Paula Fernandes Marques

Licenciada em Química Aplicada

New approach to phenanthridine alkaloids by intramolecular radical cyclization

Dissertação para obtenção do Grau de Mestre em
Química Bioorgânica

Orientador: Paula Cristina de Sério Branco, Professora Auxiliar com Agregação, Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa

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ABSTRACT

The phenanthridine core is present in several natural products namely the phenanthridine alkaloids. Their synthesis is important in the pharmaceutical industry, so the development of new synthetic methods is welcomed by them.

Radical reactions are involved in the synthesis of several natural products, among them the phenanthridine alkaloids. The use of tributyltin hydride and azobisisobutyronitrile is a common approach for the thermal generation of radicals. Beyond being an effective method, they have associated the toxic effects of the tin.

For the past few years, N-heterocyclic carbene-boranes have being used in radical reactions, as radical mediators. Applications in radical reductions and, more recently, in intramolecular cyclizations have been reported.

Here we report studies with N-heterocyclic carbene-boranes for the intramolecular cyclization of appropriated substrates for the synthesis of the phenanthridines core. For that, the substrates used include secondary and tertiary amines, an amide, and an ether. Attempts has been made to synthesise a heteroatom free substrate in order to understand the effect of the heteroatoms in the reaction, but without success. Two different N-heterocyclic carbene-boranes were synthesized based on imidazolium salts, the (1,3-dimethylimidazolium-2-yl)trihydroborate and the (3-ethyl-1-methylimidazolium-2-yl)trihydroborate.

The reactions yields were below expectations, however the cyclization products were obtained. No reduction products were identified, showing the difficulty of the boranes to react with the substrate. It was identified a complex between a tertiary amide substrate and the borane, which may be the reason for the low yields. In the reaction with the ether it seems that the complex with the NHC-borane is also formed.

It was also identified an adduct between the borane and the thiophenol, when this last one was used as co-adjuvant. The formation of that adduct should be the reason why the reactions with thiophenol had a lower yield.

Unfortunately, all the attempts to increase the yield were unsuccessful.

Keywords: NHCs, NHC-borane, phenanthridine, radical reactions.

RESUMO

Moléculas com núcleos de fenantridina estão presentes em diversos produtos naturais, nomeadamente nos alcaloides de fenantridina. A síntese deste núcleo é importante na indústria farmacêutica, por isso o desenvolvimento de novos métodos sintéticos é apreciado pelas farmacêuticas.

Na síntese de produtos naturais, tais como os alcaloides de fenantridina, estão muitas vezes envolvidas reações radicalares. Um método comum para a formação térmica de radicais requer o uso de hidreto de tributilestanho e de azobisisobutironitrilo. Apesar de ser um método eficaz, o estanho é um metal tóxico.

Durante os últimos anos, carbenos N-heterocíclicos acoplados com borano têm sido utilizados em reações radicalares, como mediadores de radicais. Na literatura é possível encontrar aplicações destes boranos em reduções radicalares e, mais recentemente, em ciclizações intramoleculares.

Nesta dissertação foi estudado o uso de carbenos N-heterocíclicos acoplados com borano na ciclização intramolecular de substratos para a síntese de núcleos de fenantridina. Para isso, foram utilizados como substratos aminas secundárias e terciárias, uma amida e um éter. Tentou-se também sintetizar um substrato sem heteoátomos de modo a perceber o efeito dos heteroátomos na reação, mas em sucesso. Foram sintetizados dois NHC-boranos – o (1,3-dimetilimidazol-2-il)trihidroborato e o (3-etil-1-metilimidazol-2-il)trihidroborato.

Os rendimentos obtidos foram abaixo do esperado, no entanto foi possível obter os produtos de ciclização. Nenhum produto de redução foi identificado, mostrado a dificuldade dos boranos para reagirem com os substratos. Foi também identificado um complexo entre uma amina terciária e o borano que pode estar na causa dos baixos rendimentos observados. Na reação com o éter parece também se formar o complexo com o NHC-borano.

Foi também identificado um aduto entre o borano e o tiofenol, quando este último foi utilizado como coadjuvante. A formação deste aduto pode ser a razão para os rendimentos baixos das reações quando é utilizado o tiofenol.

Infelizmente, todas as tentativas para o aumento do rendimento não tiveram sucesso.

Palavras-Chave: NHCs, NHC-borano, fenantridina, reações radicalares.

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LIST OF ABBREVIATIONS

AIBN – Azo-iso-butyronitrile

ATR – Attenuated Total Reflectance

^{11}B NMR – Nuclear Magnetic Resonance of Boron-11

cc – Cubic Centimetre

^{13}C NMR – Nuclear Magnetic Resonance of Carbon-13

d – Doublet

DCM – Dichloromethane

dipp – 1,3-bis(2,6-diisopropylphenyl)

DMF – N,N-dimethylformamide

dppm – bis(diphenylphosphino)methane

DTBP – di-*tert*-butyl peroxide

DTBP – di-*tert*-butyl peroxide

eq – equivalents

FAD – Flavin adenine dinucleotide

FT-IR – Fourier Transform Infra-Red

GC-MS – Gas Chromatography–Mass Spectrometry

^{1}H NMR – Nuclear Magnetic Resonance of Proton

Hz – Hertz

In – Radical Initiator

IR – Infra-Red

J – Coupling constant

m – Multiplet

MH – Radical Mediator

Min – Minutes

mm – Milimeters

MOM – Methoxymethyl

NADPH – Nicotinamide adenine dinucleotide phosphate (reduced)

NHC – N-Heterocyclic carbene

NHC-boranes – N-Heterocyclic carbene boranes

NHO – N-heterocyclic olefins

NHO-boranes – N-heterocyclic olefins boranes

nm – Nanometers

PC – Photocatalyst

PLP – Pyridoxal 5'-phosphate

ppm – parts per million

q – Quartet

rt – Room temperature

RZ – Main Compound

s – Singlet

SAM – S-Adenosyl Methionine

S_N2 – bi-Molecular nucleophilic substitution

t - Triplet

TBHN – di-*tert*-butyl hyponitrile

TBTH – Tributyltin hydride

TDT – *tert*-dodecanethiol

THF – Tetrahydrofuran

THF - Tetrehydrofuran

TLC – Thin Layer Chromatography

UV – Ultraviolet

1. INTRODUCTION

1.1 ALKALOIDS

Alkaloids are a vast family of natural products. They are commonly defined as natural compounds that possess a basic nitrogen, excluding primary metabolites like amino acids, nucleotides, and cofactors. Alkaloids are mainly found in plants, although they can also be found in some microorganisms and animals. Their principal function in plants is protection against external attacks.[1–3]

This group of molecules can have one or multiple nitrogen atoms which can be classified as primary, secondary, tertiary or quaternary. Usually, these compounds are found in Nature in the form of salts. However, when their basicity is low or they are neutral molecules, they are found as free bases.[1]

Alkaloid's classification is based on their biosynthetic origin, such as arginine, phenylalanine, piperidine, indole, etc. Other building blocks from other natural products (like acetate or shikimate) can be incorporated into alkaloids. These molecules are usually classified as "pseudoalkaloids".[1,3]

The first isolated alkaloid was morphine in 1806. Since then alkaloid isolation starts to get more importance and biological studies increased as well as studies elucidating alkaloid biosynthetic pathways. Biological studies reveal properties such as pharmaceuticals, stimulants, narcotics, and poisons.[3,4]

1.1.1 Phenanthridines

Phenanthridines are an alkaloid group that is part of the isoquinoline alkaloids family. These alkaloids have biosynthetic origin in tyrosine. Their core structure (Figure 1.1) is formed by three fused aromatic rings - one of pyridine (B) and two of benzene (A and C).[2,5,6]

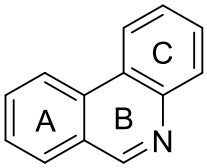


Figure 1.1 – Phenanthridine core structure.[6]

Phenanthridines are mainly found in five plant families: the *Fumariaceae* (genera *Corydalis, Dicentra,* and *Fumaria)*, the Papaveraceae (numerous genera), the *Rutaceae* (genera *Fagara*, *Zanthoxylum* and *Toddalia*), the Caprifoliaceae (genus *Symphoricarpos)* and the *Meliaceae* (genus *Xylocarpus*).[7,8]

Numerous natural products have a phenanthridine core (Figure 1.2). Some of these molecules have a great importance in the pharmaceutical and medicinal chemistry areas and several research groups worldwide have already studied it, especially quaternary phenanthridines. The factors that most influence the pharmacological activity of the molecule are the aromatic planarity, the acidity of the quaternary cation and the substituents of ring A.[7,9–11] Some of the reported pharmacological activities are antibacterial[12], antifungal[13], anti-inflammatory[14], antitumor[15], DNA intercalator[16], and protein kinase C inhibitor[17].

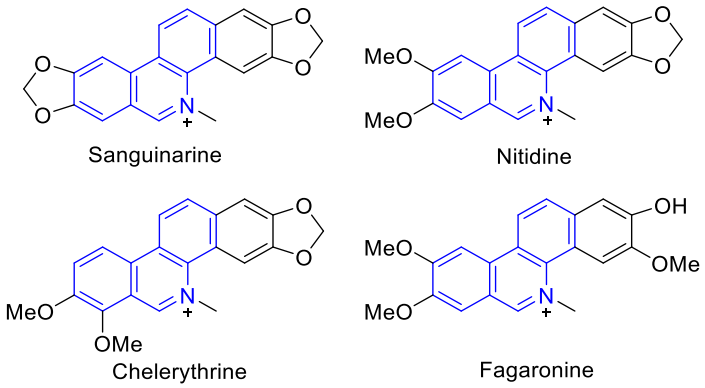


Figure 1.2 – Some natural products with a phenanthridine core. Sanguinarine has antibacterial and antifungal properties, nitidine has antitumor properties and is DNA topoisomerase inhibitor, chelerythrine has antibacterial activity and is protein kinase C inhibitor, fagaronine has antitumor properties and is a DNA topoisomerase inhibitor.[18–21]

The first step for the phenanthridine biosynthesis is the (*S*)-reticuline biosynthesis which requires two L-Tyrosine molecules (Figure 1.3). One of them is oxidized giving L-DOPA and then suffers a decarboxylation. The other L-tyrosine molecule, suffer a transamination reaction and a decarboxylation. A Mannich-like reaction occurs yielding (*S*)-norcoclaurine. The molecule is then *O*-methylated and *N*-methylated. Finally, through oxidation and another *O*-methylation, (*S*)-reticuline is obtained.[1,4]

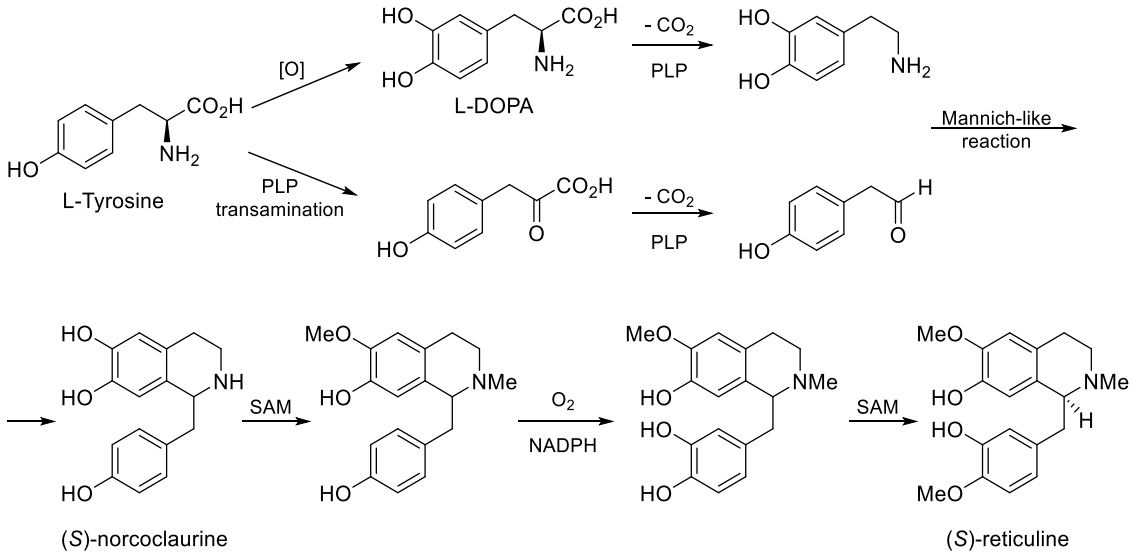


Figure 1.3 – Biosynthetic pathway of (*S*)-reticuline.[1,4]

The next step is the formation of (*S*)-scoulerine, a protoberberine (Figure 1.4). For that, is required the formation of the “berberine bridge”. An iminium ion is formed followed by a cyclization through a Mannich-like reaction. A keto-enol tautomerism allows the formation of the (*S*)-scoulerine.[1,22]

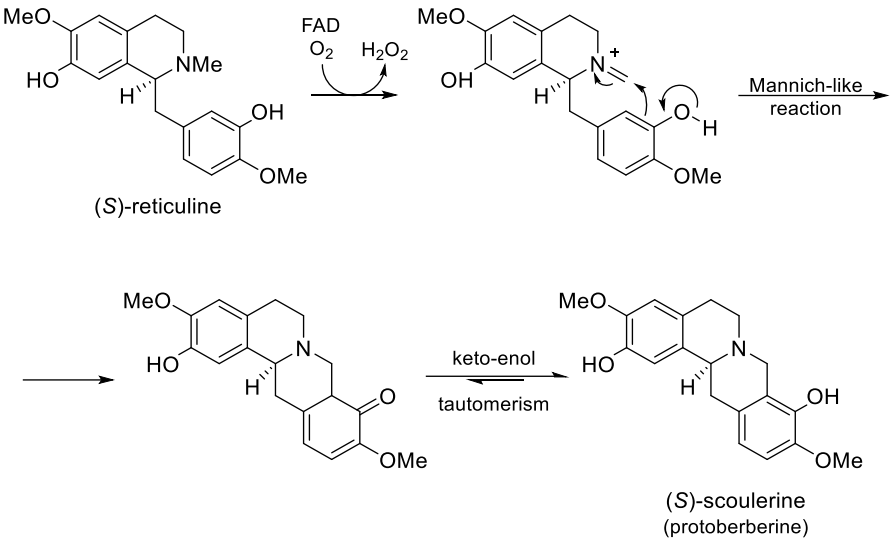


Figure 1.4 – Biosynthesis of (*S*)-scoulerine.[1,22]

Finally, to obtain the phenanthridine, the bond between the C-6 and C-7 of protoberberine cleaves and a new bond between C-6 and C-13 is created. These two steps result in phenanthridine core formation. In Figure 1.5 is represented the biosynthesis of sanguinarine, a phenanthridine alkaloid. Starting in (*S*)-scoulerine, two methylenedioxy groups must be formed. After that, an *N*-methylation occurs, followed by an oxidation. In short, the phenanthridine core is formed through the C-6/C-7 bond cleavage and the new bond formation between C-6 and C-13. An oxidative dehydration leads to sanguinarine.[8,22,23]

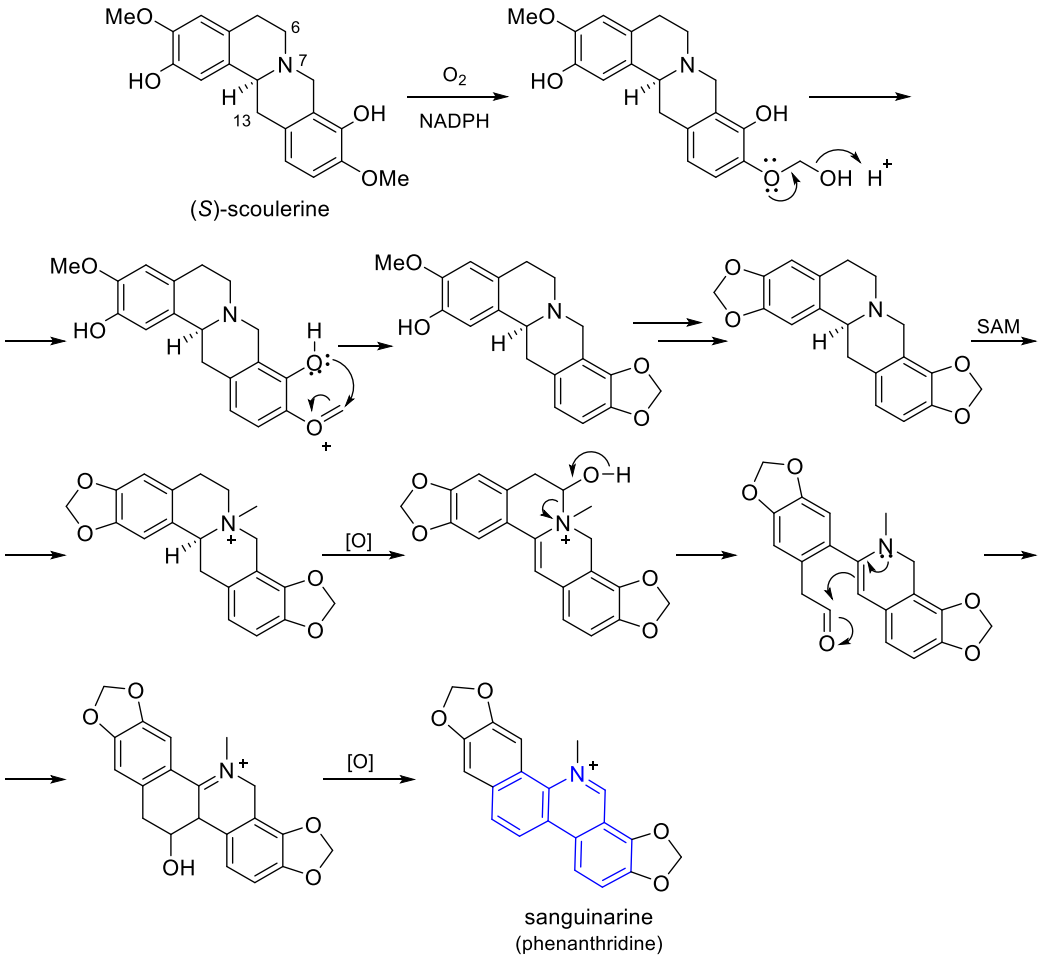


Figure 1.5 – Biosynthesis of sanguinarine, a phenanthridine alkaloid.[8,22,23]

Due to the pharmacological importance of phenanthridine, these molecules have been the target of a bigger interest in the organic synthesis since earlier times. The first time phenanthridine was synthesized was in 1889 by Pictet and Ankersmit.[24] In this reaction, phenanthridine was obtained by pyrolysis of the condensation product of benzaldehyde and aniline (Figure 1.6 a)). Some years later, in 1896, Pictet and Hubert developed a new method for phenanthridine synthesis, through a dehydration of *N*-acyl-*o*-xenylamines, with zinc chloride at high temperatures known as the Pictet-Hubert reaction (Figure 1.6 b)). In 1931, new reaction conditions were developed, leading to Morgan-Walls reaction (Figure 1.6 c)). The differences between Morgan-Walls and Pictet-Hubert are the replacement of zinc chloride for phosphorus oxychloride and the addition of nitrobenzene as solvent. Besides that, Morgan-Walls reaction allows better reaction yields.[11,24,25]

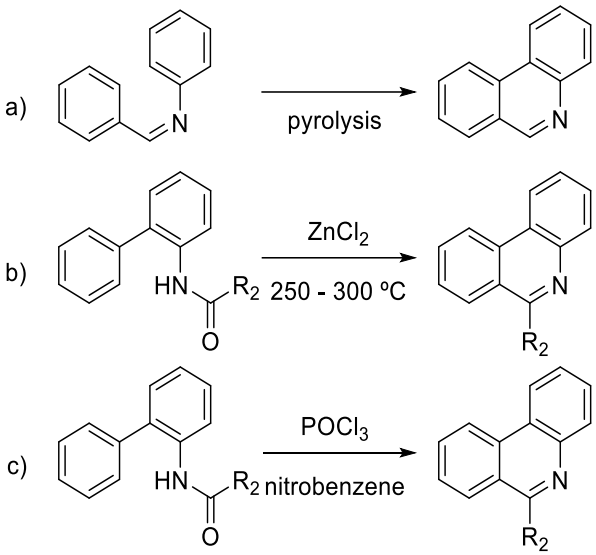


Figure 1.6 – First synthesis of phenanthridine by Pictet and Ankersmit (a), and Pictet-Hubert (b) and Morgan-Walls (c) reactions for phenanthridine synthesis.[24,25]

Since then till nowadays, a lot of new synthetic methods have been developed. The method used will depend on the structure of the molecule. Transitions metal-catalysis reactions are commonly used for phenanthridine synthesis. These reaction can be used with several different substituents. There are reports on the use of palladium, platinum, ruthenium, rhodium, rhenium, iridium, nickel, iron and cooper in this type of reactions. Palladium is the most used metal in these reactions.[11,25]

Harayama *et al.*[26] reported the synthesis of [1,3]dioxolo[4,5-j]phenanthridine and norchelerythrine with a palladium-catalysed reaction (Figure 1.7). The synthesis of halobenzoic acids with amine gives haloamides. The amides were protected with MOM, giving the protected haloamide. Then, palladium-catalysed intramolecular reaction was made with P(*o*-Tol)$_3$, Ag_2CO_3, and catalytic amount of $Pd(OAc)_2$, The cyclization product reacted with $LiAlH_4$, for reducing the carbonyl group, and HCl, to deprotect the amine. Phenanthridine alkaloids are thus obtained with good yields.[26]

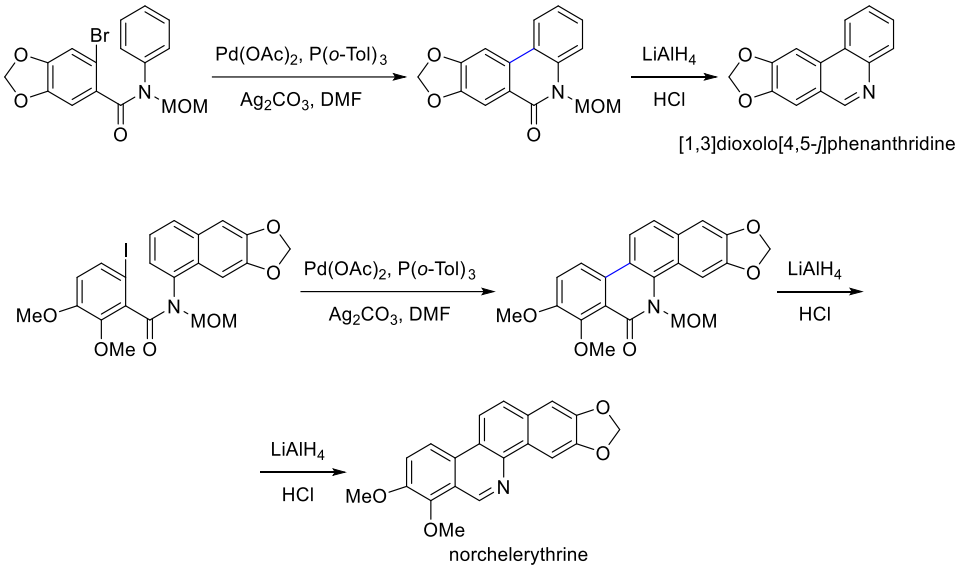


Figure 1.7 – Reaction scheme of palladium-catalysed intramolecular cyclization for [1,3]dioxolo[4,5-j]phenanthridine and norchelerythrine.[26]

Radical reactions are also common used for phenanthridine synthesis. The most common reaction is an intramolecular radical cyclization, through a biphenyl starting material. However exists numerous possibilities for these reactions with several starting materials, and catalysts. It can be used both carbon or nitrogen centred radicals.[27]

Rosa *et al.*[28] synthesized several molecules with a phenanthridine core using tributyltin hydride (TBTH), a radical propagator (Figure 1.8). This reaction starts with an initiation step, where the radical initiator, AIBN (azo-iso-butyronitrile), is thermally activated. The formed radical reacted with TBTH, forming a tributyltin radical, thus beginning the radical's propagation. The tributyltin radical reacted with *N*-(*o*-bromobenzyl)aniline originating a phenyl radical, which undergoes a intramolecular radical cyclization. To close the propagation cycle, the cyclized molecule reacted with TBTH, leading to phenanthridine and a new tributyltin radical, which will repeat the catalytic cycle. When there is no more starting material in the reaction, the tributyltin radicals react with each other, leading to the termination step.[28]

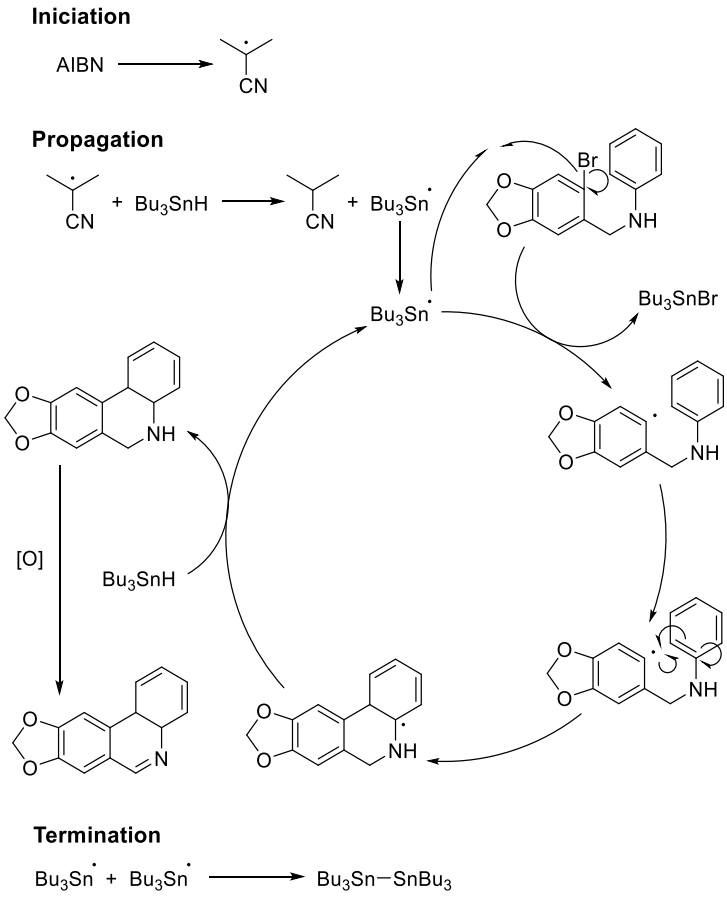


Figure 1.8 – Reaction scheme of intramolecular cyclization with TBTH for [1,3]dioxolo[4,5-j]phenanthridine.[28]

More recently, a new photoredox process for the synthesis of phenanthridines was developed by Rohe *et al.*[29] (Figure 1.9). A biphenyl isocyanide react with an alkyl radical. The alkyl radical is formed by their reaction with a photocatalyst (PC) – $[[Au_2(dppm)_2]Cl_2$. The photocatalyst is activated by irradiation with visible light, giving the radical photocatalyst. The reaction between the alkyl radical and the biphenyl isocyanide gives imidoyl radical, which undergoes a cyclization through an intramolecular radical reaction. Then, the catalytic cycle is closed and a redox reaction forms an arenium ion intermediate. The deprotonation of the intermediate ion leads to the phenanthridine.[27,29]

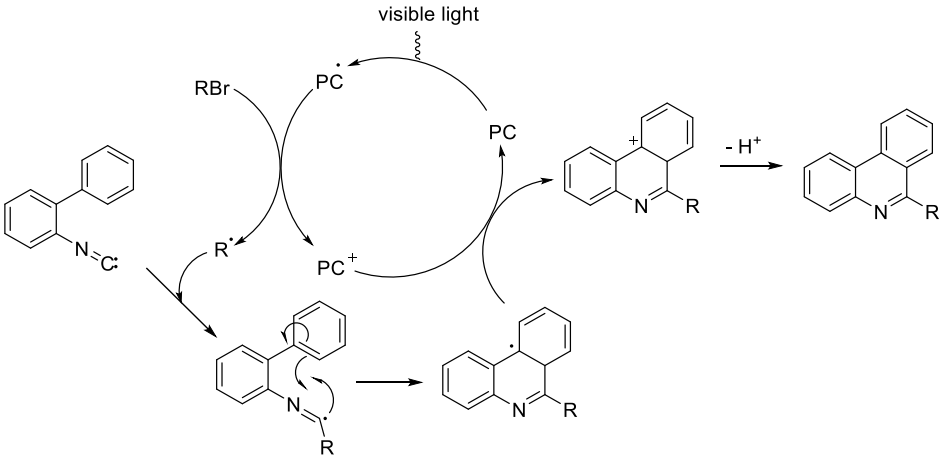


Figure 1.9 – Reaction scheme of photocatalyzed intramolecular cyclization for [1,3]dioxolo[4,5-j]phenanthridine.[27,29]

Despite the synthesis with transition metal-catalysis or radical reactions, other processes are used such as aza-Wittig reactions[30], anionic ring closure reactions[31], and metal-free reactions, like nitrogenation of 2-acetylbiphenyls[9].

Although the phenanthridine alkaloids that were approached previously are heterocyclic aromatic compounds in the following chapter it's intend to do an introduction to other nitrogen heterocyclic compounds paying attention to its applicability in synthetic procedures.

1.2 HETEROCYCLIC COMPOUNDS

Heterocyclic compounds are one of the biggest groups of organic compounds. These compounds are defined as cyclic compounds that have at least one different atom then carbon in its structure being the nitrogen atom the most seen, followed by oxygen and sulphur atoms. They can be aromatic or saturated compounds.[32,33]

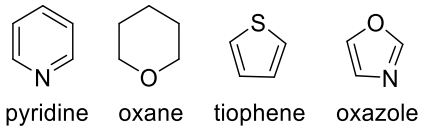


Figure 1.10 – Examples of heterocyclic compounds.[33]

These molecules have a lot of biological and industrial interests. Heterocyclic molecules are of particular interest in the pharmaceutical area, being found in some medicines.[32]

1.2.1 Imidazole

Imidazole (Figure 1.11) is an heterocyclic compound that belongs to the azoles family. Azoles family are defined as five-membered heterocyclic compounds that have at least one nitrogen atom like imidazole, triazole, oxazole, and thiazole.[33,34]

This molecule is both a good hydrogen bonding acceptor and donor. It is also planar, aromatic, and exists in the form of two tautomers.[33–35]

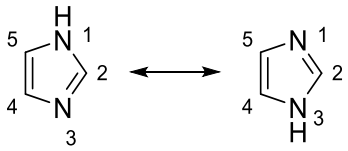


Figure 1.11 – Structure of the two imidazole tautomers.[33,36]

Imidazole is formed by three carbon atoms and two nitrogen atoms, in the positions 1 and 3. The non-bonding electrons in the nitrogen in the position 1 contribute to the aromaticity of the system and the nitrogen in the position 3 are in an sp^2 orbital.[33,36]

Imidazole is an amphoteric compound. This means that can either react as an acid or a base. Imidazole is a weak acid, their pK_a is 14.5. The pK_a of the conjugate acid of imidazole is 7.0.[33,36]

This molecule is used in several reactions. Among them are complexation with metals, metalation reactions, and reactions with electrophiles (which can originate imidazolium salts) and nucleophiles.[33,35]

Imidazole is found in some natural products (Figure 1.12). The amino acid histidine is one of them, such as histamine, a vasodilator that results of enzymatic decarboxylation of histidine. Imidazole is also present in vitamin B_{12} and DNA purines (adenine and guanine).[32,33,35] It also have pharmacological activities, mainly due to hydrogen bonds, such as antiviral[37], antifungal[38], anti-inflammatory[39], and antibacterial[40].

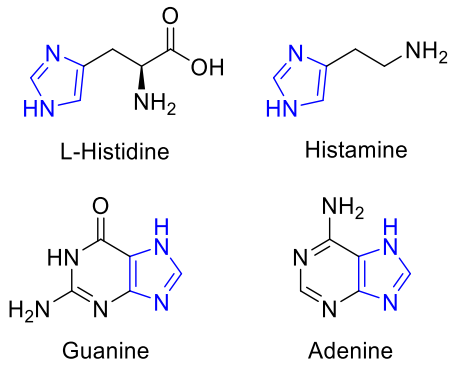


Figure 1.12 – Examples of molecules found in Nature with imidazolium core.[33,35]

1.2.2 Imidazolium Salts

The alkylation of the two nitrogen atoms of imidazole leads to imidazolium salts. In these reactions, the nitrogen atom in position 3 reacts as a nucleophile. Due to this nucleophilic character, there is no need for the use of a strong base. An S_N2 reaction is performed with an haloalkane. If a second mole of haloalkane is available, the other nitrogen atom is functionalized leading to an imidazolium salt (Figure 1.13).[33,35,41]

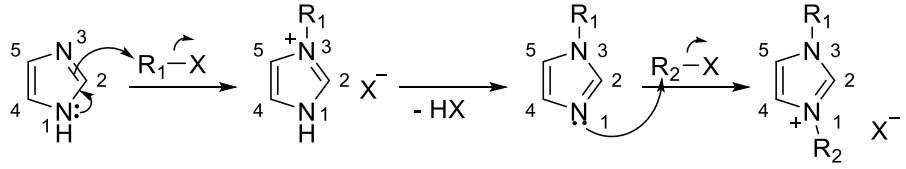


Figure 1.13 – Mechanism for the preparation of imidazolium salts.[33]

Some imidazolium salts can be characterized as ionic liquids, which are liquid electrolytes made of ions that have a melting point under 100 ºC. The complex interaction of Coulombic, hydrogen bonding, and Van-der-Waals interactions of the ionic liquid ions, gives rise to unique properties of these liquids. Ionic liquids are used as solvents in several areas like catalysis, biocatalysis, synthetic chemistry, and electrochemistry areas.[41,42]

Despite the use as solvents, imidazolium salts have other applications. Some of these applications are their use as nanocomposites, CO_2 absorbents, templates for synthesis of functionalized carbohydrates, and also used to extract metal ions from aqueous solutions and coat metal nanoparticles. Some of these compounds have ion conductivity, too. Imidazolium salts are also precursors of N-heterocyclic carbenes (NHCs).[35,41]

Furthermore, imidazolium salts have also pharmacological activities, such as antimicrobial action[38], antiarrhythmics[43], and anti-metastic agents[44]. Some imidazolium polymers have been used as antimicrobials.[45] Comparing to imidazole, imidazolium salts have weaker hydrogen bonding, but they can interact electrostatically. Cytotoxicity of imidazolium salts depends on the anion and on the length of the alkyl chains on the imidazole ring nitrogen. Cytotoxicity is increased by longer alkyl chains.[35,41]

These molecules can also be found in Nature. Lepidiline A and Lepidiline B (Figure 1.14) are two examples of these natural products. They are extracted from the roots of *Lepidium meyenii*.[41]

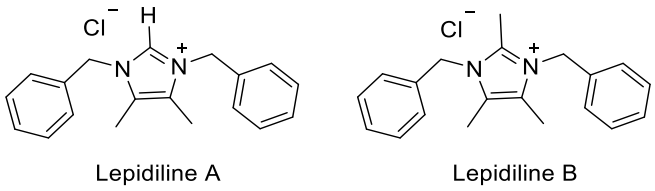


Figure 1.14 – Example of imidazolium salts present in Nature.[41]

1.2.3 N-Heterocyclic Carbenes

Carbenes are neutral compounds usually represented as :CR_2. They are defined as divalent carbon atoms that have six-electrons in their valence layer, two of them are nonbonding electrons and the remaining are in the establish bonds. Being electrodeficients these species are very reactive. Thus, carbenes are extremely electrophilic and the majority of their reactions are insertion reactions.[46–48]

Carbenes can have their nonbonding electrons paired (singlet state) or unpaired (triplet state). In the singlet state, the carbon atom has an sp^2 hybridization. In the triplet state, it can have an sp hybridization (if the molecule has a linear structure) or an sp^2 hybridization, which is the most common one. The triplet state correspond usually to the lower energy state while the singlet state has a highest energy. The structure of the molecule namely the characteristics of the carbon substituents influence the structure to be in a singlet or triplet state.[47,48]

N-heterocyclic carbenes (NHCs) are, as the name suggests, carbenes in a nitrogen heterocyclic compounds. The heterocycle must have at least one nitrogen atom, like those of the azoles family. Although, the ring size can be bigger or smaller than five atoms. The ones approached in this dissertation are based on the imidazole ring.[46]

With the deprotonation of the azolium salts with a strong base, NHCs are obtained. Potassium *tert*-butoxide (*t*-BuOK) or sodium hexamethyldisilazide ($NaN(Si(CH_3)_3)_2$) can be used to perform this reaction.[46,48,49]

In 1991, was reported the first isolated NHC, 1,3-di(adamantyl)imidazol-2-ylidene (Figure 1.15). It was obtained as a crystal by Arduengo *et al*.[50] Although carbenes are very reactive species, this molecule is stable which allowed its characterization, confirming the presence of the carbene. After that, a lot of studies start with NHCs.[46,50,51]

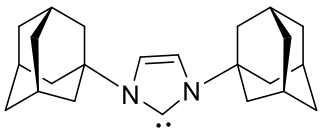


Figure 1.15 – Structure of the first isolated NHC.[50]

NHCs are singlet state carbenes that are favoured by the cyclic structure of NHCs. This structure implies the bent geometry of the carbene, which has an sp^2-like hybridization (Figure 1.16). The structure is also stabilized by σ-electron-withdrawing and π-electron-donating by a mesomerical effect, that donates electron density into the empty π-orbital, as well as by an inductive effect that lower the energy of the σ-orbital. The different R and the backbone substituents can also help to stabilize or destabilizing this structure. Aromaticity of the molecules can help to lower the energy.[46,48]

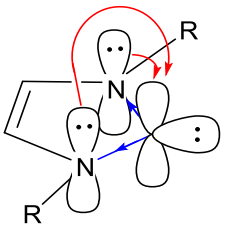


Figure 1.16 – General structure of imidazole-2-ylidenes. The σ-electron-withdrawing are represented in blue and the π-electron-donating are represented in red.[46]

The singlet state provides a nucleophilic character to these compounds, thus being able to act as σ-donors. Therefore, coordination to transition metals and *p*-block elements, and organocatalysis are some reported utilizations of NHCs. In the field of coordination with transition metals, the applications are coordination to surfaces, metallopharmaceuticals, organometallic materials, and homogeneous catalysis. Examples of applications of the organometallic materials

are coordination polymers, photoactive materials, liquid crystals, and metal-organic frameworks. They can be used as ligands in homogeneous catalysis used in cross-coupling, olefin metathesis, and asymmetric catalysis reactions. In the case of the p-block elements, the coordination is employed on activation of small molecules. It is also applied in reactive species' stabilization, like radicals and non-metals in the zero-oxidation state. They can also be used as adducts, such as NHC-boranes and NHC-mediated activation of silicon reagents that can be used in organic synthesis. Heck and Suzuki coupling, aryl aminations, and Sonogashira couplings are some examples of reactions where NHCs coordinated with palladium react as catalysts.[41,46,51]

1.2.3.1 N-Heterocyclic Carbene Boranes

NHCs can form very stable adducts with boranes (BH_3), resulting in N-heterocyclic carbene boranes (NHC-boranes). NHC-boranes are tetravalent zwitterionic molecules. The carbene–boron interaction can be considered as a covalent bond.[46,52,53]

The most used and studied NHC-boranes are the imidazole-2-ylidene boranes (NHC-BH_3). Although, another NHC-boranes have being described, both with different rings or different borane sources, like NHC-triethylboranes (NHC-BEt_3).[49,52]

The first NHC-boranes, 1,3,4,5-tetramethylimidazol-2-ylidene, were reported by Kuhn *et al.*, in 1993.[52] The fact that these molecules are easy to synthesize and are also stable, result in the increasing interest in the chemistry of NHC-boranes from synthesis to applications.[52,53]

There are several synthetic methods for the synthesis of these compounds. NHCs react with a borane, by sharing their electron pair with the unoccupied orbital of boron (Figure 1.17 a)). Borane sources commonly used are borane·tetrahydrofuran (BH_3·THF), borane·dimethyl sulphide (BH_3·SMe_2) or borane·triethylamine (BH_3·NEt_3), thus obtaining the NHC-borane. More recently, a new and easiest method was developed, that allows to obtain the NHC-borane in only one reactional step, with the reaction of the salt of the N-heterocyclic compound with sodium borohydride ($NaBH_4$) (Figure 1.17 b)). $NaBH_4$ has the function of both a base and a borane source. Another way of synthesizing NHC-boranes can be with imidazolium-2-carboxylates (Figure 1.17 c)). 1-Methyl-imidazole react with dimethyl carbonate generating 1,3-dimethylimidazolium-2-carboxylates, which reacts with a borane source. This last step is done with heating, enabling the decarboxylation of imidazolium-2-carboxylates that form the NHC. NHC-borane is formed by the carbene reaction with the borane source.[49,52,54]

