Modified Polonovski Reactions in Ionic Liquid Solvents

By

Julia Killorn

A Thesis Submitted to

Saint Mary's University, Halifax, Nova Scotia

in Partial Fulfillment of the Requirements for

the Degree of Bachelor of Science

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Approved: Dr. Robert Singer

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Date:

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Abstract

A modified Polonovski reaction using an iron (0) catalyst has been shown to be an effective means of *N*-demethylating opiate and pseudo-opiate compounds.[1] It has also been demonstrated that the choice of solvent in this reaction is of major significance as solvent effects play a large role in yields of *N*-demethylated product; isolated yields ranged from 59% (methanol) to 97% (chloroform). The current work aims to utilize the highly polar yet non-coordinating properties of ionic liquids as a reaction solvent. Ionic liquid solvents possess the added benefit of maximizing the solubility of the *N*-oxide hydrochloride starting material necessary for the modified Polonovski reaction. Use of commercial magnetite and rust nanoparticles as catalysts in ionic liquids for the modified Polonovski reaction will be discussed.

[1] Gaik B. Kok et al. J. Org. Chem. **2010**, *75*, 4806–4811.

Acknowledgements

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Abbreviations

nZVI	Nanoscale zero valent iron
$[BMIM]^+$	1-butyl-3-methylimidazolium
$[PF_6]^-$	Hexafluorophasphate
$[NTf_2]^-$	Bis(trifluoromethanesulfonyl)imide
DXM	Dextromethorphan
SEM	Scanning electron microscopy
LC	Liquid chromatography
TLC	Thin-layer chromatography
^{1}H NMR	^{1}Hydrogen nuclear-magnetic resonance
$[BMPyr]^+$	N-butyl-N-methylpyrrolidinium
i-PrOH	Isopropanol
^{13}C NMR	^{13}Carbon nuclear-magnetic resonance
DMSO-d6	Deuterated dimethylsulfoxide
IR	Infared
ATR	Attenuated total reflection
ESI-MS	Electrospray ionization mass spectrometry
mCPBA	Metachloroperoxybenzoic acid
RPM	Rotations per minute

1. Introduction

1.1. *N*-demethylation of Alkaloids

1.1.1. Introduction to alkaloids and *N*-demethylations

According to IUPAC[1], an alkaloid is a naturally occurring compound containing a basic nitrogen. These compounds are commonly heterocyclic and are derived from plants. The plant *Papaver somniferum*, otherwise known as the poppy plant, is an example of a plant that produces naturally occurring alkaloids; referred to as opiates. Many pharmaceutically used opiates differ from those that occur naturally. In naturally occurring opiates such as morphine, codeine and thebaine, the nitrogen is bonded to a methyl group (Figure 1). However, other pharmaceuticals can be synthesized by removing the naturally occurring *N*-methyl group and replacing it with an alkyl group that gives the compound different properties.[2] This is done by selectively cleaving the *N*-CH_3 bond, changing a tertiary amine into a secondary amine, before adding the new alkyl group.

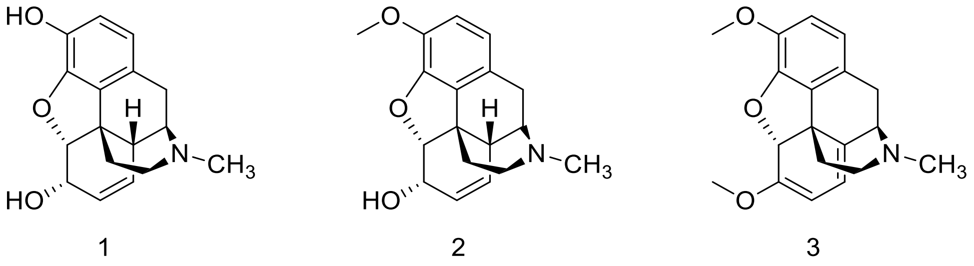


Figure 1. Structures of naturally occurring opiates, morphine, **1**, codeine, **2**, and thebaine, **3**.

N-demethylation is a key step in the synthesis of opiate alkaloid pharmaceuticals such as the opiate antagonists naloxone and naltrexone. These drugs are crucial in relieving the effects of opiate overdose. Specifically, naloxone hydrochloride is used to reverse the acute symptoms of opioid overdose and studies have found it to be a cost-effective strategy.[3] This is done by blocking the opiate receptors in the brain so that the opiate is no longer able to bind. Therefore, these drugs are used to save lives. The number of deaths related to opiate overdose are on the rise. In British Columbia alone the number of deaths in only the first half of 2016 was well over 300, which is an increase of over 74% from 2015.[4] Many of the lives lost could have been saved if drugs such as naloxone and naltrexone were made more available to the public. There has been a push to create take-home kits that may be employed in case of emergency by families and friends of drug users. As of October 3, 2016, naloxone was made available without a prescription in a nasal spray form to allow for easy administration.[5]

