-bromoisobutyranilides]

A literature search for existing preparations of α-nitroisobutyranilides finds a 1972 article by Sayo et al. [101] that discusses the decomposition of α-nitroisobutyranilides when exposed to alkali. Rather than preparing these by halo–nitro substitution, they used a reagent with the nitro already installed on the tertiary carbon. Their preparation of α-nitroisobutyranilides is to form the amide bond of the anilide by reacting an aniline with an acid chloride (75) that already contains a nitro group on the tertiary carbon.

![Illustration of Preparation of α-nitroisobutyranilides as used by Sayo et al.]

How did the nitro get onto this tertiary carbon in the first place? The above
α-nitroisobutyryl chloride reagent (75) was reported to have been prepared by chlorination of α-nitroisobutyryl acid hydrazide (76) (or its hydrochloride salt) with Cl₂ [114]. The α-nitroisobutyryl acid hydrazide was, in turn, prepared from an α-nitroisobutyryl ester that was reacted with hydrazine [80].

Preparation of tertiary α-nitrocompounds used in Sayo et al.’s 1972 paper [101]

Sayo et al. did not report the method they used to prepare α-nitroisobutyryl esters. It is possible that the ethyl α-nitroisobutyrate (65) was prepared by nitration of diethyl dimethylmalonate (77) with nitrous acid/sodium nitrite as the equivalent reaction has been carried out on diethyl ethylmalonate to give the secondary α-nitro compound [115].

Possible preparation of ethyl α-nitroisobutyrate reagent

If such a tedious route has been used to achieve the α-nitroisobutyranilides, then it appears to be of great synthetic utility to make the chemistry community aware of the shorter bromo–nitro nucleophilic substitution route used in chapter 2 of this thesis (step 2 of the RU58841 synthesis).

It is also worth noting that α-halo compounds are known to tautomerize into an enolic form when a methine group follows the carbonyl [116]. With the right conditions, this enol can be made to transfer its halogen to the methine carbon, from where it readily leaves behind an α-carbocation.
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Transfer of alpha chloride to methine carbon

A 1991 review article on the nitro group in organic synthesis by Noboru Ono briefly discusses the nitration of alkyl halides [117] and refers to the treatment of alkyl halides with sodium nitrite in DMF or DMSO as the “Kornblum reaction”. The reaction is described by Ono as high yielding for primary and secondary alkyl halides (50–70%), but low yielding (0–5%) for tertiary alkyl halides. Ono mentions the preparation of ethyl α-nitrobutyrate from ethyl α-bromobutyrate using the Kornblum reaction (as reported by Kornblum [110]) gave a 68–75%, but the fact that the nitration is occurring on a tertiary α carbon is glossed over [117]. This portion remains unedited by Ono in the 2001 edition of the same work [118]. Ono states that sodium nitrite is considerably more soluble in DMSO than in DMF, which allows a more concentrated exposure to nitrite ions and thus shorter reaction times when DMSO is used [117].

A 2005 review article by Ballini et al. which summarized the routes to achieve α-nitro ketones described them as a coveted functionality as the presence of carbonyl and nitro groups on the same carbon offers a peculiar reactivity pattern [119]. The routes to α-nitro ketones are summarized in the review paper as:

- Oxidation of nitroaldol intermediate from Henry reaction (requires an aldehyde)
- C-acylation of nitroalkanes (low yield and does not install nitro on tertiary carbon)
- Oxidation of double bond in β-nitrostyrenes (only gives access to aryl α-nitro ketones and does not install nitro on tertiary carbon) [120].
- Nitration of double bond next to trimethylsilyl oxide group with tetranitro...
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methane (expensive and hazardous reagent)

Nitration of double bond

Henry reaction via aldol intermediate

Preparations of α-nitro ketones

Of these methods, only the Henry reaction is non-restrictive enough to prepare α-nitro ketones on a large scale. The halo–nitro substitution described in this thesis therefore provides a viable alternative to the Henry reaction.

The rediscovery of this rarely-reported nitration reaction raises the following questions.

- Will it proceed just as readily with other halogens?
- Will it proceed with R groups other than methyl on the ipso carbon?
- Is there inversion/retention/racemization of configuration on a chiral tertiary carbon?
- What is the preferred model to explain the reaction mechanism?

The first three questions were not investigated in this work as the time available would not allow for the performing of that many reactions and also these experiments would have required expensive reagents. As a thorough literature review showed a total absence of rate data we decided to focus on the question of mechanism by preparing a compound
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library, collecting rate data and then using that data for Hammett plots in order to propose a mechanism. This allowed us to make use of many aniline compounds that we already had in our chemical store and only a small number more had to be purchased. The findings of the Hammett plots are discussed in the next section.

3.4.1 Mechanism of tertiary halo–nitro substitution α to a carbonyl

The mechanism of halo–nitro substitution with an alpha carbonyl may well be different to that where there is no alpha carbonyl. Certainly it does not follow the $S_N1/S_N2$ dichotomy.

In one example, Kornblum’s rule was mentioned in a 1997 paper on the synthesis of 5,5-dialkyl-3-arylamino-2-thiohydantoins by Glushkov and co-workers [121]. Here the authors expected that Kornblum’s rule would see thiocyanate ions (SCN−) attacking the carbocation from a tertiary halo compound in an $S_N1$ manner to form an isothiocyanate (R–NCS). However, as they carried out their substitutions on tertiary halo compounds with an alpha carbonyl, they observed thiocyanate products (R–SCN) which are the result of an $S_N2$ substitution (attack by the more polarizable atom on the ambident nucleophile). They postulated that the destabilizing effect of an alpha carbonyl prevented the formation of a carbocation and caused their substitution to occur by an $S_N2$ process [121]. Their language, like that of many others’, suggests that they consider $S_N1$ and $S_N2$ to be the only two options. This substitution breaking Kornblum’s rule with an ambident nucleophile reacting at the less expected atom is evidence that the substitution may well be neither $S_N1$ nor $S_N2$ in the case where the tertiary halo-carbon has a carbonyl next to it.

In order to test for this possibility and following on from step 2 of the alternative synthesis of **RU58841**, anilines of varied substitution were selected in order to prepare a library of α-bromoisobutyranilides with both greater and lesser electron withdrawing capacity than R = phenyl and also one of phenyl itself. It was observed from monitoring the rate of bromo–nitro substitution on these α-bromoisobutyranilides that the more electron withdrawn the compound, the faster the substitution took place. The compound library was then expanded by preparing two compounds with an alkyl R group in place of the aryl, namely n-butyl and benzyl. This showed that the reaction also proceeds with R = alkyl, but at a much reduced rate compared with R = aryl. The compound library was

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then expanded again by a few more compounds in order to compare rates between ortho, meta and para of the nitro, chloro and methoxy functional groups.

The reaction conditions in the bromo–nitro substitution that is the subject of this chapter include an excess of sodium nitrite. This means that the DMF is saturated with nitrite ions and that as nitrite ions become incorporated into the reactant molecule, more nitrite ions enter solution. The rate is therefore observed to be pseudo first order, where Rate = \( k'\)\([\text{start material}]\). This means that a graph of the reactant depletion versus time will make it look like first order kinetics are operative even though they may not be. Thus observation of rate in the saturated solution used to prepare our alpha nitro compounds cannot tell us anything about its mechanism.

The formation of carbocation via an \( S_N1 \) mechanism would become more difficult when the phenyl group contains more electron-withdrawing substituents, but easier when it contains more electron-donating groups. Thus if an \( S_N1 \) mechanism were operating, the substitution rate would decrease for compounds containing phenyls with electron-withdrawing substituents. However, the inductive effect of the substituents is not the only factor to influence rate – resonance effects caused by the location of the substituent on the phenyl group also play a role. These may be elucidated by comparing the rate data of compounds that have the same substituent at meta and at para using a Hammett plot.

A simple experiment to disprove an \( S_N1 \) process would be to increase the solubility of nitrite ions in DMF using a co-solvent. The presence of 5% urea has been reported (by none other than Kornblum!) to greatly increase the solubility of \( \text{NaNO}_2 \) in DMF [89]. However, it was observed from experimentation during this PhD candidature that urea doped DMF did not dissolve \( \text{NaNO}_2 \) any better than pure DMF and the reaction rate was slightly lowered which is the opposite of Kornblum et al.’s stated observation [89]. A low concentration experiment was then therefore carried out that compared a saturated solution of \( \text{NaNO}_2 \) in DMF with those that contained only 75% and 50% quantities of \( \text{NaNO}_2 \) as that of the saturated solution. In this case a rate decrease was observed with falling concentration which showed concisely that the substitution is not \( S_N1 \). This result shows that the rate-limiting step involves the nitrite ion, which has multiple mechanistic possibilities, and will be considered later in this chapter in conjunction with the Hammett plots. If the reaction rate had remained the same at lowered nitrite concentrations it would have been strong evidence of the formation of an \( S_N1 \) carbocation intermediate as the rate-limiting step.
One possible experiment to determine the mechanism would be a change of the leaving group. This experiment would not distinguish between the classical $S_{N1}/ S_{N2}$ dichotomy as a breaking the bond to the leaving group is involved in the rate-limiting step for both [78]. A change of rate with a different leaving group would show that the substitution is neither $S_{N1}$ nor $S_{N2}$. The rate will or course only be affected if the transition state is product like (Curtin-Hammett principle).

Another possibility which should be discussed is the use of a competition experiment, which is where equimolar quantities of two compounds compete for an inadequate supply of a reagent or vice versa. These can often provide valuable evidence of $S_{N1}$ versus $S_{N2}$ character of a substitution; as $S_{N2}$ is faster with softer nucleophiles, a competition experiment with a softer nucleophile than nitrite would theoretically point towards $S_{N1}$ or $S_{N2}$ as the softer nucleophile, if in a 1:1 ratio, should out-compete the nitrite in an $S_{N2}$. The trouble with this experiment is that nitrite has more than one location from which it can attack an electrophile.

One experiment to elucidate the substitution mechanism would be to prepare a hyperconjugated deuterium analogue of an $\alpha$-bromoisobutyranilide which would have different bending frequencies. The substitution rate for this deutero-compound would differ in an $S_{N1}$ process as the carbon of the carbocation intermediate would have an unoccupied $p$ orbital which would overlap differently with the $\sigma$ bonding orbitals of the vicinal C-H bonds than it will with vicinal C-D bonds.

![Deuterium analogue of an $\alpha$-bromoisobutyranilide](image)

This is method to differentiate between $S_{N1}$ and $S_{N2}$ is known as the $\beta$ isotope effect [122]. When the C–D bond is $\beta$ to the position of the bond that is breaking, as in the above example, it is capable of stabilizing the transition state by means of
hyperconjugation, thus lowering the reaction rate. This effect is known to be more pronounced when the transition state has increased carbocation character. Therefore if the deuterium analogue shown above gave a significantly slowed rate of substitution it could be taken as evidence of an \( S_N1 \) process. However, it would not be definitive as a change of rate could be observed if the transition state has properties of both \( S_N1 \) and \( S_N2 \) and seeing as how our evidence had thus far suggested exactly that, we felt that it would be an unwise use of resources to prepare this deuterium analogue and we instead pursued the compound library in order to obtain enough rate data for Hammett plots.

There are literature examples of neighbouring group participation by the carbonyl group [123, 124]. This principle could lend itself to an experiment using a prepared analogue compound with a chiral centre at the halo-carbon. Such an experiment would show whether there is neighbouring group participation in the mechanism by the carbonyl oxygen. \( S_N2 \) reactions are always accompanied by inversion of configuration. A brief substitution by the electrons on the neighbouring carbonyl O may give a retention of configuration, where two \( S_N2 \) substitutions each cause an inversion of configuration [109, 125], whereas a product with inverted configuration would hint at an \( S_N2 \) mechanism in which the carbonyl does not participate.

\[
\begin{align*}
\text{R}_1\text{CBr} & \xrightarrow{\text{NaNO}_2} \text{R}_1\text{CNO}_2 \\
\text{R}_2\text{R}_3 & \\
\text{R}_1\text{CBr} & \xrightarrow{\text{NaNO}_2} \text{R}_1\text{CNO}_2 \\
\text{R}_2\text{R}_3 & \\
\text{Br–NO}_2 \text{ substitution on a chiral carbon with } S_N2 \text{ mechanism}
\end{align*}
\]

Conversely, racemization is a key characteristic stereochemical feature of \( S_N1 \) substitutions [126] as they tend to occur in polar solvents that have the capacity to carry the anionic leaving group far away from the chiral carbon; \( S_N1 \) can be seen to give a retention or inversion in rare circumstances, but only if efforts are made to carry out the reaction in a less polar solvent — which, paradoxically, doesn’t encourage \( S_N1 \) and may
well allow an $S_N2$ pathway to dominate.

Interestingly, this experiment has been carried out by Gelbard and Colonna [81] who substituted a bromo for a nitro on a secondary $\alpha$-halo-carbon. They observed an inversion of configuration.

![Chemical structure](image)

(R)-ethyl 2-bromopropanoate  \[\text{Resin (NO}_2\text{)}\]  25 °C, 30 min Ethanol  \[\text{(S)-ethyl 2-nitropropanoate}\]

**Inversion of configuration observed during Br–NO\textsubscript{2} substitution on 2° \alpha halo-C**

They claim that the inversion of configuration of 78 occurred rapidly (under 30 min) but that a racemization was observed after 4 hours [81]. This appears to show two mechanisms: a faster, neighbouring group participating mechanism and a slower formation of an $S_N1$ intermediate, which could be nitro itself acting as a nucleophilic leaving group, where slow nitro displacement of nitro causes racemization. This is of course a secondary halo-carbon and might well follow a different mechanism to the tertiary halo-carbon substitution in the preparation of $\alpha$-nitroisobutyranilides from $\alpha$-bromoisobutyranilides. It is consistent with only some of the mechanisms postulated here in this thesis from the Hammett plot results and it appears likely to be proceeding by way of a different mechanism to the reaction on the tertiary centre of the molecules studied here in this thesis.

The topic of halo groups on a chiral centre alpha to a carbonyl was explored in a 1975 paper by Richardson and Strickland [127]. They used optical spectra to calculate the the lowest energy structural conformation of the halo group compared to the carbonyl group and declared it to be the rotamer that is eclipsed with the carbonyl group, although it should be noted that it is the reactive conformation that is important, not the ground state. Richardson and Strickland go on to note that their results were in distinct disagreement with that of their contemporaries Gaffield and Galetto who used a different method of calculation to conclude that the staggered rotamer had the lowest energy [128].

Also noteworthy is an observation from the crystallography data of 52 (from chapter 2 of
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this thesis). Using the example of tert-butyl bromide, the usual C–C–C bond angle on a tertiary-bromo carbon is 109.5° [129], but for the tertiary-bromo carbon that is alpha to a carbonyl, as it is in the α-bromoisoobutyranilide (52), the crystallography data shows a corresponding C–C–C bond angle of 111.4°. After substituting the bromo for a nitro, the α-nitroisoobutyranilide (55) has a similar C–C–C bond angle of 111.8°. Taking the classical and overly simplistic S_N1/S_N2 dichotomy as canon, if this increased C–C–C bond angle of ≈ 2° of α-bromoisoobutyranilides in crystal form is presumed to equate to the C–C–C atoms spending more time at the increased angle when the compound is in solution, it would slightly favour S_N2 over S_N1. It must be reiterated that, as will be shown in section 3.4.1.3, the mechanism has been shown by the Hammett plots to be neither S_N1 nor S_N2. It can therefore be concluded that the difference in bond angles is not significant enough to dictate mechanism.

A concerted mechanism should be considered, as well as one with neighbouring group participation.

NMR monitoring would show a long lived intermediate if it was present in substantial quantity. This was carried out by running the 55 forming reaction in an NMR tube using d_7-DMF but no intermediate could be observed. Therefore the formation of any intermediate is the rate-limiting step. If an S_N1 carbocation was the intermediate, the reaction would not be sped up by more nitrite ions, so this reaction was monitored at different nitrite concentrations.

3.4.1.1 Rate measurements

One experiment that has been carried out during this PhD candidature is monitoring the rate of formation of a library of α-nitroisoobutyranilides by GC-MS. The obtained data has been used to construct a Hammett plot which provides valuable insight into the mechanism. These results are discussed in the following pages.

The compound library included 55 and was made up of the functional groups listed in the table below.
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Table of α-nitroisobutyranilides that were analyzed for rate of Br–NO₂ substitution

<table>
<thead>
<tr>
<th>Bromo compound</th>
<th>Nitro compound</th>
<th>R-Substituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>55</td>
<td>-p-cyano-m-trifluoromethyl-phenyl</td>
</tr>
<tr>
<td>80</td>
<td>81</td>
<td>-phenyl</td>
</tr>
<tr>
<td>82</td>
<td>83</td>
<td>-p-methyl-phenyl</td>
</tr>
<tr>
<td>84</td>
<td>85</td>
<td>-o-carboethoxy-phenyl</td>
</tr>
<tr>
<td>86</td>
<td>87</td>
<td>-o-nitro-phenyl</td>
</tr>
<tr>
<td>88</td>
<td>89</td>
<td>-m-nitro-phenyl</td>
</tr>
<tr>
<td>90</td>
<td>91</td>
<td>-p-nitro-phenyl</td>
</tr>
<tr>
<td>92</td>
<td>93</td>
<td>-o-bromo-phenyl</td>
</tr>
<tr>
<td>94</td>
<td>95</td>
<td>-o-chloro-phenyl</td>
</tr>
<tr>
<td>96</td>
<td>97</td>
<td>-m-chloro-phenyl</td>
</tr>
<tr>
<td>98</td>
<td>99</td>
<td>-p-chloro-phenyl</td>
</tr>
<tr>
<td>100</td>
<td>101</td>
<td>-benzyl (not a true isobutyranilide)</td>
</tr>
<tr>
<td>102</td>
<td>103</td>
<td>-n-butyl (not a true isobutyranilide)</td>
</tr>
<tr>
<td>104</td>
<td>105</td>
<td>-o-methoxy-phenyl</td>
</tr>
<tr>
<td>106</td>
<td>107</td>
<td>-m-methoxy-phenyl</td>
</tr>
<tr>
<td>108</td>
<td>109</td>
<td>-p-methoxy-phenyl</td>
</tr>
</tbody>
</table>

The rate of conversion of bromo to nitro compound was monitored using GC-MS and the concentration values of the start material (bromo compound) were taken from an integration of the chromatogram, as were the concentration values of the product (nitro compound). The side reactions were small in total and in all cases the start material plus product made up >90% of the total signal integrations. For the purposes of graphing the reaction rate, the concentration values for start material and product were calculated as making up 100% of the total and the graphs were then plotted showing as % start material that remained in relation to the product. A further quirk in this process was that in some cases...
but not all cases, the GC-MS column (which was an SGE Analytical Science BPX5 with a column width of 0.25 mm and a film width of 0.25 μm) column had the propensity to convert some or all of the nitro product into its equivalent isocyanate m/z with the obvious loss of 2-nitropropane (m/z = 89). This appears to have correlated with another user having run TMS-chloride through the column to clean it as it seems to happen less often or not at all immediately after the column has been replaced, which occurs once per year. Because of this, the level of nitro compound product was often represented by two signals which had to be added together in order to observe the rate. The 180 °C temperature of the injector port that delivers the sample to this column may well play a part in this observed pyrolysis. There are GC-MS instruments equipped to deliver the sample to the column at room temperature, these are called ‘On-column injectors’. It would be useful to analyze the α-nitroisobutyranilides on one of these instruments to see whether the pyrolysis to the isocyanate species is observed.

The raw data obtained from the monitoring of these reactions is presented in Appendix I. An additional α-bromoisobutyranilide compound, 110, which contained a nitro group in both the 2 and 4 position of the phenyl ring, was not characterized due to extreme difficulty of isolation, but its rate of Br–NO₂ substitution to give its α-nitroisobutyranilide (111) could be easily monitored. It is therefore included in the graph to show the additional increase in rate when the compound’s R group had the electron withdrawing capacity of two nitro groups and, as expected, it proceeds much faster than the mono-nitros and the CN/CF₃ substituted compound.

Some general trends in the bromo–nitro substitution were immediately apparent before any calculations were applied to the data. The first principle that overrides all others is that the reaction goes faster when the R group is more electron withdrawing, no matter how the R group is configured. Changes such as switching between ortho, meta and para substituted groups have a comparatively small effect on rate.

The rate data are here plotted in two groups for comparison: slow and fast.
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Substitution rate for slower reacting tertiary α-bromocompounds

Substitution rate for faster reacting tertiary α-bromocompounds
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As these are pseudo first order reactions, the rate curves are all observed as a first order depletion of reactant as there is an excess of nitrite ions which are only so soluble in the DMF. As the nitrite gets used up by the reaction, more nitrite ions are able to enter solution and the nitrite concentration is essentially constant.