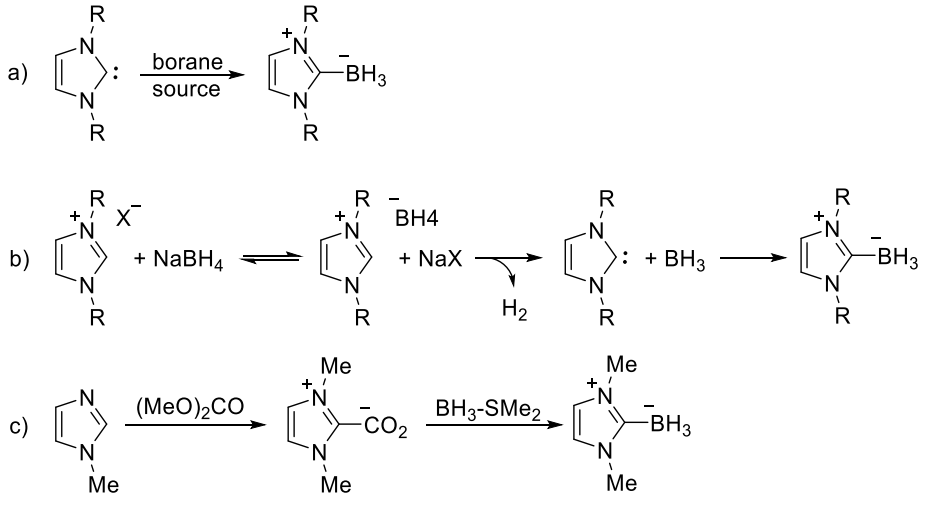


Figure 1.17 – Synthetic scheme for the NHC-boranes synthesis (a) starting from NHC and a borane source, b) with imidazolium salt and $NaBH_4$, and c) with 1-methylimidazole and dimethyl carbonate).[49,52,54]

NHC-boranes can be used in organic synthesis as reagents or catalysts. They can be used in acid/base reactions, NHC-boranes are weaker bases than sodium borohydride and react with very strong acids (pK_a<2). They react with electrophiles, usually halogenating agents, such as *N*-

bromosuccinimide (NBS), iodosuccinimide (NIS), bromine and iodine. NHC-boranes can be used as reagents in radical, ionic, and metal-catalysed reactions as well.[49,52,54–56]

NHC-boranes are also described as hypergolic. Studies are describing the use of NHC-boranes as substituents of hydrazine as fuel components in rocket propellant, being safer to use.[53,54]

1.3 RADICAL REACTIONS

It was in 1900, that Professor Moses Gomberg discovered the trivalent state of carbon. The idea was not well accepted by the scientific community at that time. Despite that initial scepticism, and after a lot of debate and investigation, a new field of chemistry emerged – the radical chemistry.[57]

Radicals are molecules where one of its atoms have one less electron in its valence layer, comparing with their fundamental state. The majority of organic molecules and solvents react with these very reactive molecules. Radicals can be classified as persistent, transient or stable. Radicals' persistence and transience are kinetic characteristics, which means that it is related to the reaction conditions. High reactions barriers lead to persistent radicals being more selective and just react by cross-reaction. Transient radicals are the opposite, they have lower reaction barriers which makes them less selective. They can react by cross-reaction or by self-termination. Whereas, stability is related to thermodynamic, depending on the electronic structure of the radical. Stability of a radical does not entail persistence.[57–60]

When radical reactions start being used, especially in the natural product synthesis, their use was restricted mostly to intramolecular reactions. One example is the synthesis of hirsutene by Curran and Rakiewicz, in 1985.[61] In this reaction intramolecular cyclizations were formed with recourse to radical reactions. Over the years radical reactions start being more used, including intermolecular reactions which was helpful for the synthesis of both simple and complex molecules. Nowadays, radical reactions participate in several reaction types, both in the investigation and industry.[57,61,62]

A radical reaction has three steps: initiation, propagation, and termination. The initiation process requires the formation of a radical through a nonradical molecule, called initiator (In). The radical initiator ($I^{\bullet}$) is formed by a homolytic cleavage through heat, light or radiation. They can also be formed through a redox process. After the radical initiator being formed, he interacts with another molecule, a radical mediator (MH) (Figure 1.18). Azo-iso-butyronitrile (AIBN), benzoyl peroxide, di-*tert*-butyl peroxide (DTBP), triethylborane or zinc chloride are some examples of initiators. Only small amounts of initiator are required and the chosen one depends on the performed reaction.[58,59,63]

The radical mediator is the molecule that "starts" the radical cycle. These molecules remove an atom or a functional group from the main molecule (RZ), which becomes a radical. An addition to a π-system can also occur. In turn, this radical main molecule reacts with a new radical mediator, not yet in the form of a radical. Before this, the main molecule can rearrange itself. Thus, the product is obtained and the radical mediator is formed again, closing the radical cycle. This is the propagation step (Figure 1.18). The most common radical mediators are reducing agents, like organometallic hydrides (tributyltin hydride (TBTH), tris(trimethylsilyl)silane, and tributylgermanium hydride).[58,59,63]

The termination step occurs when all the molecules have reacted or two radicals react with each other (Figure 1.18). Diluted solutions help extending the reaction, delaying the termination step. The propagation must be faster than termination, otherwise, no reaction occurs. This is a very common problem in radical reactions, being the greatest challenge obtaining the desired product with good yields.[58,59,63]

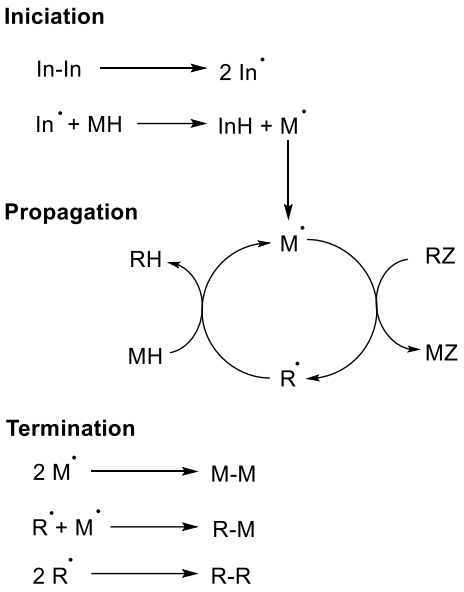


Figure 1.18 – Scheme of the three steps of a radical reaction: Initiation, Propagation and Termination (In – radical initiator, MH – radical mediator, RZ – main compound).[63]

Radical reactions are very important in organic synthesis due to the possibility of carbon-carbon bond formation. Formation of these bonds can be changeling, particularly C_{aryl}-C_{aryl} bonds. These reactions are of particular importance in the synthesis of complex molecules, like natural compounds and some pharmaceutical products. Between the several existing methods, radical reactions are an efficient method to form these bonds through a non-polar process, with only one reactional step.[28,64,65]

The first use of radical reactions to form carbon-carbon bonds was the olefin polymerization. In these reactions, only the initiator and the olefin were present, which became possible the polymerization. These reactions don't have much monitoring and the polymers can have different lengths.[58]

The formation of carbon-carbon bonds is also possible through intramolecular reactions. For these, more reaction monitoring than the necessary in the polymerization reactions is needed. These intramolecular reactions occur when the compound has a π bond, which allows the cyclization of the molecule. Molecules' reduction is also possible, but the intramolecular reaction is greatly favoured. However, there are strategies to favour the desired reaction. On one hand, high concentrations lead to reduction, on the other hand, more diluted solutions result in cyclization. Steric effects can make the intramolecular reaction product impossible to form, leading to the reduction product formation.[58,66]

1.3.1 Boranes in Radical Reactions

Boranes can be used in radical reactions as initiators or as radical mediators. The most common used borane is triethylborane, which can react in different reaction types.[67]

As a radical initiator, triethylborane/oxygen system is the most used (Figure 1.19). The autoxidation of the borane form the radical and allows the reaction to occur even at low temperatures. The importance of low-temperature reactions is the stereoselectivity control. They can also be used in water. Triethylborane can be used in reductive, fragmentation, and atom transfer reactions.[63,67]

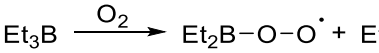


Figure 1.19 – Autoxidation of triethylborane.[63,67]

The first reported use of boranes in radical chemistry was in addition to enones and enals. It is necessary an activation of the borane with oxygen, diacetyl peroxide or with radiation. Any trialkylboranes can be used subject to these reactions, but only one alkyl group is transferred.[67]

Another borane group that have been applied in radical reducing reactions are amine-boranes ($R_3N–BH_3$). This investigation in amine-boranes as reducing agents start being developed by Roberts[68]. The addition of the amine to the borane, decrease the bond-dissociation energy of B-H bond. This decrease allows the hydride transfer that is not possible when the borane is not complexed with the amine. Even though, amine-boranes easily dissociate, originating free boranes, not allowing hydride transfer. NHC-boranes are thought to solve these problems.[56,67,69]

NHC-boranes investigation is at the beginning, however, they are seen as very promising. The bond-dissociation energy of NHC-boranes are slightly higher than tributyltin hydride, so it might be a good replacement for it. Behind all the advantages already mentioned, NHC-boranes don't have the toxic effects related to tributyltin hydride. It is also separated from the main compound without difficulty.[56,69]

Radical chain reduction of xanthates (Figure 1.20 a)) were the first examples where NHC-boranes were applied as radical reducing agents. Nevertheless, these compounds have been used in other radical chain reductions, like reductive dehalogenation (Figure 1.20 b)), and a few reductive cyclizations (Figure 1.20 c)). As initiators, both AIBN, TBHN (di-*tert*-butyl hyponitrile), and DTBP have been successfully used.[52,56,69]

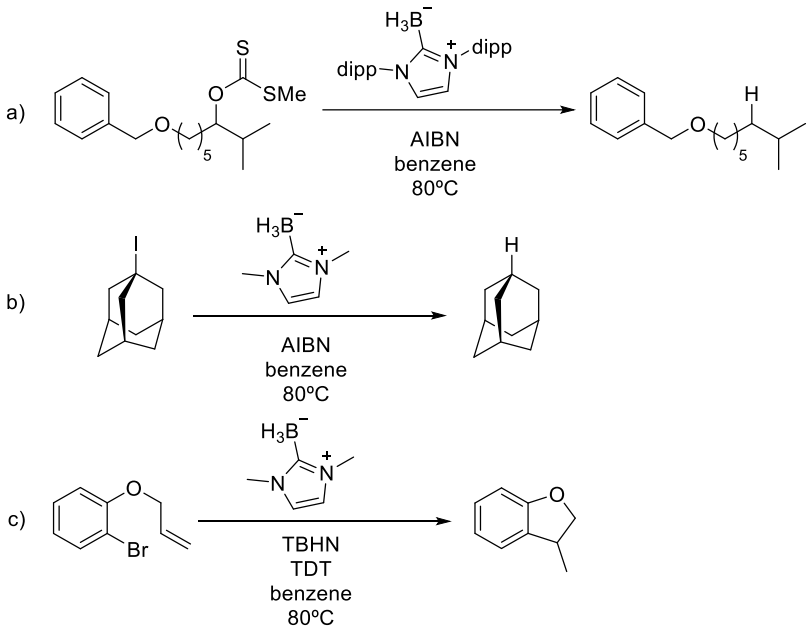


Figure 1.20 – Radical chain reduction of a xanthate with (1,3-bis(2,6-diisopropylphenyl)imidazolium-2-yl)trihydroborate and AIBN a), reductive dehalogenation of adamantly iodine with (1,3-dimethylimidazolium-2-yl)trihydroborate and AIBN b), and reductive cyclization of 1-(allyloxy)-2-bromobenzene with (1,3-dimethylimidazolium-2-yl)trihydroborate, TBHN, and *tert*-dodecanethiol (TDT) c).[52,56]

Recently have been reported that the addition of thiols (thiophenol or *tert*-dodecanethiol) help the hydride transfer process.[56]

2. RESULTS AND DISCUSSION

2.1 PREAMBLE

With the development of this work, it was intended to develop a new technique for the synthesis of molecules with a phenanthridine core using an intramolecular radical cyclization. The main advantage of this new method is the possibility of making this cyclization in one step reaction without the toxicity of TBTH or the presence of metallic catalysts.

With this purpose were synthesized several substrates for the radical reactions to be performed, namely the *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (**1**) and *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (**2**). However, to a better understand of the mechanism of the reaction other substrates were prepared. Following, these several different families of compounds were subject to the radical cyclization reaction. These families include not only the above secondary amines **1** and **2** but also tertiary amines, amides and ether compounds. These compounds will give us an inset of how the NHC-borane behaves in the presence of different functional groups.

It was also need to develop and improve the synthesis of NHC-boranes, the radical mediator to be used. NHC-boranes were synthesized in two steps, being the first one the formation of the imidazolium salt, followed by reaction with $NaBH_4$, as base and boron source.

2.2 AMINES SYNTHESIS

Due to the presence of the phenanthridine core in several natural products, it was our interest to synthesize molecules with this nucleus in the first place. Therefore, *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (**1**) and *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (**2**), two secondary amines were synthesized.

Cyclic tertiary amines are also found in many natural products so, a couple of tertiary amines were also studied as substrates for the radical cyclization, the *N*-(2'-bromobenzyl)-2,3-dihydroindole (**3**) and the *N*-(2-bromobenzyl)-*N*-methylaniline (**4**) (Figure 2.1).

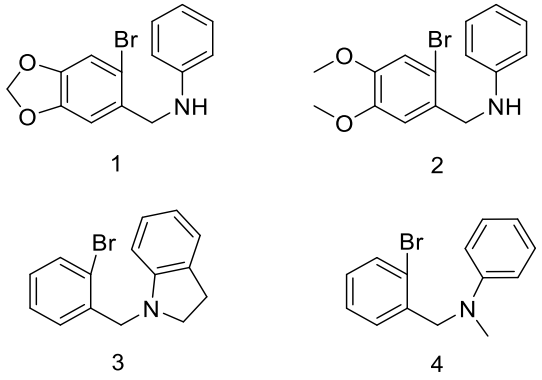


Figure 2.1 – The secondary (2-bromo-4,5-methylenedioxybenzyl)aniline (1) and *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (2), and tertiary amines *N*-(2'-bromobenzyl)-2,3-dihydroindole (3) and *N*-(2-bromobenzyl)-*N*-methylaniline (4) that were synthesized.

2.2.1 Secondary Amines

The syntheses of the secondary amines, substrates for the phenanthridine nucleus, are presented in Figure 2.2. The first step for the synthesis of these molecules was the bromination of two benzaldehydes, piperonal and veratraldehyde following the literature procedures.[70,71] Thus, the benzaldehydes react with bromine for several days to make the bromo aryl aldehydes compounds **5** and **6** respectively. The bromination of piperonal involved glacial AcOH at room temperature (rt). In the case of the veratraldehyde, was used MeOH at rt. These procedures allowed us to obtain a selective bromination in the *orto* position to the aldehyde group. Through ^{1}H NMR and IR analysis, it is possible to confirm the formation of these two compounds.

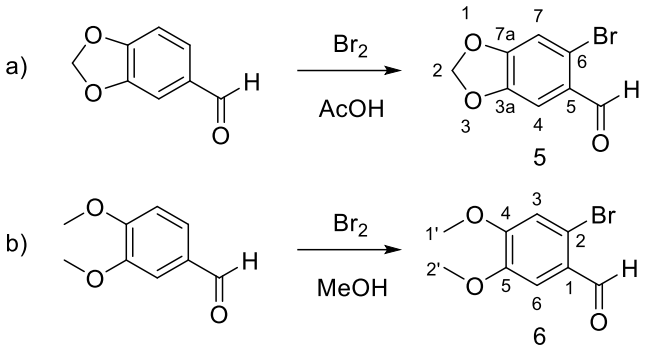


Figure 2.2 – Bromation of piperonal (a) and veratraldehyde (b) to attain the respectively bromo aryl aldehydes 5 and 6.[70,71]

In the ^{1}H NMR spectrum of 6-bromopiperonal (**5**), the presence of two singlets at 7.06 and 7.36 ppm, shows that the bromination occurred at the *orto* position to the carbonyl group. If bromination had occurred at the *orto* position to the oxygen the singlet at H-6 would be expected to be more deshelling. It is also possible to see proton 2 at 6.08 ppm and the aromatic proton 4 at 7.36 ppm. At low field is the singlet of the aldehyde proton, at 10.18 ppm, being in accordance with the literature.[70] The carbonyl group can also be found at 1670 cm^{-1} in the IR spectrum. (Appendix 1)

In the case of the 2-bromo-4,5-dimethoxybenzaldehyde (**6**), the spectrum is similar. At 7.05 ppm is the proton 3, which is next to the bromine atom. The aldehyde proton is at 10.18 ppm, at 7.41 ppm is the aromatic proton 6, and at 3.92 and 3.96 ppm are the protons 2' and 1', respectively. In the IR spectrum, the band of the carbonyl group is at 1667 cm^{-1}. The spectra data are in accordance with the literature.[71] (Appendix 2)

Then the bromo aryl aldehydes reacted with aniline under reductive conditions to attain the respective *N*-(bromobenzyl)anilines (**1** and **2**). The reaction scheme is presented in Figure 2.3. The first step is the formation of a Schiff base followed by their *in situ* reduction by $NaBH_4$. For the Schiff base formation, the bromo aryl aldehydes reacted with aniline in EtOH. After half an hour under reflux, $NaBH_4$ was added and the reaction remains for 1 hour at rt being thus obtained the desired amines, following the literature procedure.[28]

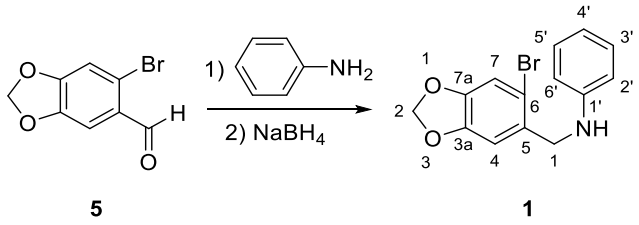
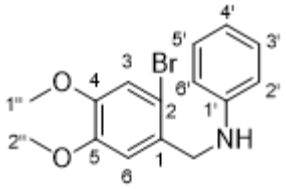


Figure 2.3 – Reaction of the bromo aryl aldehydes with aniline and sodium borohydride to attain the *N*-(bromobenzyl)anilines.

The ^{1}H NMR spectrum of **1** shows the disappearance of the signal of the aldehyde proton and the appearance of the signal at 4.31 ppm which correspond to the protons of the CH_2 group next to the nitrogen atom. In the IR spectrum the band of the carbonyl also disappears and a new one appears at 3377 cm^{-1} that corresponds to the N-H bond stretch. Methylenedioxy group protons arise at 5.94 ppm and the seven aromatic protons can also be found at the low field as a doublet at 6.63 ppm (J = 7.8 Hz) corresponding to H2' and H6', a triplet at 6.74 ppm (J = 7.4 Hz) corresponding to H4', a singlet at 6.93 ppm corresponding to H4, a singlet at 7.02 ppm corresponding to H7, and a triplet at 7.18 ppm (J = 7.4 Hz) corresponding to H3' and H5'. The data are in accordance with the literature.[28] (Appendix 3)

In the case of *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (**2**), the conclusions through the spectra analysis also confirm that the desired molecule was successfully synthezised. In the ^{1}H NMR spectrum, the protons of the CH_2 group arise at 4.34 ppm and there is no signal of the aldehyde proton. The methyl protons of the methoxyl groups arise at 3.79 and 3.86 ppm. The doublet at 6.68 ppm (J = 7.7 Hz) correspond to H2' and H6', the triplet at 6.77 ppm (J = 7.3 Hz) correspond to H4', and the double triplet at 7.18 ppm (J = 7.4, 1.9 Hz) correspond to H3' and H5'. The singlet at 6.99 ppm correspond to the H6, and the singlet at 7.03 ppm to the H3. The IR spectrum supports these data, with no carbonyl band being found, but a new band appears at 3424 cm^{-1} corresponding to N-H stretching, being in accordance with the literature.[28] (Appendix 4)



2

All the compounds were purified by flash column chromatography with **1** being synthesized with a global yield of 34 % and **2** was synthesized with a global yield of 45 %. As it was not the main objective of this work, there was no concern to improve the yield for the preparation of these compounds.

2.2.2 Tertiary Amines

Two different tertiary amines were prepared to be subject to the radical cyclization. One of them is *N*-(2'-bromobenzyl)-2,3-dihydroindole (**3**) and the reaction scheme is presented in Figure 2.4. For its synthesis, an overnight reaction between 2-bromobenzyl bromide with 2,3-dihydroindole (2 eq) in ethyl ether was performed following the literature procedure.[28] This reaction occurs through an S_N2 mechanism where the nitrogen atom of 2,3-dihydroindole molecule attacks the benzylic carbon of 2-bromobenzyl bromide. 2,3-Dihydroindole has basic character, however, it is not a very strong nucleophile. Despite that, it is strong enough to perform this S_N2 reaction through an overnight reaction without the use of a stronger base. This reaction require the use of 2 eq of 2,3-dihydroindole for trapping the HBr that is formed during the reaction.

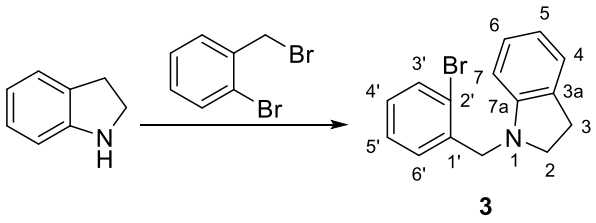


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Figure 2.4 – Reaction of the 2,3-dihydroindole with 2-bromobenzyl bromide to obtain the *N*-(2'-bromobenzyl)-2,3-dihydroindole (3).

In the ^{1}H NMR spectrum, it is possible to find at high field two triplets, at 3.45 (J = 8.3 Hz) and 3.04 ppm (J = 8.3 Hz), which correspond to the H2 and H3, respectively. The benzylic protons are found at 4.33 ppm and the aromatic protons are between 6.46 and 7.58 ppm. It should be noted that the doublet at 7.58 ppm (J = 7.9 Hz) is characteristic of an aromatic proton next to a bromine atom, confirming the desired molecule by being in accordance with the literature.[28] *N*-(2'-Bromobenzyl)-2,3-dihydroindole (**3**) was synthesized with a yield of 88 %. The IR spectrum shows a band at 3050 cm^{-1} corresponding to the aromatic C-H stretching and a band at 2922 cm^{-1} of the C-H aliphatic bond. (Appendix 5)

The other tertiary amine synthesized was *N*-(2-bromobenzyl)-*N*-methylaniline (**4**) being represented in Figure 2.5. Following a literature procedure, the molecule was also synthesized through a S_N2 reaction type.[72] The synthesis requires the use of NaH, that it is added to a solution of *N*-methylaniline in DMF, forming an *N*-methylaniline salt. Then 2-bromobenzyl bromide is added to the reaction mixture, and *N*-(2-bromobenzyl)-*N*-methylaniline (**4**) was formed.

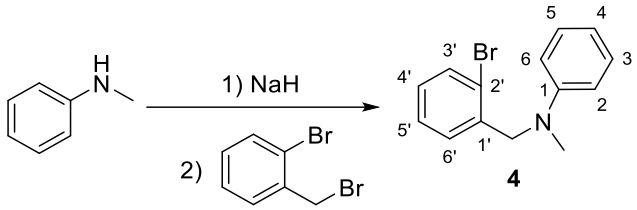


Figure 2.5 – Reaction of *N*-methylaniline with 2-bromobenzyl bromide to attain the *N*-(2-bromobenzyl)-*N*-methylaniline (4).

Through the ^{1}H NMR analysis, it is possible to prove that the desired molecule was obtained. The doublet at 7.62 ppm (J = 7.8 Hz) corresponds to the 3' proton. It is the most deshielded proton due to the proximity to the bromine atom. At 7.26 ppm, can be found a multiplet that corresponds to the protons 4', 5', and 6'. The reaming aromatic protons are between 7.21 and 6.71 ppm. At 4.59 ppm can be found the benzylic protons signal, and the singlet at the highest field (3.13 ppm) corresponds to the *N*-methyl group. The IR spectrum shows a band at 3060 and 2924 cm^{-1} corresponding to C-H aromatic bonds and C-H aliphatic bonds, respectively. The data are in accordance with the literature.[72] In a one-step reaction was possible to obtain the compound with a yield of 59 %. (Appendix 6)

2.3 AMIDE SYNTHESIS

The radical cyclization of an amide was also studied, and thus *N*-(2'-bromobenzyl)-*N*-phenylacetamide (**7**) was synthesized, following a literature procedure.[64] The reaction scheme is presented in Figure 2.6. To a solution of acetanilide in DMF was added 1.2 equivalents of NaH. The addiction of the NaH allowed the formation of the acetanilide sodium salt. After the formation of the salt, 2-bromobenzyl bromide was added to the reaction mixture, and **7** was obtained again through a S_N2 reaction mechanism.

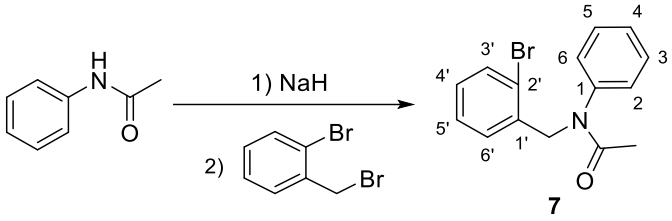


Figure 2.6 – Synthesis of *N*-(2'-bromobenzyl)-*N*-phenylacetamide (7) by the reaction of acetanilide with 2-bromobenzyl bromide.

In the ^{1}H NMR spectrum is possible to identify the protons of the acetyl group at 1.94 ppm and the protons of the CH_2 group at 5.04 ppm. In the aromatic zone, the most deshielded signal is a doublet at 7.46 ppm (J = 7.9 Hz). That signal is characteristic of aromatic protons next to a bromine atom. The remaining aromatic protons can be found in the two multiplets present in the spectra, between 7.39 – 7.21 and 7.11 – 7.03 ppm. The presence of the aromatic bonds is also confirmed by the IR spectrum, in the band at 3061 cm^{-1}. Are also seen a band of the C-H aliphatic stretch at 2971 cm^{-1} and 1657 cm^{-1} the band corresponding to the C=O bond, being in accordance with the literature.[64] The product was synthesized with a yield of 67 %. (Appendix 7)

2.4 ETHER SYNTHESIS

The ether chosen to be studied was 1-bromo-2-(phenoxymethyl)benzene (**8**) and its synthesis is presented in Figure 2.7. The synthesis involved the reaction of 2-bromobenzyl bromide with 5 equivalents of phenol. Phenol is a mild acid, thus it is not a strong nucleophile. To increase the nucleophilicity of the phenol, 5 equivalents of potassium carbonate have been placed in the reaction mixture, so that removal of the proton could be accomplished as also for the neutralization of the reaction environment.

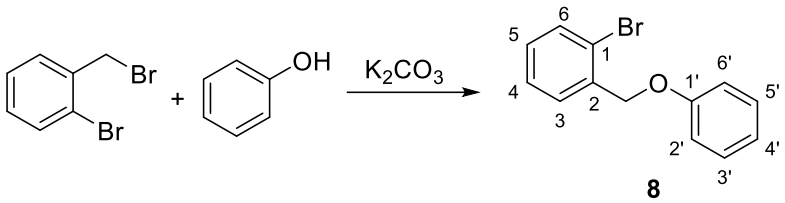


Figure 2.7 – Reaction of 2-bromobenzyl bromide with phenol to attain 1-bromo-2-(phenoxymethyl)benzene (8).

The ^{1}H NMR spectrum shows a singlet at 5.15 ppm corresponding to the CH_2 protons. The protons 2', 4', and 6' are found at the multiplet between 6.97 and 7.03 ppm. The multiplet between 7.22 – 7.17 ppm and the multiplet between 7.37 and 7.29 ppm correspond to the protons 3', 5', 3 and 5. Finally, from 7.61 to 7.55, is the multiplet corresponding to the protons 4 and 6, being the most deshielded ones.[73] The molecule was also analysed through IR spectroscopy where is viewed a band at 3061 cm^{-1} corresponding to the C-H aromatic bonds, and the C-H aliphatic bonds are found at 2970 cm^{-1}. Accordingly, 1-bromo-2-(phenoxymethyl)benzene (**8**) was synthesized with a yield of 90 %. (Appendix 8)

2.5 ETHANE-BRIDGE COMPOUNDS SYNTHESIS

To be able to study the interference of heteroatoms present in the substrates in the radical reactions it was envisaged the synthesis of 1-bromo-2-phenethylbenzene (**9**), following a literature procedure.[74] For that purpose, 2-bromobenzyl bromide reacted with 1 eq of n-BuLi, added dropwise, in THF. The reaction remained at -100 ºC for 1 hour and a TLC of the reaction showed that it was not complete. So, the reaction remained at rt overnight. After terminus and work up of the reaction and from the ^{1}H NMR analysis of the compounds attained, it is concluded that the desired product was not obtained, but were obtained the following three compounds – 1,2-bis(2-butylphenyl)ethane (**10**), 1,2-bis(2-bromophenyl)ethane (**11**), and 1,2-diphenylethane (**12**) (Figure 2.8). (Appendix 9, Appendix 10, and Appendix 11)

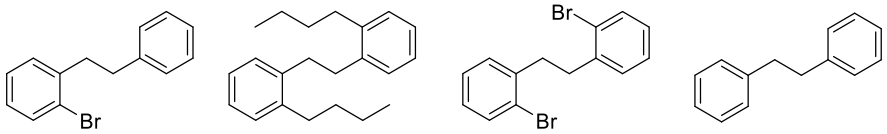


Figure 2.8 – Target compound, 1-bromo-2-phenethylbenzene (9) and the compounds obtained in the reaction, 1,2-bis(2-butylphenyl)ethane (10), 1,2-bis(2-bromophenyl)ethane (11), and 1,2-diphenylethane (12).

The major compound obtained was 1,2-bis(2-butylphenyl)ethane (**10**). This result can emerge from the fact that the reaction remained overnight at rt, as explained in Figure 2.9. The n-BuLi in the reaction had attacked the 1,2-bis(2-bromophenyl)ethane (**11**), giving **10**. The bromine-lithium exchange of **11** leads to **12**. 1,2-Bis(2-butylphenyl)ethane (**10),** 1,2-bis(2-bromophenyl)ethane (**11**), and 1,2-diphenylethane (**12**) where detected in the ^{1}H NMR spectrum from the several fractions obtained by column chromatographic purification. (Appendix 9, Appendix 10, and Appendix 11)

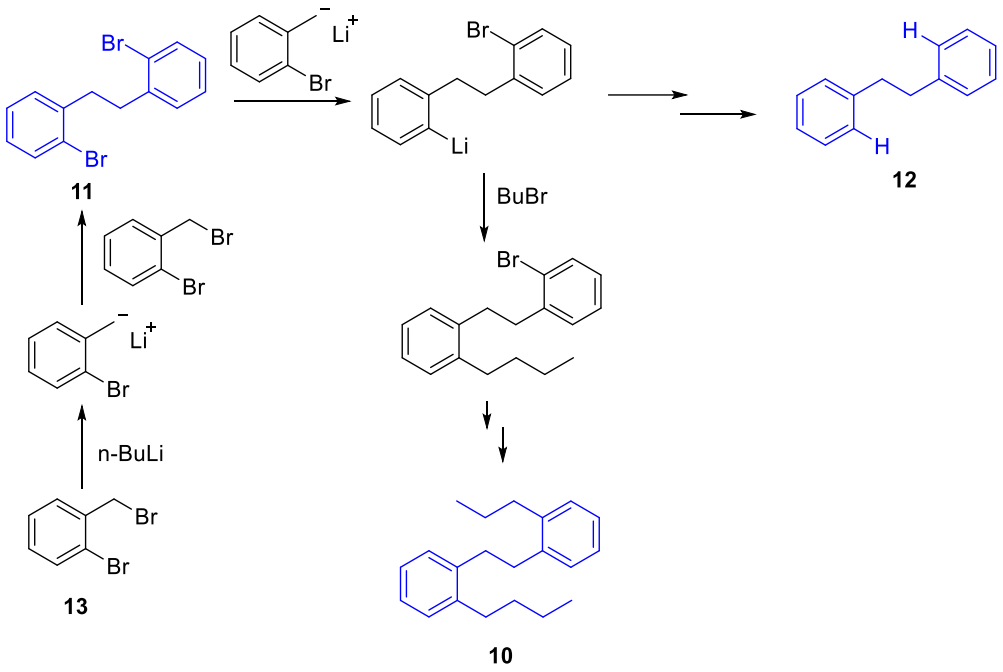


Figure 2.9 – Reaction scheme of the mechanism for the formation of the diverse products observed on reaction of 2-bromobenzyl bromide with n-BuLi.

In a new attempt the reaction rest reacting for 1 hour only, being always at -100 ºC. The remaining procedure was the same. The ^{1}H NMR spectrum shown that the molecules obtained were 1,2-bis(2-butylphenyl)ethane (**10**) and 1,2-diphenylethane (**12**). Again, it was not possible to synthesize **9** and a new reaction process was tested. This time a different strategy was approached and n-BuLi was added dropwise to a solution of benzyl bromide in THF at -78 ºC. A solution of 2-bromobenzyl bromide in THF was then added dropwise. The reaction mixture remained at -78 ºC. 1,2-Diphenylethane (**12**) and 2-bromobenzyl bromide (**13**) were detected in ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum shows only the presence of 2-bromobenzyl bromide (**13**), and not the presence of benzyl bromide (**14**). We can then assume that the formation of 1,2-diphenylethane (**12**) followed the mechanism represented in the Figure 2.10. (Appendix 9, Appendix 11, and Appendix 12)

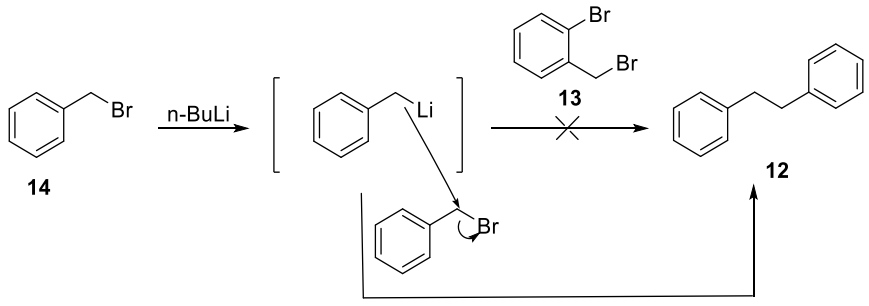


Figure 2.10 – Reaction scheme of the mechanism for the formation of 1,2-diphenylethane (12) on reaction of 2-bromobenzyl bromide (13) and benzyl bromide (14) with n-BuLi.

Following these results, THF was cooled to -90 ºC and n-BuLi was added. The temperature was always maintained at -90 ºC. Benzyl bromide was added at one time to the reaction mixture. After some minutes, a solution of 2-bromobenzyl bromide in THF was added at one time. Despite the changes in the procedure, the ^{1}H NMR shown that was also obtained 1,2-diphenylethane (**12**) and recovered 2-bromobenzyl bromide (**13**). (Appendix 11 and Appendix 12)

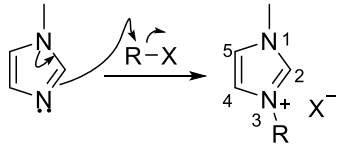
Another procedure was also tested, where 2-bromobenzyl bromide and benzyl bromide were placed in a round-bottom flask in THF. The reaction mixture was cooled to -90 ºC. n-BuLi was

added dropwise to the reaction mixture. 1,2-Bis(2-bromophenyl)ethane (**11**) and the starting materials were the molecules identified in the ^{1}H NMR spectrum. (Appendix 10)

Despite all the different approaches to the reaction, 1-bromo-2-phenethylbenzene (**9**) could not be synthesized.

2.6 IMIDAZOLIUM SALTS SYNTHESIS

The first step for the synthesis of the NHC-boranes is the formation of the imidazolium salts (**15a-d,** Figure 2.11). Therefore, through an S_N2 reaction, 1-methylimidazole reacted with different haloalkanes (a slight excess – 1.2 eq), to obtain several imidazolium salts with different groups in position 3, following literature procedures.[53,75] Therefore, four different imidazolium salts were synthesized.



15a R=Me X=I
15b R=$(CH_2)_9CH_3$ X=I
15c R=Et X=I
15d R=CH_2Ph X=Br

Figure 2.11 – Reaction mechanism for the formation of the imidazolium salts.

The 1,3-dimethylimidazolium iodine (**15a**) was obtained with a yield of 90 % and was analysed using ^{1}H NMR and IR spectroscopy. In the ^{1}H NMR spectrum, the acidic proton 2 was found at low field, at 8.67 ppm. The singlet at 7.43 ppm corresponds to the protons 4 and 5, and the singlet at 3.91 ppm integrating to 6H corresponds to the protons of the two CH_3 groups which is in accordance with the literature.[76] In the IR spectrum, it is possible to find the aromatic C-H bonds at 3068 cm^{-1}, the aliphatic C-H bonds at 2939 cm^{-1}, and the C=N stretch at 1574 cm^{-1} confirming the molecule structure. (Appendix 13)

The 3-decyl-1-methylimidazolium iodine (**15b**) was synthesized with a yield of 53 %. In the ^{1}H NMR spectrum, it was founded at low field the proton 2 at 10.10 ppm. The singlets at 7.46 and 7.35 ppm correspond to the aromatic protons 4 and 5, respectively. The *N*-methyl group is represented by the singlet at 4.11 ppm, and the triplet at 4.30 ppm (J = 7.5 Hz) corresponds to the two protons 1' from the decyl chain. The remaining protons of the decyl group are found in the multiplets between 1.87 – 1.96, and 1.17 – 1.38 ppm, being in accordance with the literature.[77] The IR spectrum shows bands at 3086 cm^{-1}, corresponding to the aromatic C-H bonds, and bands from the aliphatic C-H bonds at 2921 cm^{-1}. At 1571 cm^{-1} is a band that represents the C=N stretching. (Appendix 14)

The 3-ethyl-1-methylimidazolium iodine (**15c**) was also synthesized through an S_N2 reaction with the same mechanism as the one in the reaction discussed above. For this reaction, 1-methylimidazole was diluted in diethyl ether and iodoethane, in excess, was slowly added. The 3-ethyl-1-methylimidazolium iodine (**15c**) was synthesized with a yield of 97 % and was characterised by ^{1}H NMR and IR spectroscopy. The IR spectrum shows a band at 3081 cm^{-1} that confirms the presence of aromatic C-H bonds, at 2967 cm^{-1} are the aliphatic C-H stretch, and at 1567 cm^{-1} are the C=N stretching. In the ^{1}H NMR spectrum, the protons of the *N*-methyl group were found as a singlet at 3.90 ppm. The H7 and H8 protons of the ethyl group are present at 4.24 and 1.51 ppm, respectively. The acid proton 2 is represented by the singlet at 8.72 ppm. The singlets at 7.43 and 7.49 ppm corresponds to the protons 4 and 5, being in agreement with the literature.[78] (Appendix 15)

It was also synthesized the 3-benzyl-1-methylimidazolium bromide (**15d**) with a yield of 90 %. The molecule was characterized through ^{1}H NMR spectroscopy. The acidic proton 2 is represented by the singlet at 10.47 ppm. The aromatic protons 4 and 5 are represented by the singlet at 7.29 and by the multiplet between 7.35 – 7.40 ppm. In this multiplet are also represented the aromatic protons H2', H4', and H6'. The multiplet between 7.45 – 7.48 ppm correspond to the H3' and H5' protons. The IR spectrum confirms the presence of the aromatic C-H bonds at 3086 cm^{-1}. A band at 1563 cm^{-1} is due to the presence of C=N bonds. The CH_2 group is found, in the ^{1}H NMR, at 5.57 ppm, and the singlet at 4.06 ppm is due to the protons from the *N*-methyl group. The spectral data are in accordance with the literature.[75] (Appendix 16)

In some IR spectra of the imidazolium salts is seen a broad band around 3400 cm^{-1}. The appearance of this band is due to the presence of water in the salts, since they are hygroscopic.