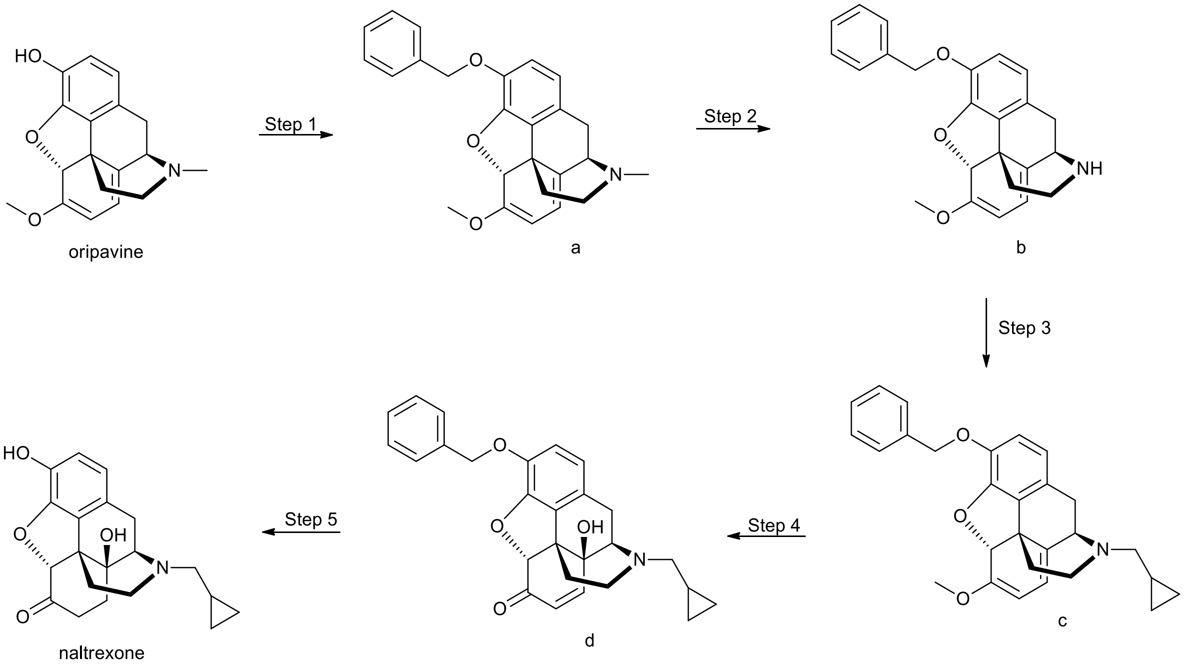


Figure 2. Synthesis of naltrexone.

This drug would not be available if not for the *N*-demethylation in the conversion of thebaine to naloxone[6] or oripavine to naltrexone (Figure 2).[7] The current work aims to improve this reaction with the use of ionic liquids and different iron sources so that these drugs can be made faster with higher yields while maintaining green solvents and catalysts to allow for use in industry.

1.1.2. History of *N*-demethylation Reactions

There are many different documented methods of *N*-demethylating a compound; however, many of them have clear shortcomings. The von Braun reaction (Figure 3) was reported in 1900 as an approach to *N*-demethylating a tertiary amine.[8]

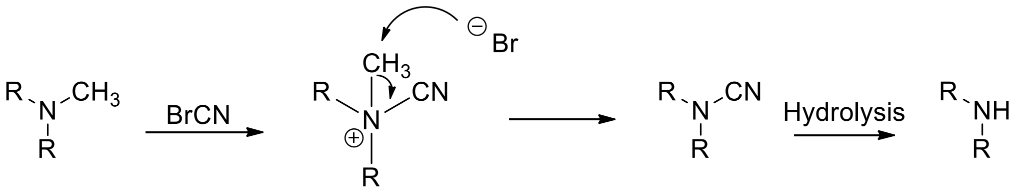


Figure 3. Von Braun reaction scheme.

This reaction yields a secondary amine through the use of cyanogen bromide followed by acid or base hydrolysis. This method of *N*-demethylating alkaloids is not used today as it requires the use of a toxic reagent, cyanogen bromide. Further advances included photooxidation, reported in 1989 (Figure 4).[9]

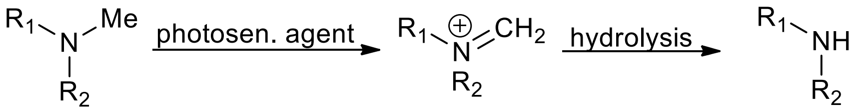


Figure 4. Photooxidation reaction scheme.

Despite being able to obtain good yields, this mechanism requires the use of expensive materials which is not desirable in large scale reactions.

1.1.3. Polonovski Reaction

The method of *N*-demethylation that is the focus of this work is the Polonovski reaction. This reaction was first reported in 1927 by Max and Mitchell Polonovski[10] and includes the conversion of a tertiary amine to a secondary amine. This conversion is done by first transforming the tertiary amine to the *N*-oxide which is then further reacted with an activating agent. The activating agent can be acylating agents, iron salts or sulfur dioxide, leading to the *N*-demethylated product.[2]

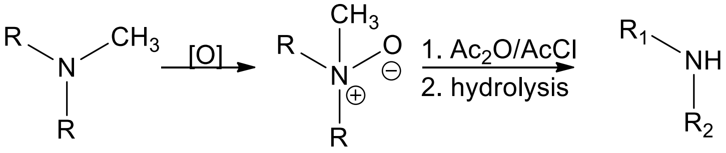


Figure 5. Scheme of Polonovski reaction.

The original Polonovski reaction utilized chloroformate esters as the activating agent (Figure 5). However, the cost of these reagents lead researchers to investigate the use of iron salts instead. In 2003, McCamley *et al.*[2] found that iron(II) salts, such as $FeSO_4 \cdot 7H_2O$, produced high yields and were a much greener alternative to the other activating agents possible for this reaction (Figure 6).

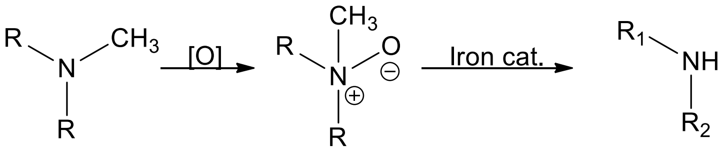


Figure 6. Scheme of Non-classical Polonovski reaction.

McCamley *et al*. proposed a mechanism for their modified Polonovski reaction (Figure 7). In this mechanism there are two successive one electron steps. Initially, the *N*-oxide, **4,** must undergo protonation to form **5**. Fe(II) will then undergo a one-electron reduction leading to the cleavage of the N-O bond and the formation of an amine radical cation, **6**. The radical cation will selectively lose an α-proton from the methyl group. This selectivity occurs due to the relative acidity of the protons in the molecule as well as steric and electronic effects. Once the α-proton is lost an electron reorganization occurs resulting in a carbon centred radical, **7**. The carbon centred radical is then oxidized by Fe(III) forming an iminium ion, **8**. Finally, hydrolysis will generate the desired secondary amine, **9**. There is a side product formed if the amine radical cation is reduced instead of oxidized. This forms the original tertiary amine of the starting material, **10**.