Reactions of ortho substituted phenyl R groups always proceeded faster than the equivalent meta or para. It may be that a substituent on the aryl ring closer to the site of halo–nitro substitution facilitates the substitution to occur, however it doesn’t seem to matter what that substituent is, as shown by the specific examples below.

Substitution rate for methoxy substituted α-bromoisobutyranilides
The above graphs show the nitro, chloro and methoxy α-bromoisobutyranilides being converted to their equivalent α-nitroisobutyranilides and a different rate can be seen for ortho, meta and para. The rate varied less between the three chloro substituted R groups.
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(~7% difference between fastest and slowest) than it did for the nitro compounds and methoxy compounds (~20% difference between fastest and slowest). Chlorine, a single atom not capable of hydrogen bonding seems less able to facilitate the nearby Br–nitro substitution than the nitro or the methoxy which both bend with free rotation and contain free electron pairs. If one were to compare Br or methyl groups between ortho, meta and para, it may be expected for them to be within 7% of each other like they were for the chloro. If one were to carry out this comparison with ethyl benzoate groups (like 85) it would be expected that the fastest and slowest would vary by ~20%. The results suggest groups placed in the ortho position do more to increase rate when they are flexible and dipolar.

One exception to the first principle of increased rate with more electron withdrawing R groups is that bromo in the ortho position goes ~5% faster than chloro in the ortho position. As bromo and chloro are quite similar, it appears that in this case the two processes at play that affect rate are close enough to observe the normally weaker steric facilitation of the nearby substitution by the larger bromo group managing to outweigh the normally stronger effect of rate increasing with electronegativity.

3.4.1.2 Rate dependence on nitrite concentration

As mentioned earlier in this chapter, an experiment to observe the effect of changes in nitrite concentration at below saturation, but still present in molar excess, was carried out using a higher dilution version of the p-cyano-m-trifluoromethyl-α-nitroisobutyranilide (55) preparation. As can be seen in the graph below, the reaction rate was lowered by ~8% under these conditions. A plot of the $52 \rightarrow 55$ reaction at saturated, 3/4 and 1/2 of saturation shows that the rate-limiting step involves the nitrite ion.
Effect of nitrite concentration on $52 \rightarrow 55$ reaction rate

It was expected that rates would be identical in the above graph and therefore these reactions were only carried out once towards the end of the PhD candidature in order to rule out $S_N1$. There was not enough time to repeat them and so not enough data was obtained to do good rate calculations as there was for the over-saturated substitutions of $\alpha$-bromo-isobutyranilides. However, the difference in rate of ~8% is too significant to be down to chance – the reactions at saturation that were each repeated multiple times never varied by more than 2%. The ionic strength of the solvent would be different at these lowered concentrations and the substitution could be going through a different mechanism. As noted earlier, this is evidence against an $S_N1$ mechanism as the rate-limiting step of an $S_N1$ reaction would be the formation of a cationic intermediate which does not require the nitrite ion to form. If this cationic intermediate were present it would grab nitrite ions more quickly than it forms and the reaction would occur equally quickly at lower nitrite concentrations. This clearly cannot be an exclusive $S_N1$ process and we can declare that the nitrite must be taking part in the rate-limiting step.

3.4.1.3 Hammett plots

First-order plots of $\ln(\%SM)$ against time have been prepared for the reactions of the compound library. The slope of these is $-k'$, where $k'$ is the pseudo-first-order rate
constant. As has been mentioned, a dilution experiment showed that the reaction rate depends also on nitrite concentration, so these reactions are only pseudo first order due to nitrite concentration remaining effectively constant throughout the reaction. The nitrite concentration was the same in each experiment: ~5 mmol of the reactant α-bromoisobutyranilide compound (1–2 g) with NaNO₂ 4.00 g (44.9 mmol) in 40 mL of DMF.

The whole of the data was plotted and a line fitted to it (shown in Appendix II). The linearity of these first order plots is reasonably good, except for the 52 → 55 reaction. In many cases, linear regression analysis (shown below each graph) showed a noticeable deviation from linearity or accuracy at the longer time scales and a second plot using mostly the earlier portion of the data gave a more accurately linear trendline which improved the $R^2$ value considerably (see Appendix II; when carried out, these are shown below the plot of the whole data). This phenomenon is to be expected given the mode in which the reaction was monitored. Each data point is derived from taking a 1 mL aliquot that was then prepared for GC-MS analysis. As each reaction was done with 40 mL of solvent, after a handful of aliquots had been taken the ratio of components present in the flask would differ markedly from what is was at the start of the reaction. The second reason the later data points ought to give a less accurate trendline is that a small amount of the formed nitro product will degrade by further reaction with nitrite ions via a nitroso intermediate to produce the alkyl nitrite by-product (this process was described by Kornblum [99] and discussed here in section 3.2).

What seemed to be the best $k'$ values for each substitution reaction were used to construct Hammett plots which are shown in Appendix III. As Hammett plots are only reliable when the electronic effects are not complicated by steric factors [130], only the data obtained for meta and para monosubstituted aromatic compounds were used. The meta examples were plotted (as $\log_{10}(k'/k'n)$): that is, divided the pseudo first-order rate constants by the value of the unsubstituted pseudo first-order rate constant) against ordinary $\sigma$ values (which are based on $K_a$ values for benzoic acids). This gave a fit that was OK, though not marvellous. It showed a positive $\rho$ value of 0.67, indicating that the transition state develops a negative charge; strictly speaking it means that the transition state’s negative charge interacts with the ring more strongly than does the negative charge of carboxylate.

The para substituted compounds are more complex to consider because
'through-conjugation' is possible, where a canonical form can be drawn that puts the charge right at the para position - and potentially on the substituent itself.

Through-conjugation canonical form

Starting with ordinary σ values (from benzoic acid $K_a$ values) the Hammett plot gave a fit that was not terribly good. A Hammett plot was constructed using $\sigma^0$ values from a compound where through-conjugation was not possible: the fit was worse. The $\sigma^+$ values were then tried based on benzylic $S_N1$ solvolysis (a positive charge next to the ring), and these have strong through-conjugation effects with electron-donating substituents: the fit was terrible. The $\sigma^-$ values were then tried, which are based on phenol $K_a$ values, so a negative charge next to the ring, and strong through-conjugation effects with electron-withdrawing substituents: this gave the best fit of all (and a $\rho$ of 1.44: in the phenol acidity standard $\rho$ is 2.01).

This result implies that not only does this reaction have a negative charge on the transition state, but that charge can readily conjugate onto the ring.

The positive $\rho$ implies a mechanism in which the nucleophile attacks first, before the leaving group leaves. One might think that the large $\rho$ and the correlation with $\sigma^-$ implies the negative charge that forms must be on the nitrogen, but this isn’t necessarily so. In amides there is strong π character in the nitrogen–carbonyl bond.
and therefore the whole group has a π system that is planar with and conjugated with the aromatic ring’s π system. Therefore the negative charge that forms could be on the amide carbonyl, or even the position α to the carbonyl, as even there it will be conjugated with the ring (cf. hydrolysis of cinnamic esters, which has \( \rho = 1.27 \)).

If the mechanism started with deprotonation of the amide NH, where would it go next? One can only imagine forming an α-lactam, which would surely break open at the carbonyl. In any case, that mechanism wouldn’t be available when the starting compound was an α-bromoester, and we know they also react [95, 109]. Hence it appears that it must start with addition at the carbonyl, or formation of an enolate. This provides several possibilities, each of which has several sub-possibilities:

1. In the rate-determining step nitrite adds to the carbonyl as nitro, forming a negative oxygen. The carbonyl re-forms pushing the nitro to do a 1,2-shift onto the adjacent atom (like a semipinacol rearrangement), displacing the halogen (which may leave first to give either a carbocation or an epoxide).

![Possible mechanism number one](image)

2. In the rate-determining step nitrite adds to the carbonyl as nitrite, forming a negative oxygen. The carbonyl re-forms, pushing the nitrite nitrogen onto the adjacent atom in a four-centre reaction and displacing the halogen (which may leave first to give either a carbocation or an epoxide).
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Possible mechanism number two

3. The negative oxygen formed in possibilities 1 or 2 could form an epoxide by displacing the adjacent bromide (which may leave first), then more nitrite could add at the other side of the epoxide. The carbonyl re-forms, pushing off the first nitrite.

Possible mechanism number three
4. The rate-determining step is nucleophilic attack by nitrite (through nitrogen) at the bromine, with enolate as leaving group and forming nitryl bromide. The enolate formed could then react with the nitryl bromide to form the nitro product.

Possible mechanism number four

While none of these options can be ruled out completely, 4 is particularly favoured as it is very similar to what happens in the specific reduction of α-halo carbonyls by soft nucleophiles. It seems unlikely that a free radical mechanism would produce the negative charge.

An interesting experiment to test for this mechanism would be to change the leaving group (bromide) to chloride.

Change of leaving group to Cl

This reaction couldn’t be carried out due to the fact that the reagent required to prepare these compounds (α-chloroisobutyryl chloride) was only available from one supplier at a prohibitively expensive price and were out of stock anyway. The two possible rate-
limiting steps are formation of the nitryl bromide and reaction of the nitryl bromide by attack from enolate. Both of these steps could proceed at a different rate with Cl in the place of Br. It is also possible that they will not proceed at all if nitryl chloride is significantly shorter lived than nitryl bromide. If the first step does proceed, the second step (attack of nitryl chloride by enolate) would proceed faster as the nitryl chloride N would be a stronger electrophile than the nitryl bromide N.

While on an academic visit it was suggested that as the reactions were carried out under air this substitution may be proceeding by means of a radical mechanism involving elemental oxygen (O₂). A later experiment ruled out this proposal as the reaction proceeded at the same rate in the absence of oxygen (section 3.5.2.1). This result is in agreement with the negative charge of the transition state.

### 3.5 Experimental procedures and characterization of novel compounds in this chapter

The library of compounds prepared in this chapter were prepared by first reacting anilines (or in two cases, benzylamine and n-butylamine are used) with α-bromoisobutyryl bromide reagent (60) in order to acylate the amino group to prepare an amide compound. These compounds were isolated and characterized. They were then exposed to NaNO₂ in DMF in order to substitute their alpha bromo for a nitro group. The procedures and characterizations for the acylations are given first, followed by those for the substitution.

IR spectra were measured from 4000–650 cm⁻¹ using a Varian 1000 FTIR spectrometer with a Diamond Attenuated Total Reflectance (ATR) attachment. Reaction rate was monitored using a Varian CP-3800 gas chromatograph equipped with an SGE Analytical Science BPX5 column (column width 0.25 mm, film width 0.25 μm) which was adjoined to a Varian Saturn 2200 GC/MS/MS. Accurate mass spectra were measured using a Waters GCT Premier HR-TOFMS equipped with an Agilent 7890 GC column. The NMR spectra were obtained using a Bruker 300 MHz spectrometer. Chemical shifts in \(^1\)H NMR spectra were reported in parts per million (ppm δ) relative to the TMS signal, measured by the chloroform signal (δ = 7.24 ppm) and the J couplings measured in Hz. Chemical shifts in \(^13\)C NMR spectra were measured relative to the central peak of the deuterochloroform signal (δ = 77.5 ppm) and the J couplings measured in Hz.

While the data for the IR and NMR spectra are listed here, images of each spectrum are listed in appendix V.
3.5.1 Acylation reactions

Unless otherwise stated, all reactions were carried out at room temperature in a 100 mL round bottom flask using ~21.5 mmol (1.5–4 g) of the reactant amine compound which was an aniline in all but two cases. 1,2-Dichloroethane (35 mL) was used as solvent in all cases. Oven dried K$_2$CO$_3$ (3.00 g, 21.7 mmol) was added to protect the reagent from water and also to convert the HBr that is yielded into KBr. A 5% molar excess of α-bromoisoobutyryl bromide (60) was added last in a dropwise fashion to the flask which had been placed onto a balance and tared. The flask was then sealed with Parafilm and the reaction allowed to stir overnight at 700 rpm.

The next morning the reaction was worked up by first placing the entire mixture onto a rotary evaporator and the solvent removed. The solids then underwent liquid/liquid extraction in ethyl acetate/water. The ethyl acetate fraction was dried over MgSO$_4$, passed through fluted filter paper and then evaporated. The resulting solids were recrystallized from methanol to give a pure product.

\[ p\text{-Cyano-m-trifluoromethyl-}\alpha\text{-bromoisoobutyranilide (52)} \]

\[ \text{54} \quad \text{60} \quad \text{52} \]

\[ p\text{-Cyano-m-trifluoromethylaniline (54)} \] (3.96 g, 21.3 mmol) gave 7.02 g (21.1 mmol, 99% yield) of pure \( p\)-cyano-m-trifluoromethyl-α-bromoisoobutyranilide (52). Characterization data for 52 are provided in chapter 2.

\[ \alpha\text{-Bromoisoobutyranilide (80)} \]
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Aniline (2.00 g, 21.5 mmol) gave 4.04 g (16.8 mmol, 78% yield) of pure \( \alpha \)-bromoisobutyranilide (80) as white needles that looked like shredded coconut, m.p. 89–92 °C; \( R_f = 0.54 \) in 4:1 hexanes/EtOAc, 0.74 in 65:35 hexanes/EtOAc and 0.95 in 1:1 hexanes/EtOAc; IR(\( \text{cm}^{-1} \)): 3275, 3042, 2993, 2924, 1660 (C=O), 1594, 1551, 1513, 1461, 1401, 1372, 1355, 1318, 1295, 1234, 1187, 1141, 962, 900, 862, 815, 767, 738, 677; \( ^1 \text{H NMR} \) (300 MHz, 26 mg : 0.4 mL CDCl\(_3\)): \( \delta \) 2.06 (6H, s, CH\(_3\)), \( \delta \) 7.15 (1H, tt, ArH\(^d\), J 2, J 8), \( \delta \) 7.36 (2H, tt, ArH\(^3\), J 2, J 8), \( \delta \) 7.54 (2H, dt, ArH\(^2\), J 2, J 8), \( \delta \) 8.46 (1H, br, s, NH); \( ^{13} \text{C NMR} \) (75 MHz, 137 mg : 0.4 mL CDCl\(_3\)): \( \delta \) 32.8 (s, C-3\(_{AB}\)), \( \delta \) 63.2 (s, C-2), \( \delta \) 120.3 (s, C-2\(^d\)), \( \delta \) 125.1 (s, C-4\(^d\)), \( \delta \) 129.3 (s, C-3\(^d\)), \( \delta \) 137.6 (s, C-1\(^d\)), \( \delta \) 170.2 (s, C-1\(^d\)); GC-(EI) TOF-HRMS: calc’d m/z for C\(_{10}\)H\(_8\)NOBr: 241.0102, observed: 241.0095.

\( p \)-Methyl-\( \alpha \)-bromoisobutyranilide (82)

\( p \)-Toluidine (2.30 g, 21.5 mmol) gave 4.72 g (18.5 mmol, 86% yield) of pure \( p \)-methyl-\( \alpha \)-bromoisobutyranilide (82) as little amber prisms, m.p. 95–98 °C; \( R_f = 0.63 \) in 4:1 hexanes/EtOAc, 0.78 in 65:35 hexanes/EtOAc and 0.93 in 1:1 hexanes/EtOAc; IR(\( \text{cm}^{-1} \)): 3297, 3195, 3032, 3006, 2984, 2919, 1652 (C=O), 1601, 1533, 1512, 1470, 1404, 1319, 1297, 1236, 1193, 1164, 1100, 1022, 1009, 946, 938, 893, 813, 767, 755, 696; \( ^1 \text{H NMR} \) (300 MHz, 35 mg : 0.4 mL CDCl\(_3\)): \( \delta \) 2.05 (6H, s, CH\(_3\)), \( \delta \) 2.33 (3H, s, ArCH\(_3\)), \( \delta \) 7.15 (2H, d, ArH\(^3\), J 8), \( \delta \) 7.42 (2H, d, ArH\(^2\), J 8), \( \delta \) 8.40 (1H, br, s, NH); \( ^{13} \text{C NMR} \) (75 MHz, 135 mg : 0.4 mL CDCl\(_3\)): \( \delta \) 21.2 (s, ArCH\(_3\)), \( \delta \) 32.8 (s, C-3\(_{AB}\)), \( \delta \) 63.4 (s, C-2), \( \delta \) 120.3 (s, C-2\(^d\)), \( \delta \) 129.7 (s, C-3\(^d\)), \( \delta \) 134.8 (s, C-1\(^d\)), \( \delta \) 135.1 (s, C-4\(^d\)), \( \delta \) 170.1 (s,
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C-1); GC-(El) TOF-HRMS: calc’d m/z for C_{11}H_{14}NOBr: 255.0259, observed: 255.0254.

**o-Carboethoxy-α-bromoisoisobutyranilide (84)**

![Diagram](image)

Ethyl anthranilate (3.60 g, 21.8 mmol) gave 6.26 g (20.1 mmol, 92% yield) of pure o-carboethoxy-α-bromoisoisobutyranilide (84) as little amber prisms, m.p. 59–61 °C; R_f = 0.63 in 4:1 hexanes/EtOAc, 0.82 in 65:35 hexanes/EtOAc and 0.95 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3189, 3117, 3076, 2974, 2937, 1696 (C=O), 1680 (C=O), 1605, 1592, 1467, 1449, 1365, 1298, 1271, 1239, 1199, 1170, 1144, 1105, 1086, 1050, 1016, 969, 947, 856, 763, 730, 700; ^1H NMR (300 MHz, 30 mg : 0.4 mL CDCl₃): δ 1.42 (3H, t, ethyl CH₃), δ 2.07 (6H, s, CH₃), δ 4.42 (2H, q, ethyl CH₂), δ 7.12 (1H, td, ArH⁴, J₂, J₈), δ 7.56 (1H, td, ArH⁵, J₂, J₈), δ 8.08 (1H, dd, ArH⁶, J₂, J₈), δ 8.70 (1H, dd, ArH³, J₂, J₈), δ 11.90 (1H, br, s, NH); ^13C NMR (75 MHz, 145 mg : 0.4 mL CDCl₃): δ 14.4 (s, ethyl CH₃), δ 32.1 (s, C-3_AB), δ 60.5 (s, C-2), δ 61.8 (s, ethyl CH₂), δ 116.2 (s, C-2'), δ 120.5 (s, C-6'), δ 123.2 (s, C-4'), δ 131.2 (s, C-3'), δ 134.7 (s, C-5'), δ 141.4 (s, C-1'), δ 168.3 (s, ester C=O), δ 171.0 (s, C-1); GC-(El) TOF-HRMS: calc’d m/z for C_{13}H_{15}NO₃Br: 312.0235, observed: 312.0222.

**o-Nitro-α-bromoisoisobutyranilide (86)**

![Diagram](image)

O-Nitroaniline (2.90 g, 21.0 mmol) gave 5.83 g (20.4 mmol, 97% yield) of pure o-nitro-α-bromoisoisobutyranilide (86) as bright yellow needles, m.p. 67–70 °C; R_f = 0.61 in 4:1 hexanes/EtOAc, 0.80 in 65:35 hexanes/EtOAc and 0.83 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3320, 3118, 2985, 1701 (C=O), 1606, 1584, 1544, 1496, 1458, 1427, 1391,
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1374, 1335, 1268, 1221, 1145, 1112, 1077, 1044, 1009, 945, 891, 862, 787, 742, 681; \(^1\)H NMR (300 MHz, 32 mg : 0.4 mL CDCl\(_3\)): \(\delta\) 2.07 (6H, s, CH\(_3\)), \(\delta\) 7.23 (1H, td, ArH\(^4\), \(J\) 2, \(J\) 8), \(\delta\) 7.68 (1H, td, ArH\(^5\), \(J\) 2, \(J\) 8), \(\delta\) 8.25 (1H, dd, ArH\(^3\), \(J\) 2, \(J\) 8), \(\delta\) 8.73 (1H, dd, ArH\(^6\), \(J\) 2, \(J\) 8), \(\delta\) 11.34 (1H, br, s, NH); \(^13\)C NMR (75 MHz, 138 mg : 0.4 mL CDCl\(_3\)): \(\delta\) 32.2 (s, C-3\(_{A/B}\)), \(\delta\) 60.7 (s, C-2), \(\delta\) 122.1 (s, C-3'), \(\delta\) 124.0 (s, C-4'), \(\delta\) 126.1 (s, C-6'), \(\delta\) 134.7 (s, C-1'), \(\delta\) 136.1 (s, C-5'), \(\delta\) 137.0 (s, C-2'), \(\delta\) 171.3 (s, C-1); GC-(EI) TOF-HRMS: calc’d \(m/z\) for C\(_{10}\)H\(_{11}\)N\(_2\)O\(_3\)Br: 285.9953, observed: 285.9949.