2.7 NHC-BORANE SYNTHESIS

After the synthesis of the imidazolium salts, it followed the synthesis of the NHC-boranes (Figure 2.12). Therefore, the imidazolium salts reacted with $NaBH_4$ (2 eq), in toluene. The reaction remains at reflux for 18h, following a literature procedure.[53] The $NaBH_4$ has a dual role in these reactions, working as a base and a source of borane. The use of the $NaBH_4$ is of great advantage because it replaces the use of strong bases and reactive borane sources.[54]

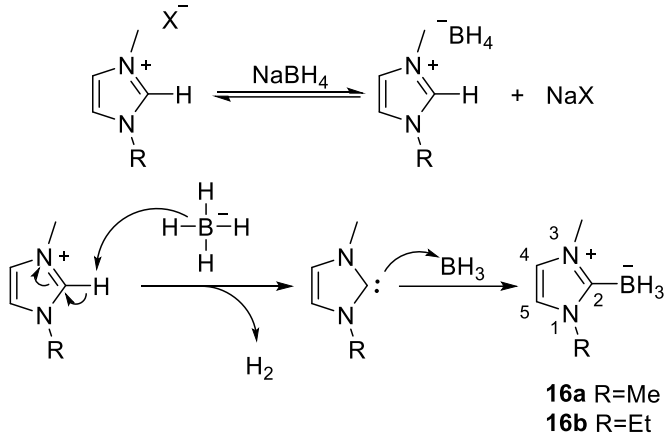


Figure 2.12 – Reaction mechanism for the synthesis of the NHC-boranes.[49]

(1,3-Dimethylimidazolium-2-yl)trihydroborate (**16a**) was successfully synthesized and was analysed with ^{1}H NMR, ^{13}C NMR, ^{11}B NMR, and IR spectroscopy. In relation to the starting material (**15a**) it was observe for **16a** a shielding of the proton signals in the ^{1}H NMR spectra. The protons of the methyl groups are observed at 3.73 ppm and the signal of the corresponding carbon atoms are at 36 ppm in the ^{13}C NMR spectrum. The singlet at 6.79 ppm in the ^{1}H NMR correspond to the aromatic protons (4 and 5). In the ^{13}C NMR, they are found at 120 ppm. In the IR spectra was observed the stretching of the aromatic C-H bond at 3130 cm^{-1}. The protons of the BH_3 group are found as a multiplet between 1.36 and 0.65 ppm in the ^{1}H NMR spectra, in the ^{11}B NMR spectra they are observed as a quadruplet at -37.49 ppm, and in the IR spectra the stretching of the B-H bond appeared at 2269 cm^{-1}. The C=N stretching can also be seen at 1476 cm^{-1} in the IR spectra. These results are in accordance with the literature report.[53] Through the spectra analysis, it was confirmed that (1,3-dimethylimidazol-3-ium-2-yl)trihydroborate (**16a**) was obtained, with a yield of 56 %. (Appendix 17)

In a two-step reaction, the NHC-borane **16a** was synthesized with a global yield of 50 %.

The formation of the NHC-borane having 3-ethyl-1-methylimidazolium iodine as starting material was also successful, with a yield of 17 %. (3-Ethyl-1-methylimidazolium-2-yl)trihydroborate (**16b**) was analysed through ^{1}H NMR, ^{13}C NMR and IR spectroscopy. In the ^{1}H NMR, at low field, the doublet at 6.81 ppm (J = 8.8 Hz) represents the aromatic protons H4 and H5. The carbon signals for CH-4/5 are at 118.19 and 120.22 ppm. The stretching of the aromatic C-H bonds corresponds to the band at 3131 cm^{-1}. The quadruplet at 4.14 ppm (J = 7.2 Hz) and the triplet at 1.36 ppm (J = 7.2 Hz) corresponds to the H7 and H8 from the ethyl group, respectively. The multiplet between 1.33 and 0.65 ppm is characteristic of the BH_3 protons, and the B-H stretching band is found at 2275 cm^{-1}. In the ^{13}C NMR, CH_2-7 is represented by the signal at 43.75 ppm and CH_3-8 by the signal at 15.47 ppm. The singlet at 3.71 ppm is due to the protons of the methyl group, and the respective carbon is found at 35.81 ppm. The quaternary carbon C-2 corresponds to a quadruplet between 170.57 and 171.79 ppm. In the IR spectrum is also seen a band at 2982 cm^{-1} that corresponds to aliphatic C-H bonds, and a band at 1475 cm^{-1} from the C=N stretching. The spectral data are in accordance with the literature.[53] (Appendix 18)

This reaction was not as effective as the previously one and this is something not yet completed understood. The global yield for the synthesis of (3-ethyl-1-methylimidazolium-2-yl)trihydroborate (**16b**) was 16 %.

The same procedure was made with 3-decyl-1-methylimidazolium iodine (**15b**). Through TLC it was noticed that a reaction has occurred, although not being complete. Even so, after the work up of the reaction the ^{1}H NMR spectrum didn't allowed the identification of the compound.

The reaction with 3-benzyl-1-methylimidazolium bromide (**15d**) followed the same procedure. Again, no product has been identified by the ^{1}H NMR spectra. For these molecule, was tried a different procedure where the reaction remained overnight at rt, and yet the desired product has not been formed.

(3-Decyl-1-methylimidazolium-2-yl)trihydroborate is not described in the literature and we do not have a justification for the reaction not to happened. In the case of (3-benzyl-1-methylimidazolium-2-yl)trihydroborate, its synthesis was reported in the literature by Gardner *et al.*[49] (3-Benzyl-1-methylimidazolium-2-yl)trihydroborate was synthesized through 3-benzyl-1-methylimidazolium iodine reaction with sodium borohydride. Since the reported reaction had as counter-ion the iodine, and our compound had bromide, the counter-ion may have an effect in the NHC-borane synthesis. More assays should be done in order to confirm these conclusions.

2.8 N-HETEROCYCLIC OLEFIN-BORANE SYNTHESIS

One of work's objective was also to verify if it was possible to do the synthesis of N-Heterocyclic Olefin-boranes (NHO-boranes) starting from 1,3-dialkyl-2-methylimidazolium salts and study its reactivity by comparison with the reactivity of NHC-boranes.

N-heterocyclic olefins (NHOs) are the alkylidene derivatives of NHCs. Like NHC-boranes, NHOs are ylidenes, but they can have an olefin structure too (Figure 2.13). The double bond has high electron density, which causes the exocyclic carbon to have a nucleophilic character and a strong Brønsted/Lewis basicity.[79,80]

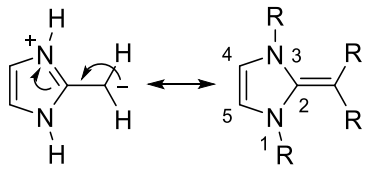


Figure 2.13 – Ylidene and olefin structures of NHOs.[80]

Beyond the *N*-substituents, NHOs can have different substituents in the exocyclic carbon. These substituents can change the reactivity of the molecules, by modifying stereochemical hindrance and stabilizing or destabilizing the electron density.[80]

NHOs properties can be compared to NHCs, although NHOs are softer donors than NHCs, due to the highly polarized exocyclic C=C double bond. The double bond has considerable electron density of high π-orbital character at the exocyclic carbon atoms.[81]

NHOs are easy to synthesize by several procedures. They have been used in CO_2 sequestration reactions[82], ring-opening polymerization reactions[83], and transesterification reactions[79].

The imidazolium salt used was one which had been synthesized in the group.[84] For the preparation of the NHO-boranes the same reaction method was used as in NHC-boranes.[53] Thus 1,2,3-trimethylimidazolium iodine, $NaBH_4$, and toluene were placed in a round-bottom flask under reflux. The reaction remained under reflux for 24 hours. The crude was analysed by ^{1}H NMR spectroscopy, and the desired product was not identified.

The $NaBH_4$ may not be strong enough to remove a proton from the exocyclic carbon since the exocyclic carbon has strong basicity.[80] The reaction should be repeated with a strong base and a borane source, in order to understand if the NHO-borane is formed.

2.9 RADICAL CYCLIZATION REACTIONS

The NHC-boranes prepared were used as radical mediators on the radical intramolecular cyclization of the substrates synthetized and described in chapters 2.2 to 2.4. It was followed the same procedure to all the radical reactions, therefore to a benzene solution of the substrate it was added the NHC-borane followed by AIBN dissolved in benzene. AIBN was added slowing through several hours, using a syringe equipped with an automatic injector. The reactions were performed under N_2 atmosphere. Whenever the TLC showed NHC-borane still present in the reaction, more AIBN was added to consume all the borane.

Curran *et al.* reported that the addition of catalytic amounts of thiols to radical reactions using NHC-boranes helped to enhance the yields by helping in the hydrogen transfer process. So, whenever specified, 0.2 equivalents of thiophenol were added to improve the reaction.[56]

In all the reactions, was detected the formation of the parent imidazole salt.

2.9.1 Using *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (1) as a substrate

The first substrate to be subject to a radical intramolecular cyclization was *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (**1**) with (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**) as a radical mediator (Figure 2.14). To a benzene solution of **1** and NHC-borane (**16a**) under reflux was added drop-wise, during 15 h to 18 h, a solution of 0.2 eq of AIBN in dry benzene. As reported in experimental procedure more AIBN was added (until were reached 0.8 equivalents). Even so, the total consume of **1** was not observed. The cyclization product, [1,3]dioxolo[4,5-j]phenanthridine (**17**) was obtained with a poor yield of 13 % and it was recovered 58 % of the substrate 1 (Table 2.1, entry 1).

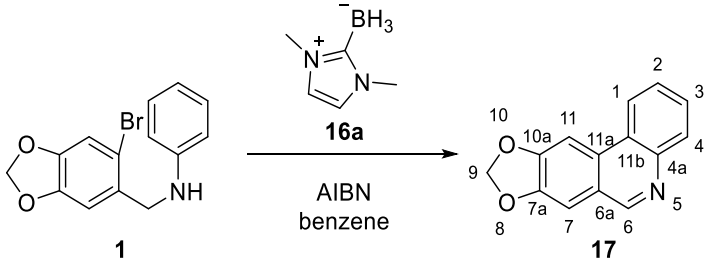


Figure 2.14 – Reaction scheme of the radical intramolecular cyclization of 1.

Further studies envisaging the methodology were focus on the solvent preparation as also the use of additives as thiophenol or the amount of AIBN. In relation to the solvent despite the benzene used was dried using molecular sieves, it could rest some oxygen traces in it that could interfere with the reaction outcome. So, to prepare an oxygen free benzene, the solvent was subject to freeze drying through vacuum and N_2 cycles (Table 2.1 entry 2). No substantial differences were observed with **17** being obtained with16 % yield and was recovered 65 % of the starting material.

To realize if the problem was in the radical initiator, a new radical reaction was carried out with di-*tert*-butyl peroxide (DTBP) as a radical initiator (0.2 eq), but the yield was lower than the reactions with AIBN (Table 2.1, entry 3) so the radical initiator to be used in the following experiments remained the AIBN. The next change that was made involved drying the solvent, benzene, with sodium wire and exclusion of oxygen through bubbling a stream of N_2 (Table 2.1, entry 4). A slight increase in the yield was observed being the selected method for the next reactions.

Table 2.1 – Reactional conditions for the radical cyclization of *N*-(bromo-4,5-methylenedioxybenzyl)aniline (1).

Entry	Solvent preparation	Radical Initiator (eq)	PhSH (eq)	NHC-borane (eq)	Yield (%)
1	*Sieves*	AIBN (0.8)[a)]	-	1.1[e)]	13
2	Freeze Drying	AIBN (0.6)[b)]	-	1.6[e)]	16
3	Freeze Drying	DTBP (0.2)	-	1.1[e)]	2
4	Sodium Wire	AIBN (0.6)	-	1.1[e)]	22
5	Freeze Drying	AIBN (0.4)[c)]	0.05	1.3[e)]	11
6	Freeze Drying	AIBN (0.8)[d)]	0.1	2.3[e)]	21
7	Sodium Wire	AIBN (0.6)	0.2	1.2[e)]	7
8	Sodium Wire	AIBN (0)	-	1.2[e)]	-
9	Sodium Wire	AIBN (0.6)	-	1.2[f)]	13

a) Initially were added 0.2 eq, and then more 3 x 0.2 eq were added in batch **for 7 days. b) The reaction started with 0.2 eq and then more 2 x 0.2 eq were joined to the reaction mixture in batch during 6 days. c) Initially were added 0.2 eq, and then more 0.2 eq were added in batch for 2 days. d) Initially were added 0.2 eq, and then more 2 x 0.2 eq were added in batch for 10 days. e) The NHC-borane used was the 16a. f) The NHC-borane used was 16b.**

It was also studied the addition of thiophenol (PhSH) to the reactions. The literature report the use of thiophenol as catalyst, helping the hydrogen transference.[56] The reaction procedure stayed the same, but 0.05 eq of thiophenol was now added to the reaction mixture and a discourage result was obtained (Table 2.1, entry 5). Increasing the amount of the additive to 0.1 eq as also the amount of AIBN and the radical mediator **16a** (2.3 eq) did not point to major improvements (Table 2.1, entry 6). Was also made a reaction with 0.2 eq of thiophenol (Table 2.1, entry 7) but the yield was even lower. With all this results it was not possible to understand why the reactions do not had any progress.

Therefore, it was made a blank assay in order to verify the stability of the NHC-borane in the presence of the substrate. The procedure was the same, but no AIBN was joined to the reaction mixture (Table 2.1, entry 8). The crude only show the presence of the two substrates (Appendix 19). It can thus be concluded that there are no side reaction between the substrate and the NHC-borane that were interfering with the radical reaction. As for the blank assay between **16a** and AIBN (0.6 eq) was expected a reaction had to occur since this is the initial step on the radical reaction.[28,56] In the complex mixture formed it was possible to identify some imidazolium salt (**15a**) being formed, meaning that a reaction occurred.

Even with all the optimizations, the yield of the reaction was below expectations. Nevertheless, the desired intramolecular cyclization product, [1,3]dioxolo[4,5-j]phenanthridine (**17**), was synthesized. The synthesis of the compound is confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopy. In the ^{1}H NMR are found 7 aromatic protons between 7.36 and 9.11 ppm, and at 6.19 ppm is a singlet that corresponds to the methylenedioxy group's protons (Appendix 20). In the IR spectrum, bands correspondent to aromatic C-H bonds are found at 3044 cm^{-1}, and C=N stretching at 1464 cm^{-1}. The ^{13}C NMR is in accordance with the literature.[85] The mechanism proposed for the reaction is presented in the Figure 2.15. The formed ring is of six atoms, so the cyclization is designated 6-endo-trig by the Baldwin's classification. The cyclization is favoured by the Baldwin's rules.[86]

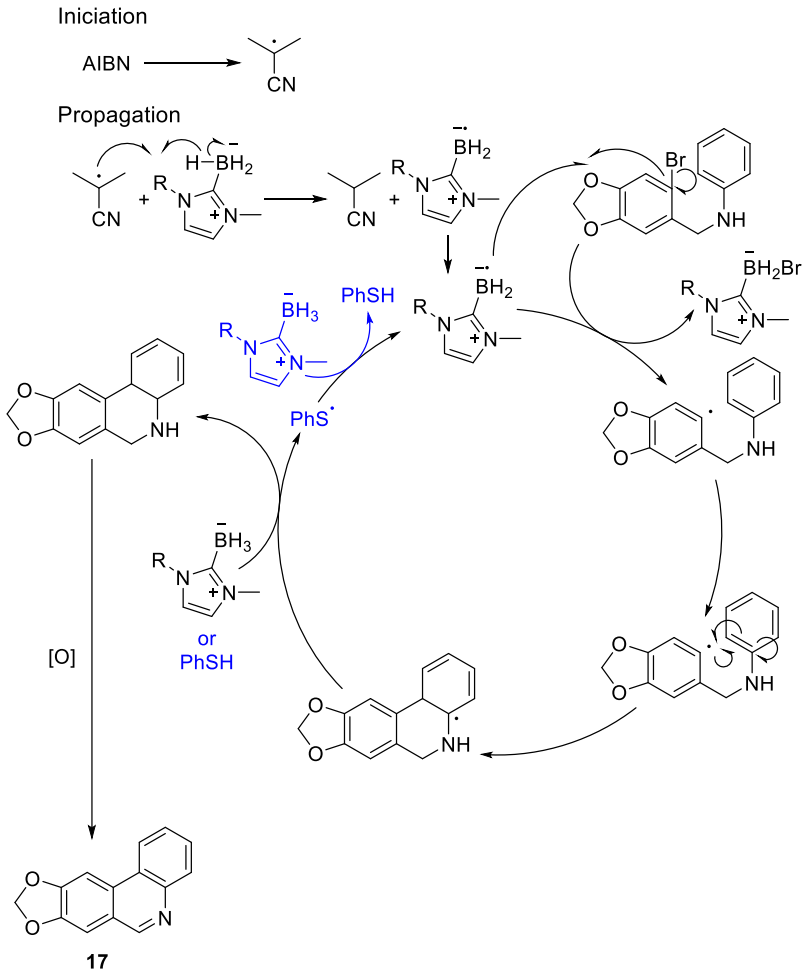


Figure 2.15 – Proposed mechanism for the radical cyclization reaction with the NHC-borane. In blue is represented the radical cyclization catalysed with thiophenol.

The intramolecular radical cyclization with *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (**1**) as a substrate was also made with a different NHC-borane – the (3-ethyl-1-methylimidazolium-2-yl)trihydroborate (**16b**) (Table 2.1, entry 9). The procedure was the same as previously presented, as well as the proposed mechanism (Figure 2.15). [1,3]Dioxolo[4,5-j]phenanthridine (**17**) was synthesized with an yield of 13 % and was recovered 79 % of **1**. The use of (3-ethyl-1-methylimidazolium-2-yl)trihydroborate (**16b**) showed no marked difference in the reaction yield, comparing with the reactions in which was used **16a**.

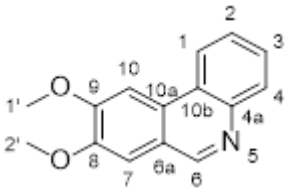
With this whole set of results was not clear the reason why the yields were so low, despite all the AIBN and NHC-borane in excess. It should also be noted that no reduction product was detected (substitution of bromine by hydrogen). This means that the radical anion of the NHC-borane has poor ability to react with the substrate abstracting the bromine atom. However that is not what is reported in the literature.[56] Therefore, different substrates with different functional groups were tested in order to understand what happen.

2.9.2 Using *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (2) as a substrate

The radical cyclizations of *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (**2**) was also studied. The best conditions observed for the radical cyclization of **1** reported in section 2.9.1 were chosen to perform these reactions namely the solvent, benzene, dried with sodium wire and exclusion of oxygen. Two assays were performed, one with AIBN (0.6 eq) and the NHC-borane (**16a**) (1.2 eq), and another using thiophenol (0.2 eq) as additive.

It was made a blank assay with the same procedure presented in 2.9.1. No reaction occurred between *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (**2**) and the NHC-borane (**16a**) (Appendix 21).

The intramolecular radical cyclization product, 8,9-dimethoxyphenanthridine (**18**), was obtained in both reactions and it was confirmed by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. The protons corresponding to the methoxyl group are presented at high field, at 4.08 and 4.15 ppm in ^{1}H NMR spectra, and at 56.32 and 56.40 ppm in the ^{13}C NMR spectra. The aromatic protons H7 and H10 are represented by the singlets at 7.37 and 7.89 ppm, respectively. The triplet doublet at 7.68 ppm (J = 19.7/7.1 Hz) corresponds to the H2 and H3, and the doublets at 8.18 and 8.46 ppm (J = 8.0 Hz) correspond to H4 and H1, respectively. The most deshielded proton is the H6, being found at 9.16 ppm. In the ^{13}C NMR spectra the aromatic protons are found from 102.00 to 153.53 ppm, being in accordance with the literature.[87] In the IR spectrum are seen a band at 2956 cm^{-1} that corresponds to the aromatic C-H bonds, and a band at 3071 cm^{-1} corresponding to the C=N stretching. The proposed reaction mechanism is the same presented in Figure 2.15. (Appendix 22)



18

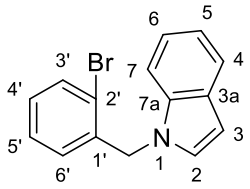
The yield obtained in the reaction without thiophenol was 34 %, and was recovered 64 % of **2**. In the reaction with thiophenol the yield was 8 % and 76 % of **2** was recovered.

Again, the yields were below expectations, and a lot of starting material were recovered. It was not possible to understand again why the yield of the thiophenol catalysed reactions were lower. No reduction product was detected (substitution of bromine by hydrogen).

2.9.3 Using *N*-(2'-bromobenzyl)-2,3-dihydroindole (3) as a substrate

Trying to understand better the role of the nitrogen atom, a reaction was performed with *N*-(2'-bromobenzyl)-2,3-dihydroindole (**3**). The reaction's procedures was the same as the above reactions, having been made one reaction with thiophenol (0.2 eq) and another without this additive. In both reactions were used 0.6 eq of AIBN and 1.2 eq of **16a**. The cyclization product was not obtained, but 1-(2'-bromobenzyl)-1H-indole (**19**) was formed. (Appendix 23)

1-(2'-Bromobenzyl)-1H-indole (**19**) was characterized with ^{1}H NMR and IR spectroscopy. The doublet at 7.68 ppm (J = 8.0 Hz) correspond to the proton H3', being characteristic of an aromatic proton next to a bromine atom. The multiplets between 7.55 and 7.64 ppm, and between 7.22 and 7.31 ppm correspond to the protons H6' and H4', respectively. The singlet at 5.40 ppm corresponds to the benzylic carbon. The protons H5', H4, H5, H6, and H7 are represented by the multiplet between 7.09 and 7.21 ppm. The doublet at 6.60 ppm (J = 3.1 Hz) corresponds to H2, and the multiplet between 6.50 and 6.55 correspond to H3. The IR spectrum shows a band at 3055 cm^{-1} corresponding to the aromatic C-H stretching and a band at 2925 cm^{-1} of the C-H aliphatic bond (Appendix 24).[88] The mechanism proposed for the formation of **19** is presented in the Figure 2.16.



19

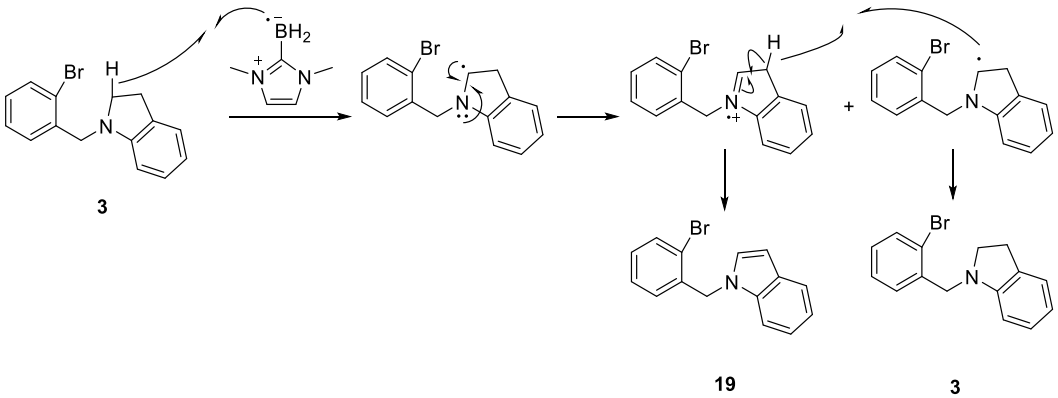


Figure 2.16 – Proposed mechanism for products observed in the radical reaction using *N*-(2'-bromobenzyl)-2,3-dihydroindole (3) as substrate.

Even after a chromatographic column, it was not possible to obtain **19** pure. So, the yields were calculated using the ^{1}H NMR spectra. Compound **19** was obtained with a yield of 28 % and

was recovered 47 % of the starting material **3**. In the reaction with thiophenol the yield was 18 % and was recovered 25 % of **3**.

In the reaction without thiophenol was also found a mixture whose ^{1}H NMR is presented in Figure 2.17. This correspond to a fraction of the chromatographic column. From the analysis of the ^{1}H NMR it can be observed on the spectra two different structures, one that correspond to compound **16a** (assigned in blue) and the other structures assigned in red that may correspond to a, by us, postulated complex between the borane compound and the product of the reaction. For this analysis accounts the two singlets at 3.73 and 6.79 ppm that have origin in the NHC-borane scaffold and are in a proportion of 1:1 with the aromatic protons at down field. At high field, between 0.69 and 2.17 ppm can be observed a set of signals that may be due to **16a** but also to the B-H present in the borane complex shown.

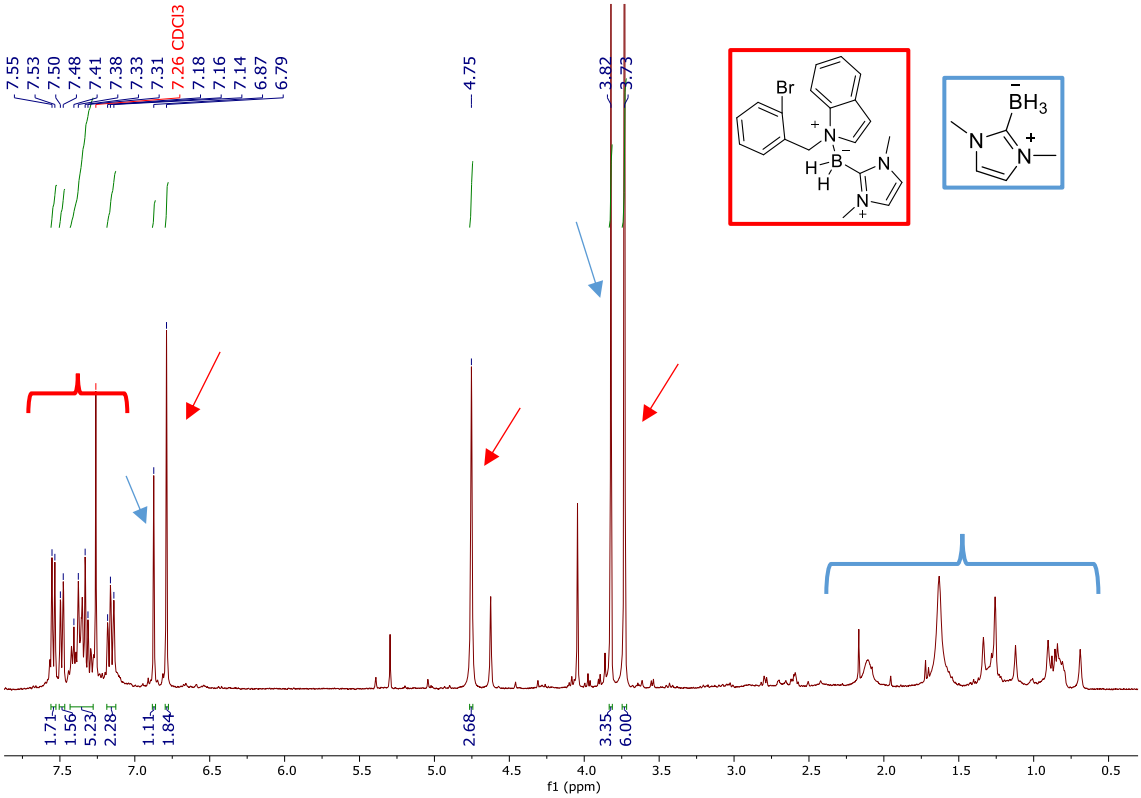


Figure 2.17 – ^{1}H NMR spectrum of the NHC-borane 16a (represented in blue) and of the complex between the borane (16a) and the reaction product (represented in red).

The formation of this adduct may be the reason why the reaction do not progress. However, it was not detected in the previous reactions. That may be due to the small amount of some fractions isolated that made the analysis unfeasible. It should also be noted that no cyclization product were obtained. The 2,3-dihydroindole group, should have some steric effect that prevent the reaction to occur. It should also be noted that, in spite of the fact that the yields were not better than in the other reactions, less starting material have been recovered.

2.9.4 Using *N*-(2'-bromobenzyl)-*N*-methylaniline (4) as a substrate

A different tertiary amine was tested and the methodology followed was the same as in the previous reactions. Therefore, *N*-(2'-bromobenzyl)-*N*-methylaniline (**4**) reacted with AIBN (0.6 eq) and the NHC-borane (**16a**) (1.2 eq), and another assay where thiophenol (0.2 eq) was joined to the reaction mixture. The reaction scheme is presented in Figure 2.18.

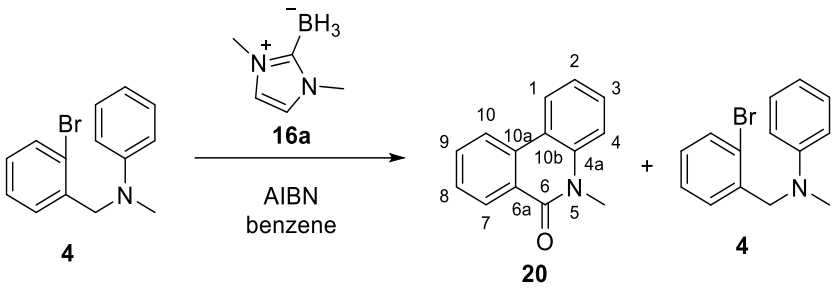


Figure 2.18 – Reaction scheme of the radical intramolecular cyclization of 4.

In both reactions was obtained the cyclization product oxidized in the benzylic carbon (5-methylphenanthridin-6(5H)-one - **20**). A band at 1647 cm^{-1} demonstrates the presence of the carbonyl group of an amide. The absence of the benzylic protons in the ^{1}H NMR spectra and the signal at 165.62 ppm, characteristic of carbonyl carbon of an amide in the ^{13}C NMR spectra also confirm the presence of this oxidized compound. The protons of the methyl group are represented by the singlet at 3.83 ppm in the ^{1}H NMR, and the respective carbon at 30.15 ppm in the ^{13}C NMR spectrum. The remaining aromatic protons of 5-methylphenanthridin-6(5H)-one (**20**) were identified between 7.34 and 8.56 ppm, with an integration for 8 protons. The data are in accordance with the literature.[89] The carbons signals on the ^{13}C NMR spectra are also in accordance with the literature, although the compound is not pure (Appendix 25). In the IR spectrum can also be seen a band at 3067 cm^{-1} corresponding to the aromatic C-H stretching. It was also made a blank assay between **4** an **16a**, like in the previous reactions. The ^{1}H NMR spectrum of the crude showed that no reaction has occurred. (Appendix 26)

The yield of the reaction catalysed with thiophenol was 8 % and in the reaction without the catalyst was 21 %.

Again, changes in the structure of the molecule do not lead to changes in reaction yields. In this case an intramolecular cyclization was possible, unlike in the reaction with the tertiary amine **3**. However, the reduction product (substitution of bromine by hydrogen) was still not detected.

2.9.5 Using *N*-(2'-bromobenzyl)-*N*-phenylacetamide (7) as a substrate

Trying to understand better the role of the nitrogen atom in these reactions, the amide **7** was used as substrate. The same methodology was used in the *N*-(2'-bromobenzyl)-*N*-phenylacetamide (**7**) radical intramolecular cyclization (Figure 2.19), and a blank assay was also made. The crude of the blank test was analysed by ^{1}H NMR, showing that no reaction had occurred. (Appendix 27)

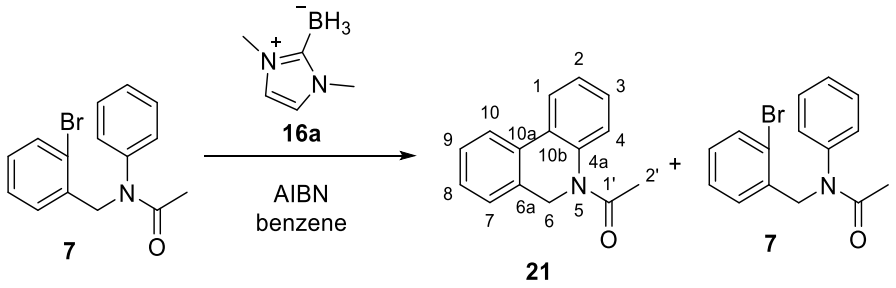


Figure 2.19 – Reaction scheme of the radical intramolecular cyclization of 7.

In the reaction with thiophenol, through ^{1}H NMR, was identified the cyclization product – 1-(phenanthridin-5(6H)-yl)ethan-1-one (**21**). The aromatic protons are founded in two set of multiplets between 7.77 and 7.82 ppm and between 7.29 and 7.38 ppm. The singlet at 5.05 ppm correspond to the H6, and the singlet at 1.94 correspond to the H2'. The signals are in accordance with those reported in the literature.[89] This compound was also identified by GC-MS with a retention time of 11.32 min (Figure 2.20 c)). In the mass spectra is found the molecular ion at *m/z* 223, and a fragmentation at *m/z* 180 (loss of CH_3CO). The other compound observed in the GC-MS spectra at 11.22 min confirm the presence of the starting material, which is in accordance

with the ^{1}H RMN (Figure 2.20 b)). Here again it was not possible to identify the reduction product (substitution of bromine by hydrogen). The molecular ion was not possible to be observed but the $[M-Br]^{+}$ at *m/z* 224 is present. The two peaks with *m/z* 169 and 171 with almost the same intensity are indicative of a fragment with bromine, which is in accordance with the cleavage of the phenylacetamide fragment. The yield of the compound **21** was 9 %. It was recovered 79 % of the starting material. (Appendix 28)

a)

b)

c)

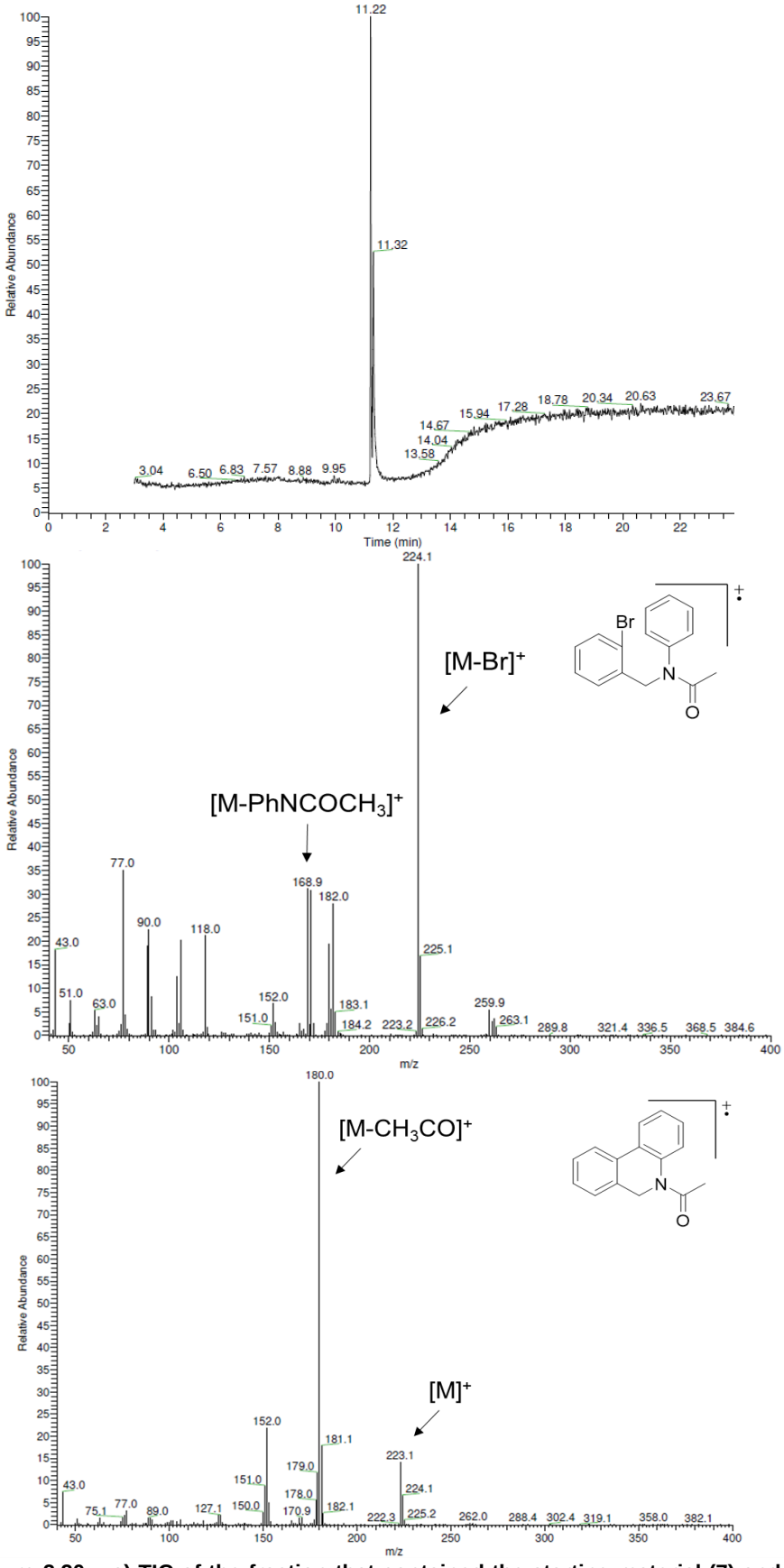


Figure 2.20 – a) TIC of the fraction that contained the starting material (7) and the cyclization product (21). b) Mass spectra of the starting material (7) at the retention time of 11.22 min. c) Mass spectra of the cyclization product (21) at the retention time of 11.32 min.

During this reaction, was also found the formation of an adduct between the NHC-borane and the thiophenol (Figure 2.21), which was identified by ^{1}H NMR and GC-MS. In the ^{1}H NMR spectrum, the presence of a doublet and two triplets at 7.36, 7.10, and 6.97 ppm respectively confirm the presence of a monosubstituted benzene ring. The singlet at 6.82 ppm corresponds to aromatic protons of the imidazole, and the two methyl groups are represented by the singlet at 3.73 ppm. Lastly, the BH_2 group protons are represented by a broad multiplet between 2.34 and 3.05 ppm. In the ^{1}H NMR spectrum can also be seen that some NHC-borane remains in this fraction. The signals of the ^{1}H NMR spectrum for the thiol-NHC-borane adduct are in accordance with the literature.[90] (Appendix 29) The analysis by GC-MS confirms the presence of the thiol-NHC-borane adduct, at 11.20 min (Figure 2.22). The molecular ion is at *m/z* 218 and the fragmentations at *m/z* 109 (thiophenol ion and NHC-borane ion), and at 77 (phenyl ion) are in accordance with the structure. It was also founded other peaks in the chromatogram at 3.97 min and 7.05 min that may arise from the instability of the compound in the conditions of analysis. Namely, the peak at 3.97 min due to thiophenol that was not identified in the ^{1}H NMR spectra. At retention time of 7.05 min a compound presenting a $[M]^+$ of *m/z* 109 and a fragmentation at *m/z* 66 (loss of BH_2 and the two methyl groups) corresponds to NHC-borane (M-H), justify the instability of the adduct.[90] This adduct was not detected in the other reactions, but it may be the reason why the reactions where it was added thiophenol had lower yields than the ones without the thiophenol.

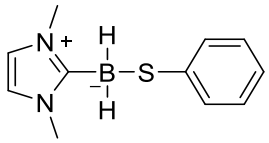


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Figure 2.21 – Structure of the adduct formed between the NHC-borane and thiophenol (22).