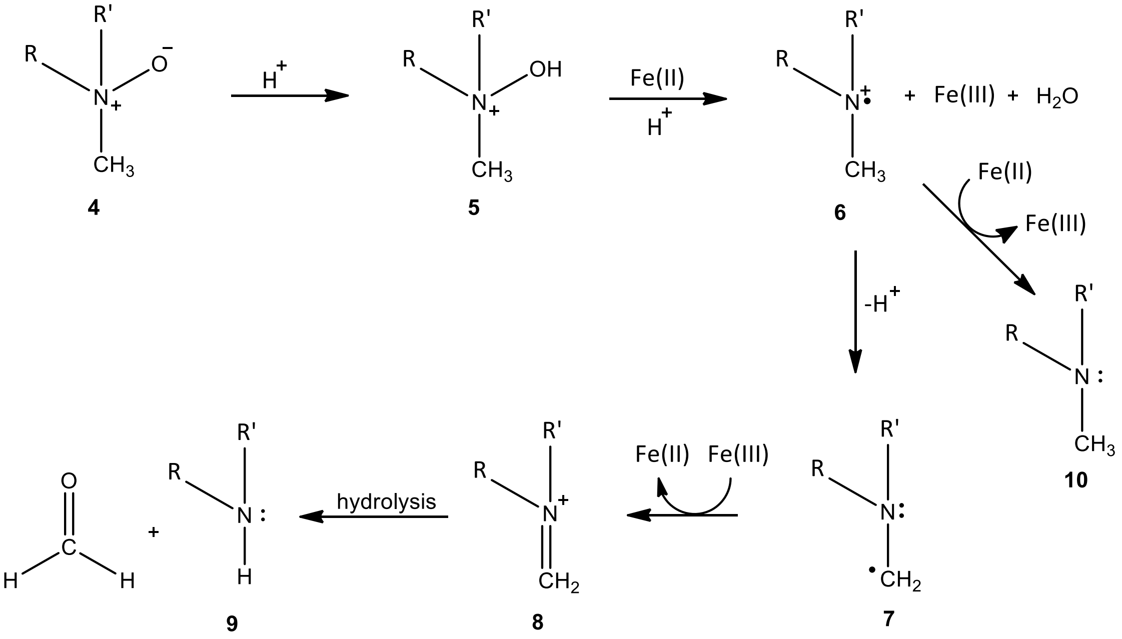


Figure 7. Proposed mechanism of the modified Polonovski reaction.

1.2. Iron sources

1.2.1. Nanoscale Zero Valent Iron

Based on the proposed mechanism shown in Figure 7, Kok *et al*[11] investigated the catalytic capability of iron(0) dust in the Polonovski reaction. The proposed mechanism depends on the Fe(II)/Fe(III) redox system. However, iron can also exist in the zero oxidation state. The presence of Fe(0)/Fe(II)/Fe(III) redox potentials allow for Fe(0) to be a possible source of electrons in this reaction. Previous work in the Singer Group[12] demonstrated that the use of nanoscale zero valent iron (nZVI) represents yet another improvement on the classical Polonovski reaction. The nZVI functions as a heterogeneous catalyst. In heterogeneous catalysis the catalyst is in a different phase than that of the reactants. In this case the reactants are dissolved in a solvent and therefore in the liquid phase whereas the nZVI is a solid catalyst. This reaction will involve the adsorption of the reactants onto the solid catalyst followed by a surface reaction (electron transfer) of the adsorbed species and finally desorption of products.[13] Due to the reduced particle size of nZVI it performs this reaction very well. The size of a nanoparticle is typically between 1-100 nm.[14] When the particle size decreases the surface area to volume ratio increases. This increase in surface area results in more active sites available for reactions to occur. Therefore, nanoparticles have increased reactivity compared to a larger particle size.

1.2.2. Magnetite Nanoparticles

Magnetite is one of the most abundant metal oxides on earth. It has the chemical formula Fe_3O_4 and contains both iron(II) and iron(III) ions. It can be found in igneous as well as sedimentary rocks. Magnetite nanoparticles have been shown to have many applications including heavy metal removal[15], magnetic resonance imaging[16], targeted drug delivery[17], magnetic data storage[18], and catalytic materials.[19] In the current research magnetite nanoparticles are utilized as an iron catalyst in the modified Polonovski reaction. As seen in the proposed mechanism (Figure 7) the presence of Fe(II) and Fe(III) are required for this reaction to proceed. Since magnetite is made up of Fe(II) and Fe(III) species, this will lead to enhanced reactivity. Magnetite nanoparticles, as with all nanoparticles, can be synthesized by many different techniques. These methods can be split into two general approaches: bottom-up and top-down. The bottom-up approach produces nanoparticles starting from single atoms, whereas the top-down approach produces nanoparticles from breaking down bulk solids with an external force.[14] As with any nanoparticle, the particle size, shape, and dispersity of magnetite nanoparticles is dependent on the method of synthesis.[20] The most common method of synthesizing magnetite nanoparticles, coprecipitation, is an example of the bottom-up approach. This is done by co-precipitating ferrous and ferric (iron II and III) ions in alkaline medium.[21] Other common bottom-up methods include thermal decomposition[22] and sol-gel[23] techniques. Magnetite nanoparticles can also be formed *via* the top-down methods such as crushing, milling, or grinding. Co-precipitation may be considered the most economic and practical way to produce magnetite nanoparticles; however, bulk magnetite is a mineral and therefore crushing, milling and grinding are alternative environmentally friendly routes[21] despite being energy intensive.

1.2.3. Rust nanoparticles

Rust is an iron oxide and has the chemical formula Fe_2O_3 and contains solely Fe(III) ions. It is most commonly formed when iron, or an iron alloy such as steel, undergoes an oxidation due to the presence of oxygen and water. Rust has a negative connotation associated with it as it is known to destroy cars and tools, and can be economically draining. In the case of the modified Polonovski reaction it could be quite beneficial. As previously stated, iron catalysts have been shown to work in this reaction and are a green alternative to the harsher reagents historically used. Using rust is a green approach as it is formed naturally by allowing iron to oxidize in a wet environment. The only perceived problem is that the proposed mechanism for the Polonovski reaction requires the presence of not only iron(III) but also iron(II). If there is only iron(III), such as in rust, the reaction should not proceed. An easy solution to this dilemma is the addition of an iron(II) salt such as $Fe_2SO_4 \cdot 7H_2O$. In order to maintain the similar reactivity to the current benchmark (nZVI) the rust used will also be nanoscale (10-100 nm).