\textit{m-Nitro-a-bromoisobutyranilide (88)}

\[\text{O}_2\text{N} \quad \text{NH}_2 \quad \text{Br} \quad \text{Br} \quad \text{88} \quad \text{O}_2\text{N} \quad \text{Br} \]

\textit{m-Nitroaniline} (2.90 g, 21.0 mmol) gave 5.83 g (20.4 mmol, 97% yield) of pure \textit{m-nitro-a-bromoisobutyranilide (88)} as yellowish shards, m.p. 98–101 °C; \(R_p = 0.44\) in 4:1 hexanes/EtOAc, 0.69 in 65:35 hexanes/EtOAc and 0.92 in 1:1 hexanes/EtOAc; IR(cm\(^{-1}\)): 3370, 3090, 2980, 2931, 1694 (C=O), 1590, 1525, 1484, 1418, 1392, 1374, 1349, 1315, 1298, 1243, 1152, 1108, 1079, 1007, 958, 893, 874, 813, 735, 673, 692, 673; \(^1\)H NMR (300 MHz, 45 mg : 0.4 mL CDCl\(_3\)): \(\delta\) 2.06 (6H, s, CH\(_3\)), \(\delta\) 7.51 (1H, t, ArH\(^5\), \(J\) 8), \(\delta\) 7.90 (1H, dd, ArH\(^6\), \(J\) 2, \(J\) 8), \(\delta\) 7.99 (1H, dd, ArH\(^4\), \(J\) 2, \(J\) 8), \(\delta\) 8.46 (1H, t, ArH\(^2\), \(J\) 2), \(\delta\) 8.66 (1H, br, s, NH); \(^13\)C NMR (75 MHz, 138 mg : 0.4 mL CDCl\(_3\)): \(\delta\) 32.4 (s, C-3\(_{A/B}\)), \(\delta\) 61.9 (s, C-2), \(\delta\) 115.2 (s, C-2'), \(\delta\) 119.6 (s, C-4'), \(\delta\) 126.1 (s, C-6'), \(\delta\) 130.0 (s, C-5'), \(\delta\) 138.8 (s, C-1'), \(\delta\) 148.7 (s, C-3'), \(\delta\) 170.8 (s, C-1); GC-(EI) TOF-HRMS: calc’d \(m/z\) for C\(_{10}\)H\(_{11}\)N\(_2\)O\(_3\)Br: 285.9953, observed: 285.9963.

\textit{p-Nitro-a-bromoisobutyranilide (90)}
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\[ \text{\textbf{p-Nitroaniline (2.90 g, 21.0 mmol) gave 5.35 g (18.7 mmol, 89\% yield) of pure}} \]
\[ p\text{-nitro-\textalpha-bromoisobutyranilide (90) as tiny yellow needles, m.p. 116–120 }^\circ\text{C; R}_f = 0.40 \]
\[ \text{in 4:1 hexanes/EtOAc, 0.67 in 65:35 hexanes/EtOAc and 0.93 in 1:1 hexanes/EtOAc; IR(cm}^{-1}) : 3406, 3115, 2929, 2931, 1698 (C=O), 1612, 1596, 1534, 1496, 1404, 1334, 1300, 1243, 1194, 1177, 1142, 1101, 945, 882, 854, 831, 750, 691, 674; ^1\text{H NMR}} \]
\[ (300 MHz, 30 mg : 0.4 mL CDCl}_3): \delta 2.05 (6H, s, CH\textsubscript{3}), \delta 7.74 (2H, dt, ArH\textsubscript{2}, J 2, J 8), \delta 8.23 (2H, dt, ArH\textsubscript{3}, J 2, J 8), \delta 8.72 (1H, br, s, NH); ^13\text{C NMR (75 MHz, 122 mg : 0.4 mL CDCl}_3): \delta 32.4 (s, C-3\textsubscript{AB}), \delta 62.1 (s, C-2), \delta 119.7 (s, C-2'), \delta 125.2 (s, C-3'), \delta 143.5 (s, C-1'), \delta 144.1 (s, C-4'), \delta 170.7 (s, C-1); GC-(EI) TOF-HRMS: calc'd m/z for C\textsubscript{10}H\textsubscript{11}N\textsubscript{2}O\textsubscript{3}Br: 285.9953, observed: 285.9929. \]

\textbf{o-Bromo-\textalpha-bromoisobutyranilide (92)}

\[ o\text{-Bromoaniline (3.70 g, 21.5 mmol) gave 6.79 g (21.3 mmol, 99\% yield) of pure}} \]
\[ o\text{-bromo-\textalpha-bromoisobutyranilide (92) as a clear, low-viscosity amber oil; R}_f = 0.70 in 4:1 \]
\[ \text{hexanes/EtOAc, 0.85 in 65:35 hexanes/EtOAc and 0.96 in 1:1 hexanes/EtOAc; IR(cm}^{-1}) : 3352, 2984, 2934, 1685 (C=O), 1588, 1520, 1434, 1300, 1155, 1110, 1025, 939, 745, 683; ^1\text{H NMR}} \]
\[ (300 MHz, 144 mg : 0.4 mL CDCl}_3): \delta 2.06 (6H, s, CH\textsubscript{3}), \delta 7.01 (1H, td, ArH\textsubscript{4}, J 2, J 8), \delta 7.33 (1H, td, ArH\textsubscript{5}, J 2, J 8), \delta 7.56 (1H, dd, ArH\textsubscript{3}, J 2, J 8), \delta 8.32 (1H, dd, ArH\textsubscript{5}, J 2, J 8), \delta 9.04 (1H, br, s, NH); ^13\text{C NMR (75 MHz, 144 mg : 0.4 mL CDCl}_3): \delta 32.7 (s, C-3\textsubscript{AB}), \delta 62.7 (s, C-2), \delta 114.4 (s, C-2'), \delta 121.8 (s, C-6'), \delta 125.9 (s, C-5'), \delta 128.6 (s, C-3'), \delta 132.6 (s, C-4'), \delta 135.8 (s, C-1'), \delta 170.3 (s, C-1); GC-(EI) \]

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TOF-HRMS: calc’d m/z for C_{10}H_{11}NOBr_2: 318.9207, observed: 318.9194.

\textit{o-Chloro-\alpha-bromoisobutyranilide (94)}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{chart1}};
\end{tikzpicture}
\end{center}

\textit{o-Chloroaniline (2.75 g, 21.6 mmol) gave 5.23 g (18.9 mmol, 88\% yield) of pure o-chloro-\alpha-bromoisobutyranilide (94) as a clear, low-viscosity amber oil; R_f = 0.66 in 4:1 hexanes/EtOAc, 0.86 in 65:35 hexanes/EtOAc and 0.96 in 1:1 hexanes/EtOAc; IR(cm\textsuperscript{-1}): 3365, 2985, 2934, 1686 (C=O), 1593, 1514, 1439, 1304, 1154, 1111, 1054, 1034, 940, 746, 698; \textit{1}H NMR (300 MHz, 139 mg : 0.4 mL CDCl\textsubscript{3}): \delta 2.04 (6H, s, CH\textsubscript{3}), \delta 7.04 (1H, td, ArH\textsuperscript{1}, J \textsubscript{2}, J \textsubscript{8}), \delta 7.26 (1H, td, ArH\textsuperscript{2}, J \textsubscript{2}, J \textsubscript{8}), \delta 7.36 (1H, dd, ArH\textsuperscript{3}, J \textsubscript{2}, J \textsubscript{8}), \delta 8.30 (1H, dd, ArH\textsuperscript{4}, J \textsubscript{2}, J \textsubscript{8}), \delta 9.04 (1H, br, s, NH); \textit{13}C NMR (75 MHz, 139 mg : 0.4 mL CDCl\textsubscript{3}): \delta 32.8 (s, C-3\textsubscript{A/B}), \delta 62.9 (s, C-2), \delta 121.5 (s, C-6\textsuperscript{'}), \delta 124.0 (s, C-2\textsuperscript{'}), \delta 125.4 (s, C-5\textsuperscript{'}), \delta 128.0 (s, C-3\textsuperscript{'}), \delta 129.4 (s, C-4\textsuperscript{'}), \delta 134.7 (s, C-1\textsuperscript{'}), \delta 170.4 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C_{10}H_{11}NOClBr: 274.9713, observed: 274.9710.

\textit{m-Chloro-\alpha-bromoisobutyranilide (96)}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.5\textwidth]{chart2}};
\end{tikzpicture}
\end{center}

\textit{m-Chloroaniline (2.75 g, 21.6 mmol) gave 5.88 g (21.3 mmol, 99\% yield) of pure m-chloro-\alpha-bromoisobutyranilide (96) as white needles with a slight redness to them, m.p. 91–95 °C; R_f = 0.53 in 4:1 hexanes/EtOAc, 0.78 in 65:35 hexanes/EtOAc and 0.94 in 1:1 hexanes/EtOAc; IR(cm\textsuperscript{-1}): 3291, 2998, 2977, 2931, 1663 (C=O), 1593, 1521, 1424, 1285, 1244, 1162, 1109, 919, 875, 860, 782, 758, 697, 682; \textit{1}H NMR (300 MHz, 31 mg : 0.4 mL CDCl\textsubscript{3}): \delta 2.06 (6H, s, CH\textsubscript{3}), \delta 7.14 (1H, dt, ArH\textsuperscript{4}, J \textsubscript{2}, J \textsubscript{8}), \delta 7.28 (1H, t, ArH\textsuperscript{5}, J \textsubscript{8}), \delta 7.39 (1H, dq, ArH\textsuperscript{6}, J \textsubscript{2}, J \textsubscript{8}), \delta 7.70 (1H, t, ArH\textsuperscript{5}, J \textsubscript{2}), \delta 8.47 (1H, br, s,}

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\( ^{13} \text{C NMR (75 MHz, 136 mg : 0.4 mL CDCl}_{3} \): \delta 32.8 (s, C-3_{A/B}), \delta 62.9 (s, C-2), \delta 118.5 (s, C-6'), \delta 120.5 (s, C-2'), \delta 125.3 (s, C-4'), \delta 130.3 (s, C-5'), \delta 135.1 (s, C-3'), \delta 139.0 (s, C-1'), \delta 170.6 (s, C-1); GC-(EI) TOF-HRMS: \text{calc'd } m/z \text{ for } C_{10}H_{11}NOClBr: 274.9713, \text{ observed: 274.9686.}

\textit{p-Chloro-\alpha\text{-bromoisobutyranilide (98)}}

\text{p-Chloroaniline (2.75 g, 21.6 mmol) gave 4.45 g (16.1 mmol, 75% yield) of pure } p\text{-chloro-\alpha\text{-bromoisobutyranilide (98) as colourless needles, m.p. 119–121 °C; } R_f = 0.52 \text{ in 4:1 hexanes/EtOAc, 0.78 in 65:35 hexanes/EtOAc and 0.91 in 1:1 hexanes/EtOAc; IR(} \text{cm}^{-1} \text{): 3285, 3188, 3122, 3071, 2988, 2941, 2895, 1656 (C=O), 1591, 1552, 1529, 1478, 1459, 1418, 1398, 1372, 1351, 1305, 1287, 1254, 1240, 1187, 1142, 1092, 1074, 999, 962, 914, 904, 888, 864, 854, 792, 704, 683; \textsuperscript{1}H NMR (300 MHz, 43 mg : 0.4 mL CDCl}_{3} \): \delta 2.04 (6H, s, CH}_{3}), \delta 7.30 (2H, dt, ArH^3, J_2, J_8), \delta 7.49 (2H, dt, ArH^2, J_2, J_8), \delta 8.45 (1H, br, s, NH); \textsuperscript{13} \text{C NMR (75 MHz, 157 mg : 0.4 mL CDCl}_{3} \): \delta 32.6 (s, C-3_{A/B}), \delta 62.8 (s, C-2), \delta 121.7 (s, C-2'), \delta 129.3 (s, C-3'), \delta 130.1 (s, C-4'), \delta 136.2 (s, C-1'), \delta 170.3 (s, C-1); GC-(EI) TOF-HRMS: \text{calc'd } m/z \text{ for } C_{10}H_{11}NOClBr: 274.9713, \text{ observed: 274.9706.}

\textit{N-Benzyl-\alpha\text{-bromoisobutyramide (100)}}

\text{Benzyamine (2.30 g, 21.5 mmol) gave 4.33 g (17.0 mmol, 79% yield) of pure}
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\[ \text{N-benzyl-\textalpha-bromoiso} \text{butyramid}e \ (100) \] as a fine white powder, m.p. 77–80 °C; \( R_f \) = 0.38 in 4:1 hexanes/EtOAc, 0.64 in 65:35 hexanes/EtOAc and 0.90 in 1:1 hexanes/EtOAc; IR(\cm\textsuperscript{-1}): 3300, 3065, 3030, 2973, 2939, 2920, 1642 (C=O), 1533, 1495, 1471, 1453, 1418, 1355, 1292, 1195, 1102, 1081, 1014, 922, 826, 752, 729, 699, 693; \textsuperscript{1}H NMR (300 MHz, 23 mg : 0.4 mL CDCl\textsubscript{3}): \( \delta \) 1.99 (6H, s, CH\textsubscript{3}), \( \delta \) 4.47 (2H, d, CH\textsubscript{2} J 8), \( \delta \) 7.02 (1H, br, s, NH), \( \delta \) 7.30 (2H, m, ArH\textsuperscript{2}), \( \delta \) 7.34 (2H, m, ArH\textsuperscript{3}), \( \delta \) 7.36 (1H, m, ArH\textsuperscript{4}); \textsuperscript{13}C NMR (75 MHz, 125 mg : 0.4 mL CDCl\textsubscript{3}): \( \delta \) 32.7 (s, C-3\textsubscript{A/B}), \( \delta \) 44.5 (s, CH\textsubscript{2}), \( \delta \) 62.9 (s, C-2), \( \delta \) 127.7 (s, C-2\'), \( \delta \) 127.8 (s, C-4'), \( \delta \) 129.0 (s, C-3'), \( \delta \) 138.0 (s, C-1'), \( \delta \) 172.2 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C\textsubscript{11}H\textsubscript{14}NOBr: 255.0259, observed: 255.0265.

\textit{a-Bromo-N-butylisobutyramid}e (102)

\( n \)-Butylamine (1.60 g, 21.9 mmol) gave 3.05 g (13.8 mmol, 63% yield) of pure \textit{a-bromo-N-butylisobutyramid}e (102) as a clear, pale yellow, low-viscosity oil; IR(\cm\textsuperscript{-1}): 3348, 2959, 2932, 2873, 1649 (C=O), 1528, 1465, 1437, 1370, 1301, 1282, 1225, 1190, 1112, 738; \textsuperscript{1}H NMR (300 MHz, 26 mg : 0.4 mL CDCl\textsubscript{3}): \( \delta \) 0.96 (3H, t, Alkyl\textsuperscript{4} J 8), \( \delta \) 1.38 (2H, sextet, Alkyl\textsuperscript{3} J 8), \( \delta \) 1.54 (2H, sextet, Alkyl\textsuperscript{2} J 8), \( \delta \) 1.97 (6H, s, CH\textsubscript{3}), \( \delta \) 3.28 (2H, sextet, Alkyl\textsuperscript{1} J 8), \( \delta \) 6.73 (1H, br, s, NH); \textsuperscript{13}C NMR (75 MHz, 147 mg : 0.4 mL CDCl\textsubscript{3}): \( \delta \) 13.9 (s, C-4'), \( \delta \) 20.2 (s, C-3'), \( \delta \) 31.5 (s, C-2'), \( \delta \) 32.8 (s, C-3\textsubscript{A/B}), \( \delta \) 40.3 (s, C-1'), \( \delta \) 63.3 (s, C-2), \( \delta \) 172.0 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C\textsubscript{8}H\textsubscript{16}NOBr: 221.0415, observed: 221.0417.

\textit{o-Chloro-a-bromoiso}butyrani\textit{lide} (104)
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\[ \text{O-Methoxyaniline (2.40 g, 21.6 mmol) gave 4.92 g (18.2 mmol, 84\% yield) of pure o-chloro-α-bromoisobutyranilide (104) as a clear, brown-metallic oil; Rf = 0.60 in 4:1 hexanes/EtOAc, 0.81 in 65:35 hexanes/EtOAc and 0.93 in 1:1 hexanes/EtOAc; IR(c/m\(^{-1}\)): 3380, 2983, 2936, 2839, 1677 (C=O), 1600, 1522, 1486, 1459, 1433, 1336, 1290, 1250, 1218, 1176, 1157, 1110, 1047, 1026, 940, 773, 744; }^{1}\text{H NMR (300 MHz, 28 mg : 0.4 mL CDCl\(_3\))}: \delta 2.06 (6H, s, CH\(_3\)), \delta 3.92 (3H, s, O–CH\(_3\)), \delta 6.90 (1H, dd, ArH\(^5\), J\(_2\), J\(_8\)), \delta 6.98 (1H, td, ArH\(^5\), J\(_2\), J\(_8\)), \delta 7.08 (1H, td, ArH\(^4\), J\(_2\), J\(_8\)), \delta 8.33 (1H, dd, ArH\(^6\), J\(_2\), J\(_8\)), \delta 9.13 (1H, br, s, NH); }^{13}\text{C NMR (75 MHz, 133 mg : 0.4 mL CDCl\(_3\))}: \delta 32.5 (s, C-3\(_{A/B}\)), \delta 56.0 (s, O–CH\(_3\)), \delta 62.8 (s, C-2), \delta 110.2 (s, C-3'), \delta 119.5 (s, C-6'), \delta 121.0 (s, C-5'), \delta 124.4 (s, C-4'), \delta 127.4 (s, C-1'), \delta 148.5 (s, C-2'), \delta 169.9 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C\(_{11}\)H\(_{14}\)NO\(_2\)Br: 271.0208, observed: 271.0195.

**m-Chloro-α-bromoisobutyranilide (106)**

\[ \text{m-Methoxyaniline (2.40 g, 21.6 mmol) gave 5.44 g (20.1 mmol, 93\% yield) of pure m-chloro-α-bromoisobutyranilide (106) as white needles, m.p. 112–114 °C; Rf = 0.47 in 4:1 hexanes/EtOAc, 0.75 in 65:35 hexanes/EtOAc and 0.93 in 1:1 hexanes/EtOAc; IR(c/m\(^{-1}\)): 3454, 3340, 3003, 2961, 2942, 2897, 1660 (C=O), 1597, 1546, 1528, 1510, 1462, 1442, 1414, 1375, 1355, 1299, 1232, 1183, 1172, 1141, 1111, 1032, 962, 902, 865, 823, 764; }^{1}\text{H NMR (300 MHz, 31 mg : 0.4 mL CDCl\(_3\))}: \delta 2.10 (6H, s, CH\(_3\)), \delta 3.86 (3H, s, O–CH\(_3\)), \delta 6.75 (1H, dd, ArH\(^4\), J\(_2\), J\(_8\)), \delta 7.05 (1H, dd, ArH\(^6\), J\(_2\), J\(_8\)), \delta 7.30 (1H, dd, ArH\(^5\), J\(_2\), J\(_8\)), \delta 7.37 (1H, t, ArH\(^2\), J\(_2\)), \delta 8.49 (1H, br, s, NH); }^{13}\text{C NMR (75 MHz, 31 mg : 0.4 mL CDCl\(_3\))}: \delta 32.9 (s, C-3\(_{A/B}\)), \delta 55.7 (s, O–CH\(_3\)), \delta 63.5 (s, C-2), \delta 105.8 (s,
C-6'), δ 111.3 (s, C-2'), δ 112.4 (s, C-4'), δ 130.1 (s, C-5'), δ 139.0 (s, C-1'), δ 160.6 (s, C-3'), δ 170.3 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C_{11}H_{14}NO_{2}Br: 271.0208, observed: 271.0216.