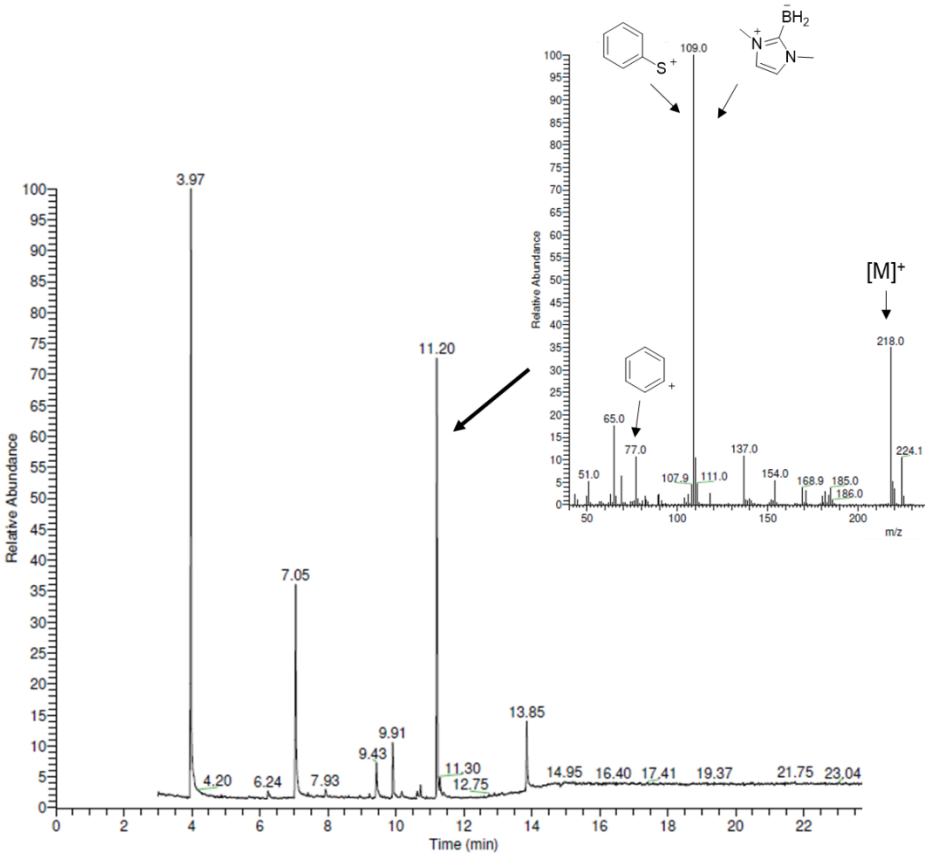


Figure 2.22 – TIC and mass spectrum of the thiol-NHC-borane adduct at retention time of 11.20 min.

In the reaction without the thiophenol, the several fractions were only analysed by ^{1}H NMR. Through the spectrum, the cyclization product (**21**) was identified, but other compound are present in a complex mixture. Comparing this spectrum with the spectrum of the reaction with thiophenol, we can see that the spectra are similar (Figure 2.23). Without any further analysis, it can be concluded that besides the cyclization compound (**21**), it is still present starting material (**7**) in the fraction. The yield of the cyclization product (**21**) was 8 %. It was recovered 80 % of the starting material.

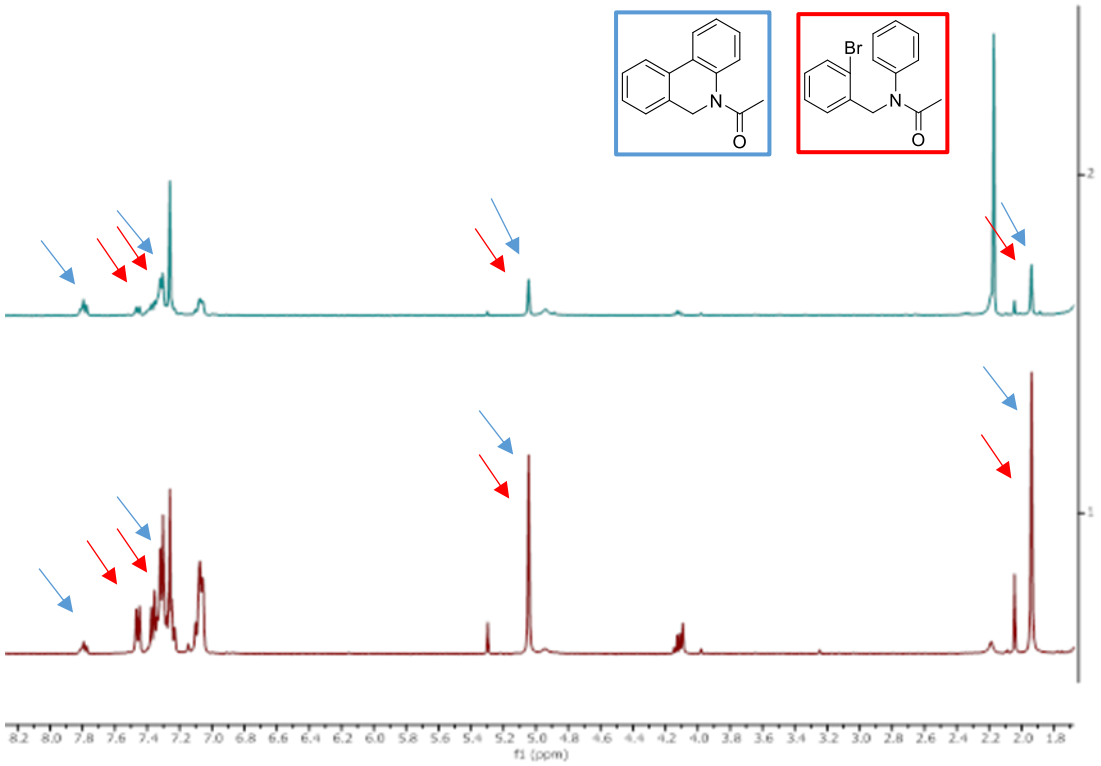


Figure 2.23 – Comparison between the spectra of the reaction with thiophenol (green) and the reaction without (red). In blue is assigned to the cyclization product (21) and in red is represented the starting material (7).

2.9.6 Using 1-bromo-2-(phenoxymethyl)benzene (8) as a substrate

Lastly, the radical reaction was performed using an ether (**8**). The heteroatom has been changed to see the influence of the different heteroatoms in the reaction. The reaction with 1-bromo-2-(phenoxymethyl)benzene (**8**) was performed with AIBN and the NHC-borane (**16a**). The reaction stayed overnight and was stopped when no NHC-borane (**16a**) was present in the reaction (followed by TLC). Despite the NHC-borane (**16a**) has all been consumed, the reaction's TLC does not show an evolution of the reaction. Thus the reaction's crude was analysed through ^{1}H NMR spectroscopy. The ^{1}H NMR showed that was only present the starting material, meaning that no reaction occurred. Since the NHC-borane was consumed and the ^{1}H NMR spectrum only showed the presence of the starting material, a proposed mechanism is presented in Figure 2.24.

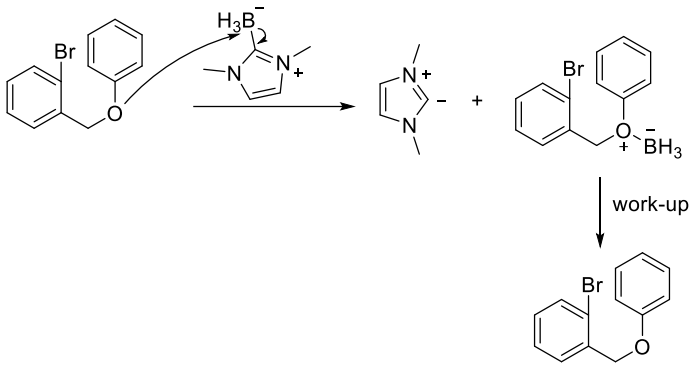


Figure 2.24 – Proposed mechanism for the radical reaction with 1-bromo-2-(phenoxymethyl)benzene (8).

A reaction using thiophenol was not performed.

The interaction of the NHC-borane with the oxygen atom looks to be stronger as a result of a better sobreposition of the oxygen lone pair with the boron empty π orbital and also due to a good leaving group, the NHC.

The obtained result of this reactions is very interesting, since Pan *et al.*[56] reported, in 2012, the 5-exo-trig radical cyclization of *O*-allyl-2-bromophenol (Figure 2.25) with 83 % yield. The radical initiator used is different of the ones tested in this dissertation, as well as the thiol. In further studies, it would be interesting to make a reaction using 1-bromo-2-(phenoxymethyl)benzene (**8**) as a substrate, but with TBHN and TDT.

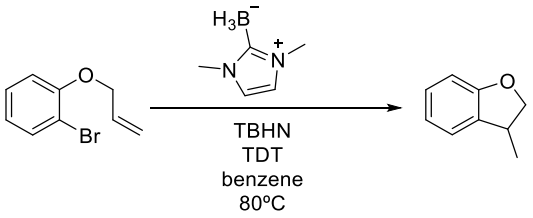


Figure 2.25 – Radical cyclization of *O*-allyl-2-bromophenol using (1,3-dimethylimidazolium-2-yl)trihydroborate, TBHN, and *tert*-dodecanethiol (TDT).[56]

3. CONCLUSIONS

In order to perform radical reactions with the main goal of synthesizing heterocyclic compounds, several bromo aryl substrates were successfully synthesized, namely two secondary amines, two tertiary amines, an amide, and an ether. Attempts were made to synthetize a free heteroatom substrate, but without success.

The reaction between 1-metilimidazolium and different haloalkanes has given rise to four different imidazolium salts. To attain the N-heterocyclic carbene-boranes compounds, the imidazolium salts reacted with sodium borohydride which works as base and borane source. From the four different imidazolium salts, only two NHC-boranes were synthetized – the (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**) and the (3-ethyl-1-methylimidazolium-2-yl)trihydroborate (**16b**).

The bromo aryl substrates were subject to radical cyclizations using the synthetized NHC-boranes as radical propagators. Most of the cyclization products were obtained, although in low yields. The reaction optimization was not successful, despite all attempts. It were tested several solvent preparations methods like, drying with sieves, freeze drying through vacuum and N_2 cycles, and drying with sodium wire. The last seem to be the most appropriated one, but the differences observed were few. Two different radical initiators were also tested – AIBN and DTBP. Between the two radical initiators AIBN showed better yields being the chosen one. The two synthetized NHC-boranes were also tested but no difference was seen between them. Substrates with different functional groups were tested although the obtained results did not change significantly. In the reaction with *N*-(2'-bromobenzyl)-2,3-dihydroindole (**3**) as a substrate, no cyclization product was formed. The obtained product was 1-(2'-bromobenzyl)-1H-indole (**19**), and a complex between the (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**) and the reaction product **19** was identified. Even though this complex was not identified in any other reaction, it may be the cause for the low yields observed in all the reactions – the ability of the NHC-borane to coordinate with heteroatoms. In the reaction with 1-bromo-2-(phenoxymethyl)benzene (**8**), the cyclization product was not obtained, but a reaction took placed since it was observed consume of the NHC-borane (**16a**). But, surprisingly, at the end of the reaction only the starting material, **8**, could be observed with recovery of the imidazolium salt (**15a**). The formation of a complex between the 1-bromo-2-(phenoxymethyl)benzene (**8**) and the NHC-borane may explain the result observed. It should be noted that no reduction products (substitution of bromine by hydrogen) were detected, at least in amounts that could be detected by us using ^{1}H NMR spectroscopy. That could indicate an inability for the NHC-borane to remove the bromine atom from the substrate, since recurrently considerable amounts of starting materials were recovered during these reactions.

It was reported in the literature that the addition of thiophenol to the reactions would increase the hydrogen transference process. In contrast to what is reported in the literature, the radical reactions with thiophenol made in this dissertation had even lower yields than the reactions without. An adduct between the thiophenol and the NHC-borane was identified in one of the reactions. The formation of this adduct may be the motive for the low yields in these reactions.

Few radical cyclization reactions using NHC-carbenes are reported in the literature, but the ones reported have good yields. So, it was not very clear why the reactions reported in these work were unsuccessful. Future work could be directed to the use of TBHN as radical mediator and TDT as thiol.

4. EXPERIMENTAL SECTION

4.1 PREAMBLE

All reagents and solvents used during this work were commercially acquired and used without further purification. The solvents were dried according to the literature procedures[91], except for benzene which has been dried with sodium wire.

All the reactions were followed by thin-layer chromatography (TLC) on Merck Kieselgel GF 254 silica plates supported in aluminium with a thickness of 0.2 mm. Their revelation was made using ultraviolet (UV) light at 254 and/or 366 nm and different TLCs visualization reagents when needed.

When needed, the reactions' crude was purified with flash column chromatography with Merck Kieselgel 60 silica (230 – 400 mesh). There were also used preparative chromatography for the purification of the compounds. In this case, was used Merck Kieselgel GF 254 silica plates supported in aluminium with a thickness of 0.2 mm or supported in a glass with a thickness of 0.5 or 1.0 mm.

The synthesized products were analysed with Nuclear Magnetic Resonance (NMR) spectroscopy, being used the Bruker Avance III 400 MHz spectrometer. ^{1}H NMR, ^{13}C NMR, and ^{11}B NMR spectra were recorded at 400, 101, and 128 MHz, respectively. Deuterated chloroform ($CDCl_3$) and deuterium oxide (D_2O) were used as solvents. Their chemical shifts were used as reference. The NMR signals were presented in the following order: deuterated solvent, chemical shift (δ, in ppm), signal multiplicity (s – singlet, d – doublet, t – triplet, q – quartet and m - multiplet), coupling constant (J, in Hz), the relative intensity of each signal (nH, where n is the number of protons) and the corresponding position in the molecule (Hx, where x is the carbon number).

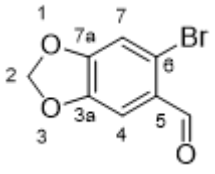
The compounds were also analysed through infrared spectroscopy (Perkin Elmer, Spectrum Two spectrophotometer) equipped with attenuated total reflectance (ATR). The description shows the more significant frequencies. The spectra description follows the following layout: sample support, maximum absorption frequency (ν_{max}, in cm^{-1}), and the corresponding functional group.

The gas chromatography–mass spectrometry (GC-MS) was acquired in an Agitent 6890N chromatographer coupled with a Thermo DSQ mass spectrometer. The chromatographic conditions were the following: DB5 column, 30 m of length, 0.25 mm of diameter, 0.25 µm of film; temperature injector of 250 ºC, temperature program: 40 ºC, 20 ºC/min until 320 ºC; split ratio: 5:1 or 30:1; 1 mL/min flow rate; 5 µL of injected sample.

4.2 BENZALDEHYDES BROMINATION

4.2.1 6-Bromopiperonal (5)

In a round bottom flask, it was added 0.5109 g (3.40 mmol, 1 eq) of piperonal in 3 mL of glacial AcOH. The reaction was stirred for five minutes and then, Br_2 was added dropwise (0.16 mL, 3.12 mmol, 1 eq). The reaction remained stirring for several days. To speed up the reaction it were added three portions of 0.16 mL of Br_2 and 1.9 mL of glacial AcOH, for 7 days, until the piperonal is all consumed.



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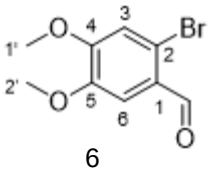
To remove the bromine still present in the reaction, a saturated solution of $Na_2S_2O_3$ was added until the orange colour disappears. Then extractions with DCM were made. Lastly, the organic fractions were washed with a 10 % solution of Na_2CO_3 and then with brine, followed by drying with sodium sulphate anhydrous and solvent removal. The recrystallization in EtOH afforded the product as white needles with a yield of 57 %. **IR (ATR) ν_{max} (cm^{-1}):** 3093 (C-H Ar), 2866 (C-H aliphatic), 1670 (C=O). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 10.18 (s, 1H, CHO), 7.36 (s, 1H, H4), 7.06 (s, 1H, H7), 6.08 (s, 2H, H2). (Appendix 1)

4.2.2 2-Bromo-4,5-dimethoxybenzaldehyde (6)

In a round bottom flask, equipped with a magnetic stirrer, it was added 493.60 mg of veratraldehyde (2.97 mmol, 1 eq) and 10 mL of MeOH. The reaction was kept at room temperature. During 15 minutes, it was added Br_2 dropwise (0.16 mL, 3.12 mmol, 1 eq). Stirring

was maintained for 4 days, until the TLC did not show the presence of veratraldehyde. It was added more 0.18 mL of Br_2 to favour the reaction.


6

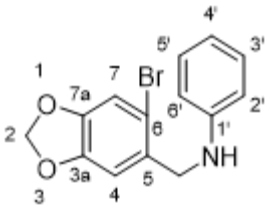
After the end of the reaction, a saturated solution of $Na_2S_2O_3$ was joined to the reaction mixture until the orange colour disappear. Then, the methanol present in the solution was evaporated and extractions were made with the aqueous residue and DCM. The organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. Recrystallization was made in 2-propanol and it affords white needles of 2-bromo-4,5-dimethoxybenzaldehyde in 56 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3009 (C-H Ar), 2866 (C-H aliphatic), 1667 (C=O). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 10.18 (s, 1H, CHO), 7.41 (s, 1H, H6), 7.05 (s, 1H, H3), 3.96 (s, 3H, H2'), 3.92 (s, 3H, H1'). (Appendix 2)

4.3 SYNTHESIS OF BROMOBENZYL DERIVATIVES

4.3.1 General Procedure for the synthesis of *N*-(bromobenzyl)anilines

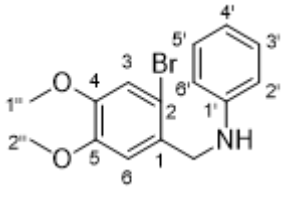
Schiff base formation and their reduction were performed *in situ*. Thus, aniline (1.3 eq) and bromobenzaldehyde (1 eq) were placed in a round bottom flask with EtOH. The reaction was heated under reflux for 30 minutes. After that time, 5 equivalents $NaBH_4$ were added. Stirring was maintained for 1 hour. Water was added to the reaction mixture and extractions with DCM were made. The organic phase was dry with anhydrous Na_2SO_4. Then, it was filtered and dried till dryness.

4.3.1.1 N-(2-Bromo-4,5-methylenedioxybenzyl)aniline synthesis (1)


1

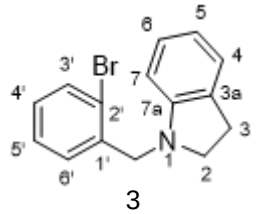
Following the procedure described in 4.3.1, and starting with bromobenzaldehyde (311.70 mg, 1.36 mmol), and aniline (0.16 mL, 1.77 mmol, 1.30 eq) in 1 mL of EtOH it was added 257 mg of $NaBH_4$ (6.80 mmol, 5 eq). *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline was obtained as a yellow solid in 59 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3377 (N-H), 3002 (C-H Ar), 2969 (C-H aliphatic). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.18 (t, J = 7.4 Hz, 2H, H3'/H5'), 7.02 (s, 1H, H7), 6.93 (s, 1H, H4), 6.74 (t, J = 7.3 Hz, 1H, H4'), 6.63 (d, J = 7.8 Hz, 2H, H2'/H6'), 5.94 (s, 2H, H2), 4.31 (s, 2H, CH_2N). (Appendix 3)

4.3.1.2 N-(2-Bromo-4,5-dimethoxybenzyl)aniline synthesis (2)


2

Following the procedure described in 4.3.1, and starting with 409.50 mg of bromobenzaldehyde (1.67 mmol), and 0.2 mL of aniline (2.17 mmol, 1.3 eq) in 1 mL of EtOH it was added 318 mg of $NaBH_4$ (8.35 mmol, 5 eq). The product was obtained as a yellow solid in 81 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3424 (N-H), 3100 (C-H Ar), 2900 (C-H aliphatic). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.18 (td, J = 7.4, 1.9 Hz, 2H, H3'/H5'), 7.03 (s, 1H, H3), 6.99 (s, 1H, H6), 6.77 (t, J = 7.3 Hz, 1H, H4'), 6.68 (d, J = 7.7 Hz, 2H, H2'/H6'), 4.34 (s, 2H, CH_2N), 3.86 (s, 3H, H1''), 3.79 (s, 3H, H2''). (Appendix 4)

4.3.2 *N*-(2'-Bromobenzyl)-2,3-dihydroindole synthesis (3)


3

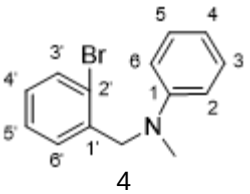
A solution of 2,3-dihydroindole (0.45 mL, 4.0 mmol, 2 eq) in 2 mL of dry ethyl ether, was cooled in an ice bath. It was slowly added a solution of 2-bromobenzyl bromide (0.494 mg, 2.0 mmol, 1 eq) in 2 mL of ethyl ether. The reaction remains stirring at room temperature overnight. The formed precipitate was removed from the reaction mixture by filtration. The solvent was evaporated and the obtained solid was purified by flash column chromatography and light brown oil was achieved in 88 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3050 (C-H Ar), 2922 (C-H aliphatic). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.58 (d, J = 7.9 Hz, 1H, H3'), 7.47 (d, J = 7.6 Hz, 1H, H6'), 7.31 – 7.25 (m, 1H, H4'), 7.17 – 7.11 (m, 2H, H5'/H7), 7.06 (t, J = 7.6 Hz, 1H, H5), 6.71 (t, J = 7.3 Hz, 1H, H6), 6.46 (d, J = 7.8 Hz, 1H, H4), 4.33 (s, 2H, CH_2N), 3.45 (t, J = 8.3 Hz, 2H, H2), 3.04 (t, J = 8.3 Hz, 2H, H3). (Appendix 5)

4.3.3 General Procedure for the synthesis of *N*-(bromobenzyl)-*N*-methylaniline derivatives

To a solution of 0.25 M of *N*-methylaniline, or similar, in *N*,*N*-dimethylformamide (DMF) under an inert atmosphere and at 0 ºC, it was added 1.2 equivalents of NaH portion-wise and the reaction remains stirring for 5 minutes. Then, a solution of 1.1 equivalents of 2-bromobenzyl bromide in DMF was added dropwise to the reaction at 0 ºC. After the addition of the benzylbromide solution, the reaction mixture remained stirring for 2 hours at rt.

After all the starting material has been consumed, the reaction mixture was quenched with saturated NH_4Cl and ethyl acetate (EtOAc) was added. Extractions with water were made. The organic phase was dried with anhydrous Na_2SO_4, filtrated, and dried till dryness.

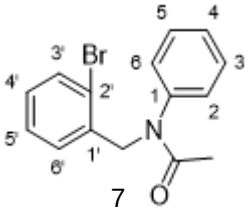
4.3.3.1 N-(2'-Bromobenzyl)-N-methylaniline synthesis (4)



4

Following the procedure described in 4.3.3, and starting with *N*-methylaniline (0.4 mL, 3.69 mmol) in 16 mL of DMF, it was added NaH (110.60 mg, 4.61 mmol, 1.2 eq). Then a solution of 2-bromobenzyl bromide (1.033 g, 4.13 mmol, 1.1 eq) in 1.5 mL of DMF was added to the reaction mixture. The product was obtained as a yellow oil in 59 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3060 (C-H Ar), 2924 (C-H aliphatic). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.62 (d, J = 7.8 Hz, 1H, H3'), 7.26 (t, J = 8.0 Hz, 3H, H4'/H5'/H6'), 7.21 – 7.13 (m, 2H, H5/H3), 6.76 (t, J = 7.3 Hz, 1H, H4), 6.71 (d, J = 8.1 Hz, 2H, H2/H6), 4.59 (s, 2H, CH_2N), 3.13 (s, 3H, CH_3). (Appendix 6)

4.3.3.2 N-(2'-Bromobenzyl)-N-phenylacetamide (7)

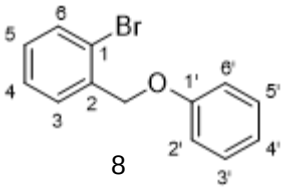


7

Following the procedure described in 4.3.3, and starting with 297 mg of acetanilide (2.20 mmol) in 5 mL of DMF, 66.18 mg of NaH (2.76 mmol, 1.2 eq) were then added. A solution of 2-bromobenzyl bromide (632 mg, 2.53 mmol, 1.1 eq) in 2 mL of DMF was added to the reaction mixture. The product was obtained as a yellow oil in 67 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3061 (C-H Ar), 2971 (C-H aliphatic), 1657 (C=O). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.46 (d, J = 7.9 Hz, 1H, H3'), 7.39 – 7.21 (m, 5H, H4'/H5'/H6'/H3/H5), 7.11 – 7.03 (m, 3H, H2/H4/H6), 5.04 (s, 2H, CH_2N), 1.94 (s, 3H, CH_3). (Appendix 7)

4.4 ETHER SYNTHESIS

4.4.1 1-Bromo-2-(phenoxymethyl)benzene synthesis (8)



8

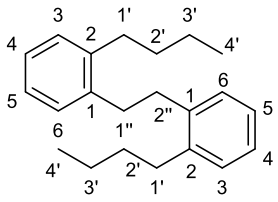
In 15 mL of acetone, it was dissolved 0.495 g of 2-bromobenzyl bromide (1 eq, 1.98 mmol), 1.402 g of potassium carbonate (5 eq, 10.14 mmol) and 1.032 g of phenol (5 eq, 10.97 mmol). The reaction stays under reflux overnight. The solvent was removed by reduced pressure. Then, the crude was dissolved in water, and extractions were made with diethyl ether. The organic layer was washed with a 10 % solution of NaOH, followed by another wash with water. Finally, the organic phase were dried with sodium sulphate, filtrated, and evaporated until dryness. The crude was purified with a chromatographic column and was obtained in the form of a colourless oil with a 90 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3061 (C-H Ar), 2970 (C-H aliphatic). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.61 – 7.55 (m, 2H, H4/H6), 7.37 – 7.29 (m, 3H, Ar-H), 7.22 – 7.17 (m, 1H, Ar-H), 7.03 – 6.97 (m, 3H, H2'/H4'/H6'), 5.15 (s, 2H, CH_2O). (Appendix 8)

4.5 ETHANE-BRIDGE COMPOUNDS SYNTHESIS

4.5.1 First Method

A solution of 493 mg of 2-bromobenzyl bromide (1 eq, 1.97 mmol) in 13 mL of THF was cooled to -100 ºC. n-BuLi (1 eq, 0.93 M, 1.97 mmol) was added dropwise to the reaction mixture. The reaction remained at -100 ºC for 1 hour and at rt overnight.

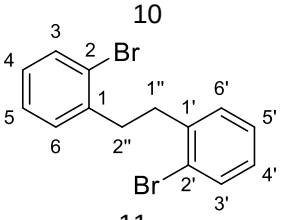
It was added 10 mL of a 0.1 M solution of HCl and the THF was evaporated. Extractions with diethyl ether were made. The organic phase was dried with anhydrous Na_2SO_4, filtrated, and dried till dryness. It was obtained a yellow oil which was purified by flash column chromatography. After purification 1,2-bis(2-butylphenyl)ethane (**10**) was obtained with 12 % yield. **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.33 – 7.21 (m, 8H, Ar-H), 2.77 – 2.70 (m, 4H, H1''/H2''), 1.73 – 1.61 (m, 6H, H1'/H2'/H3'), 1.57 – 1.43 (m, 6H, H1'/H2'/H3'), 1.04 (t, J = 7.3 Hz, 6H, H4'). (Appendix 9)



10

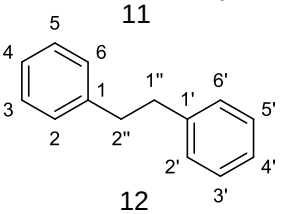
It was also obtained a fraction with a mixture of 1,2-bis(2-bromophenyl)ethane (**11**) and 1,2-diphenylethane (**12**).

1,2-Bis(2-bromophenyl)ethane (**11**) – **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.61 (d, J = 8.0 Hz, 2H, H3/H3'), 7.32 – 7.22 (m, 4H, Ar-H), 7.17 – 7.11 (m, 2H, Ar-H), 3.10 (s, 4H, H1''/H2''). (Appendix 10)



11

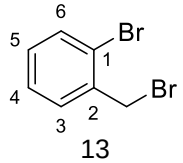
1,2-Diphenylethane (**12**) – **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.38 – 7.20 (m, 10H, Ar-H), 2.99 (s, 4H, H1''/H2''). (Appendix 11)



12

4.5.2 Second Method

A solution of 498 mg of 2-bromobenzyl bromide (1 eq, 1.99 mmol) in 13 mL of THF was cooled to -100 ºC. n-BuLi (1 eq, 1.48 M, 1.99 mmol) was added dropwise to the reaction mixture. The reaction remained at -100 ºC for 1 hour and was left to heat up to rt.



13

It was added 10 mL of a 0.1 M solution of HCl and the THF was evaporated. Extractions with diethyl ether were made. The organic phase was dried with anhydrous Na_2SO_4, filtrated, and dried till dryness. It was obtained a colourless oil which was purified by flash column chromatography. After purification 1,2-bis(2-butylphenyl)ethane (**10**) was obtained with 21 % yield. (Appendix 9)

It was also obtained 1,2-diphenylethane (**12**) with a yield of 68 %. (Appendix 11)

4.5.3 Third Method

Benzyl bromide (0.2 mL, 1.68 mmol, 1 eq) were dissolved in 5 mL of THF. The solution was cooled to -100 ºC. n-BuLi (1 eq, 1.6 M, 1.68 mmol) was added dropwise to the reaction mixture. A solution of 2-bromobenzyl bromide (432 mg, 1.73 mmol, 1 eq) in 10 mL of THF was added dropwise. The reaction remained at -78 ºC for 1 hour and, was left to heat up to rt.

It was added 10 mL of a 0.1 M solution of HCl and the THF was evaporated. Extractions with diethyl ether were made. The organic phase was dried with anhydrous Na_2SO_4, filtrated, and dried till dryness. It was obtained a colourless oil which was purified by flash column chromatography. After purification it was obtained 1,2-diphenylethane (**12**) with 66 % yield. (Appendix 11)

It was recovered 68 % of the starting material 2-bromobenzyl bromide (**13**). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.58 (d, J = 8.0 Hz, 1H, H6), 7.46 (d, J = 7.6 Hz, 1H, H3), 7.30 (t, J = 7.5 Hz, 1H, H5), 7.17 (t, J = 7.7 Hz, 1H, H4), 4.61 (s, 2H, CH_2). (Appendix 12)

4.5.4 Fourth Method

A round bottom flask with 5 mL of THF was cooled to -90 ºC. n-BuLi (1.1 eq, 1.6 M, 1.85 mmol) was added to the reaction mixture. A solution of benzyl bromide (0.2 mL, 1.68 mmol, 1 eq) in 5 mL of THF was joined to the reaction mixture. After 15 min, a solution of 2-bromobenzyl bromide (448 mg, 1.79 mmol, 1 eq) in 0.5 mL of THF was added. The reaction remained at -90 ºC for 1 hour and was left to heat up to rt.

It was added 10 mL of a 0.1 M solution of HCl and the THF was evaporated. Extractions with diethyl ether were made. The organic phase was dried with anhydrous Na_2SO_4, filtrated, and dried till dryness. It was obtained a colourless oil which was purified by flash column chromatography.

Despite purification it was obtained a mixture of 1,2-diphenylethane (**12**) and 2-bromobenzyl bromide (**13**). (Appendix 11 and Appendix 12)

4.5.5 Fifth Method

A solution of 260 mg of 2-bromobenzyl bromide (1.04 mmol, 1 eq), 0.1 mL of benzyl bromide (0.84 mmol, 1 eq), and 5 mL of THF were cooled to -90 ºC. n-BuLi (1 eq, 1.6 M, 0.84 mmol) was added dropwise to the reaction mixture. The reaction remained at -90 ºC for 1 hour and, was left to heat up to rt.

It was added 10 mL of a 0.1 M solution of HCl and the THF was evaporated. Extractions with diethyl ether were made. The organic phase was dried with anhydrous Na_2SO_4, filtrated, and dried till dryness. It was obtained a colourless oil which was purified by flash column chromatography. After purification it was obtained 1,2-bis(2-bromophenyl)ethane (**11**) with a yield of 22 %. (Appendix 10)

It was also obtained a fractions with a mixture of 1,2-bis(2-bromophenyl)ethane (**11**), 1,2-diphenylethane (**12**), and 2-bromobenzyl bromide (**13**). (Appendix 10, Appendix 11, and Appendix 12)

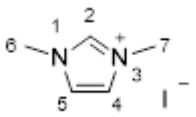
4.6 IMIDAZOLIUM SALTS SYNTHESIS

4.6.1 General Procedure

A solution of 5 M of the imidazole in DCM is placed in a round bottom flask. 1.2 equivalents of the respective haloalkane are slowly added to the solution. The reaction was followed by TLC and remain stirring until the imidazole were all consumed.

The solvent was evaporated until dryness and the compound was washed three times with ethyl acetate or diethyl ether. After that, it was dried under vacuum, which allows obtaining the imidazolium salt.

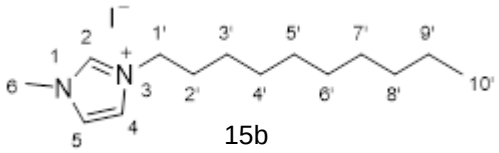
4.6.1.1 1,3-Dimethylimidazolium Iodine Synthesis (15a)



15a

Following the procedure described in 4.6.1, 0.2 mL of 1-methylimidazole (2.51 mmol) were diluted in 0.5 mL of DCM, and was added 0.18 mL of iodomethane (2.88 mmol, 1.2 eq). The product was obtained as a yellow solid in 90 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3068 (C-H Ar), 2939 (C-H aliphatic), 1574 (C=N). **^{1}H NMR (400 MHz, D_2O) δ (ppm):** 8.67 (s, 1H, H2), 7.43 (s, 2H, H4/H5), 3.91 (s, 6H, H6/H7). (Appendix 13)

4.6.1.2 3-Decyl-1-methylimidazolium Iodine Synthesis (15b)

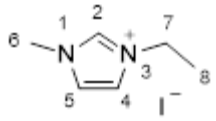


15b

Following the procedure described in 4.6.1, and starting with 0.2 mL of 1-methylimidazole (2.51 mmol) in 0.5 mL of DCM, it was added 0.6 mL of decyl iodine (3.01 mmol). The reaction remained stirring for 24 hours. The salt was obtained as a yellow oil with an yield of 53 %. **IR (ATR) ν_{max} (cm^{-1}):** 3086 (C-H Ar), 2921 (C-H aliphatic), 1571 (C=N). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 10.10 (s, 1H, H2), 7.46 (s, 1H, H4), 7.35 (s, 1H, H5), 4.30 (t, *J* = 7.5 Hz, 2H, H1'), 4.11 (s, 3H, H6), 1.96 – 1.87 (m, 2H, H2'), 1.38 – 1.18 (m, 14H, H3'/H4'/H5'/H6'/H7'/H8'/H9'), 0.86 (t, *J* = 6.8 Hz, 3H, H10'). (Appendix 14)

4.6.2 3-Ethyl-1-methylimidazolium Iodine Synthesis (15c)

Diethyl ether (2 mL) and 1-methylimidazole (0.6 mL, 7.53 mmol) were placed in a round bottom flask, under N_2 atmosphere. Iodoethane (0.7 mL, 9.03 mmol, 1.2 eq) was slowly added to the reaction mixture and the reaction remained stirring overnight, at room temperature for 2 days. More 3.2 eq of iodoethane were added until all 1-methylimidazole was consumed.



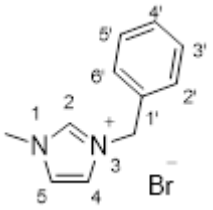
15c

The solvent was evaporated until dryness and the compound was washed three times with diethyl ether. After that, it was dried under vacuum,

and the imidazolium salt was obtained as a white solid with a 97 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3081 (C-H Ar), 2967 (C-H aliphatic), 1567 (C=N). **^{1}H NMR (400 MHz, D_2O) δ (ppm):** 8.72 (s, 1H, H2), 7.49 (s,1H, H4/H5), 7.43 (s, 1H, H4/H5), 4.24 (q, J = 7.3 Hz, 2H, H7), 3.90 (s, 3H, H6), 1.51 (t, J = 7.3 Hz, 3H, H8). (Appendix 15)

4.6.3 3-Benzyl-1-methylimidazolium Bromide Synthesis (15d)

In a round-bottom flask, 1-methylimidazole (0.5 mL, 6.27 mmol, 1 eq) and benzyl bromide (0.8 mL, 6.27 mmol, 1 eq) were placed in 5 mL of toluene. The reaction remained under reflux for 2 hours. The formation of a yellow oil is observed and the toluene was separated from the oil and the oil has been washed with toluene three times, enabling the product as a pale yellow oil, with a yield of 90 %. **IR (ATR) ν_{max} (cm^{-1}):** 3086 (C-H Ar), 1563 (C=N). **^{1}H RMN (400 MHz, $CDCl_3$) δ (ppm):** 10.47 (s, 1H, H2), 7.48 – 7.45 (m, 2H, H3'/H5'), 7.40 - 7.35 (m, 4H, H2'/H3'/H6'/H4/5), 7.29 (s, 1H, H4/5), 5.57 (s, 2H, CH_2), 4.06 (s, 3H, CH_3). (Appendix 16)



15d

4.7 NHC-BORANE SYNTHESIS

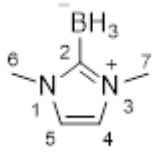
4.7.1 General Procedure

The imidazolium salt was placed in a round-bottom flask with toluene. Then was added $NaBH_4$ (1.2 – 2 eq). The reaction remained under reflux for 18 hours and was followed by TLC. The reaction's work-up was different for the two synthetized molecules.

4.7.1.1 (1,3-Dimethylimidazolium-2-yl)trihydroborate (16a)

Following the procedure described in 4.7.1, and starting with 200.20 mg of 1,3-dimethylimidazolium iodine (0.89 mmol) in 3 mL of toluene, it was added $NaBH_4$ (67.61 mg, 1.79 mmol, 2 eq).

As soon as the reaction end, the reactional mixture is passed through a pad of silica. The remaining residue was washed with ethyl acetate, passed through the previous pad of silica and evaporated to dryness. The compound was purified by a chromatographic column, and is obtained as a white solid with a 56 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3130 (C-H Ar), 3119 (C-H aliphatic), 2269 (B-H), 1476 (C=N). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 6.79 (s, 2H, H4/H5), 3.73 (s, 6H, H6/H7), 1.36 – 0.65 (m, 3H, BH_3). **^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm):** 120.03 (CH4/CH5), 36.07 (CH_3-6/CH_3-7). **^{11}B NMR (128 MHz, $CDCl_3$) δ (ppm):** -37.49 (q, J = 86.5 Hz, BH_3). (Appendix 17)

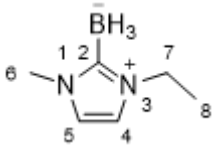


16a

4.7.1.2 (3-Ethyl-1-methylimidazolium-2-yl)trihydroborate (16b)

Following the procedure described in 4.7.1, and starting with 3-ethyl-1-methylimidazolium iodine (496.0 mg, 2.08 mmol) in 15 mL of toluene, it was added $NaBH_4$ (1.2 eq, 105.3 mg, 2.78 mmol).

The reaction's crude was purified through a chromatographic column. As eluent was used DCM/MeOH 1%. (3-Ethyl-1-methylimidazolium-2-yl)trihydroborate was obtained as a colourless liquid with a 17 % yield. **IR (ATR) ν_{max} (cm^{-1}):** 3131 (C-H Ar), 2982 (C-H aliphatic), 2275 (B-H), 1475 (C=N). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 6.81 (d, *J* = 8.8 Hz, 2H, H4/H5), 4.14 (q, *J* = 7.2 Hz, 2H, H7), 3.71 (s, 3H, H6), 1.36 (t, *J* = 7.2 Hz, 3H, H8), 1.33 – 0.65 (m, 3H, BH_3). **^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm):** 171.79 – 170.57 (C-2), 120.22 (CH-4/5), 118.19 (CH-4/5), 43.75 (CH_2-7), 35.81 (CH_3-6), 15.47 (CH_3-8). (Appendix 18)



16b

4.8 RADICAL CYCLIZATION REACTIONS

4.8.1 General Procedure

In a two-neck round bottom flask, the respective substrate was placed with the respective NHC-borane (1.2 eq) with a magnetic stirrer under N_2 atmosphere. Dried benzene was added to the reaction mixture and it was heated to reflux. AIBN (0.6 eq) was diluted in dried benzene and

it was placed in a 50 cc syringe. The syringe is placed in an automatic injector, allowing the AIBN to be added slowly overnight. When NHC-borane was still present in the reaction mixture 0.4 eq of AIBN were added to consume all the borane. After all the NHC-borane was consumed, the reaction was stopped being the reaction mixture evaporated till dryness. The crude was then purified by flash column chromatography.

4.8.2 General Procedure with thiophenol as additive

Following the same procedure as described in 4.8.1, it was added thiophenol (0.2 eq) to the reaction mixture of substrate and NHC-borane.

4.8.3 General Procedure for blank assays

For the blank assays the substrate and the NHC-borane (1.2 eq) were joined in a round-bottom flask with distilled benzene. The reaction remained under reflux overnight. The reaction mixture was dried under vacuum.