1.3. Ionic liquids

In 1914 the first ionic liquid, ethylammonium nitrate, was described by Paul Walden with a melting point of 12°C.[24] The discovery and development of the field of ionic liquids has grown substantially since then with the first water-stable imidazolium-based ionic liquid, ethylmethylimidazolium tetrafluoroborate, being reported in 1992 by Wilkes and Zaworotko.[25] Ionic liquids consist of an organic cation, such as imidazolium, pryidinium, pyrrolidium, and an inorganic anion, such as tetrafluoroborate, hexafluorophosphate, or bis(trifluoromethanesulfyl) imide.[26] The most common ionic liquids in the literature are imidazolium-based. One of the main applications of imidazolium-based ionic liquids is as solvents. The intention of the current research is to use ionic liquids as a green alternative to organic solvents, such as chloroform. Ionic liquids have been explored as solvents in many types of reactions such as hydrogenations, alkylations[27], Diels-Alder[28] and Friedel-Crafts[29] and others.

The solvents commonly used in the modified Polonovski reaction are conventional organic solvents such as chloroform and isopropanol. However, there is increasing interest in using ionic liquids as reaction solvents due to their many unique properties. Ionic liquids are characterized by their low melting points, usually < 100°C due to the weak intermolecular forces between the large, charged ions. These low melting points make most of them liquid at room temperature and stable over a wide temperature range. They also have negligible vapour pressure[30], are highly polar yet non-coordinating[27], are recyclable[31], and have good solubilising properties[32]. The ionic liquids of interest in this research are 1-butyl-3-methylimidazolium hexafluorophosphate, [BMIM] [PF_6] (Figure 8), as well as 1-buytl-3-methylimidazolium bis(trifluoromethanesulfonyl) imide, [BMIM] [NTf_2] (Figure 9).

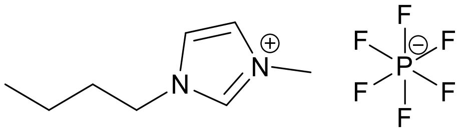


Figure 8. Structure of [BMIM] [PF_6].

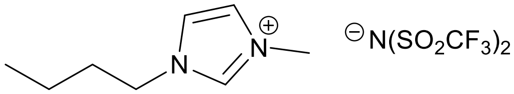
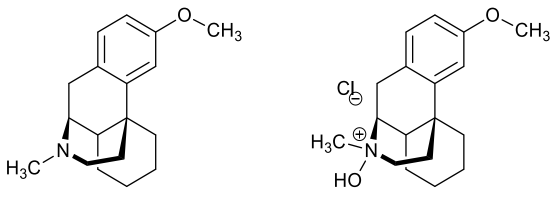


Figure 9. Structure of [BMIM] [NTf_2].

These specific ionic liquids were chosen because of many factors. Firstly, the substrate and the products are soluble in these ionic liquids. Secondly, the iron catalyst forms a suspension, making the iron and ionic liquids recyclable. Since the catalyst forms a suspension in the ionic liquids it is easily retained in the ionic liquid during the extraction process. This allows for the ionic liquid and catalyst to be reused without needing to replenish the iron. Finally, both ionic liquids have been used extensively in the Singer group and therefore the syntheses are well known and can be conducted with high yields with minimal purification required.

1.4. Opiate alkaloid model substrate

The goal of this research is to improve upon the current benchmarks for the modified Polonovski reaction, with the goal of eventually using this process in the large scale *N*-demethylation of opiate compounds. However, special permits required to work with opiates were not available and an alternative model compound was necessary. The pseudo-opiate dextromethorphan (DXM) seen in Figure 10, was chosen as an ideal substrate for multiple reasons. Not only is dextromethorphan not a controlled substance, it is also readily available, easy to work with and examples of its *N*-demethylation are present in the literature[6], which allows for direct comparison of the results obtained to the current benchmark. Dextromethorphan is considered a pseudo-opiate as it is structurally similar to opiates. It contains several ring structures that are in naturally occurring opiates and most importantly contains the characteristic *N*-methyl group. The hydrobromide salt of dextromethorphan is commercially available and can be easily converted to the starting material of the reaction, DXM *N*-oxide HCl (Figure 10).



10 11

Figure 10. Structure of pseudo opiate DXM, **10**, and DXM *N*-oxide HCl, **11**.

1.5. Objectives

This research project investigates the modified Polonovski reaction for the *N*-demethylation of alkaloids in an ionic liquid solvent. The goal of the current research is to improve upon earlier conditions of the Polonovski reaction by making the synthesis greener while maintaining the high yields and short reaction times. This reaction will be carried out using different sources of iron (nZVI, magnetite and rust) as a catalyst and different ionic liquids ([BMIM] [PF_6], and [BMIM] [NTf_2]) as the solvent. This reaction will be compared to the current benchmark, nZVI in isopropanol.

2. Results and Discussion

The ideal starting place for new research is to continue the work already published in the field. Previous work in the Singer group[12] utilizing DXM and iron as a substrate and catalyst, respectively, to perform the modified Polonovski is the obvious place to start. The current work is a continuation of the previous research using iron as a catalyst in the form of Fe(0) dust as well as nZVI. The main outcome of this research showed that when the size of the iron particles is reduced it increases the reactivity, allowing for significantly shorter reaction times. Solvent effects were shown to have a large impact on the yields obtained from this reaction regardless of catalyst.[11] Therefore, multiple solvents were investigated. When nZVI was used, isopropanol was the solvent that was found to have the best yields, reaching 86%, and short reaction times, as low as 45 minutes.[12] This represents the benchmark for this reaction. Ionic liquids are considered a green solvent and have many desirable properties that make them an interesting solvent to investigate for this reaction. In order to get a complete idea of the possible solvent effects for the *N*-demethylation of DXM, 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM] [PF_6] was chosen.