*p-Chloro-α-bromoisobutyranilide (108)*

\[
\begin{align*}
\text{NH}_2 & \quad \text{Br} & \quad \text{Br} \\
\text{O} & \quad & \text{O} \\
\text{Br} & \quad & \text{Br}
\end{align*}
\]

*p-Methoxyaniline* (2.40 g, 21.6 mmol) gave 5.80 g (21.4 mmol, 99% yield) of pure *p*-chloro-α-bromoisobutyranilide (108) as white needles, m.p. 88–89 °C; R\(_t\) = 0.46 in 4:1 hexanes/EtOAc, 0.72 in 65:35 hexanes/EtOAc and 0.91 in 1:1 hexanes/EtOAc; IR(cm\(^{-1}\)): 3319, 3007, 2982, 2962, 2841, 1654 (C=O), 1601, 1539, 1508, 1468, 1444, 1412, 1372, 1316, 1300, 1273, 1232, 1223, 1197, 1184, 1164, 1106, 1031, 952, 933, 890, 831, 809, 763, 751, 675; \(^1\)H NMR (300 MHz, 25 mg : 0.4 mL CDCl\(_3\)): δ 2.07 (6H, s, CH\(_3\)), δ 3.82 (3H, s, O–CH\(_3\)), δ 6.90 (2H, dt, ArH\(^3\), J \(=\) 2, J \(=\) 8), δ 7.45 (2H, dt, ArH\(^2\), J \(=\) 2, J \(=\) 8), δ 8.40 (1H, br, s, NH); \(^13\)C NMR (75 MHz, 25 mg : 0.4 mL CDCl\(_3\)): δ 32.4 (s, C-3\(_{\text{A/B}}\)), δ 55.5 (s, O–CH\(_3\)), δ 63.3 (s, C-2), δ 114.6 (s, C-3'), δ 121.8 (s, C-2'), δ 130.5 (s, C-1'), δ 156.8 (s, C-4'), δ 169.9 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C_{11}H_{14}NO_{2}Br: 271.0208, observed: 271.0197.

### 3.5.2 Substitution reactions

Unless otherwise stated, all reactions were carried out at room temperature in a 100 mL round bottom flask using ~5 mmol (1–2 g) of the reactant α-bromoisobutyranilide compound (1–2 g) with NaNO\(_2\) (4.00 g, 44.9 mmol) in DMF (40 mL) and a magnetic stirrer at 700 rpm.

The rates were monitored periodically by the removal of 1 mL of the reacting mixture and doing a mini liquid/liquid extraction using 2 mL of DCM and washing four times.
with 3 mL of water in a 5 mL screw cap vial. The DCM layer was then dried over anhydrous MgSO₄ and transferred to a GC-MS vial by passing it through a Pasteur pipette that had been prepared with a small amount of cotton.

The time between each aliquot was determined for each reaction by trial in an initial rough experiment. The reaction was then run again and aliquots taken for GC-MS at strategic time intervals. After running many of these reactions, an educated guess at the rate of reaction in some cases provided an adequate spacing of the aliquots on the first try and when this happened no repeat reaction was required.

Unless otherwise stated, the reactions were worked up upon completion using the following method. The DMF was removed by rotary evaporator with water bath at 70 °C and vacuum of 25 Torr, with Dow Corning high vacuum grease freshly applied to the joins and Keck clips used to hold the flask onto a non-reversible splash-guard.
The solids were then dissolved into water/ethyl acetate for liquid/liquid extraction. The ethyl acetate fraction was evaporated and the solids from this were analyzed by TLC in order to detect the Rf of the product and that of the impurities. The product was then purified by a column that was prepared dry and then solvent added. The crude mixture was adsorbed onto ~10 g of 43–60 μ silica by dissolving it in DCM, adding the silica and then placing the flask onto a rotary evaporator and gently removing most of the DCM. The last of the DCM was removed from the silica/crude compound mixture by attaching the flask to house vacuum and repeatedly (and gently!) vacuuming and purging the flask until a free flowing powder was obtained. A 40 mm diameter glass-frit vacuum column was placed under vacuum and ~150 g of 43–60 μ silica was carefully placed in the column. The prepared silica/crude compound mixture was then carefully added to the top of the clean silica using a glass funnel. This method typically produced 800–1300 mg of highly pure α-nitroisobutyranilide compound as observed by NMR.

In two cases, the reactant compound was not a true α-bromoisobutyranilide as the phenyl groups had been substituted with benzyl (101) and n-butyl (103).

*p-Cyano-m-trifluoromethyl-α-nitroisobutyranilide (55)*
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52 (p-cyano-m-trifluoromethyl-α-bromoisobutyranilide) (1.68 g, 5.03 mmol) was added to NaNO₂ and DMF. The reaction was worked up by addition of 20 mL of deionized water which caused the product to begin to precipitate. The flask was placed in a crystal fridge overnight and then the crystals collected by Büchner funnel filtration to give 1.88 g of intensely white needles 2 to 10 mm in length, these were found to be p-cyano-m-trifluoromethyl-α-nitroisobutyranilide (55) that had co-crystallized with DMF in a 1:1 ratio (86% yield when corrected for the DMF), m.p. 129–131 °C; A DMF free version of this compound could be prepared by repeated liquid/liquid extraction using water/ethyl acetate which provides a white amorphous powder of the same MP. Characterization data for 55 are provided in chapter 2.

α-Nitroisobutyranilide (81)

80 (α-Bromoisobutyranilide) (1.20 g, 4.98 mmol) gave 870 mg (4.18 mmol, 84% yield) of pure α-nitroisobutyranilide (81) as an extremely shiny crystalline powder with a hint of orange, m.p. 104–107 °C; Rᵣ = 0.32 in 4:1 hexanes/EtOAc, 0.56 in 65:35 hexanes/EtOAc and 0.87 in 1:1 hexanes/EtOAc; IR(κ⁻¹): 3256, 3199, 3136, 3076, 1655 (C=O), 1598, 1549, 1538, 1492, 1459, 1440, 1399, 1373, 1352, 1321, 1266, 1233, 1189, 1143, 963, 894, 859, 752, 695, 666; ¹H NMR (300 MHz, 26 mg : 0.4 mL CDCl₃): δ 1.94 (6H, s, CH₃), δ 7.17 (1H, tt, ArH¹, J₂, J₈), δ 7.34 (2H, tt, ArH³, J₂, J₈), δ 7.48 (2H, dt, ArH², J₂, J₈), δ 7.98 (1H, br, s, NH); ¹³C NMR (75 MHz, 26 mg : 0.4 mL CDCl₃): δ 24.9 (s, C-3ₐ/B), δ 91.6 (s, C-2), δ 120.8 (s, C-2'), δ 125.8 (s, C-4'), δ 129.5 (s, C-3'), δ 136.8 (s,
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C-1'), δ 164.7 (s, C-1); GC-(EI) TOF-HRMS: calc'd m/z for C_{10}H_{12}N_{2}O_{3}: 208.0848, observed: 208.0846.

*p-Methyl-α-nitroisobutyranilide* (83)

82 (p-Methyl-α-bromoisobutyranilide) (1.28 g, 5.02 mmol) gave 970 mg (4.37 mmol, 87% yield) of pure p-methyl-α-nitroisobutyranilide (83) as orange shards of various morphology, m.p. 115–118 °C; R_f = 0.38 in 4:1 hexanes/EtOAc, 0.61 in 65:35 hexanes/EtOAc and 0.87 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3274, 3120, 3042, 2932, 2924, 2893, 2860, 1660 (C=O), 1594, 1550, 1522, 1513, 1460, 1436, 1401, 1372, 1355, 1318, 1295, 1259, 1234, 1187, 1179, 1141, 961, 900, 862, 815, 770, 738, 678; ¹H NMR (300 MHz, 21 mg : 0.4 mL CDCl₃): δ 1.93 (6H, s, CH₃), δ 2.32 (3H, s, ArCH₃), δ 7.13 (2H, d, ArH³, J 8), δ 7.35 (2H, d, ArH², J 8), δ 7.91 (1H, br, s, NH); ¹³C NMR (75 MHz, 42 mg : 0.4 mL CDCl₃): δ 21.3 (s, ArCH₃), δ 24.9 (s, C-3_A/B), δ 91.6 (s, C-2), δ 121.1 (s, C-2'), δ 129.9 (s, C-3'), δ 134.3 (s, C-1'), δ 135.5 (s, C-4'), δ 164.9 (s, C-1); GC-(EI) TOF-HRMS: calc'd m/z for C_{11}H_{14}N_{2}O₃: 222.1004, observed: 222.1006.

*o-Carboethoxy-α-nitroisobutyranilide* (85)

84 (o-Carboethoxy-α-bromoisobutyranilide) (1.56 g, 5.00 mmol) gave 1381 mg (4.95 mmol, 99% yield) of pure o-carboethoxy-α-nitroisobutyranilide (85) as white, amorphous powder, m.p. 84–87 °C; R_f = 0.43 in 4:1 hexanes/EtOAc, 0.69 in 65:35 hexanes/EtOAc and 0.93 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3177, 3120, 3082, 2991, 1699

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(C=O), 1685 (C=O), 1608, 1594, 1551, 1529, 1466, 1455, 1366, 1351, 1303, 1277, 1251, 1238, 1182, 1139, 1090, 1016, 857, 763, 700; ^1^H NMR (300 MHz, 25 mg : 0.4 mL CDCl_3): δ 1.42 (3H, t, ethyl CH_3), δ 1.98 (6H, s, CH_3), δ 4.41 (2H, q, ethyl CH_2), δ 7.16 (1H, td, ArH^4, J 2, J 8), δ 7.57 (1H, td, ArH^5, J 2, J 8), δ 8.08 (1H, dd, ArH^6, J 2, J 8), δ 8.66 (1H, dd, ArH^3, J 2, J 8), δ 11.81 (1H, br, s, NH); ^1^C NMR (75 MHz, 68 mg : 0.4 mL CDCl_3/0.1 mL d_6-DMSO): δ 14.9 (s, ethyl CH_3), δ 24.3 (s, C-3_A/B), δ 62.5 (s, ethyl CH_2), δ 92.3 (s, C-2), δ 118.9 (s, C-2'), δ 122.0 (s, C-6'), δ 125.2 (s, C-4'), δ 131.6 (s, C-3''), δ 135.1 (s, C-5') δ 139.8 (s, C-1'), δ 166.5 (s, C-1), δ 168.2 (s, ester C=O); GC-(EI) TOF-HRMS: calc’d m/z for C_{13}H_{15}N_{2}O_{5}: 279.0981, observed: 279.0972.

**o-Nitro-α-nitroisobutyranilide (87)**

86 (o-Nitro-α-bromoisobutyranilide) (1.36 g, 4.74 mmol) gave 1000 mg (3.95 mmol, 83% yield) of pure o-nitro-α-nitroisobutyranilide (87) as a deep yellow, cauliflower-shaped crystalline nuggets, m.p. 82–84 °C; R_f = 0.38 in 4:1 hexanes/EtOAc, 0.70 in 65:35 hexanes/EtOAc and 0.90 in 1:1 hexanes/EtOAc; IR(cm^−1): 3392, 2924, 2854, 1706 (C=O), 1607, 1588, 1548, 1497, 1454, 1431, 1396, 1374, 1335, 1270, 1224, 1161, 1140, 1075, 898, 861, 854, 789, 742, 688; ^1^H NMR (300 MHz, 18 mg : 0.4 mL CDCl_3): δ 2.00 (6H, s, CH_3), δ 7.28 (1H, td, ArH^4, J 2, J 8), δ 7.70 (1H, tt, ArH^5, J 2, J 8), δ 8.27 (1H, dd, ArH^3, J 2, J 8), δ 8.71 (1H, dd, ArH^6, J 2, J 8), δ 11.09 (1H, br, s, NH); ^1^C NMR (75 MHz, 18 mg : 0.4 mL CDCl_3): δ 24.6 (s, C-3_A/B), δ 91.6 (s, C-2), δ 122.7 (s, C-3'), δ 124.9 (s, C-4'), δ 126.3 (s, C-6'), δ 134.1 (s, C-1'), δ 136.5 (s, C-5'), δ 137.2 (s, C-2'), δ 165.9 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C_{10}H_{11}N_{3}O_{5}: 253.0699, observed: 253.0705.
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**m-Nitro-α-nitroisobutyranilide (89)**

![Chemical structure of m-Nitro-α-nitroisobutyranilide (89)]

88 (m-Nitro-α-bromoisobutyranilide) (1.43 g, 4.74 mmol) gave 1028 mg (4.06 mmol, 86% yield) of pure m-nitro-α-nitroisobutyranilide (89) as a pale yellow, clean looking crystalline powder, m.p. 135–136 °C; R_f = 0.27 in 4:1 hexanes/EtOAc, 0.57 in 65:35 hexanes/EtOAc and 0.84 in 1:1 hexanes/EtOAc; IR (cm⁻¹): 3347, 3093, 2923, 1548, 1434, 1401, 1373, 1350, 1317, 1287, 1262, 1234, 1192, 1145, 1089, 1079, 970, 909, 882, 856, 824, 809, 734, 693, 671; ^1H NMR (300 MHz, 50 mg : 0.4 mL d₆-DMSO): δ 1.93 (6H, s, CH₃), δ 7.67 (1H, t, ArH^5, J 8), δ 8.01 (1H, dd, ArH^6, J 2, J 8), δ 8.07 (1H, dd, ArH^4, J 2, J 8), δ 8.61 (1H, t, ArH^6, J 2), δ 10.40 (1H, br, s, NH); ^13C NMR (75 MHz, 50 mg : 0.4 mL d₆-DMSO): δ 24.6 (s, C-3A/B), δ 92.5 (s, C-2), δ 115.7 (s, C-2'), δ 119.8 (s, C-4'), δ 127.4 (s, C-6'), δ 131.3 (s, C-5'), δ 140.2 (s, C-1'), δ 148.8 (s, C-3'), δ 167.5 (s, C-1); GC-(EI) TOF-HRMS: calc'd m/z for C_{10}H_{11}N_{3}O_{5}: 253.0699, observed: 253.0694.

**p-Nitro-α-nitroisobutyranilide (91)**

![Chemical structure of p-Nitro-α-nitroisobutyranilide (91)]

90 (p-Nitro-α-bromoisobutyranilide) (1.43 g, 4.74 mmol) gave 980 mg (3.87 mmol, 82% yield) of pure p-nitro-α-nitroisobutyranilide (91) as a fine, white fluffy powder, m.p. 138–140 °C; R_f = 0.19 in 4:1 hexanes/EtOAc, 0.45 in 65:35 hexanes/EtOAc and 0.87 in
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1:1 hexanes/EtOAc; IR (cm\(^{-1}\)): 3352, 1709 (C=O), 1615, 1597, 1547, 1506, 1464, 1409, 1400, 1374, 1346, 1307, 1249, 1221, 1181, 1160, 1142, 1115, 898, 848, 829, 816, 752, 691; \(^1\)H NMR (300 MHz, 27 mg: 0.4 mL \(d_6\)-DMSO): \(\delta\) 1.94 (6H, s, CH\(_3\)), \(\delta\) 7.94 (2H, dt, ArH\(^2\), J 2, J 8), \(\delta\) 8.29 (2H, dt, ArH\(^3\), J 2, J 8), \(\delta\) 10.50 (1H, br, s, NH); \(^13\)C NMR (75 MHz, 27 mg: 0.4 mL \(d_6\)-DMSO): \(\delta\) 24.5 (s, C-3\(_{A/B}\)), \(\delta\) 92.5 (s, C-2), \(\delta\) 121.2 (s, C-2'), \(\delta\) 125.7 (s, C-3'), \(\delta\) 144.0 (s, C-4'), \(\delta\) 145.1 (s, C-1'), \(\delta\) 167.4 (s, C-1); GC-(EI) TOF-HRMS: calc’d \(m/z\) for C\(_{10}\)H\(_{11}\)N\(_3\)O\(_5\): 253.0699, observed: 253.0702.

**o-Bromo-α-nitroisobutyranilide (93)**

![Diagram](image)

92 (o-Bromo-α-bromoisobutyranilide) (1.61 g, 5.02 mmol) gave 1082 mg (3.77 mmol, 75% yield) of pure o-bromo-α-nitroisobutyranilide (93) as an amber oil; \(R_f = 0.48\) in 4:1 hexanes/EtOAc, 0.69 in 65:35 hexanes/EtOAc and 0.91 in 1:1 hexanes/EtOAc; IR (cm\(^{-1}\)): 3398, 3339, 2997, 2925, 1699 (C=O), 1590, 1548, 1519, 1464, 1436, 1398, 1373, 1346, 1299, 1237, 1207, 1167, 1143, 1121, 1047, 1026, 896, 855, 750; \(^1\)H NMR (300 MHz, 26 mg: 0.4 mL CDCl\(_3\)): \(\delta\) 1.98 (6H, s, CH\(_3\)), \(\delta\) 7.04 (1H, td, ArH\(^4\), J 2, J 8), \(\delta\) 7.34 (1H, td, ArH\(^5\), J 2, J 8), \(\delta\) 7.56 (1H, dd, ArH\(^6\), J 2, J 8), \(\delta\) 8.24 (1H, dd, ArH\(^6\), J 2, J 8), \(\delta\) 8.52 (1H, br, s, NH); \(^13\)C NMR (75 MHz, 66 mg: 0.4 mL CDCl\(_3\)): \(\delta\) 24.9 (s, C-3\(_{A/B}\)), \(\delta\) 91.4 (s, C-2), \(\delta\) 114.8 (s, C-2'), \(\delta\) 122.6 (s, C-6'), \(\delta\) 126.8 (s, C-5'), \(\delta\) 128.9 (s, C-3'), \(\delta\) 132.8 (s, C-4'), \(\delta\) 134.9 (s, C-1'), \(\delta\) 164.9 (s, C-1); GC-(EI) TOF-HRMS: calc’d \(m/z\) for C\(_{10}\)H\(_{11}\)N\(_3\)O\(_3\)Br: 285.9953, observed: 285.9961.

**o-Chloro-α-nitroisobutyranilide (95)**

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94 (o-Chloro-α-bromoisobutyrnilide) (1.38 g, 4.99 mmol) gave 955 mg (3.94 mmol, 79% yield) of pure o-chloro-α-nitroisobutyrnilide (95) as an amber oil; Rf = 0.43 in 4:1 hexanes/EtOAc, 0.70 in 65:35 hexanes/EtOAc and 0.90 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3352, 2998, 2922, 2852, 1697 (C=O), 1594, 1549, 1518, 1467, 1441, 1398, 1373, 1347, 1302, 1238, 1168, 1144, 1128, 1055, 1035, 897, 856, 751, 690; ¹H NMR (300 MHz, 21 mg : 0.4 mL CDCl₃): δ 1.97 (6H, s, CH₃), δ 7.11 (1H, td, ArH¹, J 2, J 8), δ 7.30 (1H, td, ArH⁵, J 2, J 8), δ 7.40 (1H, dd, ArH³, J 2, J 8), δ 8.26 (1H, dd, ArH⁶, J 2, J 8), δ 8.58 (1H, br, s, NH); ¹³C NMR (75 MHz, 39 mg : 0.4 mL CDCl₃): δ 24.9 (s, C-3ₓ/ᵧ), δ 91.5 (s, C-2), δ 122.2 (s, C-6'), δ 124.2 (s, C-2'), δ 126.2 (s, C-5'), δ 128.2 (s, C-3'), δ 129.5 (s, C-4'), δ 133.8 (s, C-1'), δ 164.7 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C₁₀H₁₁N₂O₃Cl: 242.0458, observed: 242.0462.

**m-Chloro-α-nitroisobutyrnilide (97)**

96 (m-Chloro-α-bromoisobutyrnilide) (1.38 g, 4.99 mmol) gave 1135 mg (4.68 mmol, 94% yield) of pure m-chloro-α-nitroisobutyrnilide (97) as a light orange crystalline mass with multiple nucleation points, m.p. 125–128 °C; Rf = 0.47 in 4:1 hexanes/EtOAc, 0.72 in 65:35 hexanes/EtOAc and 0.89 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3385, 3188, 3122, 3071, 2988, 2941, 2895, 1656 (C=O), 1590, 1552, 1528, 1478, 1459, 1418, 1398, 1372, 1351, 1304, 1287, 1254, 1240, 1231, 1187, 1142, 1092, 1074, 999, 914, 904, 888, 854, 791, 704, 682; ¹H NMR (300 MHz, 18 mg : 0.4 mL CDCl₃): δ 1.82 (6H, s, CH₃), δ 6.99 (1H, d, ArH¹, J 8), δ 7.14 (1H, td, ArH³, J 2, J 8), δ 7.43 (1H, d, ArH⁶, J 8), δ 7.64 (1H, m, ArH⁵), δ 9.38 (1H, br, s, NH); ¹³C NMR (75 MHz, 18 mg : 0.4 mL CDCl₃/2 drops
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d₆-DMSO): δ 24.7 (s, C-3Å/B), δ 91.2 (s, C-2), δ 118.9 (s, C-6'), δ 121.0 (s, C-2'), δ 124.7 (s, C-4'), δ 129.8 (s, C-5'), δ 134.2 (s, C-3'), δ 139.3 (s, C-1'), δ 165.8 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for C₁₀H₁₁N₂O₃Cl: 242.0458, observed: 242.0475.