4.8.3.1 Using N-(2-bromo-4,5-methylenedioxybenzyl)aniline (1) as a substrate

As described in 4.8.1 and in 4.8.2, 49.9 mg of *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (**1**) were mixed with 29.0 mg of NHC-borane (**16a** or **16b**), and 22.5 mg of AIBN slowly added during 17 h. Whenever specified in Table 4.1 thiophenol, was joined (4 µL) to the reaction mixture. [1,3]Dioxolo[4,5-j]phenanthridine (**17**) was obtained as a yellow solid after purification. **IR (ATR) ν_{max} (cm^{-1})**: 3044 (C-H aromatic), 1464 (C=N). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)**: 9.01 (s, 1H, H6), 8.30 (d, J = 8.1 Hz, 1H, H1), 8.07 (d, J = 8.1 Hz, 1H, H4), 7.83 (s, 1H, H11), 7.61 (t, J = 7.6 Hz, 1H, H3), 7.55 (t, J = 7.5 Hz, 1H, H2), 7.17 (s, 1H, H7), 6.09 (s, 2H, H9). **^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm):** 152.06, 151.39, 148.53, 143.40, 130.79, 129.65, 128.42, 127.10, 124.45, 123.04, 122.20, 105.80, 102.21, 100.17. (Appendix 20)

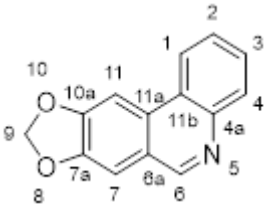


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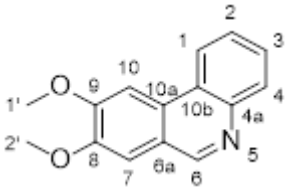
Table 4.1 – Reactional conditions of the radical reaction with *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (1) as a substrate.

Entry	Solvent preparation	Radical Initiator (eq)	PhSH (eq)	NHC-borane (eq)	Yield (%)
1	*Sieves*	AIBN (0.8)[a)]	-	1.1[e)]	13
2	Freeze Drying	AIBN (0.6)[b)]	-	1.6[e)]	16
3	Freeze Drying	DTBP (0.2)	-	1.1[e)]	2
4	Sodium Wire	AIBN (0.6)	-	1.1[e)]	22
5	Freeze Drying	AIBN (0.4)[c)]	0.05	1.3[e)]	11
6	Freeze Drying	AIBN (0.8)[d)]	0.1	2.3[e)]	21
7	Sodium Wire	AIBN (0.6)	0.2	1.2[e)]	7
8	Sodium Wire	AIBN (0.6)	-	1.2[f)]	13

a) Initially were added 0.2 eq, and then more 3 x 0.2 eq were added in batch for 7 days. b) The reaction started with 0.2 eq and then more 2 x 0.2 eq were joined to the reaction mixture in batch during 6 days. c) Initially were added 0.2 eq, and then more 0.2 eq were added in batch for 2 days. d) Initially were added 0.2 eq, and then more 2 x 0.2 eq were added in batch for 10 days. e) The NHC-borane used was the 16a. f) The NHC-borane used was 16b.

It was also made a blank assay following the procedure described in 4.8.3, with 47.2 mg of *N*-(2-bromo-4,5-methylenedioxybenzyl)aniline (**1**) and 22.1 mg (1.2 eq) of (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)**: 7.16 (t, J = 7.4 Hz, 2H), 7.01 (s, 1H), 6.91 (s, 1H), 6.79 (s, 2H), 6.72 (t, J = 7.2 Hz, 1H), 6.59 (d, J = 7.8 Hz, 2H), 5.93 (s, 2H), 4.29 (s, 2H), 3.73 (s, 6H), 1.35 – 0.67 (m, 3H). (Appendix 19)

4.8.3.2 Using N-(2-bromo-4,5-dimethoxybenzyl)aniline (2) as a substrate



18

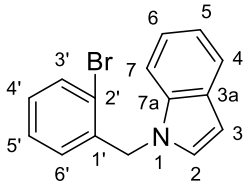
Following the procedure described in 4.8.1 and in 4.8.2, 49.8 mg of *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (**2**) was joined with 21.0 mg of NHC-borane (**16a**), and 17 mg of AIBN were slowly added during 17 h. Whenever specified in Table 4.2,Table 4.1 thiophenol (4 µL) was joined to the reaction mixture. 8,9-Dimethoxyphenanthridine (**18**) was obtained as a yellow solid after purification. **IR (ATR) ν_{max} (cm^{-1}):** 3071 (C-H aromatic), 1502 (C=N). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 9.16 (s, 1H, H6), 8.46 (d, *J* = 8.0 Hz, 1H, H1), 8.18 (d, *J* = 8.0 Hz, 1H, H4), 7.89 (s, 1H, H10), 7.68 (dt, *J* = 19.7, 7.1 Hz, 3H, H2/H3), 7.37 (s, 1H, H7), 4.15 (s, 3H, H1'), 4.08 (s, 3H, H2'). **^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm**): 153.53, 151.24, 150.29, 143.11, 129.63, 128.73, 128.21, 127.02, 123.99, 121.92, 121.72, 108.09, 102.00, 56.40, 56.32. (Appendix 22)

Table 4.2 – Reactional conditions of the radical reaction with *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (2) as a substrate.

Entry	Solvent preparation	Radical Initiator (eq)	PhSH (eq)	NHC-borane (eq)	Yield (%)
1	Sodium Wire	AIBN (0.6)	-	1.2	34
2	Sodium Wire	AIBN (0.6)	0.2	1.2	8

It was also made a blank assay following the procedure described in 4.8.3, with 46.1 mg of *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (**2**) and 19.7 mg (1.2 eq) of (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)**: 7.17 (t, J = 7.4 Hz, 2H), 7.03 (s, 1H), 6.94 (s, 1H), 6.79 (s, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.8 Hz, 2H), 4.32 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.73 (s, 6H), 1.35 – 0.67 (m, 2H). (Appendix 21)

4.8.3.3 Using N-(2'-bromobenzyl)-2,3-dihydroindole (3) as a substrate



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Following the procedure described in 4.8.1 and in 4.8.2, 95.6 mg of *N*-(2'-bromobenzyl)-2,3-dihydroindole (**3**) were mixed with 45.5 mg of NHC-borane (**16a**), and 38.5 mg of AIBN were slowly added during 17 h. In the reaction with thiophenol, was joined 8 µL of thiophenol to the reaction mixture. 1-(2'-Bromobenzyl)-1H-indole (**19**) was obtained as a dark solid after purification. **IR (ATR) ν_{max} (cm^{-1}):** 3055 (C-H Ar), 2925 (C-H aliphatic). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 7.68 (d, J = 8.0 Hz, 1H, H3'), 7.64 – 7.55 (m, 1H, Ar-H), 7.31 – 7.22 (m, 1H, Ar-H), 7.21 – 7.09 (m, 5H, Ar-H), 6.60 (d, J = 3.1 Hz, 1H, Ar-H), 6.55 – 6.50 (m, 1H, Ar-H), 5.40 (s, 2H, CH_2). (Appendix 24)

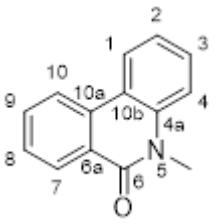
Table 4.3 – Reactional conditions of the radical reaction with *N*-(2'-bromobenzyl)-2,3-dihydroindole (3) as a substrate.

Entry	Solvent preparation	Radical Initiator (eq)	PhSH (eq)	NHC-borane (eq)	Yield (%)
1	Sodium Wire	AIBN (0.6)	-	1.2	28
2	Sodium Wire	AIBN (0.6)	0.2	1.2	18

It was also made a blank assay following the procedure described in 4.8.3., with 24.8 mg of *N*-(2'-bromobenzyl)-2,3-dihydroindole (**3**) and 12.5 mg (1.2 eq) of (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)**: 7.58 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.17 – 7.08 (m, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.79 (s, 2H), 6.68 (t, J = 7.4 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1H), 4.31 (s, 2H), 3.73 (s, 6H), 3.43 (t, J = 8.2 Hz, 2H), 3.03 (t, J = 8.3 Hz, 2H), 1.36 – 0.67 (m, 3H). (Appendix 23)

4.8.3.4 Using N-(2-bromobenzyl)-N-methylaniline (4) as a substrate

As described in 4.8.1 and in 4.8.2, 49.6 mg of *N*-(2-bromobenzyl)-*N*-methylaniline (**4**) and 24.9 mg of NHC-borane (**16a**) were mixed, and 18.8 mg of AIBN was slowly added through 17 h. In the reaction with thiophenol was joined 4 µL of thiophenol. 5-Methylphenanthridin-6(5H)-one (**20**) was obtained as a brown solid. **IR (ATR) ν_{max} (cm^{-1}):** 3067 (C-H aromatic), 1647 (C=O). **^{1}H RMN (400 MHz, $CDCl_3$) δ (ppm):** 8.56 (d, J = 7.9 Hz, 1H, H1), 8.32 – 8.28 (m, 2H, H3/H4), 7.77 (t, J = 7.7 Hz, 1H, H2), 7.61 – 7.53 (m, 2H, H9/H10), 7.44 (d, J = 8.4 Hz, 1H, H7), 7.34 (t, J = 7.5 Hz, 1H, H8), 3.83 (s, 3H, CH_3). **^{13}C RMN (126 MHz, $CDCl_3$) δ (ppm):** 165.62, 138.19, 133.69, 132.58, 129.74, 129.07, 128.12, 125.75, 123.40, 122.65, 121.77, 120.21, 115.23, 30.15. (Appendix 25)



20

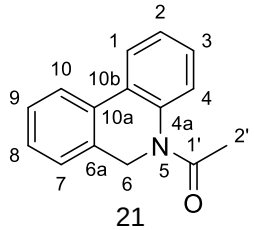
Table 4.4 – Reactional conditions of the radical reaction with *N*-(2-bromobenzyl)-*N*-methylaniline (4) as a substrate.

Entry	Solvent preparation	Radical Initiator (eq)	PhSH (eq)	NHC-borane (eq)	Yield (%)
1	Sodium Wire	AIBN (0.6)	-	1.2	21
2	Sodium Wire	AIBN (0.6)	0.2	1.2	8

It was also made a blank assay following the procedure described in 4.8.3, with 49.0 mg of *N*-(2-bromobenzyl)-*N*-methylaniline (**4**) and 26.5 mg (1.2 eq) of (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)**: 7.62 (d, J = 7.7 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.20 – 7.13 (m, 2H), 6.84 (s, 2H), 6.78 – 6. 68 (m, 3H), 4.59 (s, 2H), 3.78 (s, 6H), 3.13 (s, 3H), 1.41 – 0.69 (m, 3H). (Appendix 26)

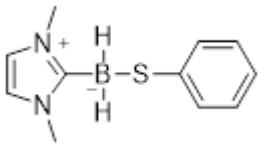
4.8.3.5 Using N-(2'-bromobenzyl)-N-phenylacetamide (7) as a substrate

As described in 4.8.1 and in 4.8.2, 48.2 mg of *N*-(2'-bromobenzyl)-*N*-phenylacetamide (**7**), 21.7 mg of NHC-borane (**16a**), and 16.8 mg of AIBN was slowly added through 17 h. In the reaction with thiophenol, was joined 4 µL of thiophenol. 1-(Phenanthridin-5(6H)-yl)ethan-1-one (**21**) was obtained as a yellow solid, after purification**. ^{1}H RMN (400 MHz, $CDCl_3$) δ (ppm)**: 7.82 – 7.77 (m, 2H, Ar-H), 7.38 – 7.29 (m, 6H, Ar-H), 5.05 (s, 2H, H6), 1.94 (s, 3H, H2'). **GC-MS:** tr 11.32, *m/z* 223. (Appendix 28)



21

It was also identified a thiophenol-NHC adduct (**22**). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)**: 7.36 (d, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 2H), 6.97 (t, *J* = 7.1 Hz, 1H), 6.82 (s, 2H), 3.73 (s, 6H), 3.05 – 2.34 (bm, 2H). **GC-MS:** tr 11.20, *m/z* 218. (Appendix 29)



22

Table 4.5 – Reactional conditions of the radical reaction with *N*-(2'-bromobenzyl)-*N*-phenylacetamide (7) as a substrate.

Entry	Solvent preparation	Radical Initiator (eq)	PhSH (eq)	NHC-borane (eq)	Yield (%)
1	Sodium Wire	AIBN (0.6)	-	1.2	8
2	Sodium Wire	AIBN (0.6)	0.2	1.2	9

It was also made a blank assay following the procedure described in 4.8.3, with 24.6 mg of *N*-(2'-bromobenzyl)-*N*-phenylacetamide (**7**) and 10.9 mg (1.2 eq) of (1,3-dimethylimidazolium-2-yl)trihydroborate (**16a**). **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)**: 7.41 (d, J = 7.9 Hz, 1H), 7.34 – 7.17 (m, 5H), 7.06 – 7.00 (m, 3H), 6.75 (s, 2H), 5.00 (s, 2H), 3.69 (s, 6H), 1.90 (s, 3H), 1.31 – 0.62 (m, 3H). (Appendix 27)

4.8.3.6 Using 1-bromo-2-(phenoxymethyl)benzene (8) as a substrate

As described in 4.8.1, 101.5 mg of 1-bromo-2-(phenoxymethyl)benzene (**8**) and 49.7 mg of NHC-borane (**16a**) were mixed, and 40.2 mg of AIBN was slowly added through 17 h. **^{1}H NMR**

(400 MHz, $CDCl_3$) δ (ppm): 7.61 – 7.55 (m, 2H, H4/H6), 7.37 – 7.29 (m, 3H, H3'/H5'/H5), 7.22 – 7.17 (m, 1H, H3), 7.03 – 6.97 (m, 3H, H2'/H4'/H6'), 5.15 (s, 2H, CH_2O). (Appendix 8)

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6. APPENDIX

APPENDIX 1 – 6-BROMOPIPERONAL (5)

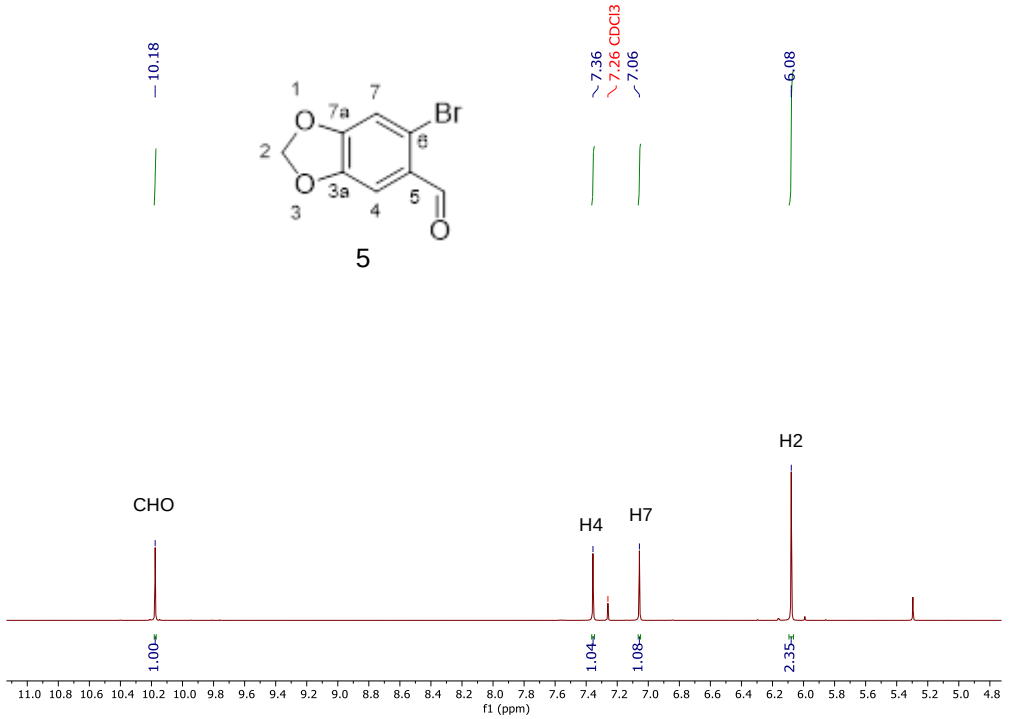


Figure 6.1 – ^{1}H NMR spectrum of 6-bromopiperonal (5).

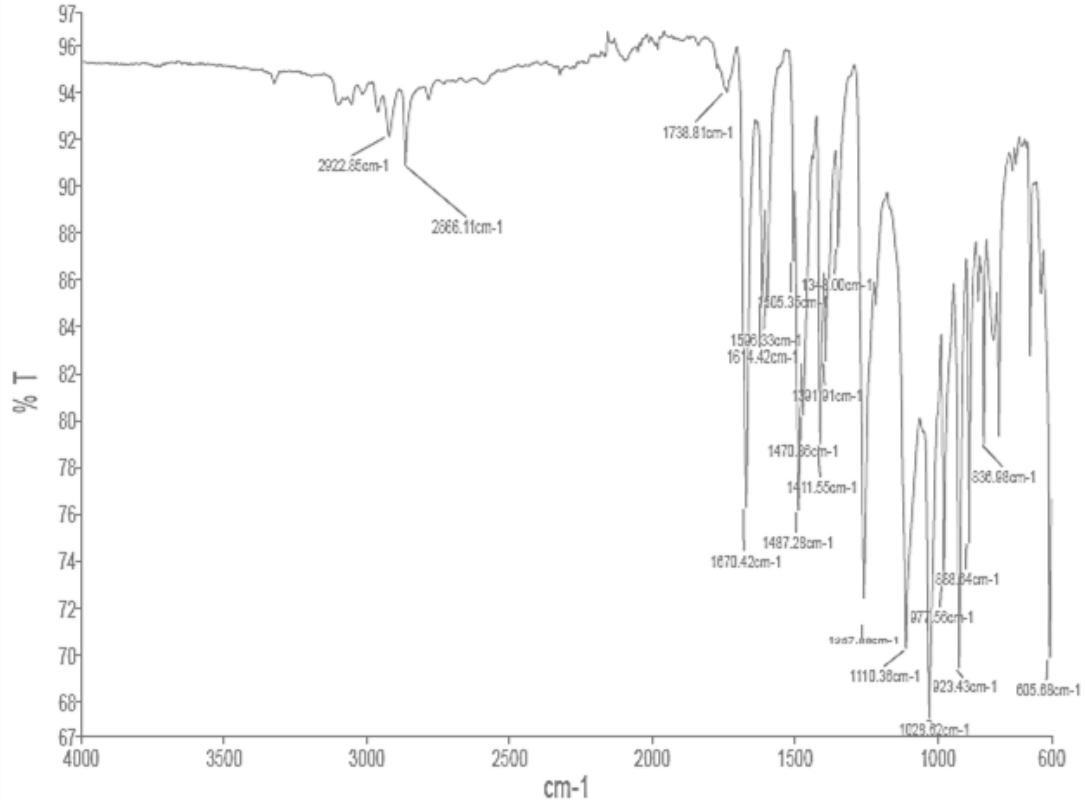


Figure 6.2 – IR spectrum of 6-bromopiperonal (5).

APPENDIX 2 – 2-BROMO-4,5-DIMETHOXYBENZALDEHYDE (6)

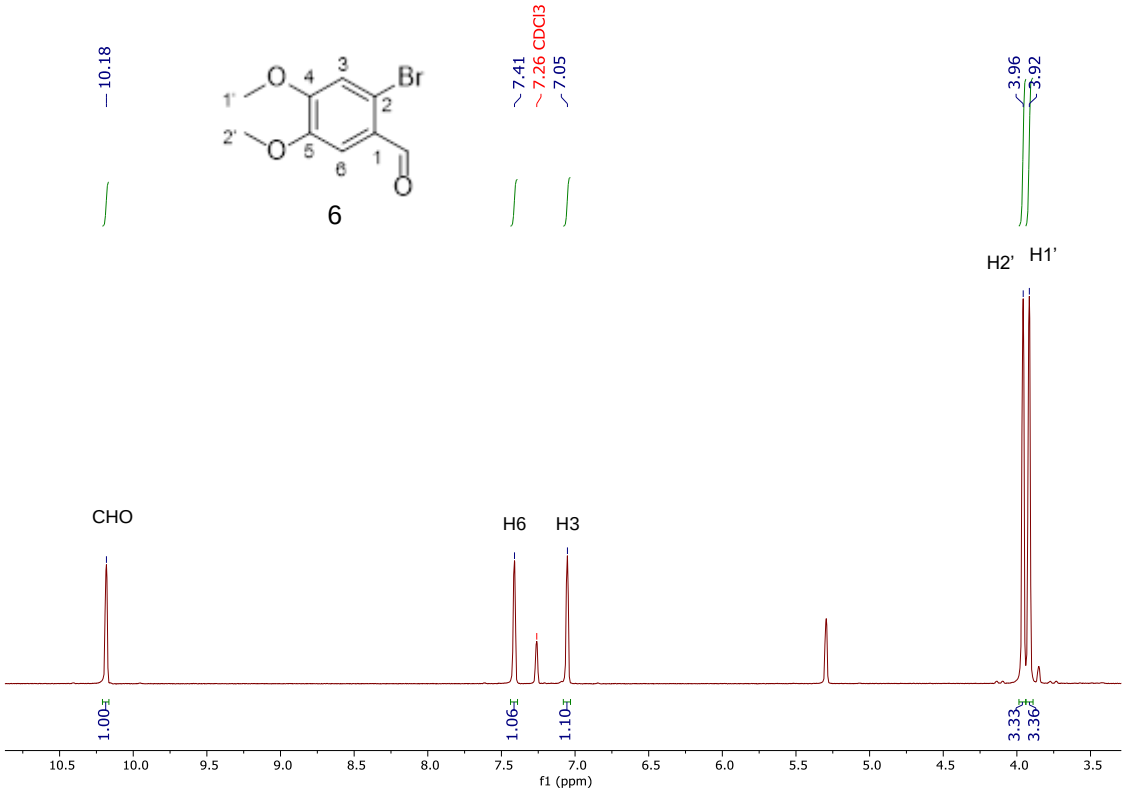


Figure 6.3 – ^{1}H NMR spectrum of 2-bromo-4,5-dimethoxybenzaldehyde (6).

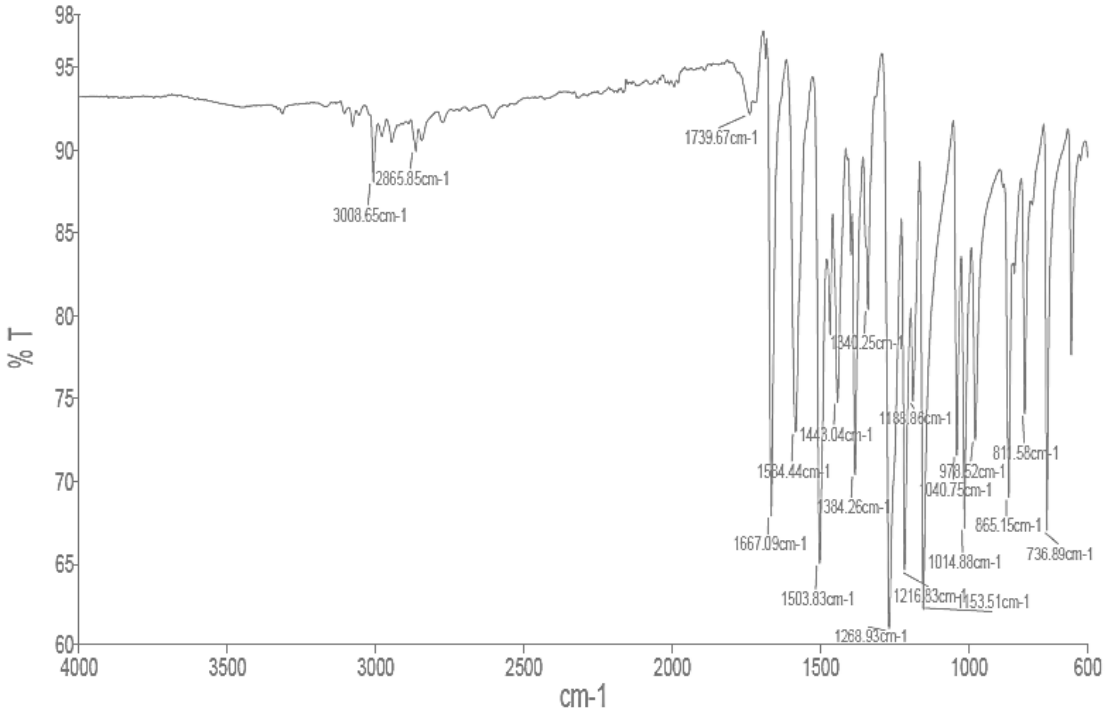
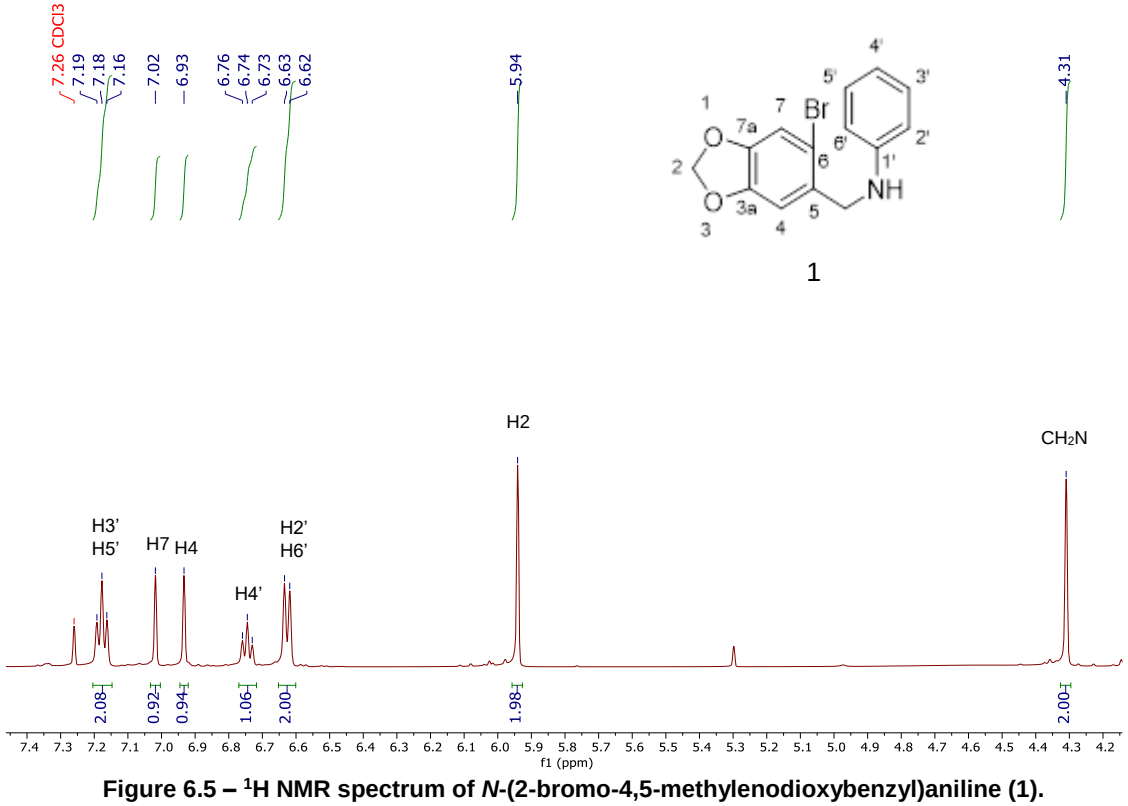


Figure 6.4 - IR spectrum of 2-bromo-4,5-dimethoxybenzaldehyde (6).

APPENDIX 3 – *N*-(2-BROMO-4,5-METHYLENEDIOXYBENZYL)ANILINE (1)



1

Figure 6.5 – ^{1}H NMR spectrum of *N*-(2-bromo-4,5-methylenodioxybenzyl)aniline (1).

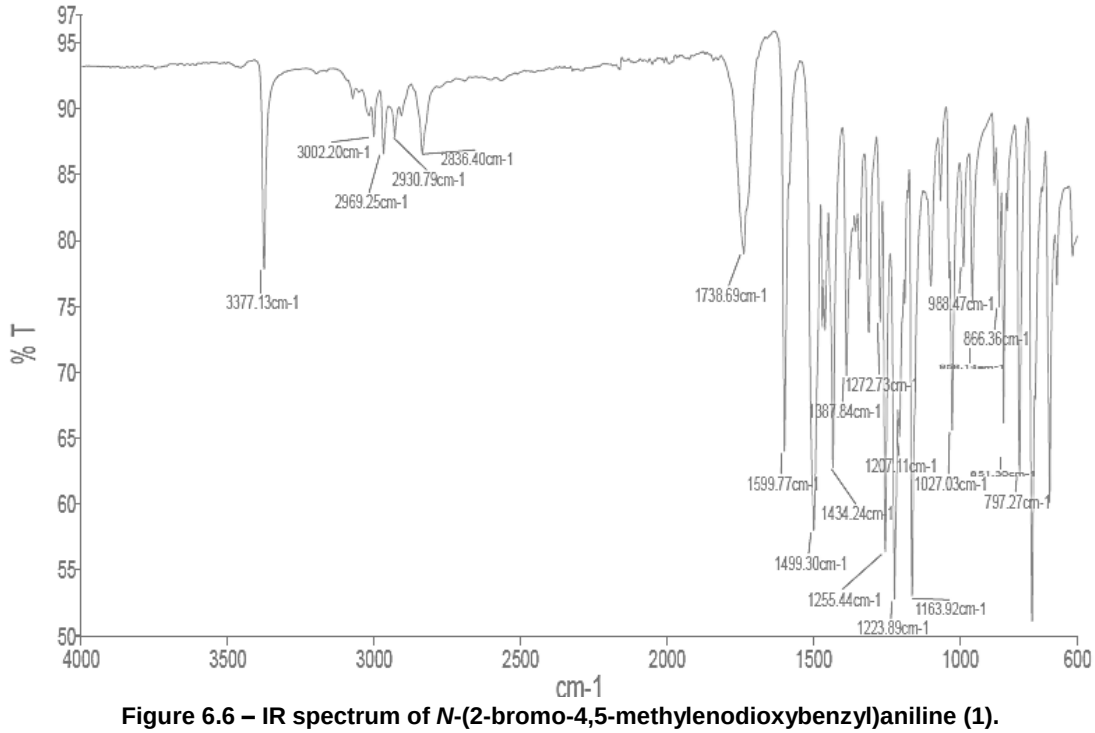


Figure 6.6 – IR spectrum of *N*-(2-bromo-4,5-methylenodioxybenzyl)aniline (1).

APPENDIX 4 – *N*-(2-BROMO-4,5-DIMETHOXYBENZYL)ANILINE (2)

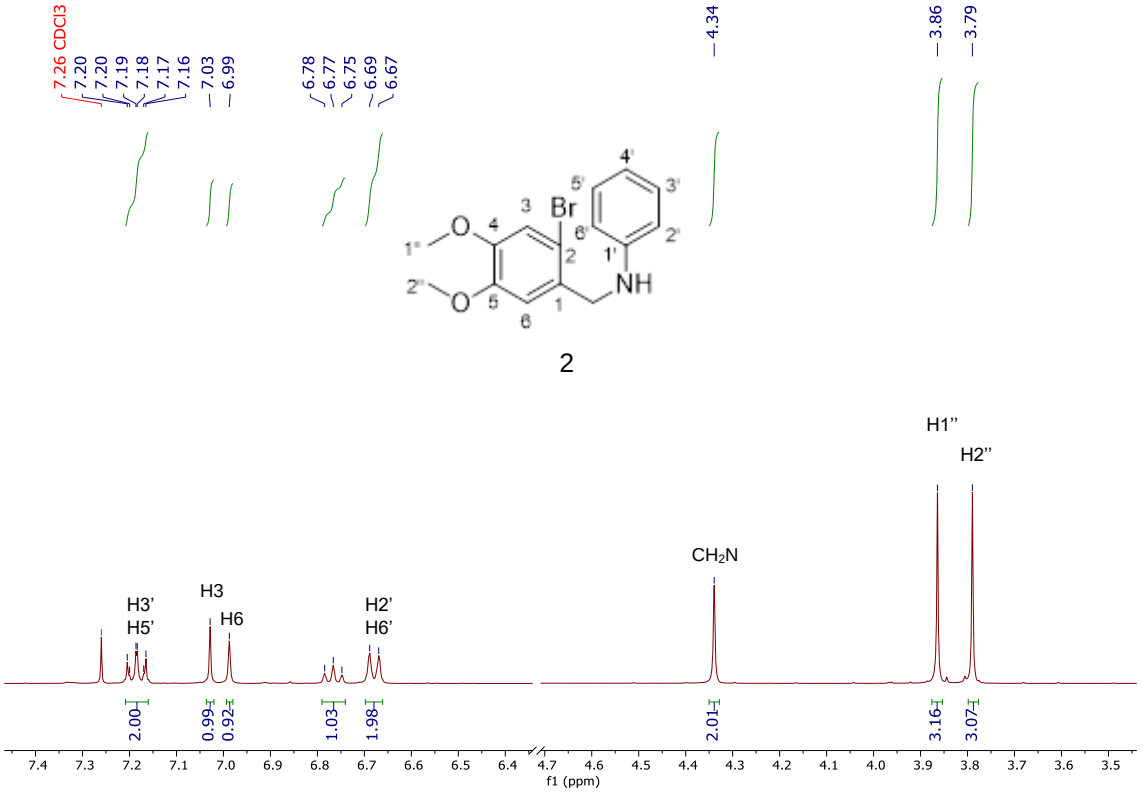


Figure 6.7 – ^{1}H NMR spectrum of *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (2).

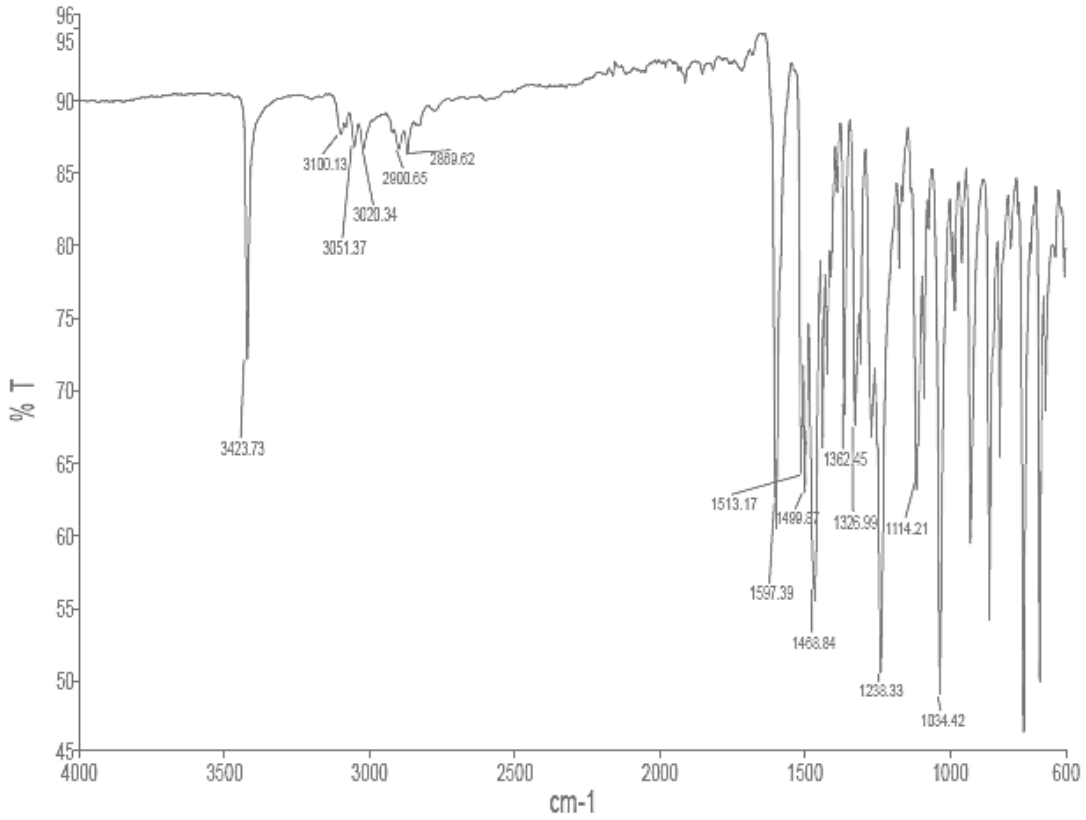


Figure 6.8 – IR spectrum of *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (2).

APPENDIX 5 – *N*-2'-BROMOBENZYL-2,3-DIHYDROINDOLE (3)

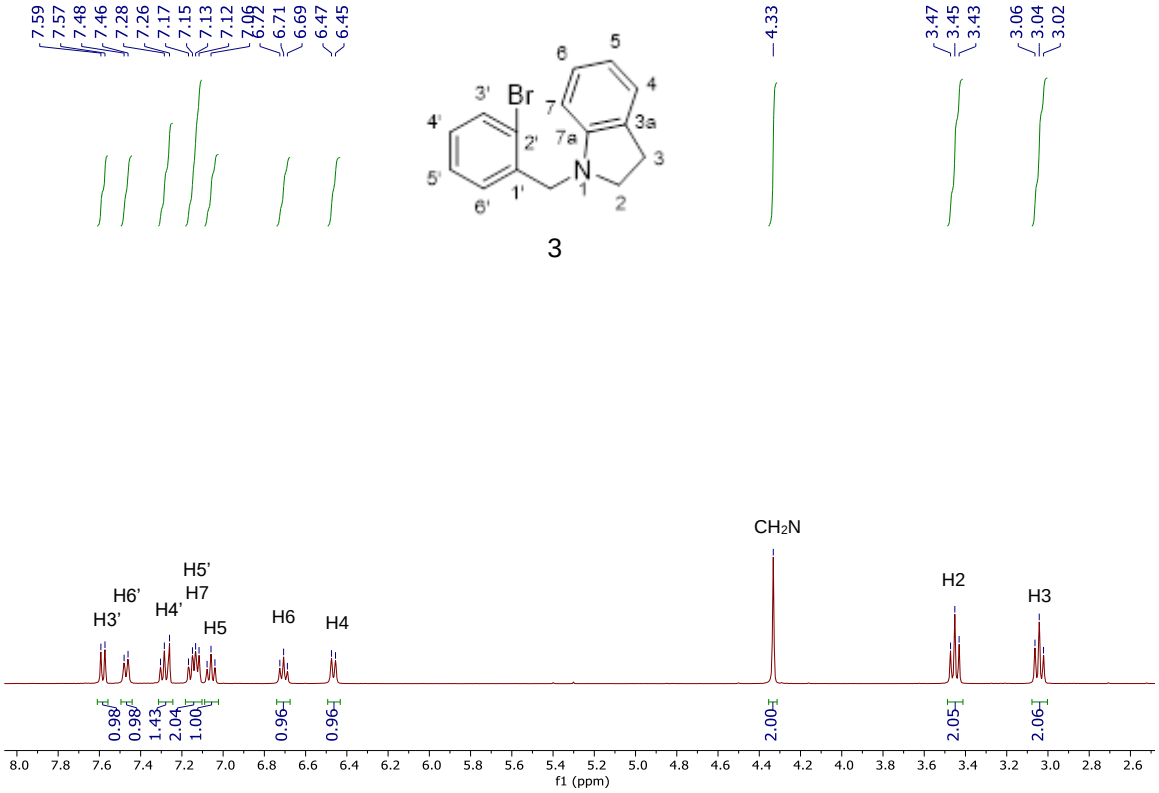


Figure 6.9 – ^{1}H NMR spectrum of *N*-2'-bromobenzyl-2,3-dihydroindole (3).