The nZVI was synthesized in [BMIM] [PF_6] and water and the reaction yielded 47% nor-product. This is significantly lower than the average 86% yields of nZVI in isopropanol. During the trials of this reaction the nZVI continually oxidized before the dextromethorphan was added, as well as during the course of the reaction, signified by the change of the nanoparticles from black to orange. Once the nZVI is oxidized there is only Fe(III) present and the reaction cannot proceed. It was speculated that the ionic liquid would function as a capping agent for the nanoparticles allowing them to not be oxidized as readily; however, this did not appear to be the case. Due to an inability to obtain consistent results and better yields the focus of the research was directed towards different iron sources in the isopropanol as well as different ionic liquids.

The magnetite nanoparticles were purchased from Sigma Aldrich and, therefore, the reactants were added to a round bottom flask and utilized with no additional preparation required. Characterization of the nanoparticles was conducted using a TESCAN MIRA 3 LMU Variable Pressure Schottky Field Emission Scanning Electron Microscope located at Saint Mary’s University.

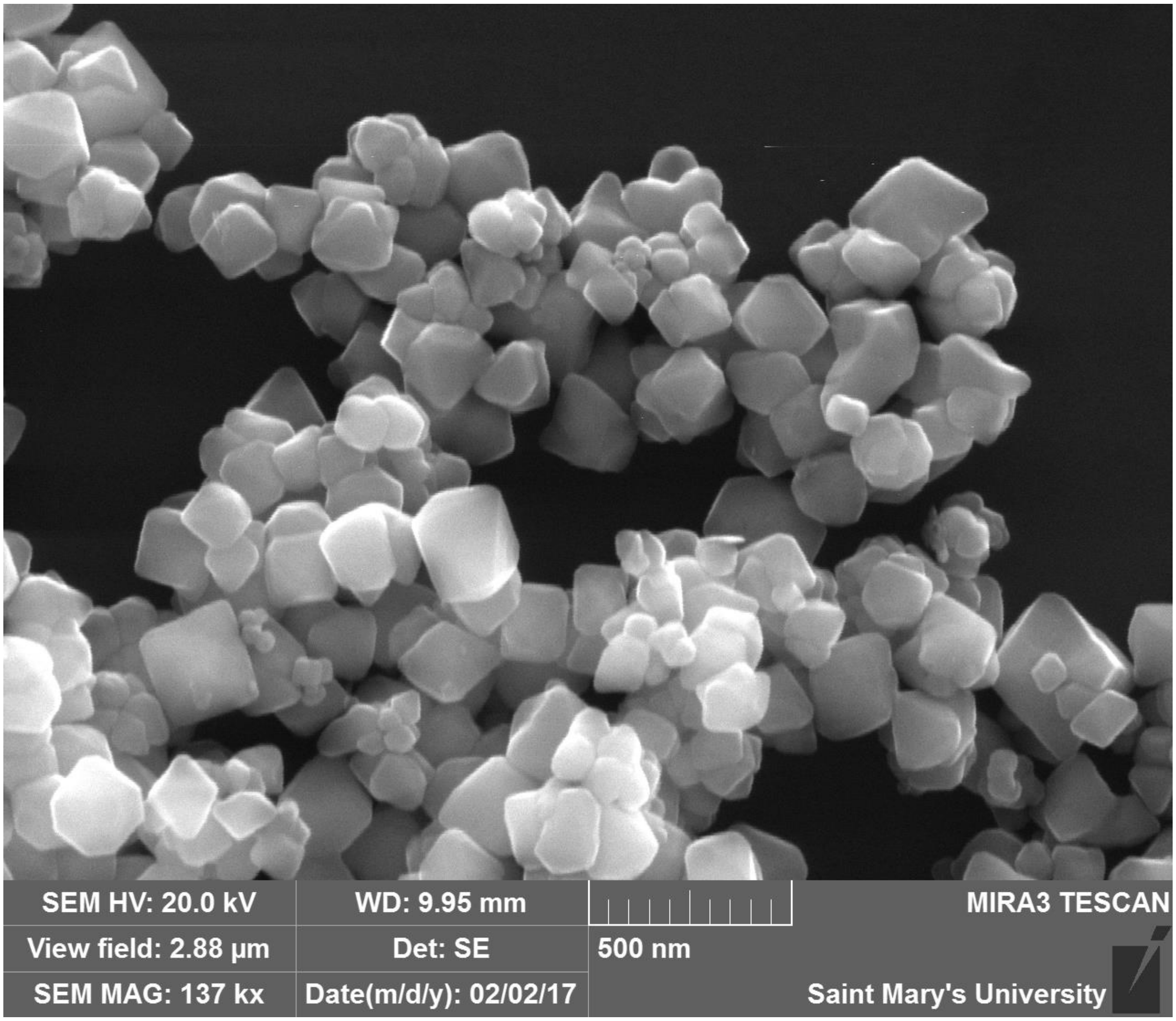


Figure 11.1. SEM image of magnetite nanoparticles, 500 nm scale.