*p-Chloro-α-nitroisobutyranilide (99)*

98 (p-Chloro-α-bromoisobutyramide) (1.38 g, 4.99 mmol) gave 1070 mg (4.41 mmol, 88% yield) of pure p-chloro-α-nitroisobutyranilide (99) as a pale yellow, clean looking crystalline powder, m.p. 124–127 °C; Rₐ = 0.38 in 4:1 hexanes/EtOAc, 0.67 in 65:35 hexanes/EtOAc and 0.90 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3303, 3195, 3126, 3057, 3002, 2924, 2854, 1664 (C=O), 1599, 1547, 1533, 1492, 1460, 1400, 1379, 1353, 1308, 1287, 1241, 1188, 1145, 1087, 1014, 960, 904, 864, 820, 747, 708, 695, 667; ¹H NMR (300 MHz, 21 mg : 0.4 mL CDCl₃): δ 1.94 (6H, s, CH₃), δ 7.30 (2H, d, ArH³, J 8), δ 7.44 (2H, d, ArH², J 8), δ 8.01 (1H, br, s, NH); ¹³C NMR (75 MHz, 21 mg : 0.4 mL CDCl₃): δ 25.0 (s, C-3Å/B), δ 91.7 (s, C-2), δ 122.3 (s, C-2'), δ 129.5 (s, C-3'), δ 131.0 (s, C-4'), δ 135.5 (s, C-1'), δ 164.8 (s, C-1); GC-(EI) TOF-HRMS: calcd m/z for C₁₀H₁₁N₂O₃Cl: 242.0458, observed: 242.0477.

*N-Benzyl-α-nitroisobutyramide (101)*

100 (N-Benzyl-α-bromoisobutyramide) (1.40 g, 5.47 mmol) was added to NaNO₂ and DMF and the reaction heated at 120 °C for 4 h. After cooling the standard workup
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Method gave 952 mg (4.29 mmol, 78% yield) of pure N-benzyl-α-nitroisobutyramide (101) as white, crystalline, cauliflower-shaped nodules, m.p. 87–88 °C; Rf = 0.23 in 4:1 hexanes/EtOAc, 0.49 in 65:35 hexanes/EtOAc and 0.76 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3295, 3088, 3028, 3003, 2930, 1652 (C=O), 1547, 1496, 1453, 1427, 1405, 1374, 1356, 1312, 1288, 1236, 1209, 1162, 1077, 1055, 1029, 1000, 865, 747, 732, 698, 671; ¹H NMR (300 MHz, 19 mg : 0.4 mL CDCl₃): δ 1.85 (6H, s, CH₃), δ 4.45 (2H, d, CH₂ J 8), δ 6.46 (1H, br, s, NH), δ 7.22–7.37 (5H, m, ArH); ¹³C NMR (75 MHz, 55 mg : 0.4 mL CDCl₃): δ 24.8 (s, C-3ₐB), δ 44.4 (s, CH₂), δ 91.0 (s, C-2), δ 127.8 (s, C-2’), δ 128.1 (s, C-4’), δ 129.1 (s, C-3’), δ 137.5 (s, C-1’), δ 167.2 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C₁₁H₁₄N₂O₃: 222.1004, observed: 222.1001.

*N-Butyl-α-nitroisobutyramide (103)*

102 (N-Butyl-α-nitroisobutyramide) (1.30 g, 5.86 mmol) was added to NaNO₂ and DMF and the reaction heated at 120 °C for 4 h. After cooling the standard workup method gave 653 mg (3.47 mmol, 59% yield) of pure N-butyl-α-nitroisobutyramide (103) as orange, translucent, shard-shaped crystals, m.p. 61–64 °C; IR(cm⁻¹): 3322, 3085, 2957, 2934, 2874, 1654 (C=O), 1620, 1542, 1465, 1440, 1403, 1374, 1355, 1301, 1287, 1205, 1157, 867; ¹H NMR (300 MHz, 21 mg : 0.4 mL CDCl₃): δ 0.92 (3H, t, Alkyl¹ J 8), δ 1.32 (2H, sextet, Alkyl³ J 8), δ 1.49 (2H, sextet, Alkyl² J 8), δ 1.83 (6H, s, CH₃), δ 3.27 (2H, sextet, Alkyl¹ J 8), δ 6.15 (1H, br, s, NH); ¹³C NMR (75 MHz, 21 mg : 0.4 mL CDCl₃): δ 14.0 (s, C-4’), δ 20.2 (s, C-3’), δ 24.9 (s, C-3ₐB), δ 31.5 (s, C-2’), δ 40.3 (s, C-1’), δ 91.1 (s, C-2), δ 167.0 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C₈H₁₆N₂O₃: 188.1161, observed: 188.1173.

*α-Methoxy-α-nitroisobutyranilide (105)*
104 (α-Methoxy-α-bromoisobutyranilide) (1.40 g, 5.15 mmol) gave 868 mg (3.65 mmol, 71% yield) of pure α-methoxy-α-nitroisobutyranilide (105) as tiny, pretty, orange prisms or various morphology, m.p. 67–70 °C; Rf = 0.40 in 4:1 hexanes/EtOAc, 0.65 in 65:35 hexanes/EtOAc and 0.89 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3331, 3043, 3005, 2964, 2936, 2901, 2838, 1675 (C=O), 1594, 1553, 1521, 1493, 1460, 1432, 1403, 1375, 1357, 1322, 1287, 1262, 1220, 1177, 1142, 1112, 1042, 1025, 963, 899, 862, 849, 780, 748, 739, 724, 666; ¹H NMR (300 MHz, 19 mg : 0.4 mL CDCl₃): δ 1.95 (6H, s, CH₃), δ 3.91 (3H, s, O–CH₃), δ 6.90 (1H, dd, ArH³, J 2, J 8), δ 6.97 (1H, td, ArH¹, J 2, J 8), δ 7.10 (1H, td, ArH², J 2, J 8), δ 8.28 (1H, dd, ArH⁶, J 2, J 8), δ 8.62 (1H, br, s, NH); ¹³C NMR (75 MHz, 57 mg : 0.4 mL CDCl₃): δ 24.9 (s, C-3AB), δ 56.2 (s, O–CH₃), δ 91.6 (s, C-2), δ 110.4 (s, C-3'), δ 120.3 (s, C-6'), δ 121.4 (s, C-5'), δ 125.3 (s, C-4'), δ 126.9 (s, C-1'), δ 148.7 (s, C-2'), δ 164.4 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C₁₁H₁₄N₂O₄: 238.0954, observed: 238.0952.

**m-Methoxy-α-nitroisobutyranilide (107)**

106 (m-Methoxy-α-bromoisobutyranilide) (1.40 g, 5.15 mmol) gave 981 mg (4.12 mmol, 80% yield) of pure m-methoxy-α-nitroisobutyranilide (107) as a crystalline mass of orange tipped needles, m.p. 97–99 °C; Rf = 0.29 in 4:1 hexanes/EtOAc, 0.55 in 65:35 hexanes/EtOAc and 0.85 in 1:1 hexanes/EtOAc; IR(cm⁻¹): 3276, 3223, 3154, 3007, 2943, 2838, 1665 (C=O), 1614, 1597, 1539, 1489, 1451, 1427, 1397, 1373, 1344, 1320, 1301, 1277, 1267, 1208, 1182, 1149, 1031, 953, 844, 788, 764, 749, 727, 686; ¹H NMR (300 MHz, 28 mg : 0.4 mL CDCl₃): δ 1.93 (6H, s, CH₃), δ 3.80 (3H, s, O–CH₃), δ 6.72
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(1H, dd, ArH\textsuperscript{4}, J 2, J 8), δ 6.96 (1H, dd, ArH\textsuperscript{6}, J 2, J 8), δ 7.22 (1H, t, ArH\textsuperscript{5}, J 8), δ 7.26 (1H, d, ArH\textsuperscript{2}, J 2), δ 7.98 (1H, br, s, NH); \textsuperscript{13}C NMR (75 MHz, 120 mg : 0.4 mL CDCl\textsubscript{3}): δ 24.6 (s, C-3\textsubscript{A/B}), δ 55.5 (s, O–CH\textsubscript{3}), δ 91.5 (s, C-2), δ 106.8 (s, C-6'), δ 111.6 (s, C-2'), δ 113.2 (s, C-4'), δ 130.0 (s, C-5'), δ 138.0 (s, C-1'), δ 160.4 (s, C-3'), δ 165.2 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C\textsubscript{11}H\textsubscript{14}N\textsubscript{2}O\textsubscript{3}: 238.0954, observed: 238.0954.

\textit{p-Methoxy-\alpha-nitroisobutyrnilide (109)}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {108};
\node at (2,0) {109};
\draw[->] (0.5,0) -- node[above] {NaNO\textsubscript{2}} (2.5,0);
\end{tikzpicture}
\end{center}

\textbf{108} (\textit{p-Methoxy-\alpha-bromoisobutyranilide}) (1.40 g, 5.15 mmol) gave 1078 mg (4.53 mmol, 77% yield) of pure \textit{p-methoxy-\alpha-nitroisobutyranilide (109)} as tiny, pretty, pale yellow needles, m.p. 69–71 °C; R\textsubscript{f} = 0.16 in 4:1 hexanes/EtOAc, 0.48 in 65:35 hexanes/EtOAc and 0.80 in 1:1 hexanes/EtOAc; IR(cm\textsuperscript{-1}): 3346, 3003, 2961, 2939, 2898, 2840, 1660 (C=O), 1597, 1545, 1530, 1510, 1462, 1440, 1414, 1403, 1375, 1356, 1311, 1299, 1268, 1232, 1184, 1173, 1141, 1112, 1031, 962, 901, 863, 850, 824, 764; \textsuperscript{1}H NMR (300 MHz, 28 mg : 0.4 mL CDCl\textsubscript{3}): δ 1.92 (6H, s, CH\textsubscript{3}), δ 3.79 (3H, s, O–CH\textsubscript{3}), δ 6.86 (2H, d, ArH\textsuperscript{3}, J 8), δ 7.37 (2H, d, ArH\textsuperscript{2}, J 8), δ 7.87 (1H, br, s, NH); \textsuperscript{13}C NMR (75 MHz, 120 mg : 0.4 mL CDCl\textsubscript{3}): δ 24.9 (s, C-3\textsubscript{A/B}), δ 55.8 (s, O–CH\textsubscript{3}), δ 91.5 (s, C-2), δ 114.5 (s, C-3'), δ 122.9 (s, C-2'), δ 129.8 (s, C-1'), δ 157.5 (s, C-4'), δ 164.9 (s, C-1); GC-(EI) TOF-HRMS: calc’d m/z for C\textsubscript{11}H\textsubscript{14}N\textsubscript{2}O\textsubscript{4}: 238.0954, observed: 238.0971.

\textbf{3.5.2.1 \textit{Br–NO\textsubscript{2} Substitution in the absence of O\textsubscript{2}}}  

Preparation of \textit{p-cyano-m-trifluoromethyl-\alpha-nitroisobutyranilide (55)} was carried out using two 100 mL Schlenk flasks. Into one flask was placed 1.68 g of \textit{p-cyano-m-trifluoromethyl-\alpha-bromoisobutyranilide (52)} and into the other was placed 4.00 g of NaNO\textsubscript{2}. A 20 mL portion of DMF was added to each of flask which was then sealed with a rubber septum and placed under positive pressure of nitrogen. The nitrogen
used was prepared in the bottom of the building by taking runoff from a liquid nitrogen tank. This nitrogen was passed through a Dreschel bottle containing a solution of 5 g pyrogallol in 100 g KOH/100 mL water. This is a known method of deoxygenating gases [131]. The red colour that develops from the oxidation of pyrogallate was observed not to get any darker even after 24 h of bubbling.

Nitrogen passing through a pyrogallol solution before entering the reaction flask

Using this nitrogen which was free of O₂, both flasks had nitrogen bubble through them for 30 min in order to displace any dissolved O₂ from the DMF. After this time, the contents of the flask containing the dissolved compound (52) were transferred to the flask containing the NaNO₂ using a 20 mL glass syringe. The reaction was then monitored periodically by GC-MS and was seen to follow the same rate as that observed when the reaction was done under air.

3.5.2.2 Br–NO₂ Substitution at low nitrite concentration

Preparation of p-cyano-m-trifluoromethyl-α-nitroisobutyranilide (55) was carried out in tandem in three 100 mL flasks of the same shape and all using the same shape magnetic stirrer, stirred at 700 rpm. The flasks were in the same room, on the same bench and the reaction started at the same time. The only difference was in the amount of sodium nitrite used. Each reaction used 35 mL of DMF which was taken from the same bottle immediately before use. As it was measured that at room temperature, 50 mL of DMF was required to dissolve 205 mg of NaNO₂, the saturated reaction used 144 mg of NaNO₂, the 75% and 50% saturation reactions used 108 mg and 72 mg respectively. As

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the 50% nitrite concentration contained 1.04 mmol of NaNO₂ and as an excess of nitrite in 4:1 or greater ratio was desired, 84 mg (0.025 mmol) of 52 was used in all three reactions. The reactions were monitored by GC-MS using the same extraction method and instrument as had been used to monitor the other substitution reactions. Aliquots were taken at ~ 1 h intervals to obtain five data points for each reaction; all fifteen GC-MS sample vials were run on the same GC-MS on the same day.
4. 2-Nitropropane – A new leaving group and novel formation of an isocyanate

Both the novel ring closure explored in chapter 2 and also the pattern by which the α-nitroisobutyrilanilides prepared in chapter 3 have been seen to degrade present a potential utility. They show that a bond breakage of an amide with a neighbouring isobutyrylnitro group can occur to furnish an isocyanate. Not only does this bond breakage occur in a repeatable way, it appears likely that it can occur in a controllable way.

![Chemical structure](image)

The R group is not restricted to aryl groups and the equivalent isocyanate product has been observed on the GC-MS injector port from the compounds with alkyl R groups (103 and 101) equally readily as it has for the R = aryl compounds.

Characterizing the mechanism and conditions required for control of this chemistry is of great potential interest as both products are valuable. 2-Nitropropane is a useful solvent and can be sold as a racing fuel additive. Its properties are further discussed in 4.1. Isocyanate compounds are by no means limited to fine chemical synthesis, which in fact represents only a minimal quantity of their consumption. Large volumes of isocyanates are used to prepare carbamate pesticide compounds, while isocyanates in the form of diisocyanates are heavily used in the polyurethane industry as raw materials for manufactured goods. Millions of tonnes per year of isocyanate chemical products are consumed by both of the above categories and in widely varied molecular form. Nearly all of these isocyanates are produced by treatment with phosgene [132]; the hazards of this process are further discussed in section 4.3.

It may also prove possible to develop this reaction as a preparative synthetic route where 2-nitropropane leaves to give the isocyanate (NCO) group as an intermediate that reacts in the same pot with a target compound. This would allow α-nitroisobutyranilides to be
used as synthetic intermediates instead of using the isocyanate as a discrete compound. Such 'pre-isocyanate' reagents would retain the coveted control over reactivity that isocyanates possess, but without the short shelf life, water sensitivity and toxicity that many isocyanate products possess.

4.1 Properties of 2-nitropropane

2-Nitropropane has a dielectric constant of 25.5 [133] which makes it a mid-range solvent on the polarity scale (methanol is 33.1, water is 80.1). While it has a high enough polarity to dissolve most compounds, 2-nitropropane is far less miscible with water than 2-propanol. Even nitroethane, for example, is immiscible with water. A boiling point of 120 °C allows 2-nitropropane to readily enter the vapour phase at atmospheric pressure - it should easily be distilled away from less volatile compounds under a mild vacuum. It is stable in a bottle at room temperature and pressure and is commercially available from Sigma-Aldrich and other providers. 2-Nitropropane has a smell that is similar to 2-propanol, but slightly more metallic.

The nitro group has long been known to be capable of accepting hydrogen bonds. This effect is weaker than for that of other functional groups and it was thought to be unable to participate in hydrogen bonding until 1964 when Baitinger et al. showed that nitro compounds give rise to small intermolecular IR spectral shifts in the O–H stretching [134]. Later in 2001 Abraham and Platts [135] tabulated and compared the hydrogen bonding capability of structural groups, listing the nitro group as having one of the lowest hydrogen bond constants at 0.25, while methoxy and ethoxy groups are listed as 0.43 and 0.46 respectively.

2-Nitropropane has a more acidic proton on its 2 position than does 2-propanol. This is due to the dual effect of resonance and electron withdrawing stabilization of the anion by the nitro group, whereas the carbanion of 2-propanol would need to be stabilized by the hydroxyl which can only impart an electron withdrawing effect. Nitro has a dual resonance (mesomeric) electron-withdrawing effect and an inductive (electronegativity) electron-withdrawing effect.
Despite this capability, not much of the anion forms at room temperature.

Ionization of C acids like nitroalkanes (and recombination of the ions) is much slower than for O and N acids and so, while nitroalkanes will ionize slowly, they will ionize so slowly as to retain phase separation from water even after sitting in the same bottle for several months. However, an old bottle of a nitroalkane that contains a small amount of the brightly coloured anion can be purified of the small amount of its anionic form by placing it over water for a few days. This is a procedure that was done several times during this PhD candidature with nitroethane, which could always be brought back from orange to clear.

With these considerations, one would expect 2-nitropropane to depart from an open vessel reaction mixture under moderate heat with no vacuum. However, 2-nitropropane was not able to be captured when it was yielded from the ring-closure reaction (chapter 2’s hydantoin synthesis), nor could it be smelled on the condenser. As this was at high temperature (120 °C) and in the presence of nitrite ions, this could be due to a known side reaction where nitro compounds react with nitrite ions to undergo an elimination to form an alkene [89, 104]. Propene, the alkene formed in this case is a gas at temperatures above −50 °C and so is quite difficult to capture without special equipment.
There are no previously reported reactions where a 2-nitropropane anion acts as a leaving group to produce 2-nitropropane as a by-product. The stability of the 2-nitropropane anion suggests that it should readily act as a leaving group. Still it remains that 2-nitropropane acting as a leaving group has not hitherto been reported. 2-Nitropropane is however, known to act as an alkylating reagent when prepared in its anionic form as a sodium or lithium salt [136 (Kornblum again), 137] and this is its main appearance in the literature (or more correctly, 2-nitropropanoate is not an alkylating reagent, it itself gets alkylated). In this capacity the 2-nitropropanoate tends to O-alkylate and special efforts are devised in order to encourage it to instead C-alkylate.

4.1.1 Separation and capture of 2-nitropropane formed

It was expected that the targeted isocyanate product (57) in the reaction flask would form a carbamate by reacting with any alcohol present, thus procuring further proof of its existence. As it was desired to capture the 2-nitropropane exclusively by a reactive distillation, an alcohol with high boiling point was chosen in which to heat the α-nitroisobutyranilides so that the alcohol solvent would not distil as readily as the 2-nitropropane formed.

In order to capture 2-nitropropane, compound 55 was heated at 150 °C in a reactive distillation style apparatus under vacuum of 20 mmHg in benzyl alcohol (BP = 205 °C). These pyrolysis conditions decomposed the main part of 55 to a resin, however the captured distillate was analyzed by H-NMR and was at first found to be 2-nitropropane mixed with benzyl alcohol; when the conditions were repeated using a slightly milder vacuum the distillate was found to be pure 2-nitropropane. Both distillates obtained were confirmed to contain 2-nitropropane by the addition of a drop of 2-nitropropane purchased from Sigma-Aldrich to the NMR tubes, which were then reanalyzed by H-NMR and C-NMR to observe an increased intensity in the signals from the 2-nitropropane nuclei.
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With α-nitroisobutyranilides such as 55, the departure of 2-nitropropane leaves formation of an isocyanate as the most obvious molecular possibility (previously mentioned at the end of section 2.3). In our paper on the alternative synthesis of RU58841 [74], we put forth two mechanisms for the ring closure of 59. Our favoured mechanism is by way of an isocyanate intermediate in a 5-exo-dig ring closure. Our other mechanism, a 5-exo-trig ring closure was less favoured, partly due to steric hindrance. The α-nitroisobutyranilides have less steric hindrance than 59, but they lack the extended amide system required for this kind of nucleophilic attack to occur intramolecularly.

Attack from an outside nucleophile such as benzyl alcohol or water from silica gel cannot be ruled out, however, as we shall see, repeated observation of \( m/z \) signals that correspond to the equivalent isocyanates have led to the view that the formation of 2-nitropropane is far more likely to proceed via the isocyanate formation mechanism.

When 109 was heated in the presence of 43–60 μm silica it yielded 2-nitropropane as a clear, colourless liquid.