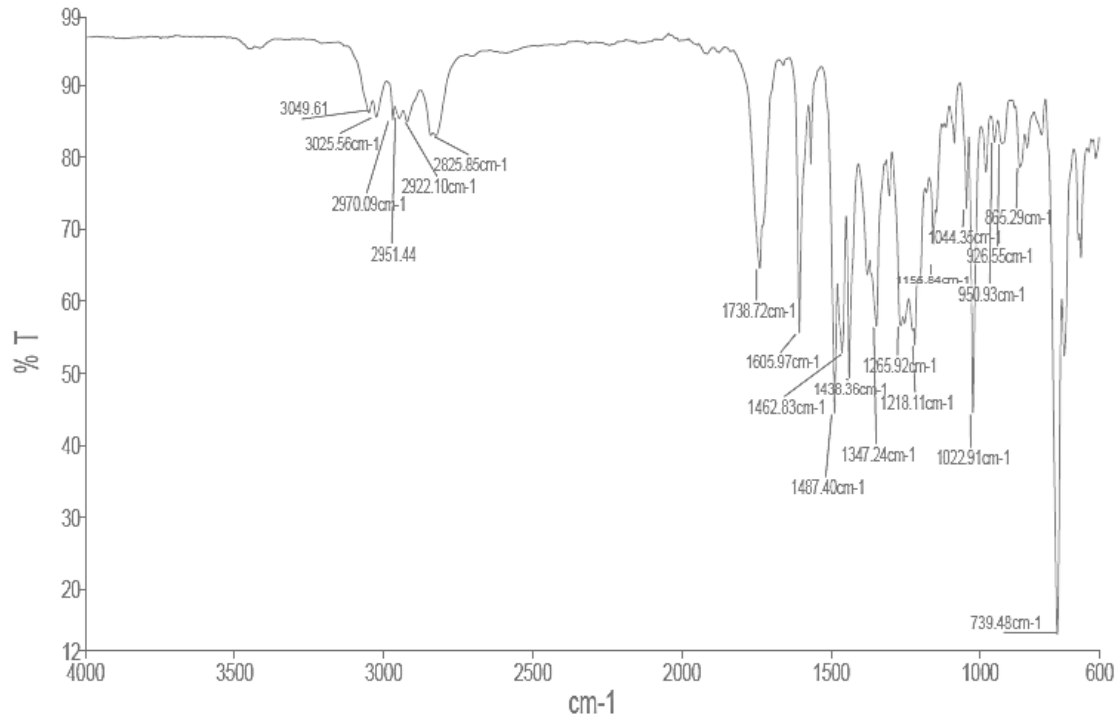


Figure 6.10 – IR spectrum of *N*-2'-bromo-2,3-dihydroindole (3).

APPENDIX 6 – *N*-(2-BROMOBENZYL)-*N*-METHYLANILINE (4)

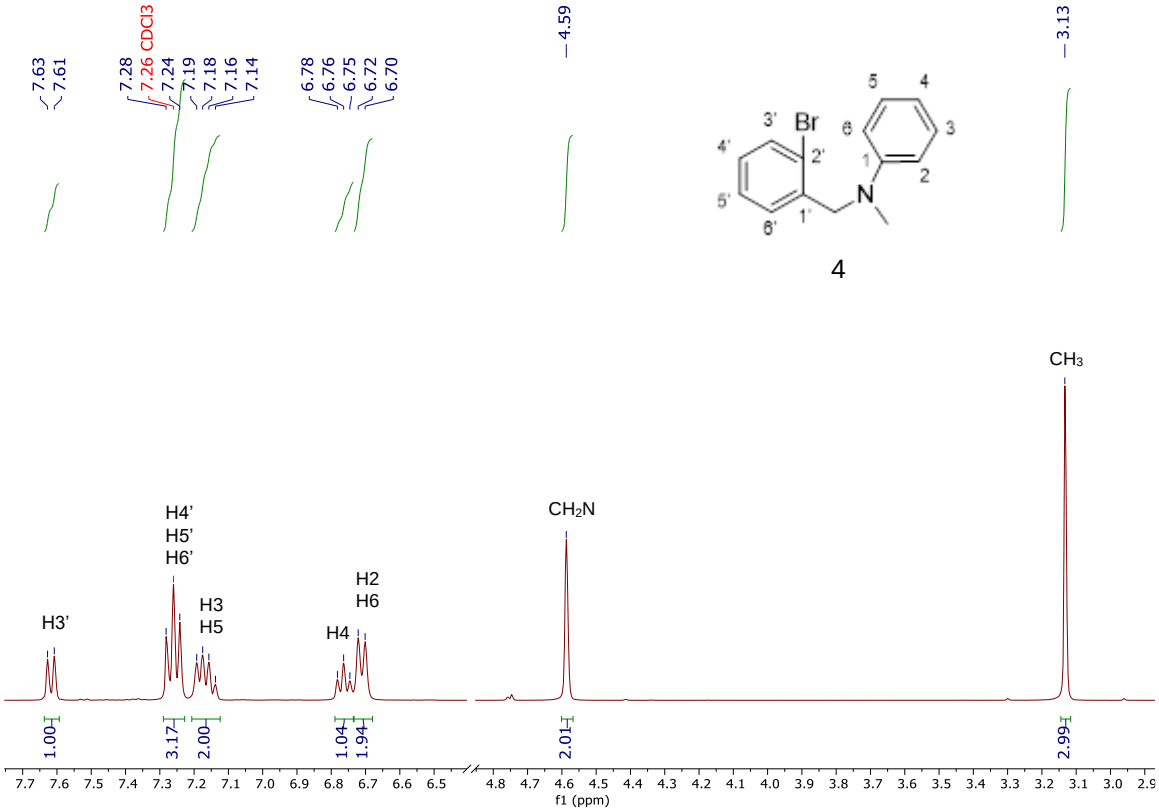


Figure 6.11 – ^{1}H NMR spectrum of *N*-(2-bromobenzyl)-*N*-methylaniline (4).

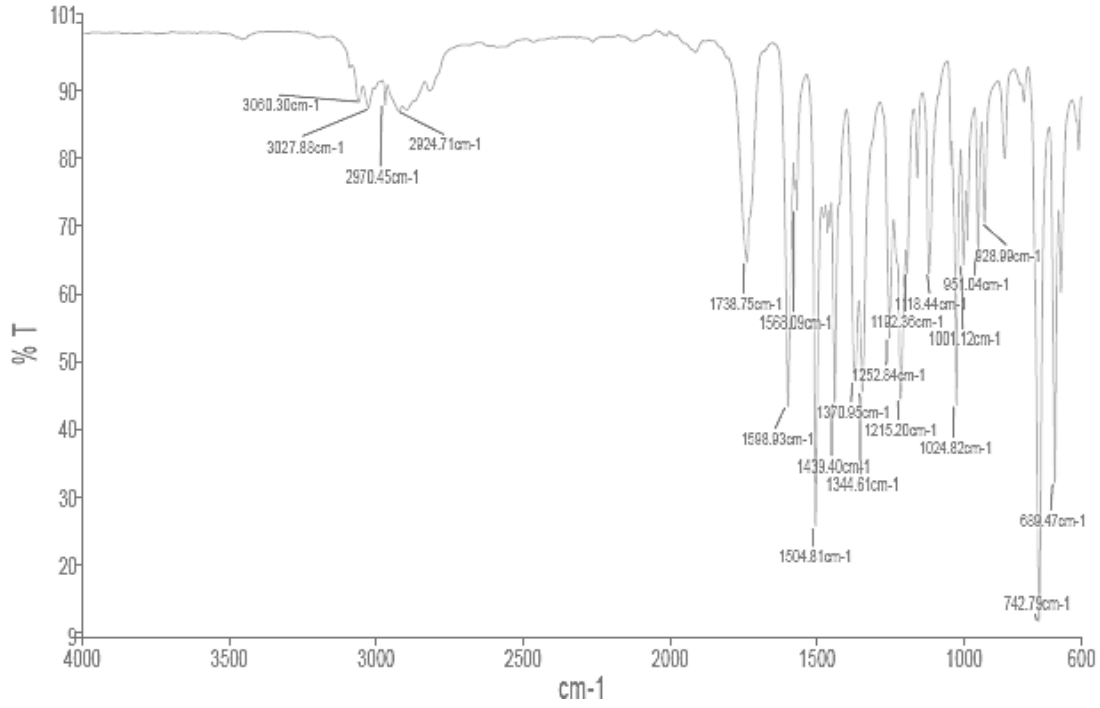


Figure 6.12 – IR spectrum of *N*-(2-bromobenzyl)-*N*-methylaniline (4).

APPENDIX 7 – *N*-(2'-BROMOBENZYL)-*N*-PHENYLACETAMIDE (7)

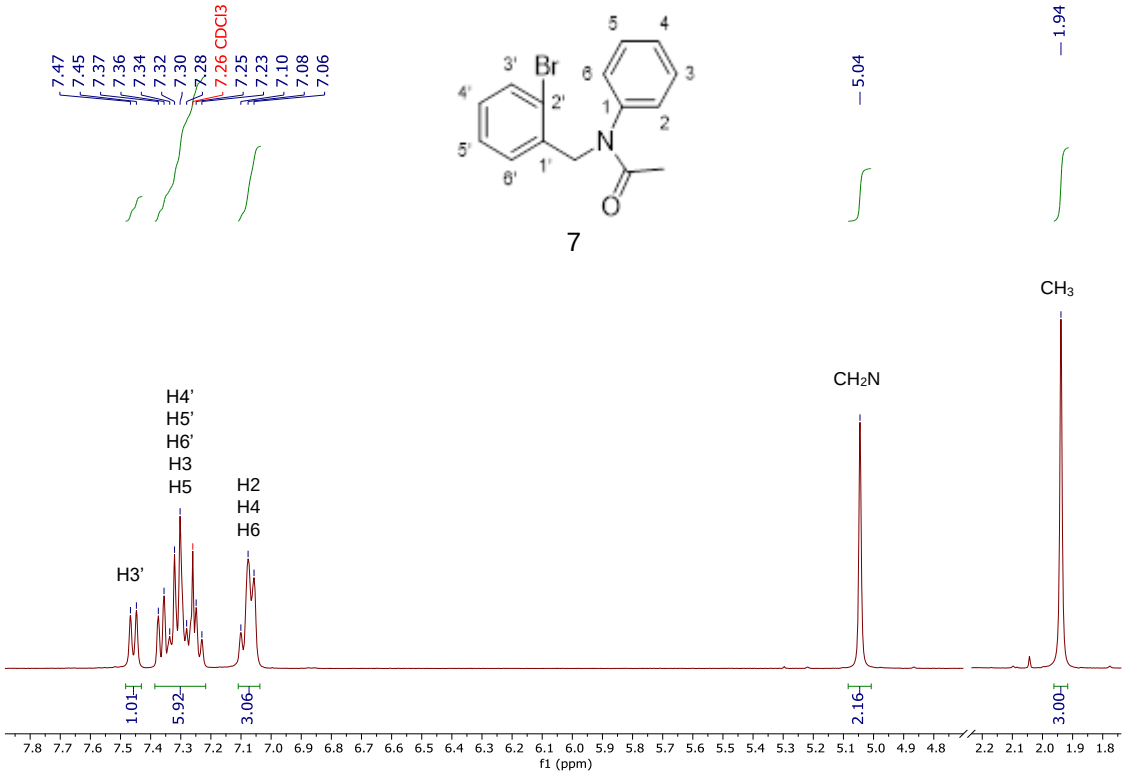


Figure 6.13 – ^{1}H NMR spectrum of *N*-(2'-bromobenzyl)-*N*-phenylacetamide (7).

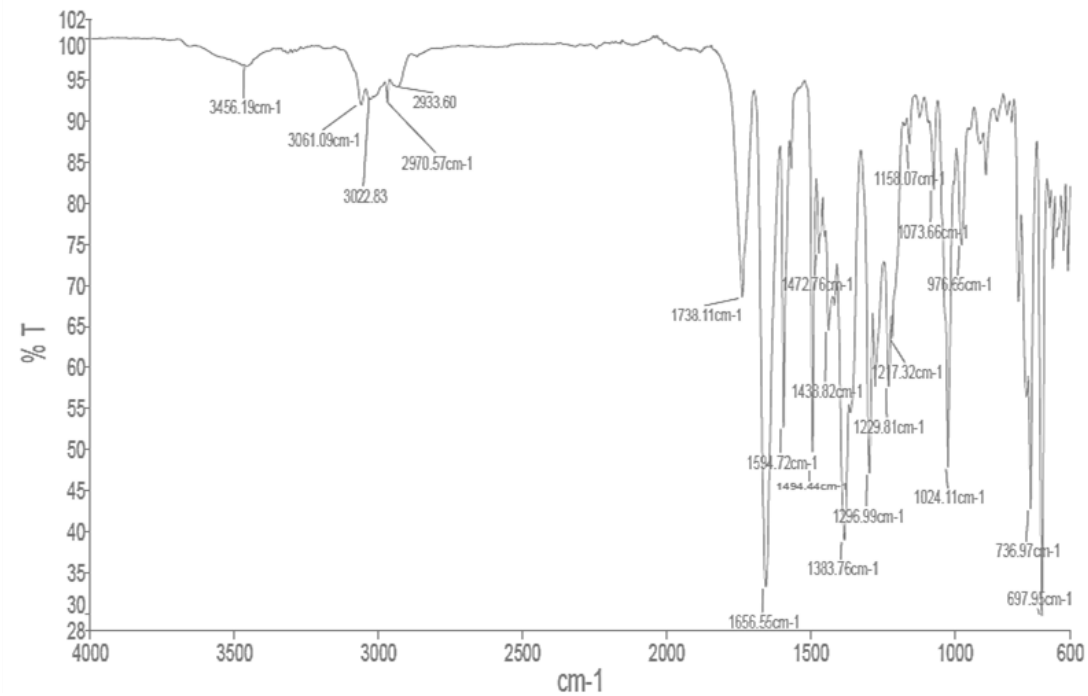


Figure 6.14 – IR spectrum of *N*-(2'-bromobenzyl)-*N*-phenylacetamide (7).

APPENDIX 8 – 1-BROMO-2-(PHENOXYMETHYL)BENZENE (8)

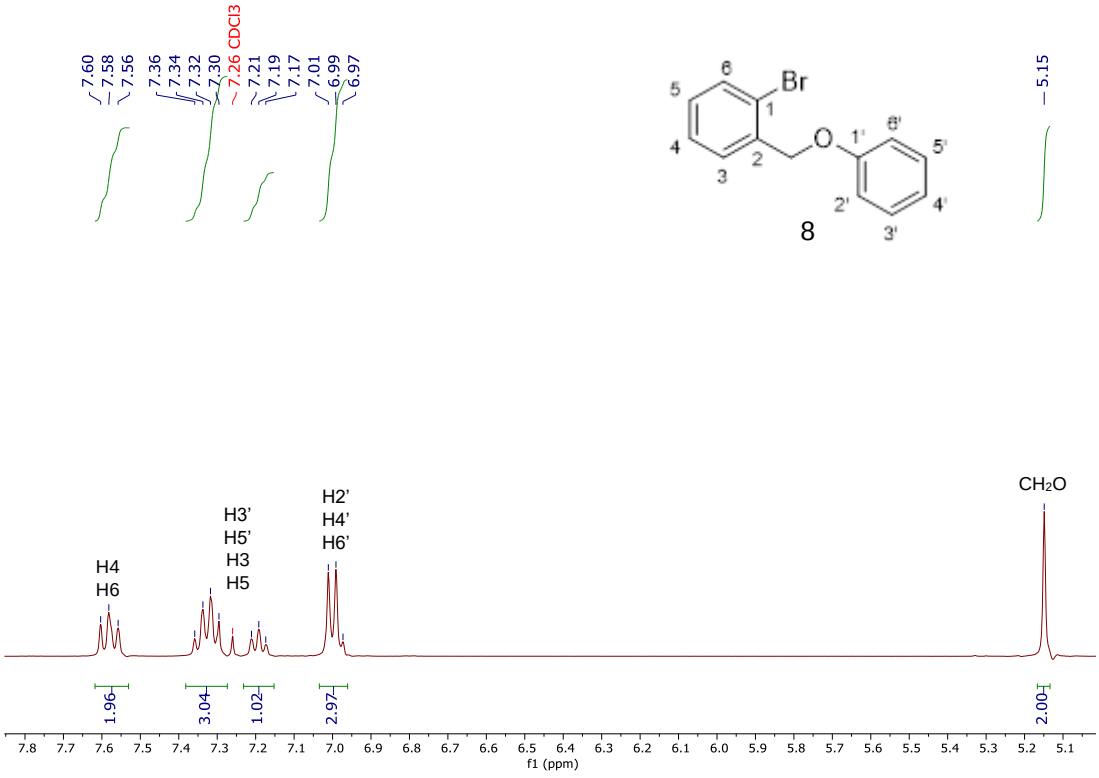


Figure 6.15 – ^{1}H NMR spectrum of 1-bromo-2-(phenoxymethyl)benzene (8).

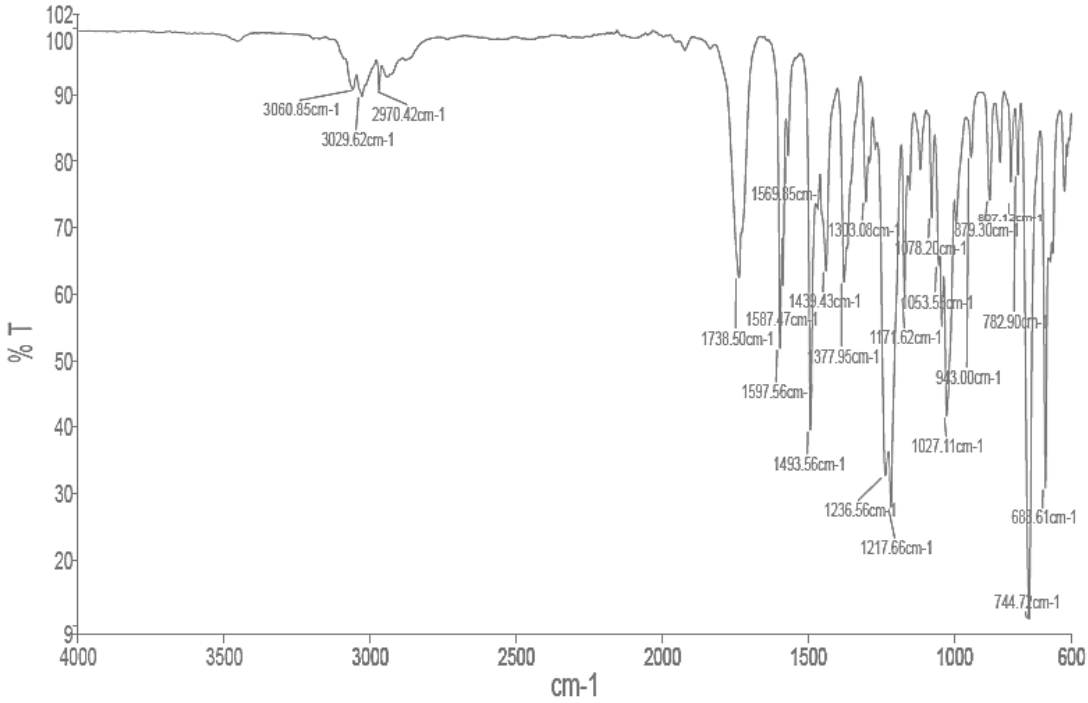
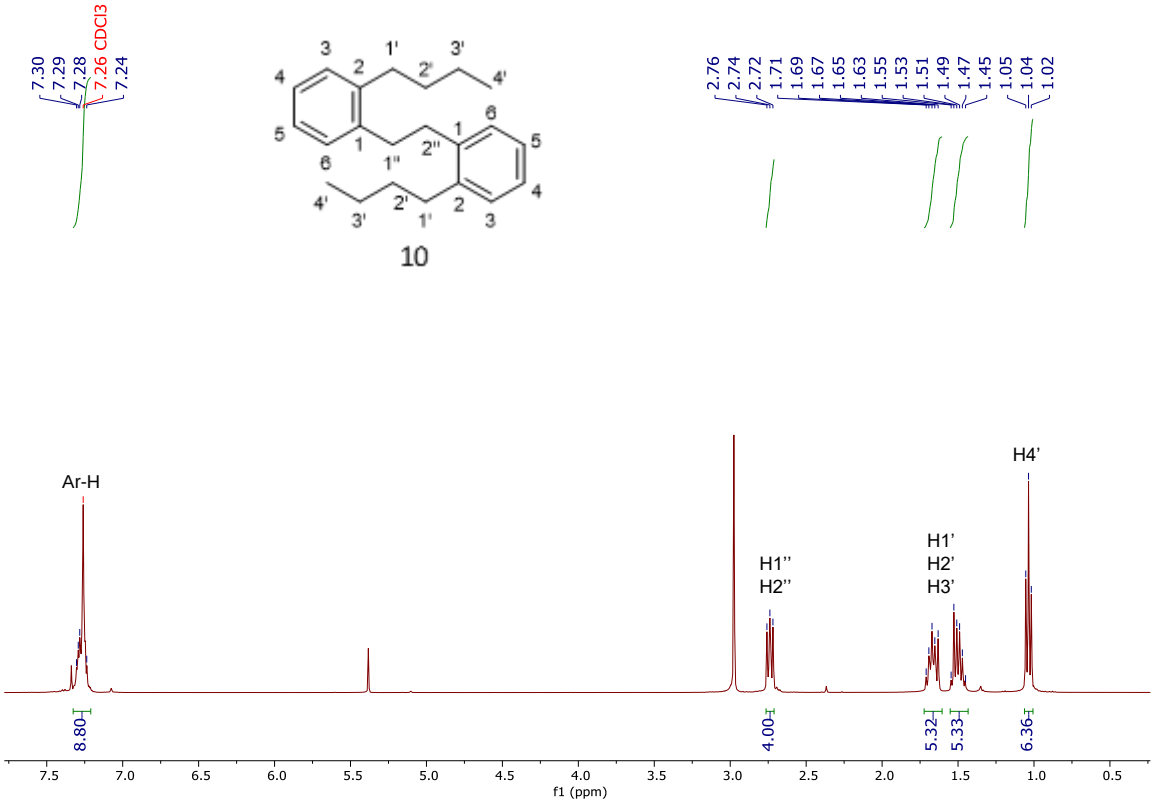


Figure 6.16 – IR spectrum of 1-bromo-2-(phenoxymethyl)benzene (8).

APPENDIX 9 – 1,2-BIS(2-BUTYLPHENYL)ETHANE (10)



APPENDIX 10 – 1,2-BIS(2-BROMOPHENYL)ETHANE (11)

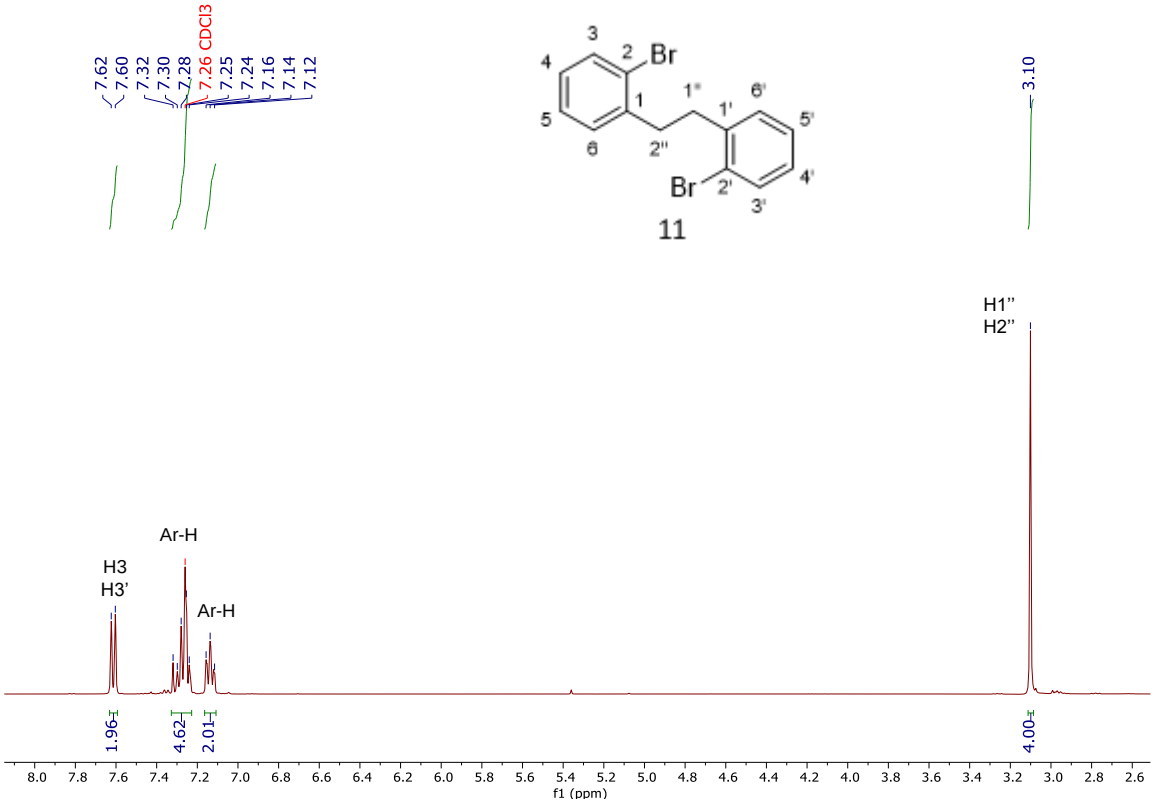


Figure 6.17 – ^{1}H NMR spectrum of 1,2-bis(2-bromophenyl)ethane (11).

APPENDIX 11 – 1,2-DIPHENYLETHANE (12)

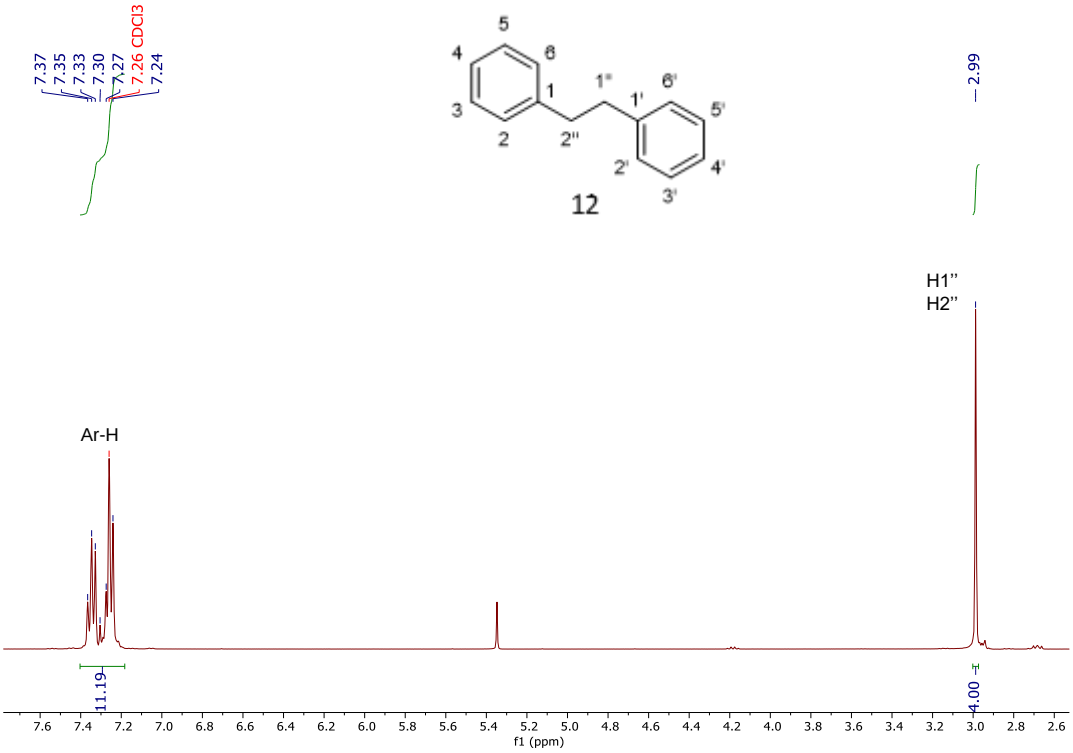


Figure 6.18 – ^{1}H NMR spectrum of 1,2-diphenylethane (12).

APPENDIX 12 – 2-BROMOBENZYL BROMIDE (13)

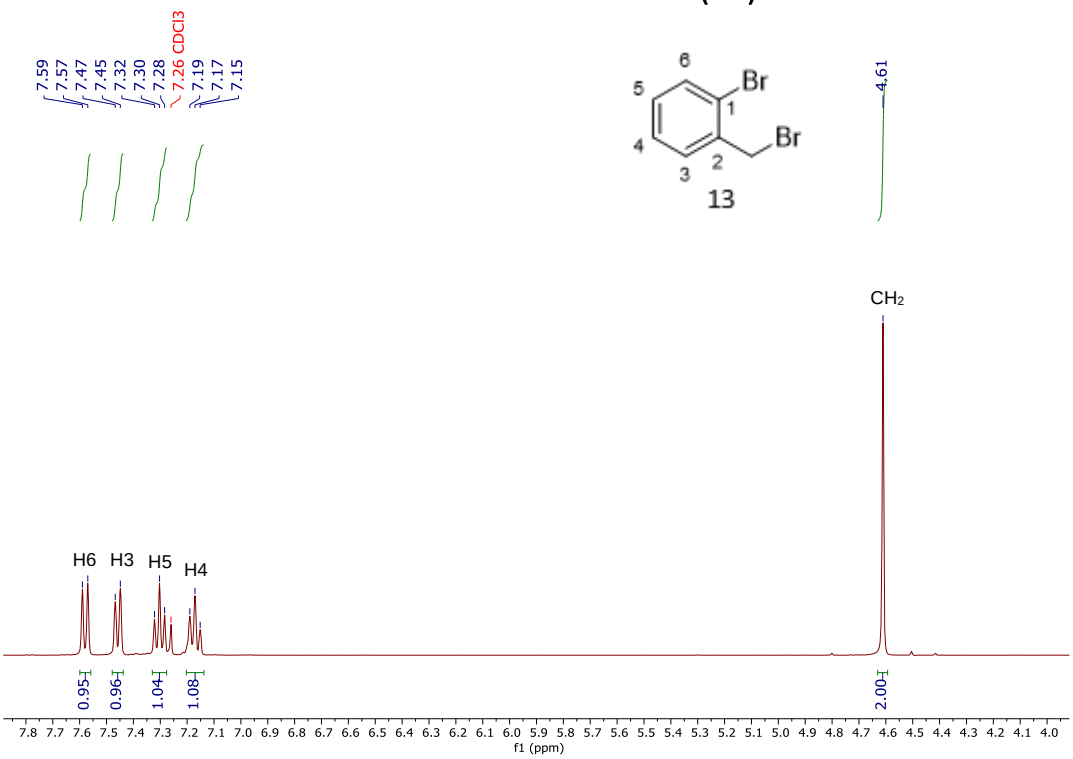


Figure 6.19 – ^{1}H NMR spectrum of 2-bromobenzyl bromide (13).

APPENDIX 13 – 1,3-DIMETHYLIMIDAZOLIUM IODINE (15A)

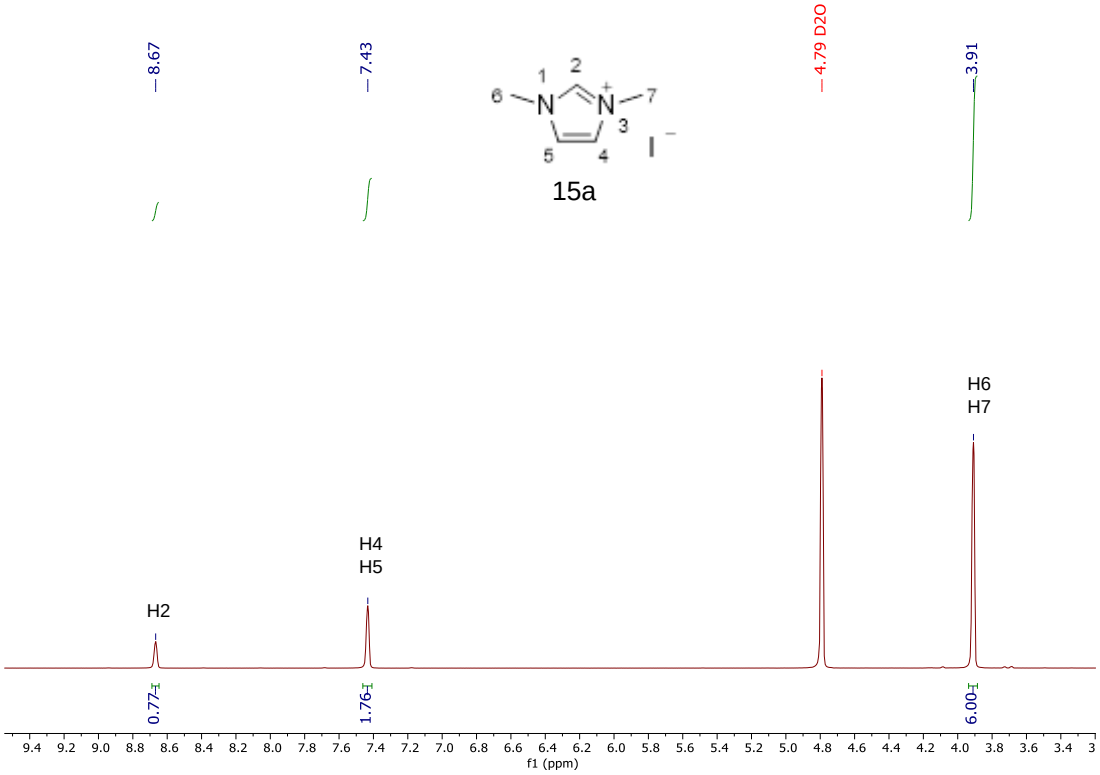


Figure 6.20 – ^{1}H NMR spectrum of 1,3-dimethylimidazolium iodine (15a).

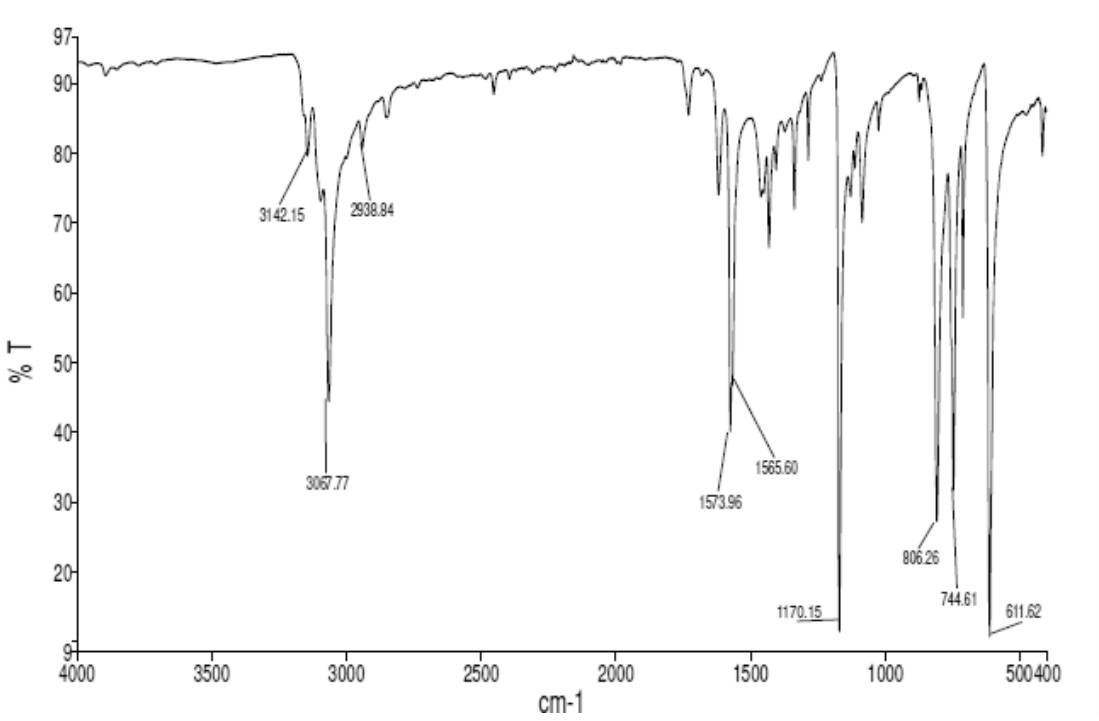


Figure 6.21 – IR spectrum of 1,3-dimethylimidazolium iodine (15a).

APPENDIX 14 – 3-DECYL-1-METHYLIMIDAZOLIUM IODINE (15B)

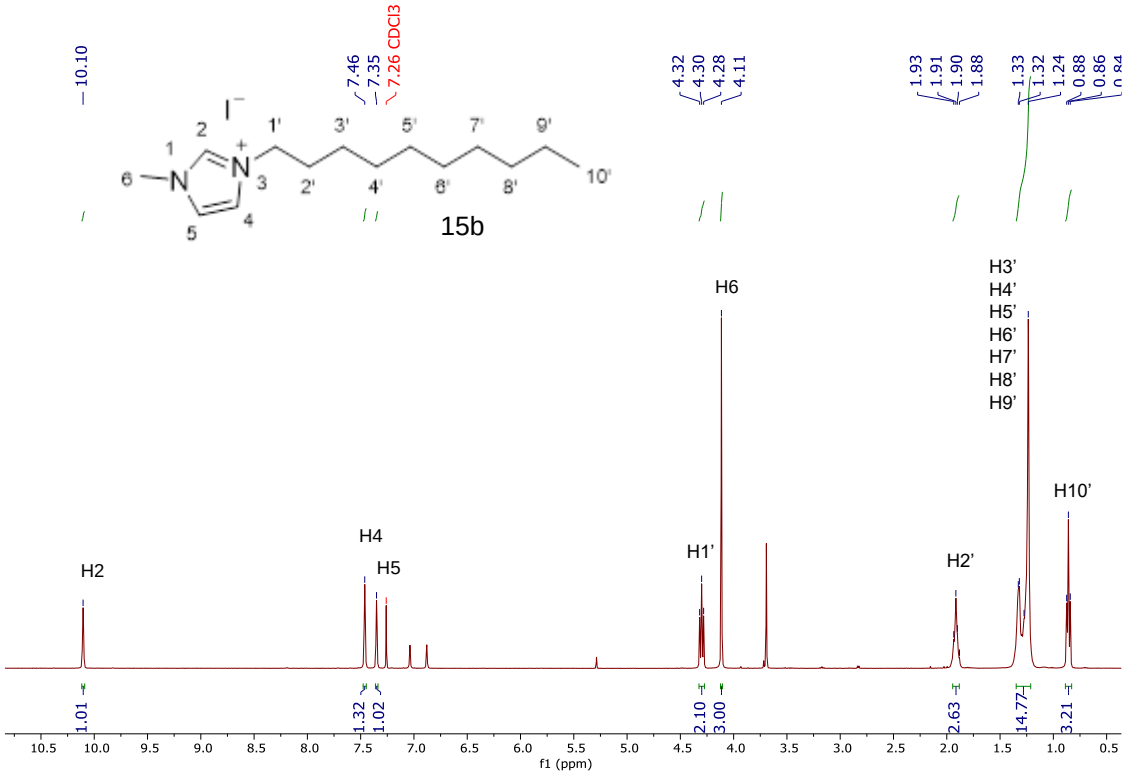


Figure 6.22 – ^{1}H NMR spectrum of 3-decyl-1-methyimidazolium iodine (15b).

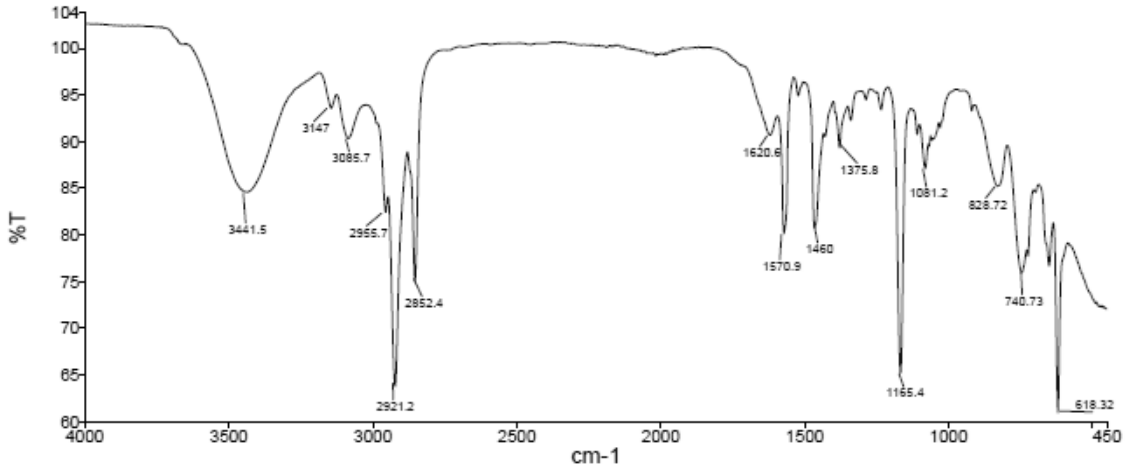


Figure 6.23 – IR spectrum of 3-decyl-1-methylimidazolium iodine (15b).