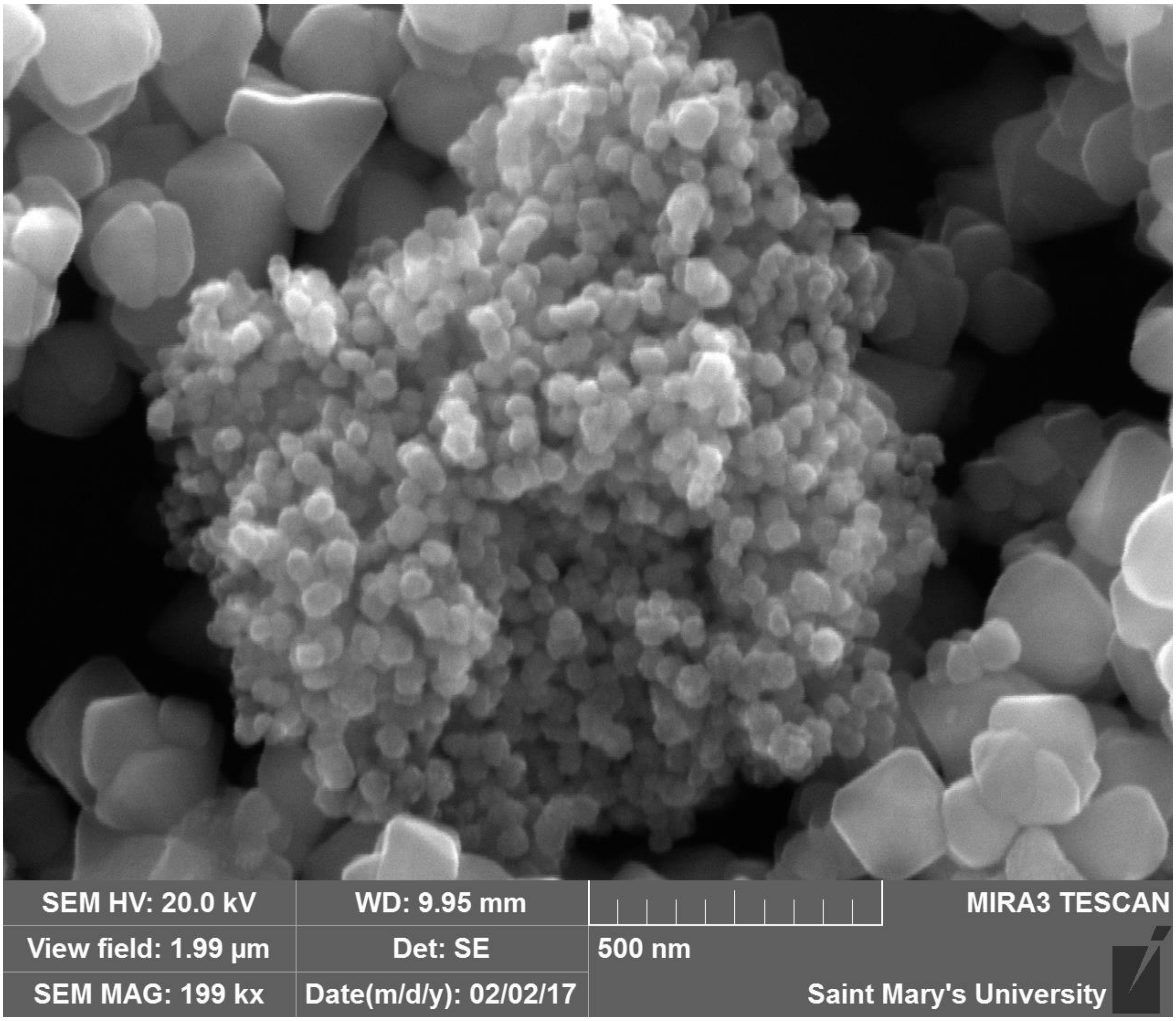


Figure 11.2. SEM image of magnetite nanoparticles, 500 nm scale, showing a cluster of smaller agglomerated nanoparticles.

The magnetite nanoparticles generally ranged from approximately 100-250 nm in size and were square in shape. The nanoparticles are relatively monodisperse although some of the nanoparticles were even smaller than 100 nm, approximately < 50 nm. As can be seen in Figure 11.2 the smaller, spherical nanoparticles are quite agglomerated and have formed a ball. This large dispersity in size and shape is not ideal for catalytic reactions. For this reaction to proceed with high yields and small reaction times a smaller particle size is desired. Due to the lack of uniform size and shape the reactivity is greatly reduced, leading to poor yields and reaction times compared to the nZVI.

The magnetite nanoparticles were first tested in isopropanol in order to compare the efficiency of the magnetite to nZVI, iron(0) dust and different iron(II) salts. This reaction was originally attempted at room temperature, as the previous reactions[2, 11, 12] required no heating. However, after 48 hours there appeared to be little to no conversion. In an attempt to speed up the reaction it was attempted again under reflux. Since this reaction is conducted in isopropanol it can easily be monitored. One way to monitor this reaction is *via* thin-layer chromatography (TLC). TLC is not a quantitative technique; instead, it only allows for the presence or absence of a reagent or product to be observed. Another technique used to monitor reactions of this nature is liquid chromatography (LC). When using LC to monitor a reaction, an aliquot is taken at certain time intervals over the course of the reaction and analyzed using an appropriate LC method. Over time the decrease of the starting material can be seen, along with an increase in two separate product peaks. The reaction with magnetite is quite simple to monitor *via* LC as the magnetite nanoparticles are magnetic and are attracted to the stir bar when the stirring is ceased therefore no nanoparticles are injected into the LC.

Preliminary LC results indicate the reaction takes more than 24 hours despite heating. The experiment was run multiple times, monitoring the reaction every couple hours. However, consistent results could not yet be obtained. During each trial the time at which the starting material peak completely disappeared, indicating 100% conversion, was not consistent. In one trial there was 100% conversion within the first 16 hours, although an additional trial is required to confirm these results. Since the time needed to achieve 100% conversion is not yet determined reactions to obtain an isolated yield were run for upwards of 2 days. For this reaction the highest yield was found to be 54% norDXM in 68 hours.

To address the main purpose of the research the reaction with magnetite was then conducted in [BMIM] [PF_6]. This reaction required optimization because, to our knowledge, no reaction of this kind has been conducted in ionic liquids. Some of the obstacles included temperature, volume of ionic liquid and reaction time. Similar to magnetite in isopropanol, the magnetite did not react very quickly at room temperature. Therefore it was heated to 95°C with a reflux condenser attached to the reaction vessel. Different volumes of ionic liquid were tested in order to further optimize the reaction. When done in isopropanol the volume used is 20mL. Due to the cost of ionic liquids, a lower volume is desirable. It has been demonstrated that 2.5mL is unsatisfactory as it is difficult to dissolve all the starting material (0.5 mmol DXM *N*-oxide HCl). Low volume of ionic liquid allows for undissolved starting material to remain on the sides of the flask throughout the reaction. This leads to longer reaction times and lower yields due to loss of sample. An increase in the volume of ionic liquid was required in an attempt to mitigate these problems. 5 mL of [BMIM] [PF_6] was used instead which lead to better dissolution of the starting materials. The dissolution of the DXM *N*-oxide HCl was still slow which may contribute to long reaction times that cannot be avoided.