The rationale for these reaction conditions is discussed in detail in section 4.4. Apart from air cooling, no coolant was required to capture 2-nitropropane and the yields appeared to be close to quantitative.
4.2 Properties of the isocyanate group

Isocyanates (often abbreviated to NCO) are compounds that contain the high energy functional group R-N=C=O. They typically do not form easily or by accident and are prized for their well characterised and selective reactivity with OH, NH & SH functional groups [138]. High yields and a lack of by-products make isocyanate compounds useful building blocks in organic synthesis and polymer chemistry [139]. The reactivity of the isocyanate group comes from the highly electron withdrawn C being readily attacked by a nucleophile, for example a deprotonated hydroxyl anion (RO'). When reacted with an OH compound, a carbamate group is produced (also known as a urethane group - RNHCOOR) and when reacted with an NH compound a urea group is formed (RNHCONHR). Reaction with SH similarly yields RNHCOR. Isocyanates can also react in an analogous way with secondary amines and carboxylic acids. Reaction with H₂O ‘quenches’ the NCO group by releasing CO₂ which leaves behind a primary amine NH₂ (which may in turn react with another isocyanate to give a urea product).

Isocyanates are typically prepared by exposing an amine compound to phosgene (ClCOCl). Phosgene is a gas which is highly toxic to humans and when it is used as a reagent for small scale fine chemical synthesis it is typically introduced in a solution of either dichloromethane or toluene. As discussed in 1.5.1, Battmann *et al.* used phosgene in toluene to prepare an isocyanate intermediate en route to their hydantoin [34]. However, in large-scale preparations—for example, the production of diisocyanates from methylenediarylamines on a tonne scale—special handling equipment allows phosgene to be introduced in its gaseous form. The scale-up plants that carry out this process must be located in areas not in close proximity to large populations and the workers must be monitored for phosgene exposure. As phosgene has been used as a chemical weapon its use remains tightly regulated.

![Chemical Reaction]

A significant portion of the cost to produce diisocyanates is surely consumed by addressing the presence of phosgene which requires special personnel and equipment.
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There have been many attempts at phosgene-free diisocyanate synthesis, of which only a few have been successful and are mostly restricted to small scales [139], ultra low temperatures [140] or to the preparation of isocyanates that are sterically hindered [141].

In the pursuit of an alternative isocyanate synthesis it is pertinent that NCO groups are highly recognisable in IR spectra by their characteristic absorbance at 2260–2290 cm\(^{-1}\) [138]. This is near the region of the C=N stretch in the cyano (nitrile) group (2210–2260 cm\(^{-1}\)) but there is no overlap and the C=N stretch of cyano is also a distinctly sharper shape and not easily confused with the broad shape given by NCO. A Google search for images shows the IR spectra for methyl and phenyl isocyanate.

![IR spectrum of methyl isocyanate](image)

This characteristic and unique IR peak allows real time monitoring of a reaction as a useful tool to confirm the presence of short-lived isocyanate species during a reaction [142]. This IR peak can also be used to indicate very conclusively whether or not a solid product from a reaction workup is an isocyanate compound.
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The use of diisocyanates to produce polyurethanes with a variety of targeted properties has been well characterized. The mechanism can be catalysed to give a great amount of control over the reaction rate and follows the general form shown below.
With alcohol:

\[ R_2 \text{O}H \quad \xrightarrow{\text{DABCO}} \quad R_2\text{O}^- \quad \xrightarrow{R_1 \text{N}} \quad R_1\text{N}^+\text{O}R_2 \quad \xrightarrow{\text{R}} \quad R_1\text{N}^+\text{OC}O\text{O}R_2 \quad \xrightarrow{\text{R}} \quad R_1\text{C}O\text{O}R_2 \quad \text{Carbamate} \]

Diazabicyclooctane catalyst (DABCO)

With amines:

\[ R_1 \text{N} \quad \xrightarrow{\text{R_2 NH}_2} \quad R_1\text{N}^+\text{O}R_2 \quad \xrightarrow{\text{R}} \quad R_1\text{N}^+\text{OC}O\text{O}R_2 \quad \xrightarrow{\text{R}} \quad R_1\text{C}O\text{N}R_2 \quad \text{Urea} \]

With water:

\[ R \text{N} \quad \xrightarrow{\text{H}O} \quad R\text{N}^+\text{OC}O \quad \xrightarrow{\text{R}} \quad R\text{N}^+\text{OC}O \quad \xrightarrow{\text{R}} \quad R\text{NH}_2 + \text{CO}_2 \quad \text{Amine} \]

**General reactivity of isocyanates**

While it is true that DABCO is not basic enough to deprotonate a stoichiometric amount of an alcohol compound in a flask, catalysis works differently - DABCO works by making a small amount of the anion of a polyol and as the reaction proceeds, heat is given off that speeds up the reaction further. Thus the DABCO only needs to protonate a catalytic amount of the alcohol in order to speed up the reaction [143].

The understanding of this mechanism is of great use to polyurethane chemists because the final properties of the polyurethane are greatly determined by the rate at which they are cured. A small amount of a specially designed amine compound added to a polyol blend will speed up the polyurethane reaction, which rests on the principle that the more
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electron-dense the amine, the more readily it will react with the electron-withdrawn carbon in the NCO group to give a urea bond. This amine compound is not a catalyst, it becomes a small portion of the polymer product. The reaction with water also increases the rate of the polyurethane reaction and the presence of a small amount of water in polyols that are used to make foams can be beneficial as the CO₂ released acts as extra blowing agent and slightly reduces the need for halocarbon additives. Polyurethanes that are made up of a higher proportion of carbamate bonds have increased hardness and rigidity and this can be achieved by using more of the small molecule polyols such as ethylene glycol.

Most polyurethane production exploits the properties of a blend of diisocyanate compounds known as ‘crude MDIs’ (Methylene Di Isocyanates). As each compound in this mixture is a solid at room temperature it would be inconvenient to mix them with the prepared polyol blends for curing. However a mixture of diisocyanates with varied ratios of between 2 and 3 NCOs per compound gives a liquid with low viscosity of ~300 cP at 22 °C.

This product is mainly a mixture is the diphenylmethane isocyanates in the 2,2, 2,4 and 4,4 configuration. The undesired 2,3-isomers must be separated as they interfere with polymerization [132]. The compound 4,4-methylene diphenyl diisocyanate (112) is a solid at room temperature with a m.p. of 40 °C. This compound is sometimes given the moniker ‘pure MDI’ in order to differentiate it from the commonly encountered ‘crude
Isocyanates and diisocyanates can also react intermolecularly to form trimers called isocyanurates which solidify the mixture and quench the reactivity of the NCO group.

This trimerization is slowed by storage at 35 °C and while it exerts a limit on the shelf life of most diisocyanates to between two and three years, the deliberate formation of isocyanurates by excess isocyanate and a catalyst which promotes this pathway is often adopted as it produces polyurethane foams with superior hardness and rigidity [144].

Catalysis of the polyurethane reaction is largely carried out by organic amines such as diazobicyclooctane (DABCO) (113) or organometallic tin and mercury compounds such as dibutyltin dilaurate (114) or phenylethylmethoxy mercury neodecanoate (115). There are hundreds of such catalysts, each of which favour either gel or foam formation. Polyurethane catalysts all have in common the affinity to accept a proton from OH, NH or SH and prevent the O, N or S from becoming positively charged [144].
Organic and organometallic catalysts for polyurethane production

The more sterically hindered organic amine catalysts favour a greater proportion of isocyanurate formation than urethane formation. It is noteworthy that in some cases, the reaction can be catalyzed by acetic acid which donates a proton to the NCO, probably to the N [144].

Most NCO compounds can survive exposure to water for a few hours at room temperature. For example 2,4-toluene diisocyanate (2,4-TDI) (116) can be run through a HPLC in either water/acetonitrile or water/MeOH. [138].

2,4-Toluene diisocyanate and 2,6-toluene diisocyanate

The NCO groups don’t lack electron density when on a toluene scaffold as the methyl is electron donating. Therefore the TDIs react slowly in the absence of a catalyst. It follows that NCOs with more electron-withdrawn R groups such as 57 and 118 will react quickly with water and probably can’t be worked up by liquid/liquid extraction.
Supercharged isocyanates where the NCO carbon is highly electron-withdrawn

These supercharged isocyanate species would therefore be more difficult to isolate and it would therefore be wise to choose an α-nitroisobutyranilide from the compound library which has less electron withdrawing capacity in order to pursue the preparation of the isocyanate as a discrete intermediate.

Solubility issues can arise when it is desired to react isocyanates with polar compounds such as proteins or amino acids, particularly with the non-polar TDIs which will phase separate from compounds like urea [138]. In this case an aprotic solvent of intermediate polarity must be used, which is typically dimethylacetamide.

Described in section 2.3 (step five) was the observation that 2-nitropropane acts as a leaving group when it exists as part of a compound attached by its central carbon to a neighbouring amide carbonyl (isobutyrylnitro group). This has been observed with the α-nitroisobutyranilides and also the ring closure of 59 to give the hydantoin 48.

Ring closure of 59 to give hydantoin (48) and 2-nitropropane
It follows that 2-nitropropane departs in a way that furnishes the larger part of the compound with an isocyanate group.

Using this process to prepare and purify the newly formed isocyanate has proven to be elusive as the reaction is difficult to control. It was observed at first that while the NCO formed readily from the more electron-withdrawn α-nitroisobutyranilides, it tended to be easily quenched by water to produce the primary amine (R-NH₂). On this basis, a compound with less electron-withdrawn R group was selected from the compound library with the rationale that the isocyanate species formed would be less reactive and easier to isolate. Further attempts were carried out on the new model compound and 2-nitropropane was again seen to act as a leaving group. The pursuit of this synthesis is described in section 4.4, with experimental procedures in 4.5.

### 4.2.1 Existing preparations of the isocyanate group

The classic method to prepare an NCO group for further reaction is by carbonylation of an R-NH₂ using phosgene. This is done on small molecule compounds at a single site and also on large scale with a mixture of diaminines to make diisocyanates for polymer chemistry.

Phosgenation is the classic and by far the most characterized carbonylation pathway to isocyanates. Phosgene can be replaced with phosgene equivalent reagents, for example
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1,1'-carbonyl diimidazole (42) which replaces HCl as a leaving group with that of imidazole. However these equivalent reagents are not as reactive as phosgene and their use requires extra efforts to purify the products since their leaving group acts as an impurity that must be removed, whereas the leaving group from carbonylation using phosgene is hydrogen chloride which readily evaporates to leave a pure product.

![1,1'-Carbonyl diimidazole](image)

**1,1'-Carbonyl diimidazole; a phosgene equivalent reagent**

While many niche methods to achieve isocyanates exist, they are typically restricted to small scale and delicate conditions. For example iso-nitriles can be oxidized to isocyanates by DMSO in DCM solvent, but this requires the use of trifluoroacetic anhydride as a high dosage catalyst and part of the reaction must be carried out at -60 °C, a thermal requirement that greatly limits its scalability [140].

![Isocyanate preparation by Le and Ganem](image)

**Isocyanate preparation by Le and Ganem**

The mechanism for the formation of the isocyanate group is not obvious and Le and Ganem have not proposed one. Dimethylsulfide is a byproduct of this reaction and the isocyanates formed are reported to be usable in pot, or they can be isolated in high purity [140].

In another recently reported method, alkyl isocyanates were prepared in near quantitative
yield from a wide variety of alcohols by exposing them to a three reagent system of triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone/tetrabutylammonium cyanate. The reaction was carried out in a 1:1:1:1 ratio in acetonitrile at room temperature. This method was shown to be selective for primary alcohols in the presence of secondary and tertiary alcohols and is also applicable to thiols and trimethylsilyl ethers [139]. Although the preparative details are reported thoroughly, a mechanism has not been proposed for this reaction.

Isocyanate preparation by Akhlaghinia

In 1995 Knölker and co-workers published a method to prepare aryl or alkyl isocyanates by exposing amines, such as 119, to di-tert-butyl dicarbonate (120) in the presence of a stoichiometric amount of 4-dimethylaminopyridine (121) at room temperature in a choice of inert solvents (acetonitrile, dichloromethane, ethyl acetate, tetrahydrofuran, toluene) [141].
Once again, the mechanism for formation of the isocyanate group has not been reported, nor is it obvious. While this is probably the best alternative synthesis of isocyanate compounds in recent years, it is still limited to sterically hindered isocyanates such as 122, which is due to reaction of the tert-butanol product with the isocyanate products formed – only the sterically hindered examples react slowly enough with tert-butanol to be worked up and isolated.

As of the 2000s, the synthesis of isocyanate compounds is not always convenient and few are available commercially [145] which is a major limitation on medicinal chemistry as many of the scaffold building techniques rely on the input of an isocyanate component. It is fair to say that the options for preparing isocyanates remain limited and it would be of great use to find a new method that is safer than phosgenation but also cheap and scalable.

4.3 Mechanistic considerations

The anilide nitrogen of the α-nitroisobutyramide group was readily seen to lose its proton in the negative ion mode on an electrospray mass spectrometer during this PhD candidature. This tells us that this is a rather acidic proton and gives a strikingly obvious mechanism for the formation of an isocyanate.

![Isocyanate formation from α-nitroisobutyramide group with 2-nitropropane leaving group](image)

The impetus for this section of the PhD project was the observation of an M−89 signal from the α-nitroisobutyranilides when run through GC-MS that could only have been an isocyanate. As the loss of the anilide proton by the above mechanism is the simplest way to arrive at an isocyanate, the first attempts at the novel preparation of isocyanates were carried out by exposing α-nitroisobutyranilides to Brønsted acids and bases. As no NCO product was ever observed this way, this seemed to disprove the most simple mechanism and other possibilities were subsequently explored. The observation of the isocyanate compounds on the GC-MS injector port gave a clue that it could involve silica acting as a
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Brønsted base.

However the ring closure to form the hydantoin which occurs in DMF as the solvent could be using dimethylamine as a Brønsted base (which is yielded upon the decomposition of a small amount of DMF). There is a plausible mechanism by which this could occur that avoids an isocyanate intermediate and the ring closure could be proceeding using both the isocyanate and the non-isocyanate pathway (shown below).

![Ring closure catalyzed by dimethylamine](image)

**Ring closure catalyzed by dimethylamine**

Or it could be that the mechanism is neither acid or base catalysed but begins with H-migration from the amide nitrogen to the nitro carbon to allow 2-nitropropane to leave first, whence a C=N bond is formed to give an NCO group.

A pericyclic mechanism can also be considered, given that the α-nitroisobutyrilide can form a locked ring-like cyclic form and preliminary hydrogen bonding would allow the formation of the *aci* form of 2-nitropropane. This would be described as a retro-ene type pericyclic mechanism as a pi bond is being replaced by a sigma bond.
If this electrocyclic mechanism were operative, it would and should be expected to be thermally activated and would require no acid or base to catalyze it, mere rapid heating would encourage it forward. It is possible that two competing mechanisms are operative where the faster mechanism dominates; one during the ring closure reaction and another during the $\alpha$-nitroisobutyranilide pyrolysis; these considerations were taken into account for the experimental design to trap the isocyanate in order to prove its existence which thus far had only been shown by the mass spectra.

### 4.3.1 Trapping isocyanate intermediate

As has been mentioned, the formation of an NCO group can be short-lived due to its ability to react with $\text{H}_2\text{O}$ to give $\text{CO}_2$ leaving group and the amine. In this case the existence of such an intermediate can be proven by the addition of a compound with which it will react more quickly than water such as an alcohol or an amine. It is known from polyurethane chemistry that aromatic primary amines with highly electron-donating aromatic R groups have an N that reacts fast with an NCO group – such a liquid aromatic amine will react with a liquid isocyanate to form a solid in 2–4 seconds when mixed together [146].

Compound 55 and analogues in the library of $\alpha$-nitroisobutyranilides have been found to decompose upon heating in the presence of silica or benzyl alcohol to yield 2-nitropropane that was captured and its identity confirmed by NMR. Given the molecular structure of $\alpha$-nitroisobutyranilides (including 55) the departure of 2-nitropropane leaves an isocyanate functional group as the only possibility.
However, it may be that the more electron-withdrawn α-nitroisobutyranilide (55) also creates the shortest-lived isocyanate product. Further evidence of isocyanate formation from 55 could be made by the isolation of a carbamate when the reaction takes place in the presence of an alcohol.

This reaction was tried with methanol and the addition of DABCO to catalyze the formation of the carbamate. Upon workup, a messy polymeric product, mostly composed of the aniline decomposition product (54) was observed. It was later realized that the temperature of the reaction (180 and then 210 °C) worked very well to release the 2-nitropropane but was too high for the isocyanate (57) to be stable as isocyanates have been reported to degrade at or above 100–120 °C [132].

Although an NCO group may be observed with real time monitoring using IR spectroscopy (as mentioned earlier, the C=N bond gives a unique and intense peak at ~2250 cm⁻¹ [140]), it can sometimes be desirable to ‘trap’ the NCO for further proof of its existence. This has been carried out using tert-butylamine when oxidizing isonitriles [140] and methanol in the Hofmann rearrangement [147] which involves heating a primary amide in methanol at reflux with a hypobromite source to give good yields of
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methyl carbamates. This proceeds via rearrangement of a nitrene to form the isocyanate intermediate [147].

Hoffmann rearrangement

The isocyanate formed by the Hofmann rearrangement is reported to be quenched by water to give the amine and CO₂ and has become a widely used technique to convert primary amides to amines.

Mechanism of Hofmann rearrangement

As the attempts at formation of isocyanates had repeatedly furnished the amine, the reaction was tried under similar conditions to a Hofmann rearrangement in order to obtain the methyl carbamate derivative. Heating 55 in MeOH with NaOH/Br₂ and also with just NaOH (the Br₂ later proved to be unnecessary) showed a complication. The start compound was gone after 4 hours reflux in MeOH, but GC-MS showed mostly the amine
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compound was obtained. A further literature search found a reference that claims carbamates are capable of giving an alkene elimination product by yielding CO₂ and leaving the primary amine behind [138] thus giving the same product as an isocyanate quenched by water. It is not clear how a methyl carbamate would behave in this type of decomposition – it only has one carbon so it ought not be capable of forming an alkene. It is possible that it leaves simply as carbene (CH₂) and then takes a proton from two waters to form methane and two hydroxide ions. Or the carbene could react with one water to form methanol. However, we were unable to find even one precedent of dihydrocarbene reacting with water. In light of this observation of carbamate degradation by alkene elimination, performing the reaction using Hofmann rearrangement conditions had not lent itself well towards showing evidence for or against an isocyanate intermediate.

![Methyl carbamate decomposition via carbene](image)

It was thought that the product may perhaps be the urea compound formed under these conditions which broke back down to the aniline (54) on the GC-MS injector port, however electrospray mass spec showed a total absence of any urea compound and the aniline (54) to indeed be the full compound. It therefore seemed that a more gentle synthesis had to be pursued if the carbamate was desired as an end product.

4.4 Towards preparation of discrete isocyanate compounds using this route

The linear synthesis of RU58841 which was the subject of chapter 2 involved the conversion of an α-bromoisobutyranilide to the equivalent α-nitroisobutyranilide.
Monitoring this reaction by GC-MS showed an m/z signal of 212 which was 89 mass units lower than expected for the nitro compound. As the compound was then analyzed by electrospray mass spec and a mass minus 1 peak of 300 was observed, it followed that the nitro compound was being readily pyrolyzed by the conditions exerted by the GC-MS, which include an injector port at 180 °C. This appeared to be strong evidence that heating in the presence of silica would allow the isocyanate (57) to form at the same time as 2-nitropropane (mass = 89) is yielded.

During the subsequent monitoring by GC-MS of reaction rate in the preparation of the α-nitroisobutyranilide compound library (which was the subject of chapter 3), it was noted that in some cases, some or all of the nitro product was observed as its equivalent at M–89 (with 89 being the mass of the 2-nitropropane). The 180 °C temperature of the injector port may well play a part in this observed pyrolysis, and, as has been mentioned, running the compounds through an ‘On-column injector’ would have been expected to show a peak at the m/z of the unpyrolyzed α nitroisobutyranilides. In some cases the isocyanate species was observed as only ~5% of the nitro product but in other cases it could be as high as 95%. This phenomenon was inconsistent and while no systematic experiments were carried out, a look back at the spectra showed that it was observed more so for the more electron withdrawn compounds. Specifically it was observed for compounds 55 (R = p-cyano-m-trifluoromethyl-phenyl), 81 (R = phenyl), 91 (R = p-nitro-phenyl), 83 (R = p-methyl-phenyl), 87 (R = o-nitro-phenyl), 89 (R = m-nitro-phenyl), 95 (R = o-chloro-phenyl), 97 (R = m-chloro-phenyl), 99 (R = p-chloro-phenyl), 93 (R = o-bromo-phenyl), 105 (R = o-methoxy-phenyl), 107 (R = m-methoxy-phenyl). However it was never observed with 109 (R = p-methoxy-phenyl), 85 (R = o-carboethoxy-phenyl), 101 (R = benzyl) or 103 (R = n-butyl).