APPENDIX 15 – 3-ETHYL-1-METHYLIMIDAZOLIUM IODINE (15C)

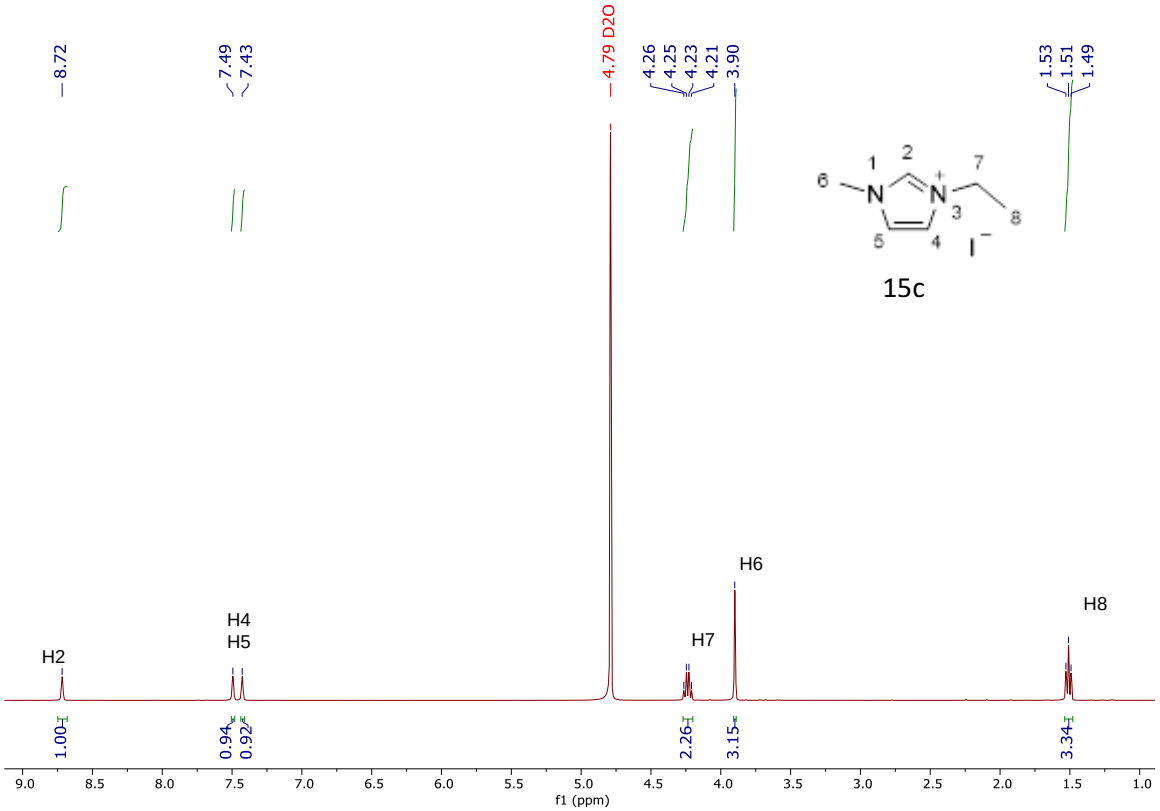


Figure 6.24 – ^{1}H NMR spectrum of 3-ethyl-1-methylimidazolium iodine (15c).

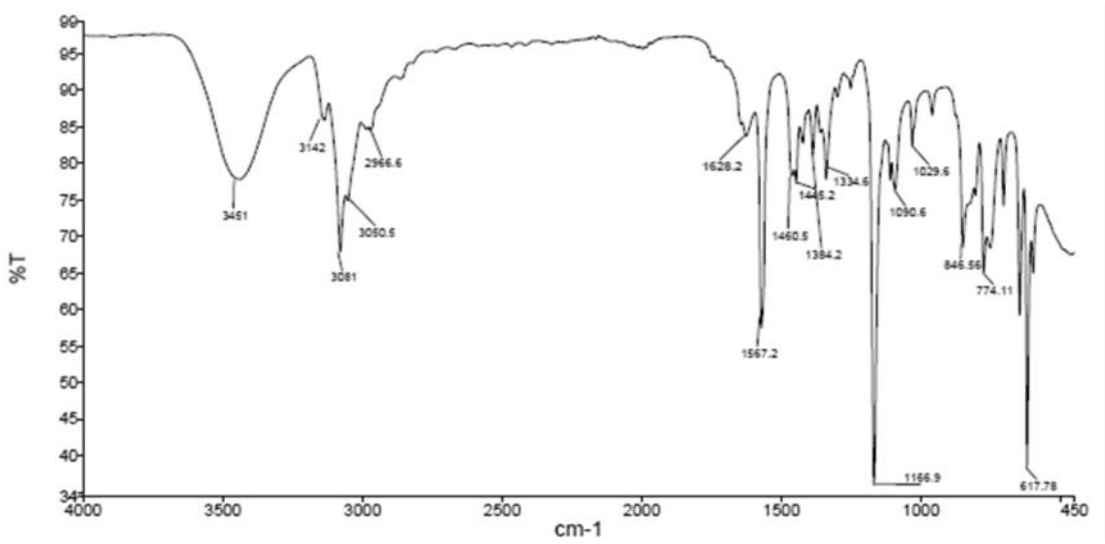


Figure 6.25 – IR spectrum of 3-ethyl-1-methylimidazolium iodine (15c).

APPENDIX 16 – 3-BENZYL-1-METHYLIMIDAZOLIUM BROMIDE (15D)

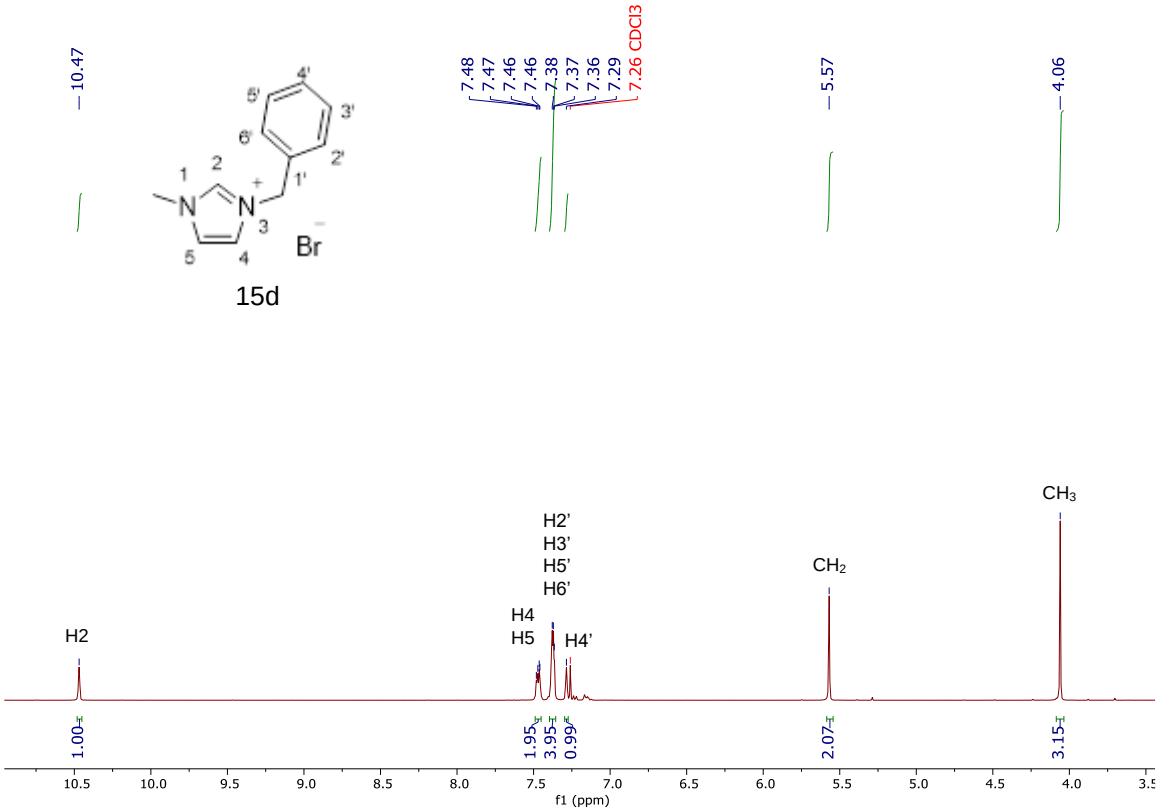


Figure 6.26 – ^{1}H NMR spectrum of 3-benzyl-1-methylimidazoilum bromide (15d).

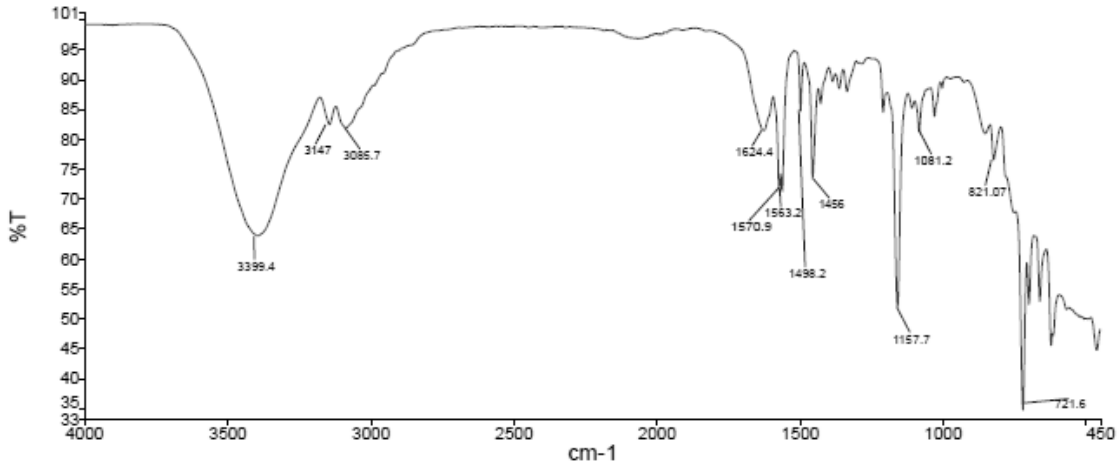


Figure 6.27 – IR spectrum of 3-benzyl-1-methylimidazolium bromide (15d).

APPENDIX 17 – (1,3-DIMETHYLIMIDAZOLIUM-2-YL)TRIHYDROBORATE (16A)

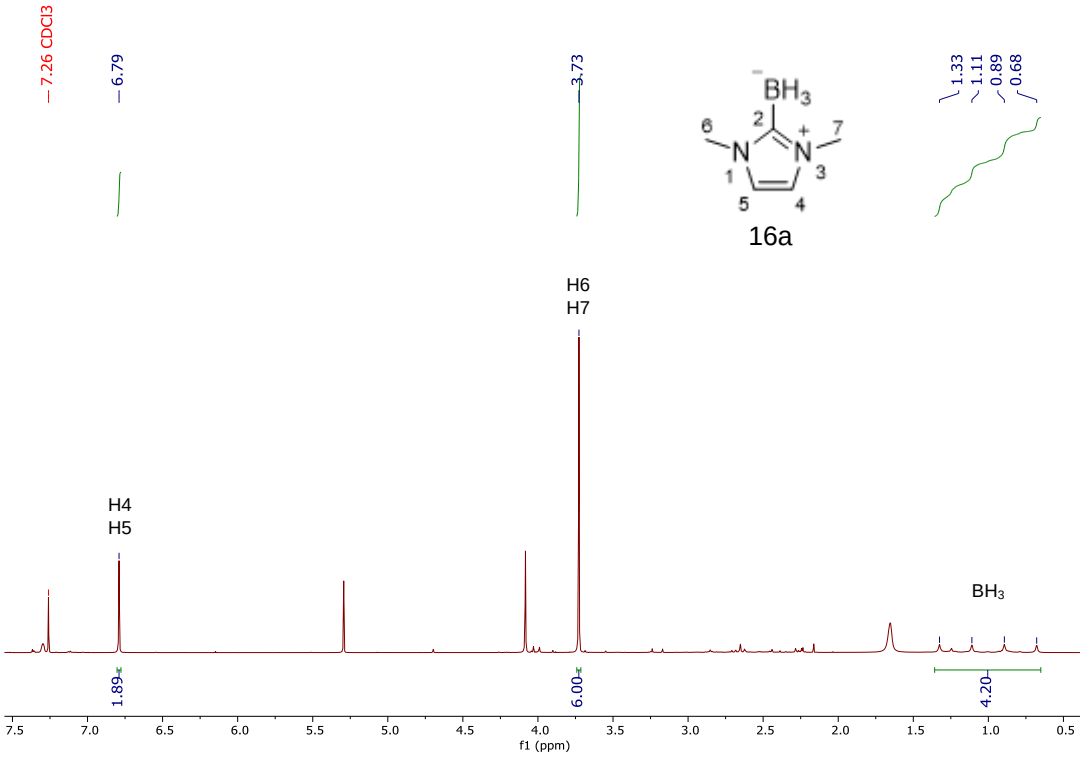


Figure 6.28 – ^{1}H MNR spectrum of (1,3-dimethylimidazolium-2-yl)trihydroborate (16a).

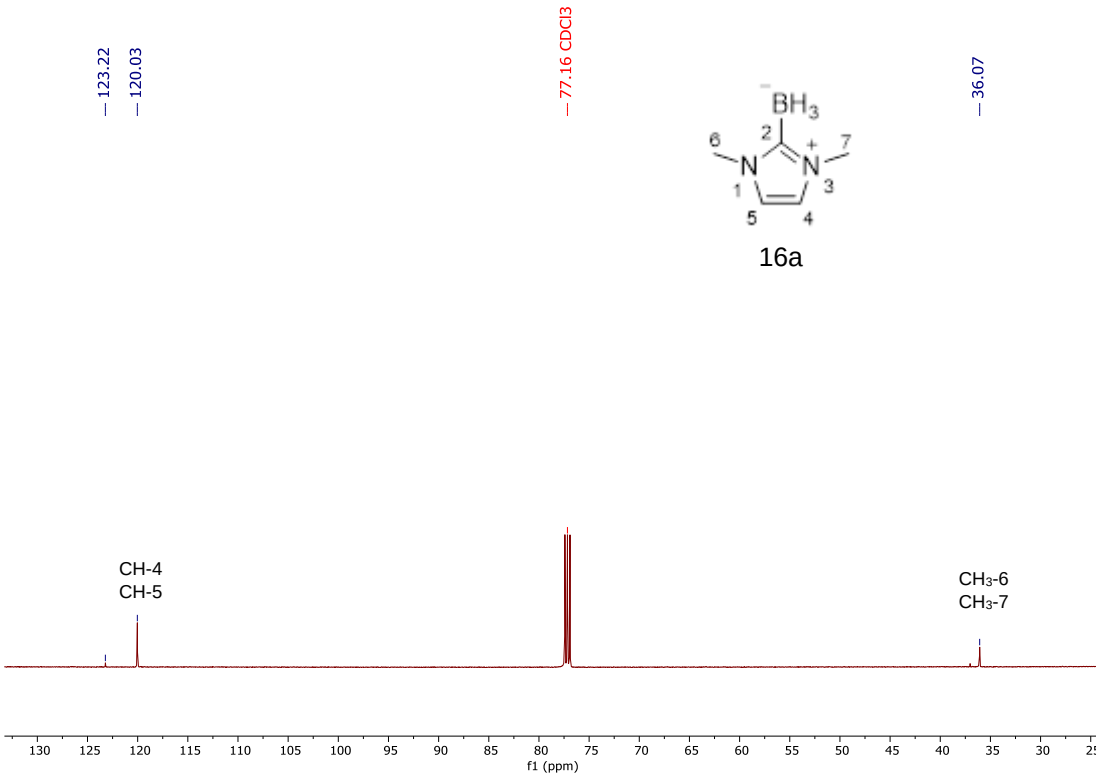


Figure 6.29 – ^{13}C MNR spectrum of (1,3-dimethylimidazolium-2-yl)trihydroborate (16a).

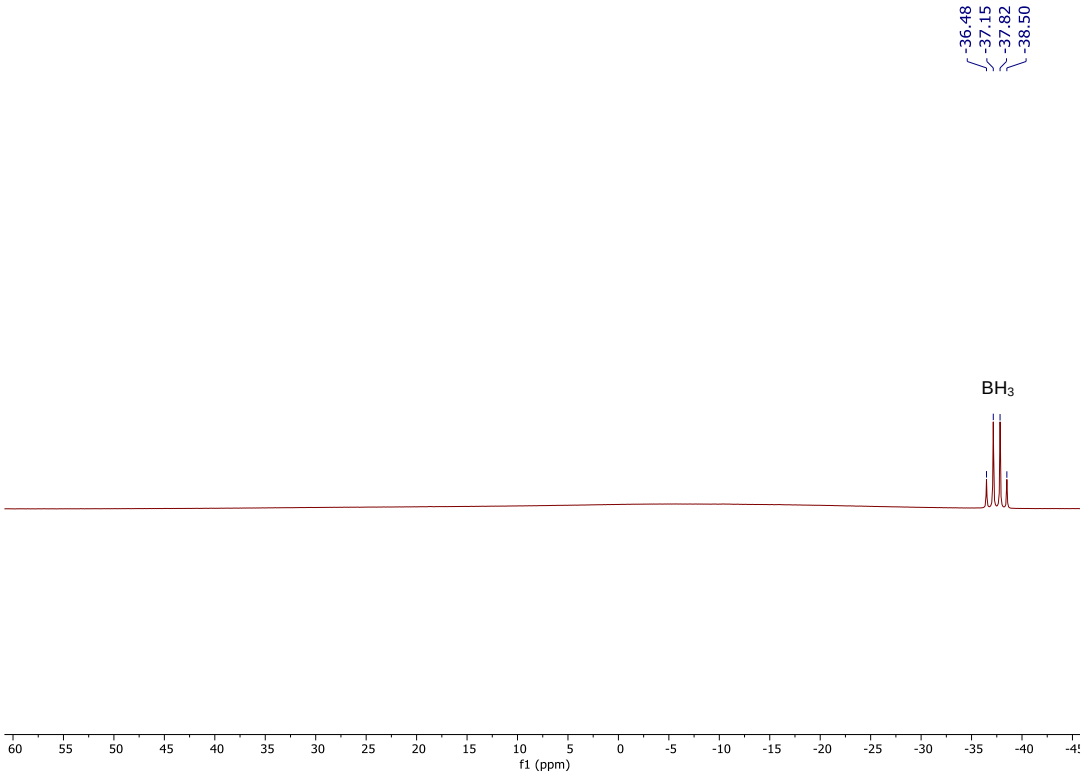


Figure 6.30 – ^{11}B MNR spectrum of (1,3-dimethylimidazolium-2-yl)trihydroborate (16a).

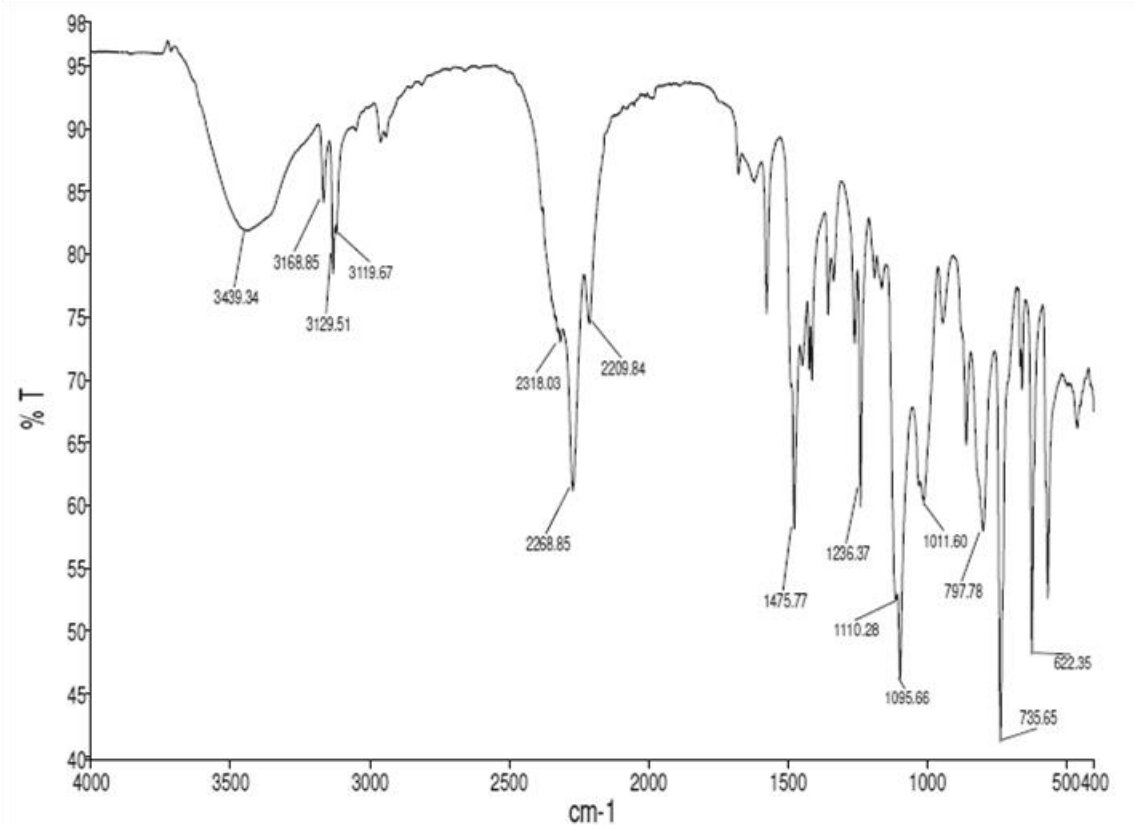


Figure 6.31 – IR spectrum of (1,3-dimethylimidazolium-2-yl)trihydroborate (16a).

APPENDIX 18 – (3-ETHYL-1-METHYLIMIDAZOLIUM-2-YL) TRIHYDROBORATE (16B)

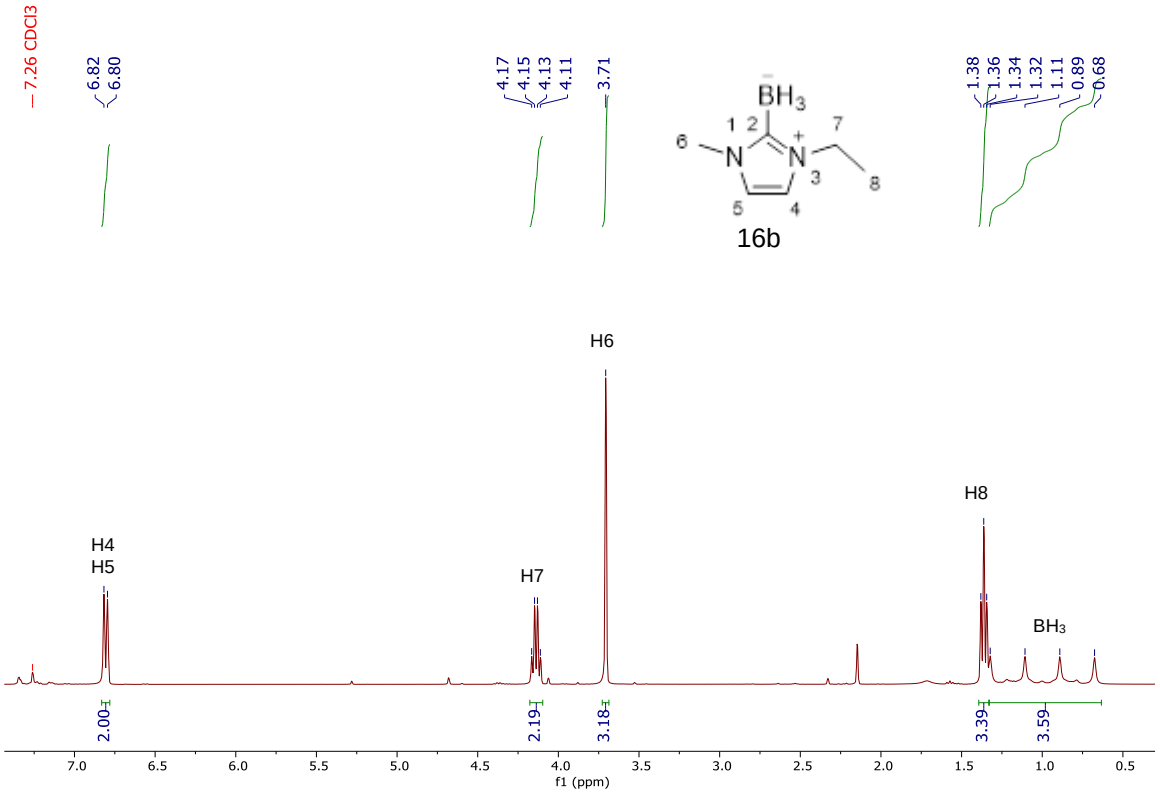


Figure 6.32 – ^{1}H NMR spectrum of (3-ethyl-1-methylimidazolium-2-yl)trihydroborate (16b).

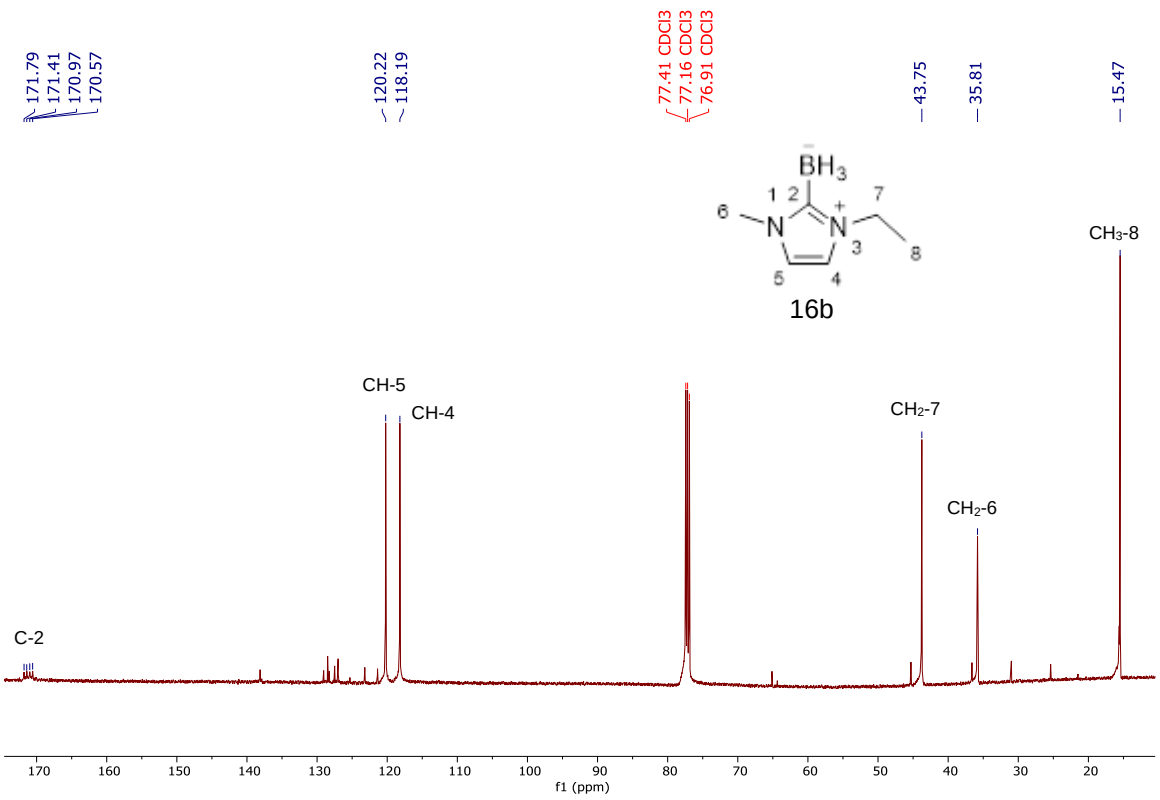


Figure 6.33 – ^{13}C NMR spectrum of (3-ethyl-1-methylimidazolium2-yl)trihydroborate (16b).

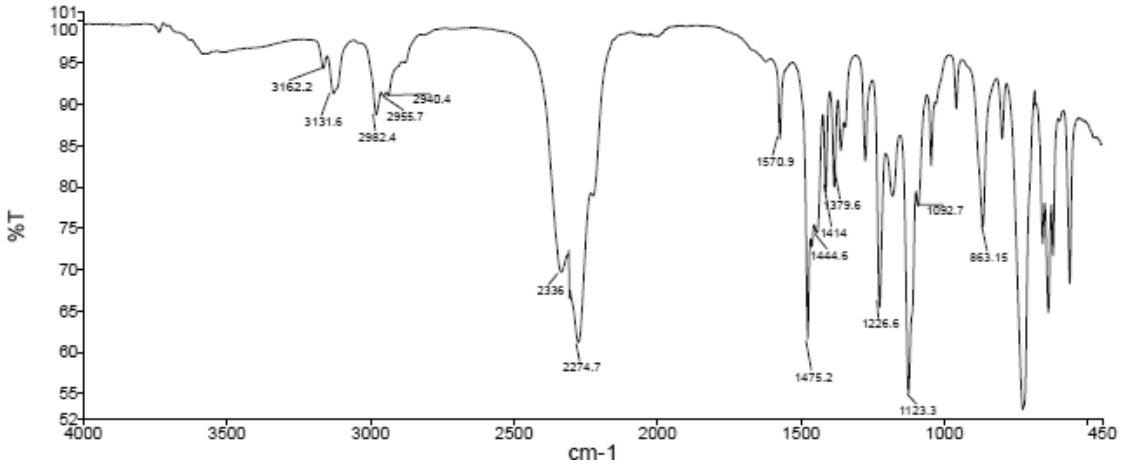


Figure 6.34 – IR spectrum of (3-ethyl-1-methylimidazolium-2-yl)trihydroborate (16b).

APPENDIX 19 – BLANK ASSAY USING *N*-(2-BROMO-4,5-METHYLENODIOXYBENZYL)ANILINE (1) AS A SUBSTRATE

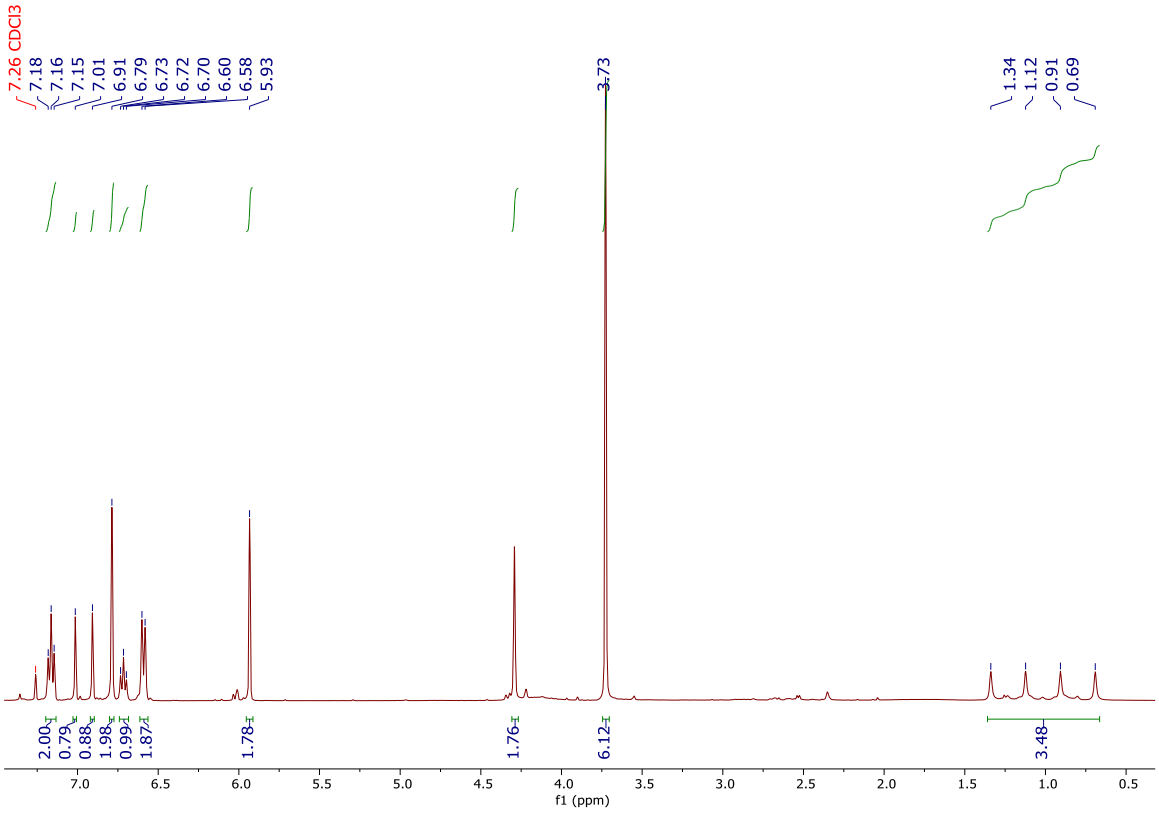


Figure 6.35 – ^{1}H NMR spectrum of the blank assay using *N*-(2-bromo-4,5-methylenodioxybenzyl)aniline (1) as a substrate.

APPENDIX 20 – [1,3]DIOXOLO[4,5-J]PHENANTHRIDINE (17)

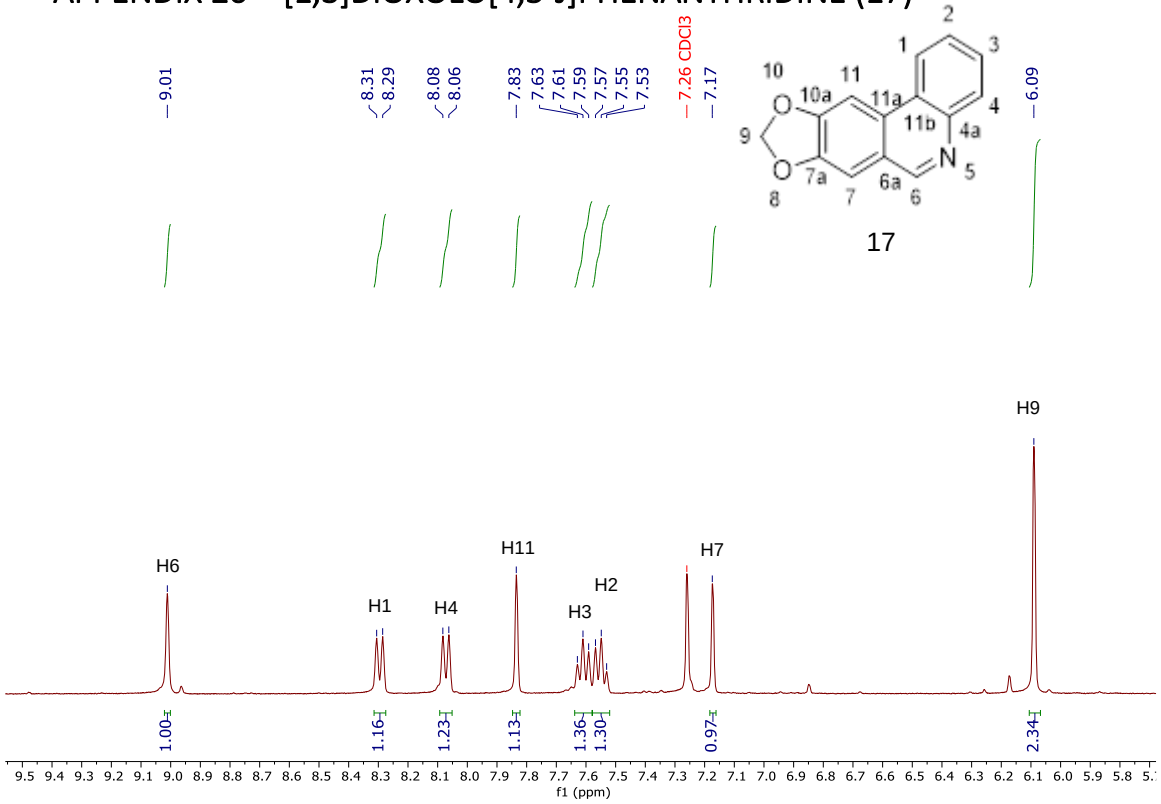


Figure 6.36 – ^{1}H NMR spectrum of [1,3]dioxolo[4,5-j]phenanthridine (17).

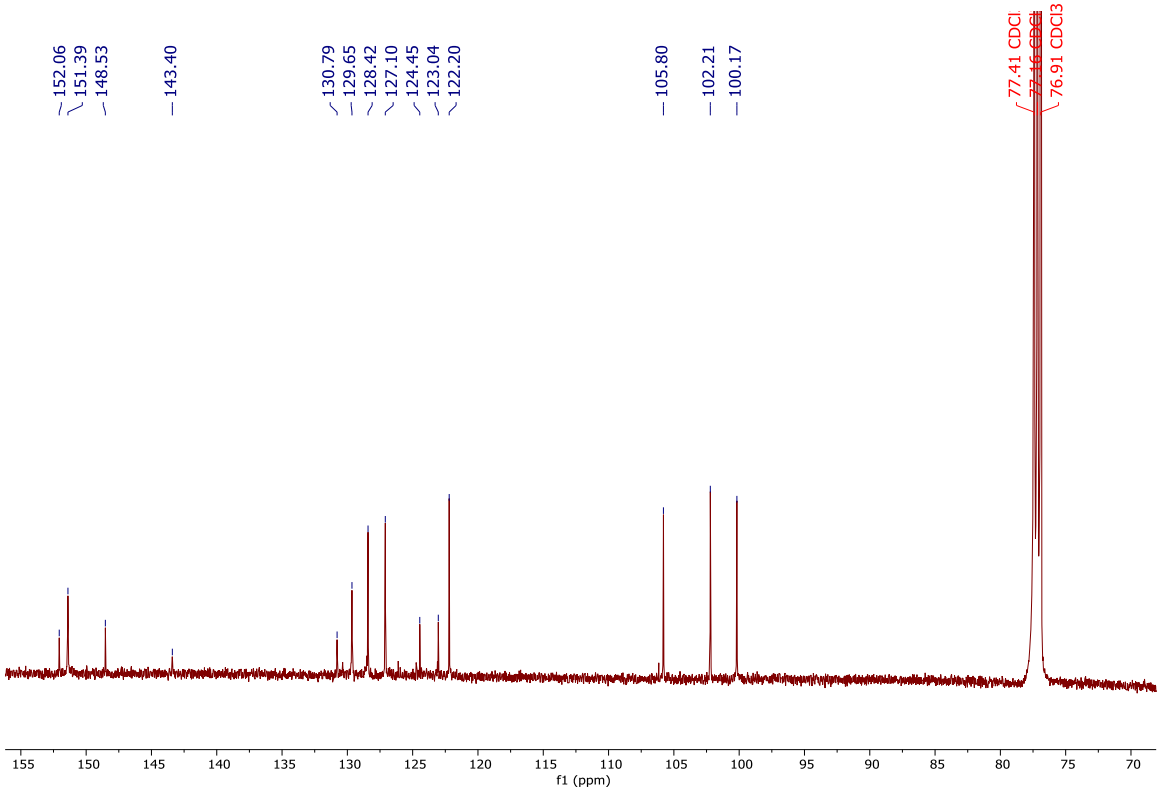


Figure 6.37 – ^{13}C NMR spectrum of [1,3]dioxolo[4,5-j]phenanthridine (17).