The reaction time also required optimization. Monitoring the reaction in an ionic liquid is much more difficult than when the same reaction is conducted in isopropanol as it cannot be monitored *via* TLC or LC. TLC cannot be used to monitor the reaction as the ionic liquid overloads the plate. When this overloading occurs the solvent cannot effectively separate the products and starting material. Extracting the products from the ionic liquid could solve this problem, however, the aliquots taken are so small that it would be useless. Monitoring the reaction *via* LC is also not ideal. Aliquots must be taken at specific time intervals to run through the LC. When this reaction is conducted in isopropanol, 0.250 mL aliquots are taken from 20 mL of isopropanol. The volume of ionic liquid is significantly less and, as a result, the volume of each aliquot would also have to be smaller. This is unrealistic and would very quickly deplete the solvent.

As the reaction could not be monitored, it was conducted for the same length of time as the isopropanol experiments in order to compare obtained yields. The reaction of magnetite in [BMIM] [PF_6] that was run for 52 hours and yielded 17% norDXM. This is significantly less than was obtained when the same reaction was conducted in isopropanol. To help determine if this drop in yield was due to the use of an ionic liquid solvent another ionic liquid was chosen.

[BMIM] [NTf_2] was chosen as it has similar properties to [BMIM] [PF_6] but with a reduced viscosity, which makes it easier to work with. The predicted obstacles for [BMIM] [NTf_2] are very similar to those encountered with [BMIM] [PF_6]. To start, 5 mL of ionic liquid was used to maximize dissolution of sample. The reaction was heated to the same temperature as [BMIM] [PF_6] and stirred. One key problem with the new ionic liquid choice is that it is soluble in chloroform. This is a problem as the work up of the reaction requires chloroform rinses of the ionic liquid to extract the product. Chloroform is used because norDXM as well as the starting material are more soluble in chloroform than they are in the ionic liquids. Therefore, the use of a new solvent to extract the products was required. [BMIM] [NTf_2] is immiscible with water, ethyl acetate and diethyl ether. Since the products and starting material are soluble in diethyl ether while the ionic liquid is not it was chosen as an ideal solvent. The ionic liquid was washed with diethyl ether and the ether layer was pipetted off the top each time. This was done to eliminate the need to drain the ionic liquid to reduce loss of sample. The ether layers were dried and a ^1H NMR was obtained.

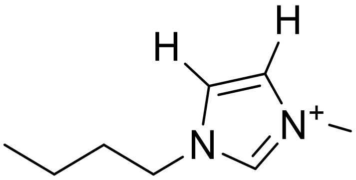


Figure 12. 1-butyl-3-methylimidazolium with hydrogens of interest shown.

The ^1H NMR appeared to contain traces of the ionic liquid with one key difference: there appear to be missing imidazolium peaks. 1-butyl-3-methylimidazolium (Figure 12) has fifteen protons but only seven unique protons. This leads to seven peaks in the ^1H NMR spectrum.

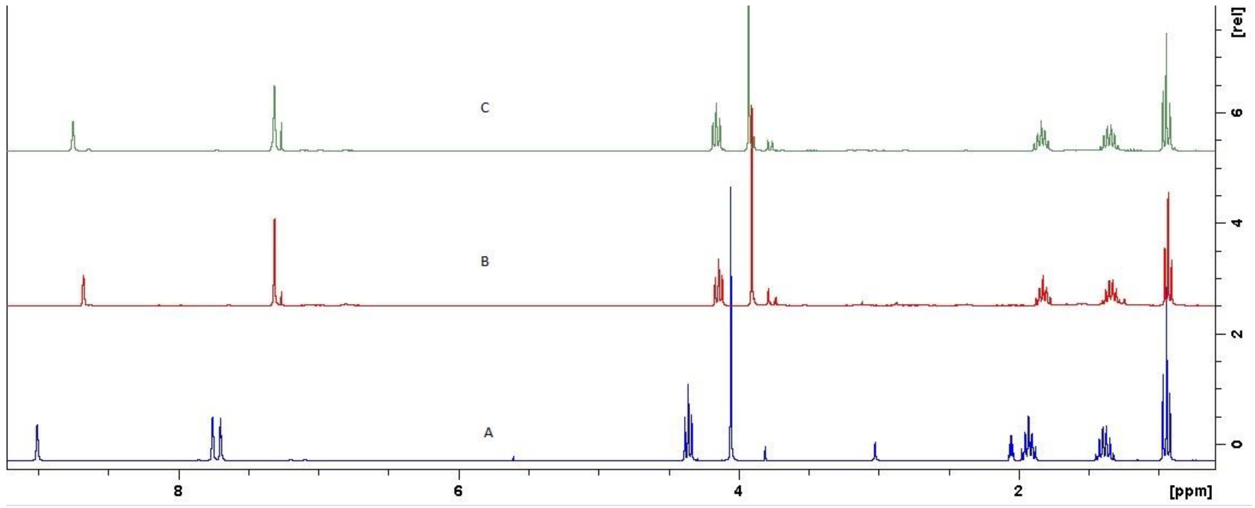


Figure 13.1. Stack of ^1H NMR of [BMIM] [NTf_2], A, ether extractions, B, and ionic liquid layer, C.