Since the ring closure reaction which is suspected to have an isocyanate intermediate occurs in DMF at 110 °C for 7 h, a significantly reduced reaction time in the presence of microwaves may say something about the mechanism and give a clue as to the best type of reagent to try in pursuit of obtaining a discrete isocyanate compound from the α-nitroisobutyranilide (a more ionic intermediary would be expected to have its rate increased). It is well known which reactions will and will not work well in microwave conditions as articulated by the work of Kappe et al. [43]. At outset of this study microwave conditions appeared to have a low likelihood of furnishing the desired isocyanate compounds and so our efforts were directed towards experiments involving
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acids, bases and rapid heating. There was not enough candidature time left to perform microwave experiments.

The α-nitroisobutyranilide with the CN/CF₃ substitution (55) was heated by a reactive distillation in benzyl alcohol at 150 °C. As the solvent distilled too readily at high vacuum the vacuum was decreased, which allowed the 2-nitropropane to distil exclusively. It was expected that the isocyanate product (57) in the reaction flask would form the carbamate equivalent by reacting with the benzyl alcohol. However, analysis of the contents of this flask showed that only resin had formed. It appeared likely that the isocyanate (57) was formed but that some of it was quenched by water back to the aniline (54) before it could be worked up. The isocyanate (57) and the aniline (54) species could polymerize at this temperature to form a urea-based resin.

Up until this point, the contents of the flasks had been analyzed by workup and subsequent IR spectra. It now seemed to make sense to monitor further attempts to prepare the isocyanate species by C-NMR. The model compound was switched to the p-methoxy derivative (109) which had three perceived advantages:

1. As the p-methoxy compound was less electron withdrawn, the isocyanate formed from it (123) would react more slowly with any water present and perhaps last long enough to work up.

2. The symmetrical substitution on the phenyl group and the absence of a CF₃ group meant that this compound had fewer C-NMR peaks. The target isocyanate product had six peaks and when quenched to aniline (54) it would have five. The originally targeted isocyanate product (CN/CF₃ compound 57) had seventeen peaks.

3. The isocyanate of the p-methoxy derivative had been prepared before by phosgenation and its C-NMR peaks were reported in literature, which would allow them to be matched.

The first experiment with the prepared 109 compound was to test for a pericyclic mechanism. This was done by dropping 1 g of 109 suddenly into a flask that was held in an oil bath at 180 °C. This flask contained only a Teflon coated magnetic stirrer bar. The flask was quickly placed under vacuum and allowed to stir for 30 min. The compound was then extracted and analyzed by C-NMR. It was observed to be even cleaner than it
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began as the tiny bit of 2-propanol from which it had been recrystallized was removed by this heating. The process was repeated at 210 °C to achieve exactly the same result. Although this result disproved the suspected retro-ene mechanism, it showed that 109 is able to withstand a temperature of 210 °C and subsequent reactions were therefore carried out at this temperature.

![Reaction Scheme](image)

**Yielding of 2-nitropropane by heating in silica gel**

The same ‘flask in hot oil bath’ method was then tried but with a little bit of 43–60 μm silica placed in the flask with the stirrer. A clear liquid rapidly evolved from the flask which was suspected and later confirmed to be 2-nitropropane. NMR analysis of the reaction flask showed no isocyanate product, only the aniline (54) was left, which could be due to the fact that silica gel always contains a little water, even when most water has been removed from it. Therefore the reaction was repeated in the presence of 2-propanol in order to react with the suspected short-lived isocyanate species to produce the carbamate. Analysis by GC-MS showed that the carbamate was produced in 7% yield, however it was combined with polymer and could not be readily viewed by NMR.

It was suspected that the reaction may be being catalyzed by Lewis acids and that the isocyanate formed may be reacting rapidly with any water present when at elevated
temperatures and so it was desired to find conditions to allow the reaction to go forward at closer to room temperature. However, no useful reactions were found to cleanly give the NCO compound (123) by using titanium tetrachloride, phosphorus tribromide, or trimethylsilyl chloride with and without DMSO (as monitored by C-NMR).

Using the methods described in the experimental section of this chapter, 2-nitropropane has been yielded from α-nitroisobutyrilnilides in the presence of benzyl alcohol and silica at temperatures of 160–210 °C. During the write-up of this thesis, it was found that it has been reported that the isocyanate group undergoes thermal degradation when heated above 100–120 °C in the absence of water and this exothermic reaction accelerates greatly to completely quench the isocyanate group at temperatures greater than 175 °C [132]. This statement of fact is in agreement with the observations of the PhD candidate and it is likely necessary to carry out the procedure at temperatures close to ambient in order to collect the isocyanate product at the same time as the 2-nitropropane. There was insufficient time to follow this new lead in the lab.

4.5 Experimental procedures and compound characterization

As the limited number of attempts to prepare and isolate the isocyanates that were formed on the GC-MS injector port all failed, some more basic evidence that the the M-89 species really was an isocyanate was sought. This was obtained by comparing fragmentation patterns of the M-89 peak with those contained in the spectral database of organic compounds (SDBS). Of the library of α-nitroisobutyrilnilides prepared in chapter 3, the hypothetical isocyanate of seven of the compounds are contained in the database (99, 95, 97, 109, 105, 107, 81). The fragmentation patterns match perfectly with the isocyanate species that is gotten for these seven compounds. These are listed in Appendix IV.

The isocyanates elute at around 50–60% of the elution time of the intact nitro compound when using the following method:

- Hold at 60 °C for 1 min
- 60 to 250 °C at 10 °C/min
- Hold at 250 °C for 5 min

This method was used with an SGE Analytical Science BPX5 column (column width 0.25 mm, film width 0.25 μm) adjoined to a Varian Saturn 2200 GC/MS/MS. The following retention times were observed:
Further validation of the earlier eluting species being an isocyanate was obtained by purchasing \( m \)-chloro-phenyl isocyanate from Sigma-Aldrich and running it through the same instrument, using the same column and the same method. Not only did the Sigma-Aldrich purchased compound elute at exactly the same time (7.653 min) as the M-89 species from \( o \)-chloro-\( \alpha \)-nitroisobutyranilide (95), but it also showed exactly the same fragmentation pattern, with \( m/z \) peaks at 153, 125, 90, 63 and 50. Hence there is no doubt that the isocyanates do form during the gas chromatography of the nitro compounds.

**Reactive distillation of 55 from benzyl alcohol.**

Benzyl alcohol (30 mL) was added to 55 (2.00 g) in a 100 mL flask that was fitted to a reactive distillation apparatus at vacuum of 20 mmHg which was then heated to 150 °C. At 100 °C onwards, the contents of the flask changed from clear, to yellow, to orange, to red. The first captured distillate was analyzed by H-NMR and was found to be 2-nitropropane mixed with benzyl alcohol; when the conditions were repeated using a slightly milder vacuum the distillate was found to be pure 2-nitropropane. In both cases it was not possible to measure the level of vacuum; the first experiment used a high vacuum pump setup that was at 0.01 mmHg but with the tap to the reactive distillation partially closed off; in the second experiment the house vacuum was used without a vacuum gauge. Both distillates obtained were confirmed to contain 2-nitropropane by the addition of a drop of 2-nitropropane purchased from Sigma-Aldrich to the NMR tubes which were then reanalyzed. What remained in the 100 mL flask was analyzed and found to be polymer in both cases.

**Reactive distillation of 109 from silica gel.**
A 250 mL flask was fitted with a magnetic stirrer bar and an air condenser and placed in a heating mantle. The flask and stirrer bar were heated to 180 °C. Compound 109 (1.00 g) was dropped suddenly into the flask through the top of the air condenser. Bubbling was observed and the reaction stopped after 90 seconds. The flask was then weighed and shown to have only 880 mg of contents. This was not enough of a mass reduction to account for the loss of 2-nitropropane to yield an isocyanate which would have left only ~500 mg of contents. It was thought that the reaction may be only partially complete. The contents were analyzed by C-NMR and found to be a purer sample of 109 that had been purified of the residual 2-propanol from its recrystallization.

The reaction was then tried again in exactly the same way but heated to 200 °C and held at this temperature for 20 min. The same result was observed.

The same reaction conditions as above were carried out but this time with 3 g of 43–60 μ silica gel having been added to the previously empty flask before heating with the stirrer bar. Upon heating towards 200 °C the silica gel in the flask yielded water which built up around the inside of the air condenser. This water was removed by placing a quickfit at the top of the condenser that was fitted to the house vacuum and heating the outside of the condenser with a Bunsen burner. Upon reaching the 200 °C temperature and adding the 1 g of 109, droplets of a clear, colorless organic looking liquid immediately materialized from the flask’s contents and condensed on the inside walls of the condenser. These droplets were harvested upon disassembly of the glassware and analyzed by NMR which showed them to be 2-nitropropane.

The reaction was then carried out again the same way as above but this time with the glassware set up so that the 2-nitropropane could be distilled straight into a flask. This setup worked and captured more 2-nitropropane, but not as much as expected; only about 2 or 3 drops were yielded.

**Trapping isocyanate as a carbamate.**

Following on from the reactive distillation of 109 from silica, the flask contents which had been analyzed by GC-MS were allowed to remain in the flask to which 30 mL of 2-propanol and was added. A 200 mg portion of DABCO was also added in order to catalyze the reaction of the isocyanate with the alcohol. The flask contents were allowed to stir at 40 °C over a weekend. The GC-MS analysis of the flask contents showed a 7% yield of the carbamate, which indicates that only 7% of the formed isocyanate had...
survived the temperature of the reactive distillation process.

**Lewis acids.**

Titanium tetrachloride is a reagent known to be a strong Lewis acid. The titanium in this species is highly oxyphilic and will react with water to give TiO$_2$ and HCl, however TiCl$_4$ is compatible with chlorinated solvents. The reaction was done in an NMR tube and monitored by C-NMR. A 100 mg portion of 109 was dissolved in CDCl$_3$ in a 5 mL beaker. A squirt of TiCl$_4$ was then added to this and the mixture quickly decanted into an NMR tube. A colour change was immediately apparent; however C-NMR showed that not a clean product was produced. Instead it appeared from the H and C-NMRs that oxygens had been removed from both the 2-nitropropane (to give 2-aminopropene) and the isocyanate (123) to give the aniline.

Given that TiCl$_4$ appeared to be too strong a Lewis acid, some intermediate strength Lewis acids were tried.

Phosphorus tribromide (PBr$_3$) is known to be able to act as a Lewis acid towards amines, but it can also act as a Lewis base towards the stronger BBr$_3$. Phosphorus tribromide is also compatible with chlorinated solvents. A 100 mg portion of 109 was dissolved in CDCl$_3$ in a 5 mL beaker. A squirt of PBr$_3$ was then added to this and the mixture quickly decanted into an NMR tube. While an immediate brown colour was observed, C-NMR showed the start material to be completely intact.
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Exposure of 109 to PBr₃

The same reaction, where 109 was exposed to PBr₃, was carried out at 70 °C in 1,2-dichloroethane using 1 g of 109, 40 mL of solvent in a 100 mL flask. It was monitored by C-NMR to give the same result as that observed in the CDCl₃/NMR tube experiment.

Trimethylsilyl chloride (TMS-Cl) was tried as it is known to be a moderate Lewis acid. Another reason for trying the reaction with TMS-Cl is that it is suspected that the isocyanate formations from α-nitroisobutyranilides on the GC-MS injector port could be a function of a previous user having run TMS-Cl through the column in an attempt to clean it. Trimethylsilyl chloride is compatible with chlorinated solvents, so the reaction was monitored in an NMR tube by C-NMR. 100 mg of 109 was dissolved in CDCl₃, a squirt of TMS-Cl was then added to this and the mixture quickly decanted into an NMR tube. The compound was observed by C-NMR to be completely intact and unaffected by TMS-Cl. The reaction was then carried out under anhydrous conditions, however instead of chlorinated solvents, DMF was tried, as it was felt that the dipolar aprotic nature of DMF may be what allows the reaction mechanism to go forward (based on the ring closure mechanism discussed previously in this thesis). The reaction was heated at reflux for 30 min and monitored by C-NMR. The start material (109) was completely unchanged by these conditions.
A publication claims that TMS-Cl reacts with a catalytic amount of DMSO to form an intermediate that acts as a stronger Lewis acid [148]. The reaction was therefore tried again at reflux with a couple of drops of d$_6$-DMSO added but the compound still remained unchanged.

These results have shown very well that Lewis acids do not catalyze the reaction. It is now clear that Brønsted bases should be pursued in order to prepare isocyanates in this way. These as well as other suggested reactions are discussed in the next chapter.
5. Key findings and future work

5.1 Outcomes and applications

A unique method for preparation of 3-aryl hydantoins has been created and described in chapter 2. This chemistry has the potential to be applied in the synthesis of other 3-aryl hydantoin compounds.

A largely unexplored substitution reaction has been characterized in chapter 3 which can be used to make α-nitroisobutyranilides as synthetic intermediates. Several mechanisms have been ruled out and a few still remain as possibilities. Further work may determine the actual mechanism from the possibilities shortlisted in chapter 3.

The pyrolysis of the α-nitroisobutyranilide compounds prepared by the substitution reaction which was the subject of chapter 3 has given insight into the mechanism for an alternative method for to yield an isocyanate compound and 2-nitropropane as a leaving group. This process was pursued as the subject of chapter 4. A future process which cleanly synthesizes both products in one step would represent a synthesis with products that have greater value than their start materials. Several conditions, such as Lewis acids and rapid heating have been ruled out. Further work to achieve this goal may now be focused on the shortened list of remaining possibilities. Brønsted bases in the presence of silica would be a sensible thing to try next.

5.2 Further work

5.2.1 RU58841 synthesis

Given the observations of pyrolysis conditions of α-nitroisobutyranilides, it would be pertinent to try exposing 55 to 2-amino-2-cyanopropane (33), possibly with heating or an acid/base reagent. If 55 pyrolyzes to give the isocyanate (57), then this would be expected to react with the 2-amino-2-cyanopropane (as it does in Batmann’s synthesis [34]) to give the RU58841 hydantoin synthon (48) in fewer steps than the synthesis outlined in chapter two.
The linear alternative RU58841 synthesis laid out in chapter 1 could be employed to make homologous compounds (differing by a CH₂ group) or analogous compounds (containing different functional groups). Several approaches are discussed in the following section.

### 5.2.1.1 Analogues of RU58841

RU58841 homologues could be prepared with a chiral methyl group on position 1 or 4 of the long chain alcohol. RU58841 analogues can also be prepared with a six-membered ring in place of the hydantoin. The possible methods to make these compounds are discussed below and the resultant compounds can be tested and compared with RU58841 for their anti-baldness activity, as well as for prostate cancer treatment.

A version of RU58841 with a six-membered moiety in place of the hydantoin (124) could be obtained in two possible ways by using the second or third compound from chapter 1’s linear synthesis. Compound 55 can be acylated using 2-bromo-2-methylpropionic acid (125) under basic conditions, the resultant compound (126) can then have its nitro group reduced to an amino, whereupon exposure of the product (127) to a carbodiimide would be expected to mediate a 6-exo-trig ring closure, which is favoured by Baldwin’s rules, to give the six-membered moiety. Alternatively, this same compound could be prepared by heating compound 59 at reflux in DMF which may furnish the same six-membered ring with accompanying loss of HBr. Such a ring closure would at first appear to be classified as 6-exo-tet and while this is favoured by Baldwin’s rules, an S_N2 substitution is unlikely at a tertiary carbon; if this ring formation does take place it is more likely to occur by the
formation of an $S_N1$ carbocation due to the loss of bromide, followed by an attack of the positively charged carbon by the free electron pair on the anilide N. In the case of two-step ring formation processes such as this the Baldwin rules don’t apply.

It may be possible to encourage the $S_N1$ process by the addition of silver ions in the form of AgBr. Both of the two processes described above are both likely to achieve the six-membered ring.

Homologues of RU58841 may also be prepared with a methylated alkyl chain; the preparation of these two species is the logical next step and to then have them tested to see whether they are more effective than the original compound at alleviating baldness. This can be carried out by using the same conditions on the final alkylation step (4-bromobutyl acetate and NaH/halogen substitution, followed by deprotection to give

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the free alcohol) but 4-bromobutyl acetate (61) can be replaced with the ring opened product of 2-methyltetrahydrofuran (128). This can be achieved by treating 2-methyltetrahydrofuran with HBr and subsequent acylation. The first part of this method was carried out during this PhD candidature but it was then decided that there was not enough time to continue to pursue it.

It was found that when the reaction was carried out using a 2 molar excess of HBr the ring opened product quickly reacted a second time with HBr to give 1,4-dibromopentane. The reaction was then carried out under anhydrous conditions using an equimolar amount of HBr in the presence of acetic anhydride, and it was found that the ring opening followed by the acylation produced no dibrominated product at all. The NMR spectra revealed a mixture of the two compounds, one of which had the methyl at the 1 position of the alkyl chain (129) and the other at the 4 position (130).

Ring opening and acylation of 2-methyltetrahydrofuran

Nothing on the preparation of these two reagents has been reported in the literature. These two ring-opened/acylated products could not be separated by distillation, not even with the use of a vigreux column. Freezing methods were also tried in hopes that one product would have a significantly different melting point to the other, but they were observed to consistently freeze and melt together. A method to visualize the TLC of these two compounds using KMnO₄ followed by gentle heating was developed when it was decided to abandon this experiment in favour of other parts of the project.
TLC of 129/130 run in 3:1 hexanes/EtOAc, stained with KMnO₄, then gently heated

This mixture of 129 and 130 had a fruity, apple-like aroma and appeared to be present in an 80:20 ratio but it was not clear which was the major compound. While they looked to be separable it must be remembered that each spot is a racemic mixture of two compounds as a chiral centre has been created at the point on the alkyl chain with the methyl group.

5.2.1.2 Blaise reaction on intermediates

Compound 59 that was prepared in step four of the RU58841 synthesis laid out in chapter two is highly suitable for a Blaise reaction. The Blaise reaction is a C–C bond forming reaction that is traditionally performed using an α-bromoester and a nitrile reactant to form a β-ketoester [149]. This reaction, originally developed in 1901, retains niche use for synthesizing molecularly diverse compounds and its mechanism does not actually require an ester, rather it only needs to be an α-bromocarbonyl compound.
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Conversion of an α-bromoester into a β-ketoester using the Blaise reaction

By applying the Blaise reaction to the compound library of α-bromoisobutyranilides, a library of β-ketoamides can be prepared for screening or further reaction.

A model reaction using compound 80 would allow confidence and optimization of this method before application to compounds with other functional groups. The R group installed at the end of the long chain moiety can include free alcohols and thioethers [149]. Amine groups are not directly compatible and require BOC protection during the Blaise reaction [150].

5.2.1.3 Towards synthesis of useful peptide macrocycles
Huang and co-workers [151] have recently isolated anti-cancer compounds that contain an 18-membered hexa-amide ring from the roots and rhizomes of the flowering plant *Rubia schumanniana*. They call these compounds rubischumanins and their structure contains a repeating amide followed by a single methylated or functionalized carbon.

Using the re-acylation technique that was used to achieve 59, analogues of the Rubischumanins could be prepared and tested for their anti-cancer properties.

### 5.2.2 Bromo–nitro substitution

Previous experiments on the halo–nitro nucleophilic substitution used primary or secondary α halo compounds were aimed to distinguish between S_N1 or S_N2 models. The experiments in this thesis substituting the tertiary α carbon have ruled out the S_N1/S_N2 dichotomy that previous authors on the topic have leaned on. However, the breadth of the reaction also needs to be explored with other carbonyl compounds such as esters (which have barely been touched) and ketones (which have not been tried at all).

The NaCN/AgCN dichotomy has long been exploited to prepare nitrile groups using NaCN and isonitrile groups using AgCN [78]. This principle could be used to distinguish between the four mechanisms presented in section 3.3 by preparing the compound library using silver nitrite instead of sodium nitrite. Any rate change could be a function of the
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solubility of AgNO₂ versus NaNO₂ in DMF and so would not be definitive evidence. However, a comparison of yield would say a lot about the mechanism. This is because Ag⁺ is known to be more capable than Na⁺ of forming silver halide with the departing halo group which in the case of halo–nitro substitutions on primary/secondary non-α carbons leaves behind a carbocation S_N1 intermediate which tends to be more readily attacked by the nitrite O (the more electronegative atom of the ambident nucleophile) to give the alkyl-nitrite product (R–O–N=O). This process significantly lowers the yield of the nitro compound. If the observed yield of nitro product is not significantly altered or is increased when the compound library is prepared using AgNO₂, it would be strong evidence that the rate determining step does not involve the departure of halide, which would make possible mechanism number 3 seem more likely.

The Hammett calculations based on the rate data have allowed a narrowing down of mechanisms. Some further experiments can be designed to give weight to the four discussed options in chapter 3. Possible mechanism number 4 involves nitryl bromide.