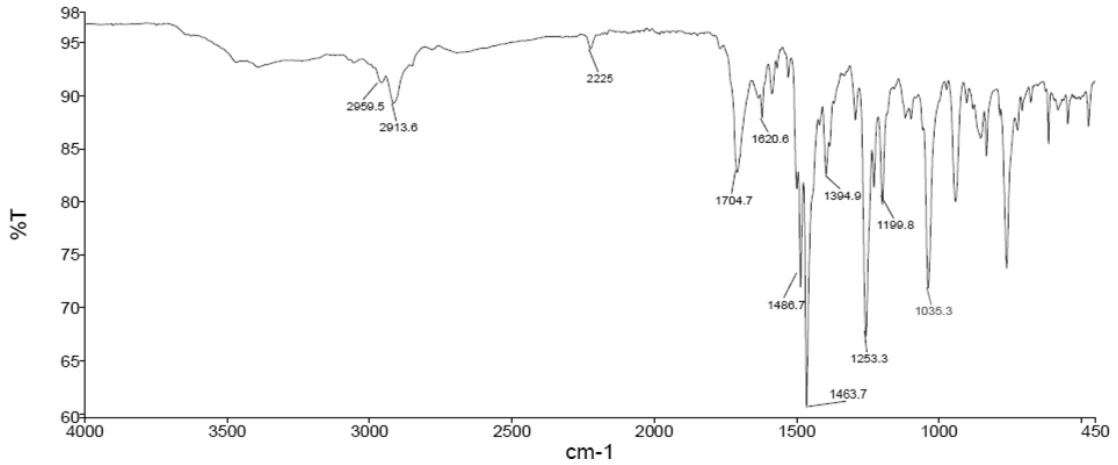


Figure 6.38 – IR spectrum of [1,3]dioxolo[4,5-j]phenanthridine (17).

APPENDIX 21 – BLANK ASSAY USING *N*-(2-BROMO-4,5-DIMETHOXYBENZYL)ANILINE (2) AS A SUBSTRATE

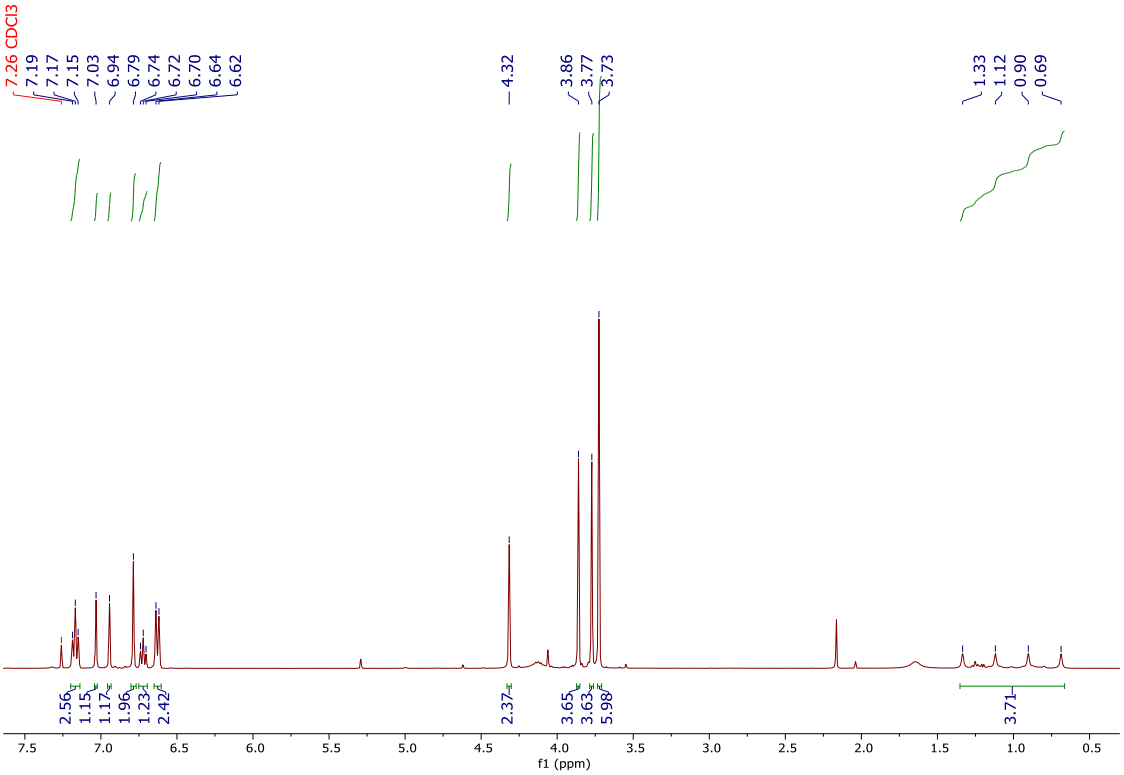


Figure 6.39 – ^{1}H NMR spectrum of the blank assay using *N*-(2-bromo-4,5-dimethoxybenzyl)aniline (2) as a substrate.

APPENDIX 22 – 8,9-DIMETHOXYPHENANTHRIDINE (18)

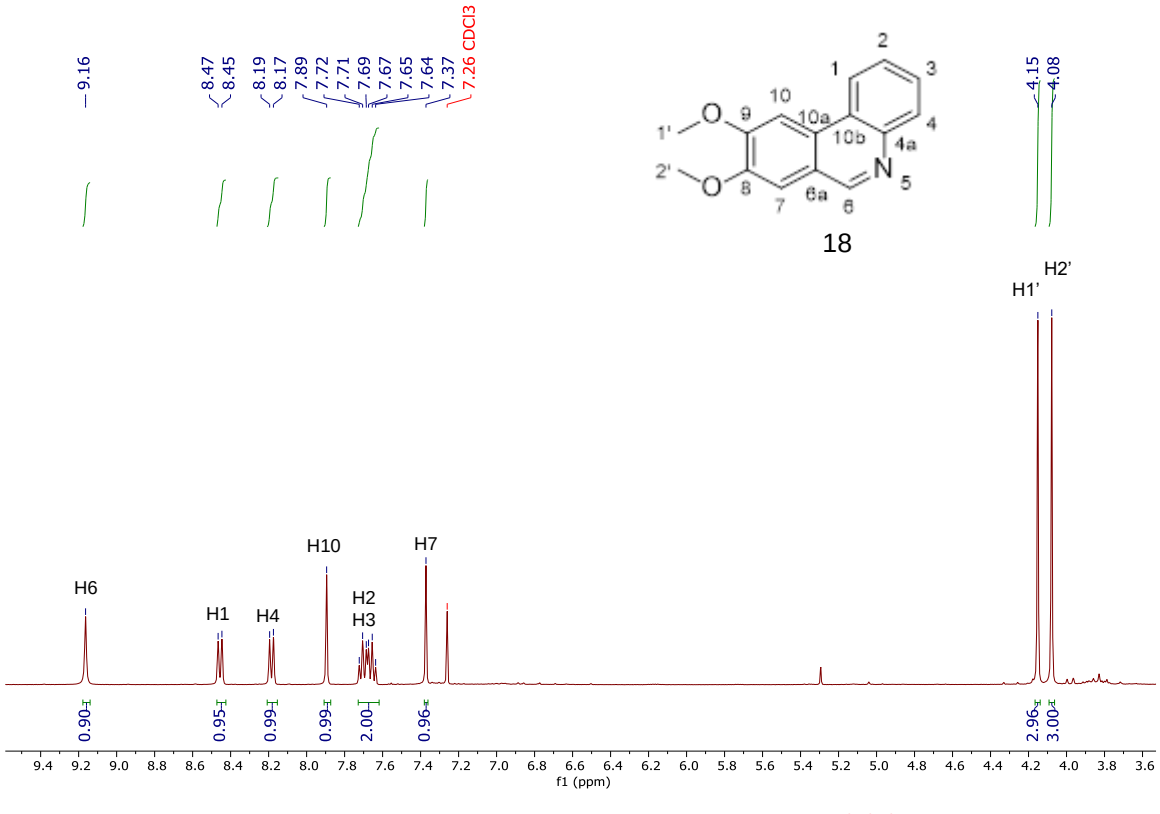


Figure 6.40 – ^{1}H NMR spectrum of 8,9-dimethoxyphenanthridine (18).

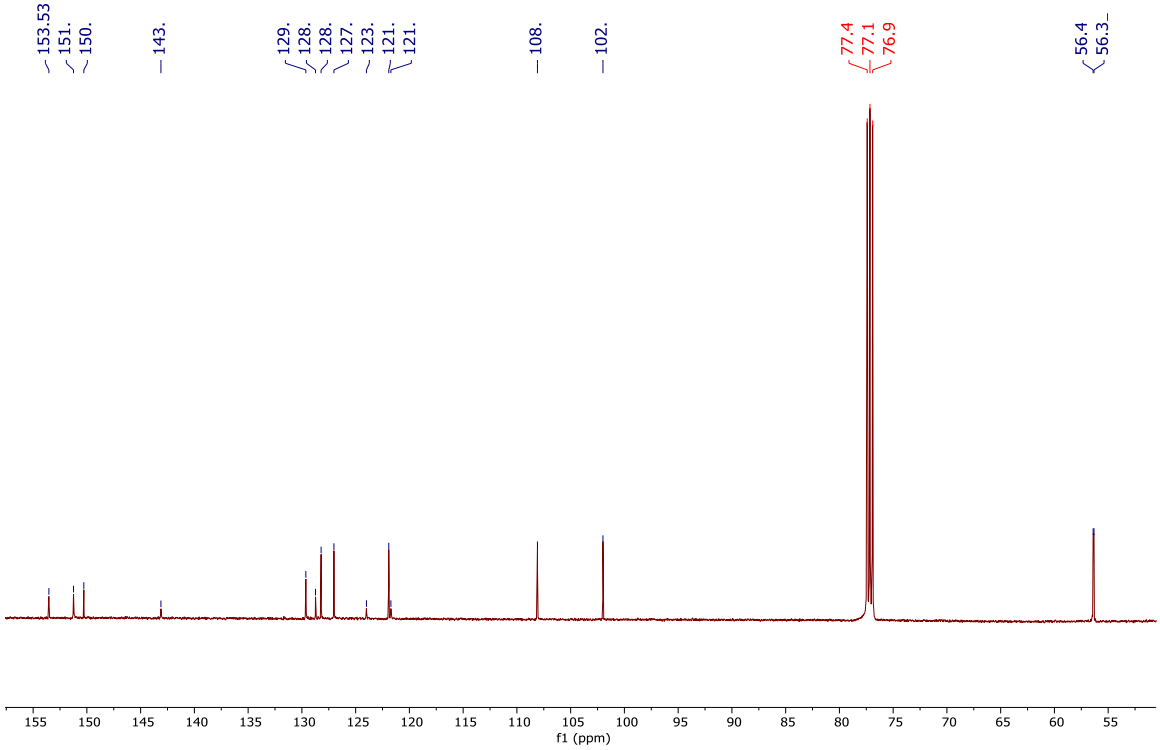


Figure 6.41 – ^{13}C NMR spectrum of 8,9-dimethoxyphenanthridine (18).

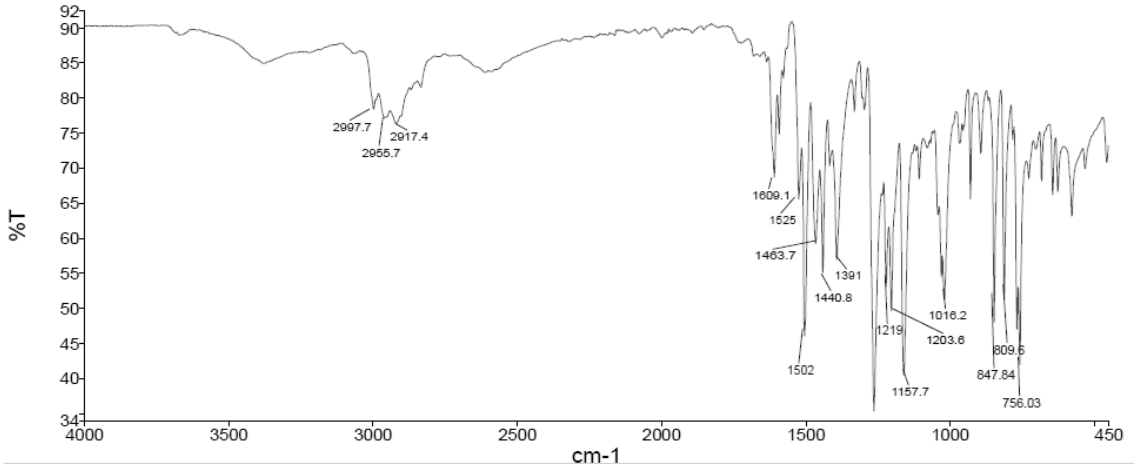


Figure 6.42 – IR spectrum of 8,9-dimethoxyphenanthridine (18).

APPENDIX 23 – BLANK ASSAY USING *N*-(2'-BROMOBENZYL-2,3-DIHYDROINDOLE (3) AS A SUBSTRATE

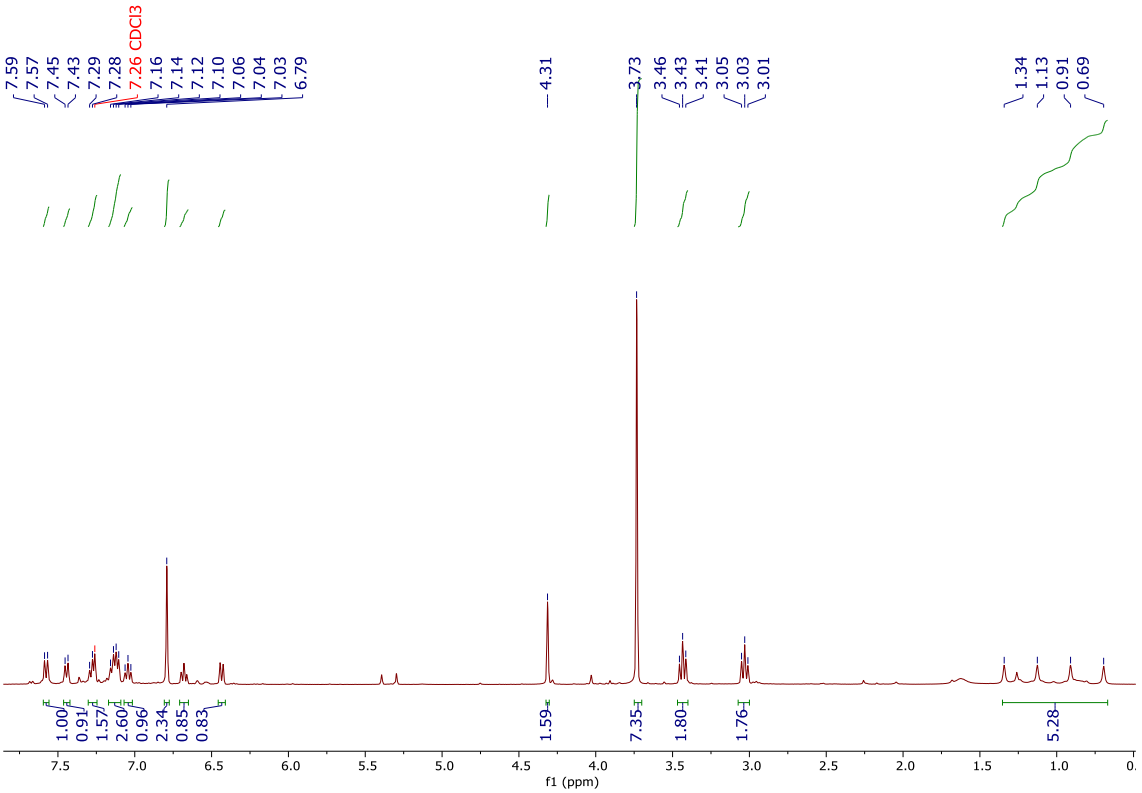


Figure 6.43 – ^{1}H NMR spectrum of the blank assay using *N*-(2'-bromobenzyl-2,3-dihydroindole (3) as a substrate.

APPENDIX 24 – 1-(2'-BROMOBENZYL)-1H-INDOLE (19)

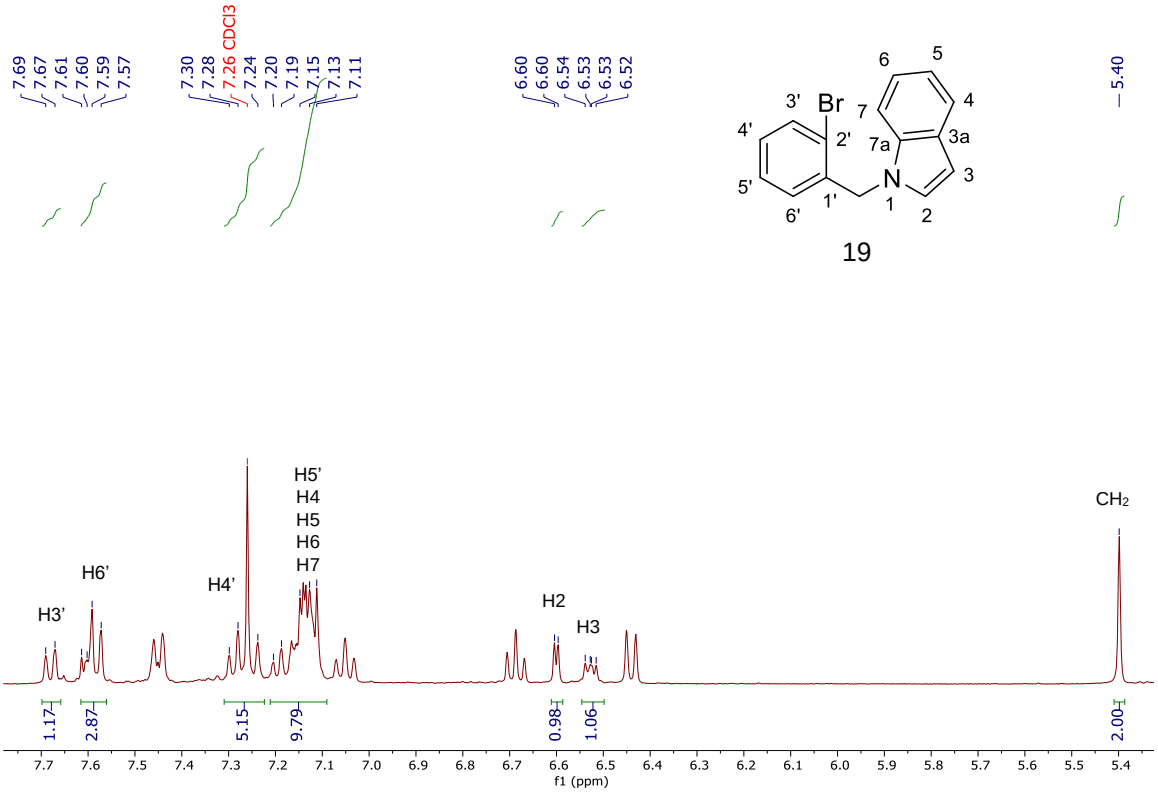


Figure 6.44 – ^{1}H NMR spectrum of 1-(2'-bromobenzyl)-1H-indole (19).

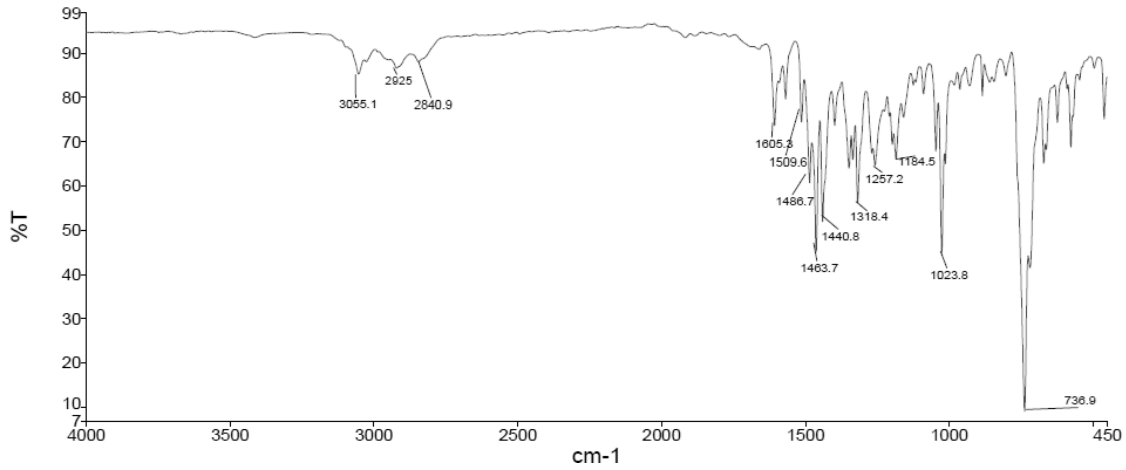


Figure 6.45 – IR spectrum of 1-(2'-bromobenzyl)-1H-indole (19).

APPENDIX 25 – 5-METHYLPHENANTHRIDIN-6(5H)-ONE (20)

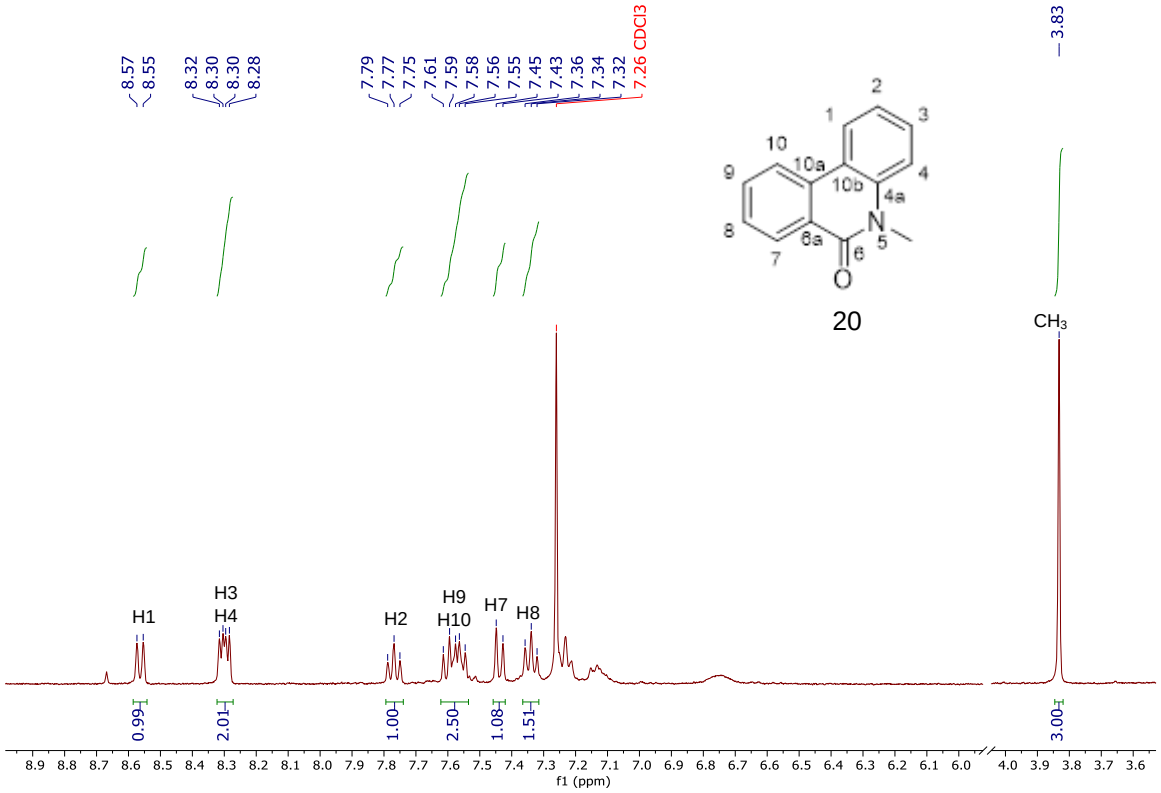


Figure 6.46 – ^{1}H NMR spectrum of 5-methylphenanthridine-6(5H)-one (20).

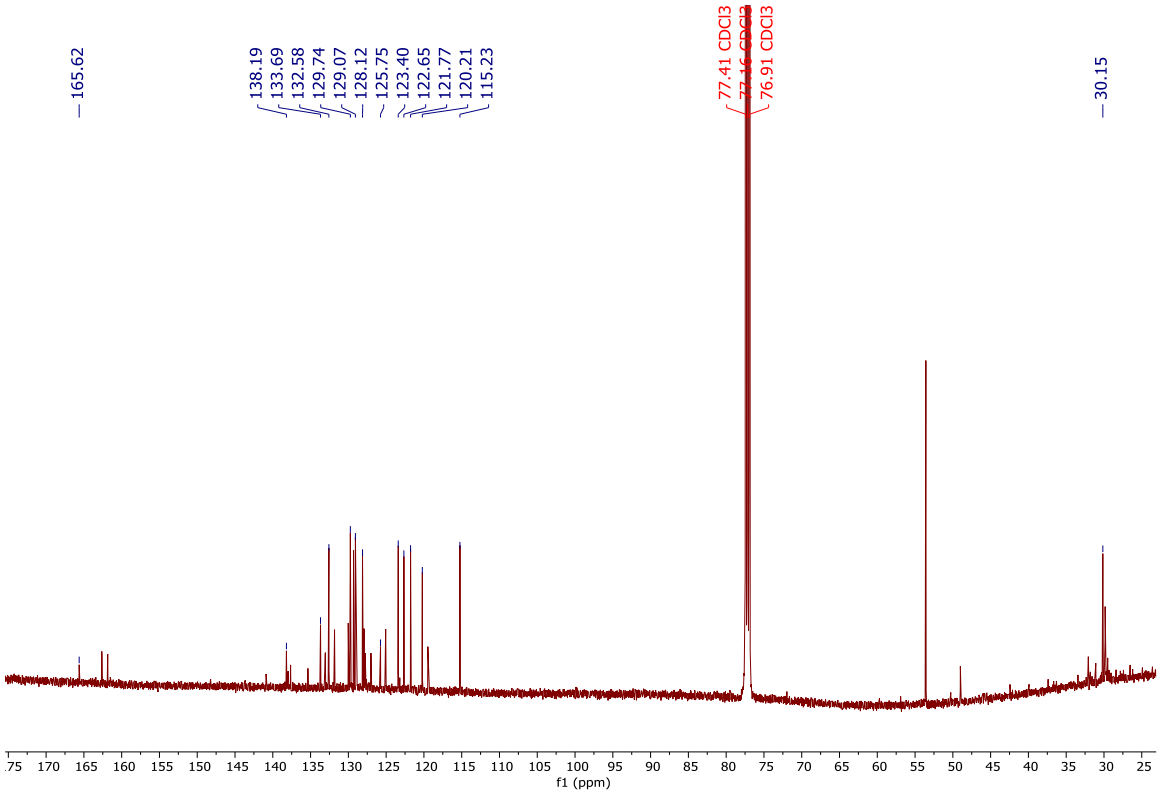


Figure 6.47 – ^{13}C NMR spectrum of 5-methylphenanthridin-6(5H)-one (20).

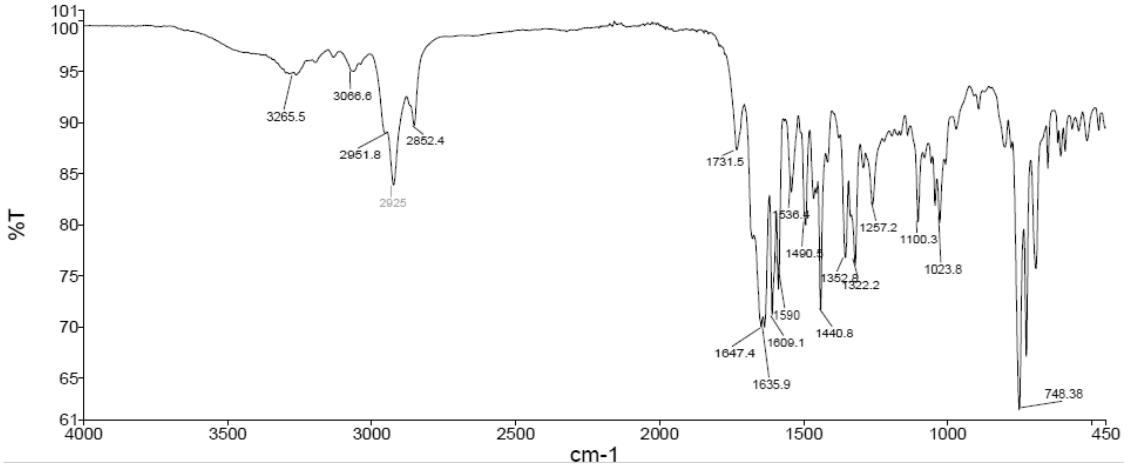


Figure 6.48 – IR spectrum of 5-methylphenanthridine-6-(5H)-one (20).

APPENDIX 26 – BLANK ASSAY USING *N*-(2-BROMOBENZYL)-*N*-METHYLANILINE (4) AS A SUBSTRATE

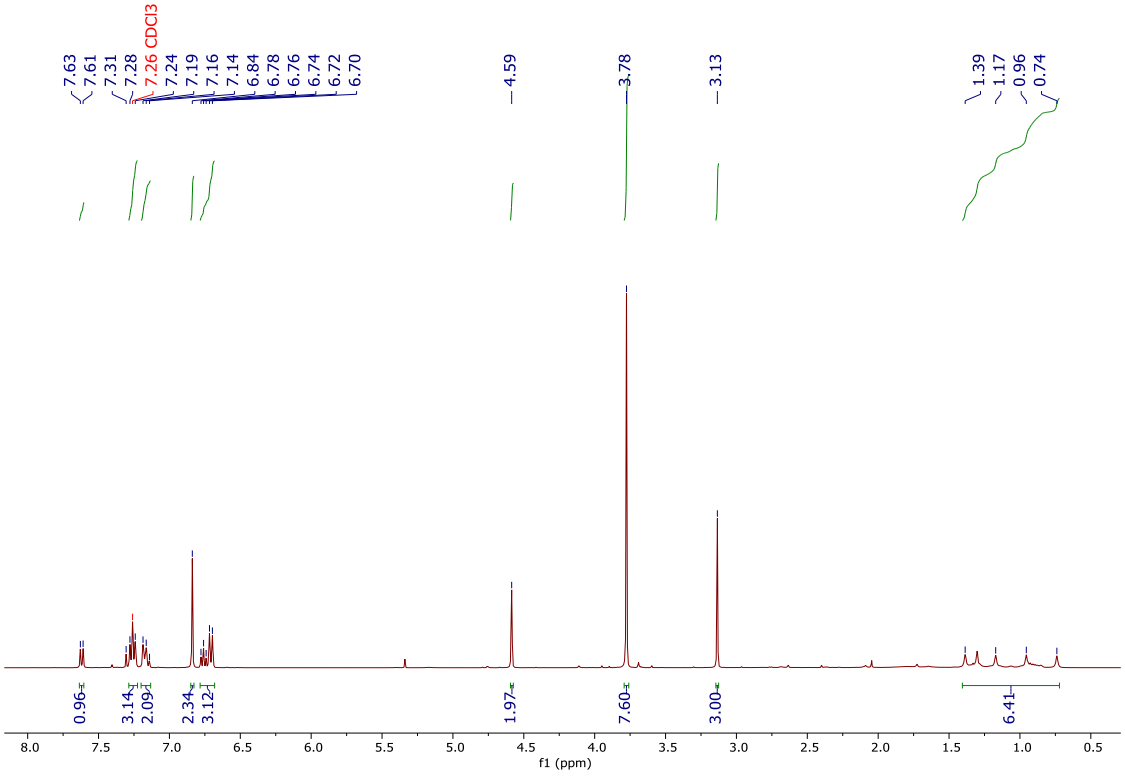


Figure 6.49 — ^{1}H NMR spectrum of the blank assay using *N*-(2-bromobenzyl)-*N*-methylaniline (4) as a substrate.

APPENDIX 27 – BLANK ASSAY USING *N*-(2-BROMOBENZYL)-*N*-PHENYLACETAMIDE (7) AS A SUBSTRATE

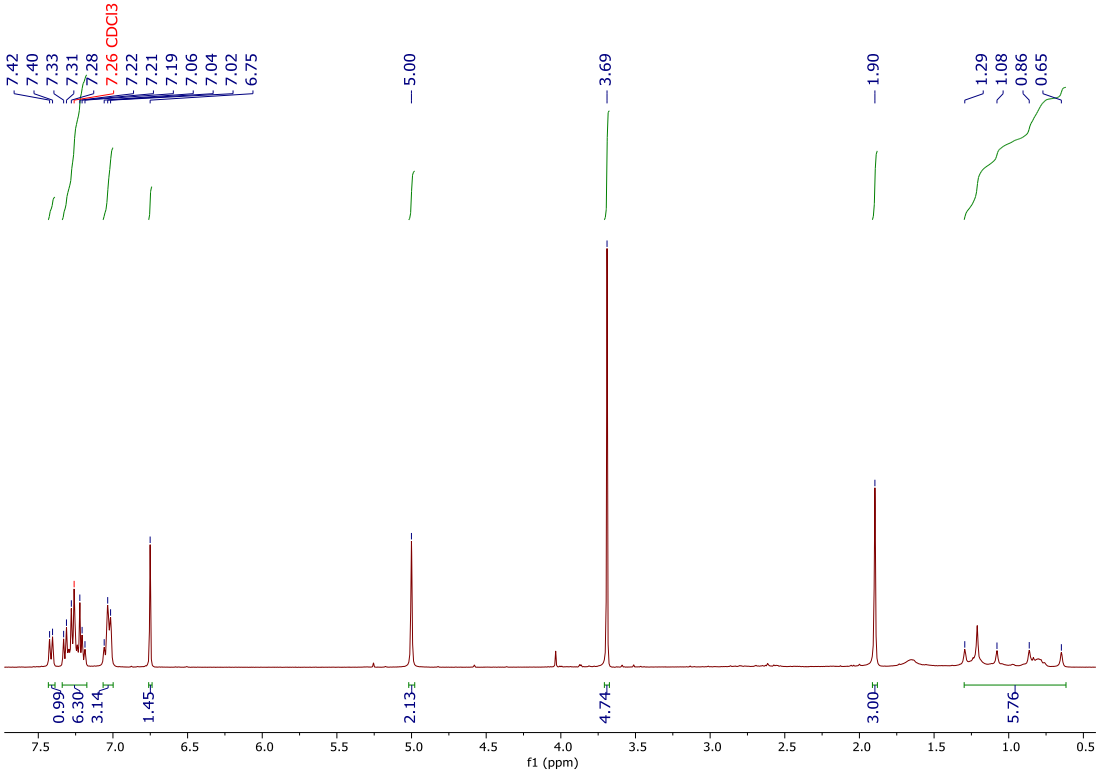
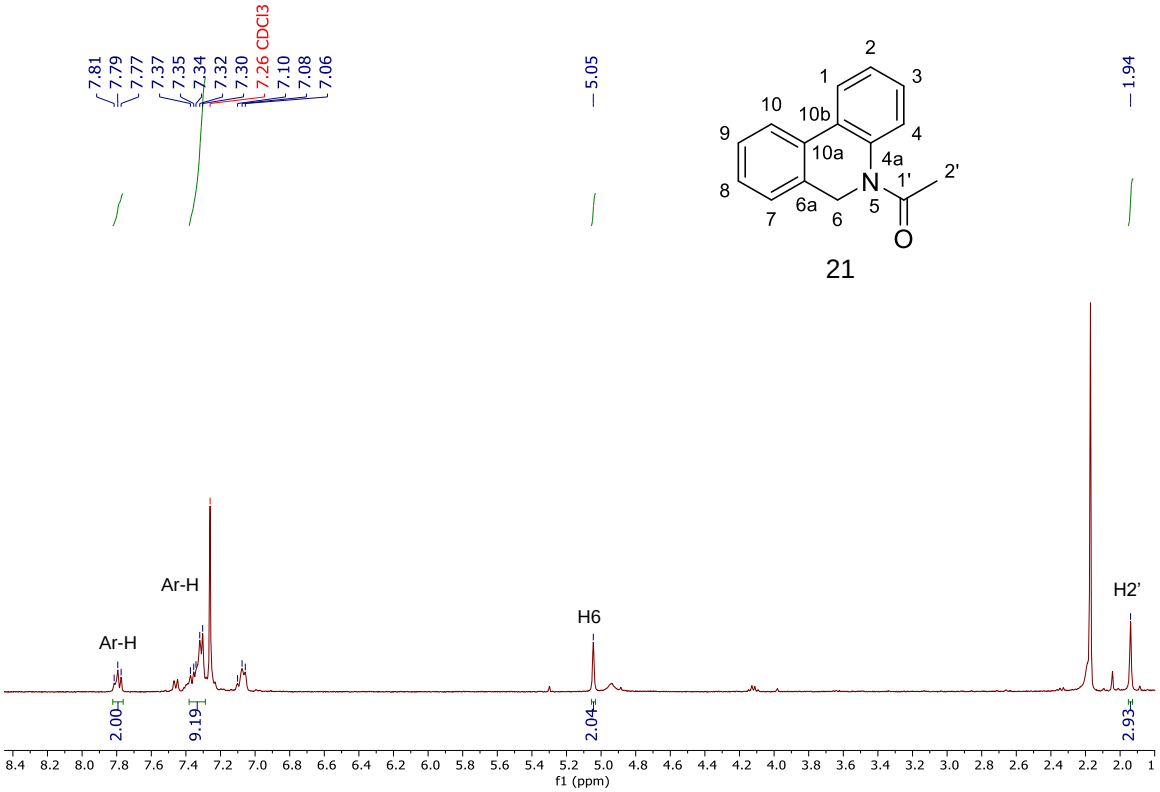


Figure 6.50 – ^{1}H NMR spectrum of the blank assay using *N*-(2-bromobenzyl)-*N*-phenylacetamide (7) as a substrate.

APPENDIX 28 – 1-(PHENANTHRIDIN-5(6H)-YL)ETHAN-1-ONE (21)



21

Figure 6.51 – ^{1}H NMR spectrum of 1-(phenanthridin-5(6H)-yl)ethan-1-one (21).

APPENDIX 29 – THIOPHENOL-NHC ADDUCT (22)

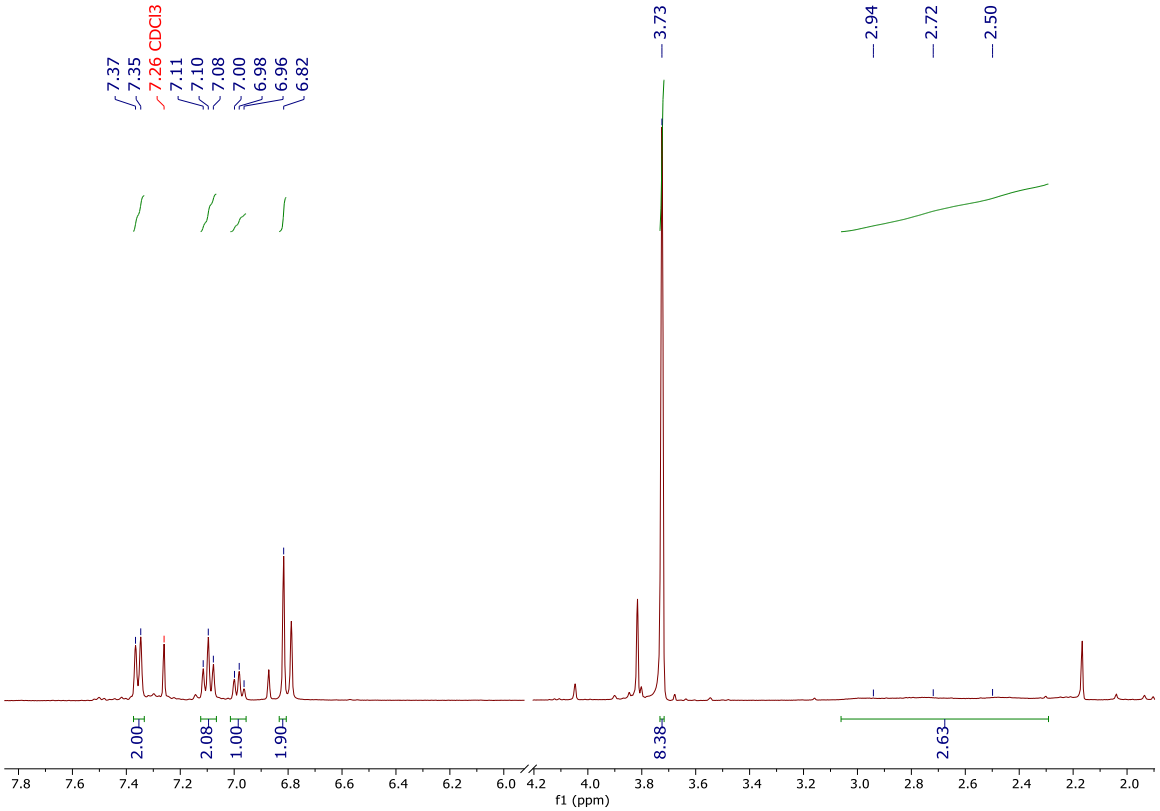


Figure 6.52 – ^{1}H NMR spectrum of the thiophenol-NHC adduct.