![Nitryl bromide](image)

Interestingly, some properties of pure nitryl bromide are known. Nitryl bromide has been prepared and characterized. It is stable for 1 h at 20 °C in the gas phase in an Ar matrix and has been observed to quantitatively isomerize to trans-bromonitrite (BrONO) in the presence of UV light [152].

![Nitryl bromide and trans-BrONO](image)

Pure nitryl bromide is known to be shorter lived than nitryl chloride [152], this may give some predicting power to the idea that it is easier to form in solution. If it is being formed in this reaction, it may be possible to vacuum it out into a sealed tube at low temperature.
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for rapid analysis by IR.

The reaction proceeding by the nitryl bromide mechanism does seem to make a lot of sense in light of both the observations here in this thesis and Kornblum’s observations. This mechanism is in line with the experiment that showed the rate-limiting step to be not influenced by the total absence of elemental oxygen.

Mechanism involving the formation and subsequent reaction of nitryl bromide

If the substitution of \(\alpha\)-bromoisobutyranilides to give \(\alpha\)-nitroisobutyranilides proceeds through formation of nitryl bromide, then the next step to test this hypothesis is to alter the leaving group from Br to Cl.

Change of leaving group to Cl

As the rate data have already been carefully collected by me for the compound library, only the rate data for the preparation of the equivalent \(\alpha\)-nitroisobutyranilides from \(\alpha\)-chloroisobutyranilides would need to be obtained in order to compare the rate of substitution for chloride versus bromide leaving group.

5.2.3 Isocyanates from \(\alpha\)-nitroisobutyranilides with
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2-nitropropane leaving group

The observations made on the mass spec provide strong evidence that the reaction that pyrolyzes α-nitroisobutyranilides to give 2-nitropropane does so by way of producing an isocyanate intermediate. Having said that, a nucleophile-driven substitution cannot be entirely ruled out based upon the evidence collected thus far.

A project to produce the isocyanate group can be developed using a di-α-nitroisobutyralnilide (132) to prepare 112 and other diisocyanates for polyurethane production. Such a process can be compared with and may compete with phosgenation, especially if it makes 2-nitropropane at the same time.

![Chemical structures](image)

**Preparation of 4,4-methylene diphenyl diisocyanate and 2-nitropropane**

Experiments carried out early in this PhD candidature that exposed 55 to Brønsted acids and bases (HCl, nitric acid, trifluoroacetic acid, sodium hydroxide) appeared not to achieve the desired isocyanate compound (57), which is why Lewis acids were instead eventually pursued. However Lewis acids have been shown here in chapter 4 not to facilitate the reaction. Silica, however, always has some water associated with it which could be allowing it to act as a nucleophile. It would therefore be worthwhile placing the compound into 2-nitropropane and heating at 80–90 °C in the presence of silica.

The extra 2-nitropropane formed by this process could be distilled off under mild vacuum and used for the next batch while the diisocyanate remains in the reaction flask, where it can be collected.

Further, given the rate observations (discussed in chapter 3) the mechanism seems more likely to be one that is encouraged by the taking of a proton (Brønsted base) or the presence of electron dense reagent (nucleophile). Subsequent experiments should therefore involve exposing the α-nitroisobutyranilide compound to bases and nucleophiles. One such experiment that would be of interest is to expose
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α-nitroisobutyranilides to phenyl sodium (C₆H₅Na) or trityl sodium (133) in an aprotic solvent. If the isocyanate is produced it should quickly react with the alcohol solvent and make the cabamate product. The successful base can then be applied to the α-nitroisobutyranilide with dimethylacetamide as a solvent in the presence of a more precious alcohol.

An α-nitroisobutyranilide exposed to trityl sodium to produce an isocyanate in situ

This would become a method of using α-nitroisobutyranilides as protected isocyanate reagents that react predictably and have a long shelf life. The 2-nitropropane leaving group would not react with the isocyanate, unlike Knölker’s isocyanate synthesis which yields tert-butanol as a leaving group [141].
6. References and appendices

6.1 References. Journals are abbreviated as listed by Berkeley at: http://www.efm.leeds.ac.uk/~mark/ISIabbr/.


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[33] [http://www.youtube.com/watch?v=jp_XISpHYfc](http://www.youtube.com/watch?v=jp_XISpHYfc)


[45] *German patent*, number 310 427, Referred to in reference [44], Authors and date unknown.


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A novel hydantoin synthesis and exploration of related reactions


[72] H. M. Hügel, C. J. Rix and K. Fleck. Comparison of copper(II) acetate promoted N-arylation of 5,5-dimethylhydantoin and other imides with triarylbumthanes and aryl

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A novel hydantoin synthesis and exploration of related reactions


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A novel hydantoin synthesis and exploration of related reactions


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Appendix I: Data from Br–NO₂ substitution rates

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6.2 Appendix II: Plots of ln(% start material) against time for Br–NO₂ substitution

Regression statistics are shown below each plot.
A novel hydantoin synthesis and exploration of related reactions

First-order plot of $\ln(\% SM)$ against time for $80 \rightarrow 81$ reaction

Regression Statistics

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A novel hydantoin synthesis and exploration of related reactions

 Improved first-order plot of ln(%SM) against time for $80 \rightarrow 81$ reaction

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A novel hydantoin synthesis and exploration of related reactions

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First-order plot of ln(%SM) against time for 100 → 101 reaction

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Improved first-order plot of ln(%SM) against time for 100 → 101 reaction

\[ y = -0.0039x + 4.6026 \]

**Regression Statistics**

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First-order plot of ln(%SM) against time for 84 → 85 reaction

**Regression Statistics**

- Multiple R: 0.999267
- R Square: 0.998535
- Adjusted R Square: 0.998423
- Standard Error: 0.066973
- Observations: 15
A novel hydantoin synthesis and exploration of related reactions

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Improved first-order plot of ln(%SM) against time for 84 → 85 reaction

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**Regression Statistics**

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Observations 8

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First-order plot of ln(%SM) against time for 102 → 103 reaction

Regression Statistics

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Observations

9

ANOVA

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Regression Statistics

Multiple R 0.999095
R Square 0.99819
Adjusted R Square 0.998009
Standard Error 0.033645

First-order plot of ln(%SM) against time for 94 → 95 reaction

\[
y = -0.0267x + 4.604
\]
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Observations 12

ANOVA

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First-order plot of ln(%SM) against time for 96 → 97 reaction

Regression Statistics

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Adjusted $R^2$ Square 0.990125
Standard Error 0.149079
Observations 12

ANOVA

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Improved first-order plot of $\ln(\%SM)$ against time for 96 → 97 reaction

$y = -0.0257x + 4.628$
A novel hydantoin synthesis and exploration of related reactions

Regression Statistics

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ANOVA

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Intercept 4.628036 0.015638 295.9403 1.9E-17 4.591974 4.664098 4.591974 4.664098

X Variable 1 -0.0257 0.000372 -69.1629 12 -0.02655 -0.02484 -0.02655 -0.02484

First-order plot of ln(%SM) against time for 98 → 99 reaction
Regression Statistics

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ANOVA

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A novel hydantoin synthesis and exploration of related reactions

Improved first-order plot of $\ln(\%SM)$ against time for $98 \rightarrow 99$ reaction

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$y = -0.032x + 4.6225$
A novel hydantoin synthesis and exploration of related reactions

First-order plot of ln(%SM) against time for 92 → 93 reaction

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Coefficients

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y = -0.0306x + 4.5995
A novel hydantoin synthesis and exploration of related reactions

**Improved first-order plot of ln(%SM) against time for 92 → 93 reaction**

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First-order plot of ln(%SM) against time for 52 → 55 reaction

Regression Statistics

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ANOVA

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Coefficients

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A novel hydantoin synthesis and exploration of related reactions

**Regression Statistics**

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**First-order plot of ln(%SM) against time for 90 → 91 reaction**

**Regression Statistics**
- Multiple R: 0.997018
- R Square: 0.994045
- Adjusted R Square: 0.993775
- Standard Error: 0.104324
- Observations: 24

**ANOVA**

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A novel hydantoin synthesis and exploration of related reactions

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![Improved first-order plot of ln(%SM) against time for 90 → 91 reaction](image)

Improved first-order plot of ln(%SM) against time for 90 → 91 reaction

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Regression Statistics

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ANOVA

Regression Statistics

Multiple R 0.989449
R Square 0.979009
Adjusted R Square 0.97751
Standard Error 0.149962
Observations 16

First-order plot of ln(%SM) against time for 82 → 83 reaction
A novel hydantoin synthesis and exploration of related reactions

Significance

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Improved first-order plot of ln(%SM) against time for 82 → 83 reaction

Regression Statistics

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First-order plot of \( \ln(\%SM) \) against time for 86 → 87 reaction

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First-order plot of ln(%SM) against time for 88 → 89 reaction

Regression Statistics

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Standard Error 0.052065
Observations 15

**ANOVA**

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**Improved first-order plot of ln(%SM) against time for 88 → 89 reaction**

**Regression Statistics**

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Adjusted R Square 0.99067
Standard Error 0.029052
Observations 9

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First-order plot of ln(\%SM) against time for 108 → 109 reaction

Regression Statistics

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Multiple R: 0.997978
R Square: 0.995959
Adjusted R Square: 0.995784
Standard Error: 0.061472
Observations: 25

ANOVA

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y = -0.0131x + 4.5944
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**Improved first-order plot of ln(%SM) against time for 108 → 109 reaction**

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First-order plot of ln(\%SM) against time for 104 → 105 reaction

![Graph showing a first-order plot of ln(%SM) against time for the reaction 104 → 105. The equation of the line is y = -0.0253x + 4.5772.]

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First-order plot of ln(\%SM) against time for 106 → 107 reaction

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Improved first-order plot of ln(\%SM) against time for 106 → 107 reaction

Regression Statistics

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6.4 Appendix III: Hammett plots

Hammett plot of *meta* substituents

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<th>$\log_{10}(k'/k_{H})$</th>
<th>$\sigma_m$</th>
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<tr>
<td>80→81</td>
<td>H</td>
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<td>0</td>
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<tr>
<td>96→97</td>
<td>Cl</td>
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<tr>
<td>88→89</td>
<td>NO₂</td>
<td>0.048456</td>
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<tr>
<td>106→107</td>
<td>CH₃O</td>
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<td>-0.02134</td>
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</table>
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Hammett plot of para substituents with ordinary $\sigma$

$y = 0.8939x + 0.0186$
$R^2 = 0.9186$
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Hammett plot of para substituents with $\sigma^+$

Hammett plot of para substituents with $\sigma^-$
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**Hammett plot of para substituents with $\sigma^-$**

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<th>$\sigma^-$_{p}</th>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>0.084694</td>
<td>0.221</td>
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</tbody>
</table>

- The $\sigma$ values from J. Shorter, "Compilation and critical evaluation of structure-reactivity parameters and equations - Part I: Values of $\sigma_m$ and $\sigma_p$ based on the ionization of substituted benzoic acids in water at 25°C (Technical Report)", *Pure Appl. Chem.*, 66, 2451–2510 (1994).
- The $\sigma^+_{p}$ values from H.C. Brown & Y. Okamoto, "Electrophilic Substituent Constants", *J. Amer. Chem Soc.*, 80, 4979 (1958), and have been returned to the original 3 d.p.
- The green $\sigma^-$_{p} value is from G. Chuchani & A. Frohlich, "The pKₐ Values of Mono-substituted Phenols and Benzenethiols and the Conjugation of Substituents having a Strong +K Effect", *J. Chem. Soc. (B)*, 1971, 1417–1420.

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6.5 Appendix IV: Fragmentation patterns of isocyanates obtained from α-nitroisobutyranilides on GC-MS injector port compared with those from SDBS

\( o \)-Chloro-α-nitroisobutyranilide (95): \( m/z = 153, 125, 90, 63 \) and 50.
\( o \)-Chloro-phenyl isocyanate from SDBS: 153, 125, 90, 63 and 50.

\( m \)-Chloro-α-nitroisobutyranilide (97): \( m/z = 153, 125, 90, 63 \) and 50.
\( m \)-Chloro-phenyl isocyanate from SDBS: 153, 125, 90, 63 and 50.

\( p \)-Chloro-α-nitroisobutyranilide (99): \( m/z = 153, 125, 90, 63 \) and 50.
\( p \)-Chloro-phenyl isocyanate from SDBS: 153, 125, 90, 63 and 50.

\( o \)-Methoxy-α-nitroisobutyranilide (105): \( m/z = 149, 134, 120, 106, 93, 78, 63 \) and 51.
\( o \)-Methoxy-phenyl isocyanate from SDBS: 149, 134, 120, 106, 93, 78, 63 and 51.

\( m \)-Methoxy-α-nitroisobutyranilide (107): \( m/z = 149, 134, 119, 106, 91, 78, 63 \) and 51.
\( m \)-Methoxy-phenyl isocyanate from SDBS: 149, 134, 119, 106, 91, 78, 63 and 51.

\( p \)-Methoxy-α-nitroisobutyranilide (109): \( m/z = 149, 134, 121, 106, 91, 78, 63 \) and 51.
\( p \)-Methoxy-phenyl isocyanate from SDBS: 149, 134, 121, 106, 91, 78, 63 and 51.

α-Nitroisobutyranilide (81): \( m/z = 119, 91, 64 \) and 51.
Phenyl isocyanate from SDBS: 119, 91, 64 and 51.
6.6 Appendix V: IR and NMR spectra of novel compounds.

From Chapter 2.

All infra red spectra in this section were taken using the KBr disc method.

NMR conditions are given below each spectrum.
A novel hydantoin synthesis and exploration of related reactions

20 mg of 52 in 0.4 mL CDCl$_3$, 300 MHz, 256 scans
A novel hydantoin synthesis and exploration of related reactions

40 mg of 52 in 0.4 mL d₆-DMSO, 75 MHz, 2048 scans
A novel hydantoin synthesis and exploration of related reactions

48 mg of 55 in 0.4 mL d$_7$-DMF, 300 MHz, 256 scans
A novel hydantoin synthesis and exploration of related reactions

48 mg of 55 in 0.4 mL d$_7$-DMF, 75 MHz, 20000 scans
A novel hydantoin synthesis and exploration of related reactions

75 mg of \( 49 \) in 0.5 mL \( d_6\)-DMSO, 300 MHz, 1024 scans. The small amount of aniline impurity is due to the acid/base workup of \( 49 \).
C-NMR of \textbf{49} was run using the same tube as H-NMR from above, 75 MHz, 55000 scans
A novel hydantoin synthesis and exploration of related reactions

32 mg of 59 in 0.4 mL d_{6}-DMSO, 300 MHz, 128 scans
32 mg of 59 in 0.4 mL d₆-DMSO, 75 MHz, 55000 scans
A novel hydantoin synthesis and exploration of related reactions

20 mg of 48 in 0.4 mL CD$_3$CN, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

20 mg of 48 in 0.4 mL CD$_3$CN, 75 MHz, 13000 scans
A novel hydantoin synthesis and exploration of related reactions

20 mg of **RU58841** in 0.4 mL CDCl$_3$, 300 MHz, 64 scans
A novel hydantoin synthesis and exploration of related reactions

20 mg of RU58841 in 0.4 mL CDCl₃, 75 MHz, 14262 scans
From Chapter 3.

All infra red spectra in this section were taken using the diamond ATR method.

NMR conditions are given below each spectrum.
A novel hydantoin synthesis and exploration of related reactions

26 mg of 80 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

137 mg of 80 in 0.4 mL CDCl₃, 75 MHz, 21737 scans
A novel hydantoin synthesis and exploration of related reactions

26 mg of 81 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

26 mg of 81 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

35 mg of 82 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

135 mg of 82 in 0.4 mL CDCl$_3$, 75 MHz, 14000 scans

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A novel hydantoin synthesis and exploration of related reactions

21 mg of 83 in 0.4 mL CDCl₃, 300 MHz, 16 scans
42 mg of 83 in 0.4 mL CDCl$_3$, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

30 mg of 84 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

1425 mg of 84 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

25 mg of 85 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

68 mg of 85 in 0.4 mL d$_6$-DMSO/0.1 mL CDCl$_3$, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

32 mg of 86 in 0.4 mL CDCl₃, 300 MHz, 32 scans
A novel hydantoin synthesis and exploration of related reactions

138 mg of 86 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

18 mg of 87 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

18 mg of 87 in 0.4 mL CDCl$_3$, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

45 mg of 88 in 0.4 mL CDCl$_3$, 300 MHz, 32 scans
A novel hydantoin synthesis and exploration of related reactions

138 mg of \( \text{88} \) in 0.4 mL CDCl\(_3\), 75 MHz, 14000 scans

\[ \text{89} \]

\[ \text{89} \]
50 mg of **89** in 0.4 mL d$_6$-DMSO, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

50 mg of 89 in 0.4 mL d_6-DMSO, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

30 mg of 90 in 0.4 mL CDCl$_3$, 300 MHz, 32 scans

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A novel hydantoin synthesis and exploration of related reactions

122 mg of 90 in 0.4 mL CDCl\textsubscript{3}, 75 MHz, 19456 scans

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A novel hydantoin synthesis and exploration of related reactions

27 mg of 91 in 0.4 mL d$_6$-DMSO, 300 MHz, 32 scans
A novel hydantoin synthesis and exploration of related reactions

27 mg of 91 in 0.4 mL d_6-DMSO, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

144 mg of 92 in 0.4 mL CDCl₃, 300 MHz, 8 scans
A novel hydantoin synthesis and exploration of related reactions

144 mg of 92 in 0.4 mL CDCl$_3$, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

26 mg of 93 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

66 mg of 93 in 0.4 mL CDCl\textsubscript{3}, 75 MHz, 14000 scans

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A novel hydantoin synthesis and exploration of related reactions

139 mg of 94 in 0.4 mL CDCl₃, 300 MHz, 8 scans
A novel hydantoin synthesis and exploration of related reactions

139 mg of 94 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

21 mg of 95 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

39 mg of 95 in 0.4 mL CDCl$_3$, 75 MHz, 13000 scans
A novel hydantoin synthesis and exploration of related reactions

31 mg of 96 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

136 mg of 96 in 0.4 mL CDCl$_3$, 75 MHz, 15000 scans
A novel hydantoin synthesis and exploration of related reactions

18 mg of 97 in 0.4 mL CDCl₃/2 drops d₆-DMSO, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

18 mg of 96 in 0.4 mL CDCl$_3$/2 drops d$_6$-DMSO, 75 MHz, 15000 scans
A novel hydantoin synthesis and exploration of related reactions

43 mg of 98 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

157 mg of 98 in 0.4 mL CDCl$_3$, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

21 mg of 99 in 0.4 mL CDCl₃, 300 MHz, 16 scans

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A novel hydantoin synthesis and exploration of related reactions

21 mg of 99 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

23 mg of 100 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

125 mg of 100 in 0.4 mL CDCl₃, 75 MHz, 13720 scans
A novel hydantoin synthesis and exploration of related reactions

19 mg of 101 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

55 mg of 101 in 0.4 mL CDCl₃, 75 MHz, 14000 scans

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A novel hydantoin synthesis and exploration of related reactions

26 mg of 102 in 0.4 mL CDCl₃, 300 MHz, 65 scans
A novel hydantoin synthesis and exploration of related reactions

147 mg of 102 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

16 mg of 103 in 0.4 mL CDCl₃, 300 MHz, 16 scans

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21 mg of **103** in 0.4 mL CDCl$_3$, 75 MHz, 17407 scans

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A novel hydantoin synthesis and exploration of related reactions

28 mg of 104 in 0.4 mL CDCl₃, 300 MHz, 32 scans
A novel hydantoin synthesis and exploration of related reactions

133 mg of 104 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

19 mg of 105 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

57 mg of 105 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

31 mg of \textbf{106} in 0.4 mL CDCl$_3$, 300 MHz, 128 scans
A novel hydantoin synthesis and exploration of related reactions

31 mg of 106 in 0.4 mL CDCl₃, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

28 mg of 107 in 0.4 mL CDCl₃, 300 MHz, 16 scans
A novel hydantoin synthesis and exploration of related reactions

120 mg of **107** in 0.4 mL CDCl₃, 75 MHz, 15000 scans
A novel hydantoin synthesis and exploration of related reactions

25 mg of 108 in 0.4 mL CDCl₃, 300 MHz, 350 scans

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A novel hydantoin synthesis and exploration of related reactions

25 mg of 108 in 0.4 mL CDCl$_3$, 75 MHz, 14000 scans
A novel hydantoin synthesis and exploration of related reactions

24 mg of 109 in 0.4 mL CDCl₃, 300 MHz, 32 scans
A novel hydantoin synthesis and exploration of related reactions

24 mg of 109 in 0.4 mL CDCl₃, 75 MHz, 36302 scans