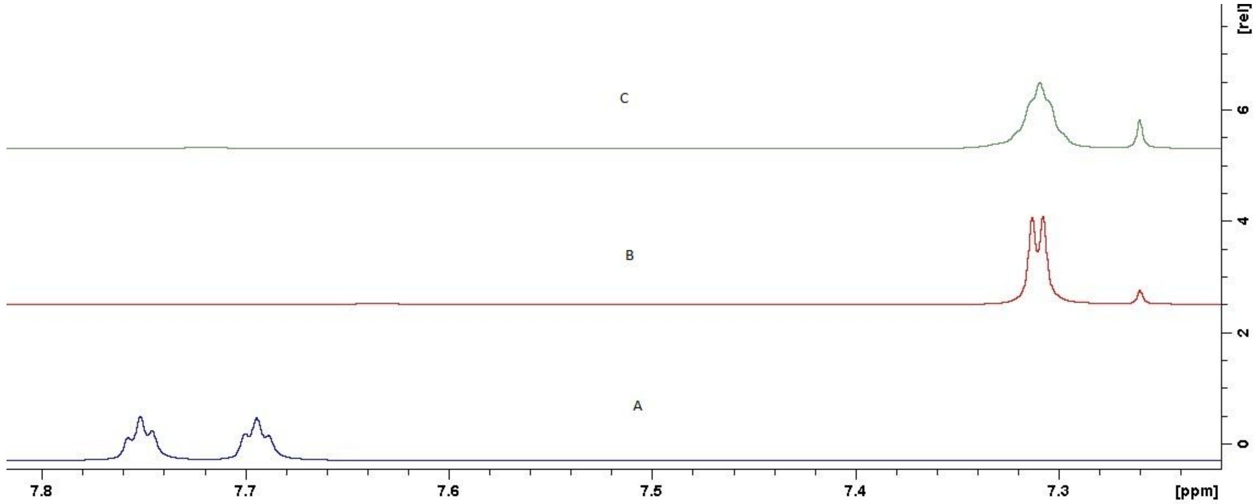


Figure 13.2. Magnification of peaks of interest in ^{1}H NMR of [BMIM] [NTf_2], A, ether extractions, B, and ionic liquid layer, C.

The peaks that appear in the ether extractions that are different from those in pure [BMIM] [NTf_2] involve the hydrogens highlighted in Figure 11. These hydrogens appear in the NMR of 1-butyl-3-methyl-imidazolium as two triplets (7.68 and 7.75 ppm) but in the ether extracts there is a doublet present (7.31 ppm). This is surprising as [BMIM] [NTf_2] should not be present in the ether layer as it is immiscible and there should be no decomposition occurring. This reaction was repeated and the same results could be obtained reproducibly. The ^{1}H NMR of the remaining ionic liquid was also obtained. Surprisingly the obtained NMR looked very similar to that of the ether extracts but instead of a doublet only one triplet is present (7.31 ppm). The ^{1}H NMR of pure [BMIM] [NTf_2] as well as the ether extract and ionic liquid layer can be seen in Figure 13.1 and 13.2.

This result is strange as there was no evidence of the [BMIM] [PF_6] decomposing despite the same reaction conditions. It is unexpected that this decomposition of [BMIM] [NTf_2] would occur solely because of heat as it has been shown that [BMIM] [NTf_2] does not decompose at temperatures below 401°C.[33] To confirm this [BMIM] [NTf_2] was stirred under the same reaction conditions both with and without magnetite nanoparticles. These experiments yielded the same NMR as the ionic liquid layer of the reaction containing magnetite and starting material. Therefore it was assumed that there was some sort of reaction occurring between the [NTf_2]$^-$ anion and the [BMIM]$^+$ cation. To see if a similar reaction would proceed with a different cation the same reaction was conducted with [BMPyr] [NTf_2] as the ionic liquid. This reaction was done using the same reaction conditions as the previous ionic liquids. [BMPyr] [NTf_2] is also soluble in chloroform so diethyl ether washes were done to extract the product.

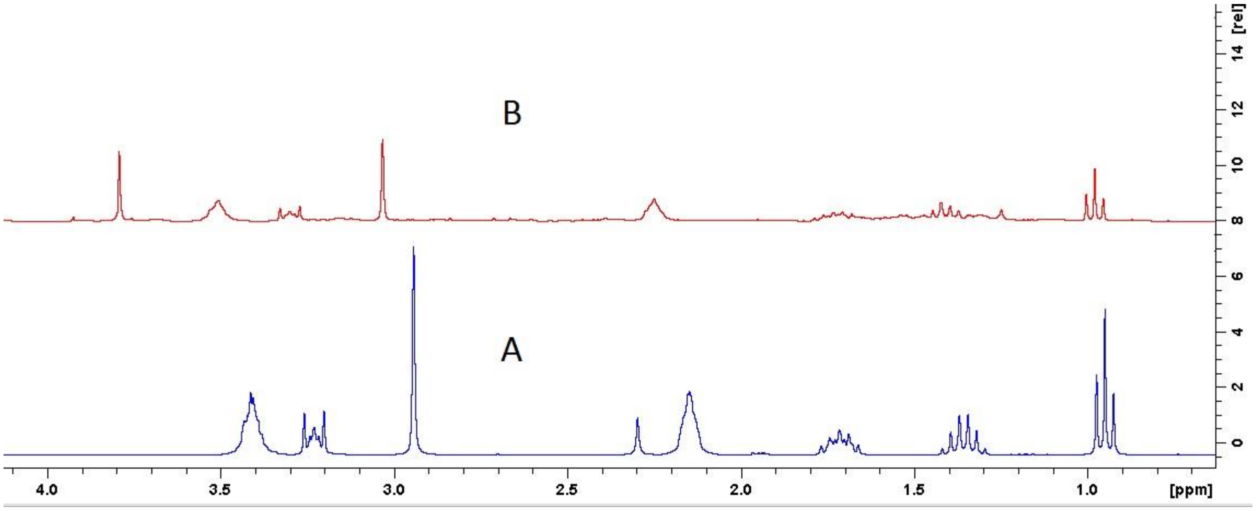


Figure 14. Stack of ^{1}H NMRs of [BMPyr] [NTf_2], A, ether extractions, B.

The ^{1}H NMR of this reaction showed some product formation but once again there was evidence of the ionic liquid decomposing. The reasoning for this decomposition of ionic liquids containing the [NTf_2]$^-$ anion is unknown and, as this problem could not easily be addressed the next step was to continue using different sources of iron.

The next source of iron to be investigated was rust nanoparticles. The rust was also purchased from Sigma Aldrich and therefore no preparation was required for this reaction. Rust nanoparticles were characterized with the SEM as well.

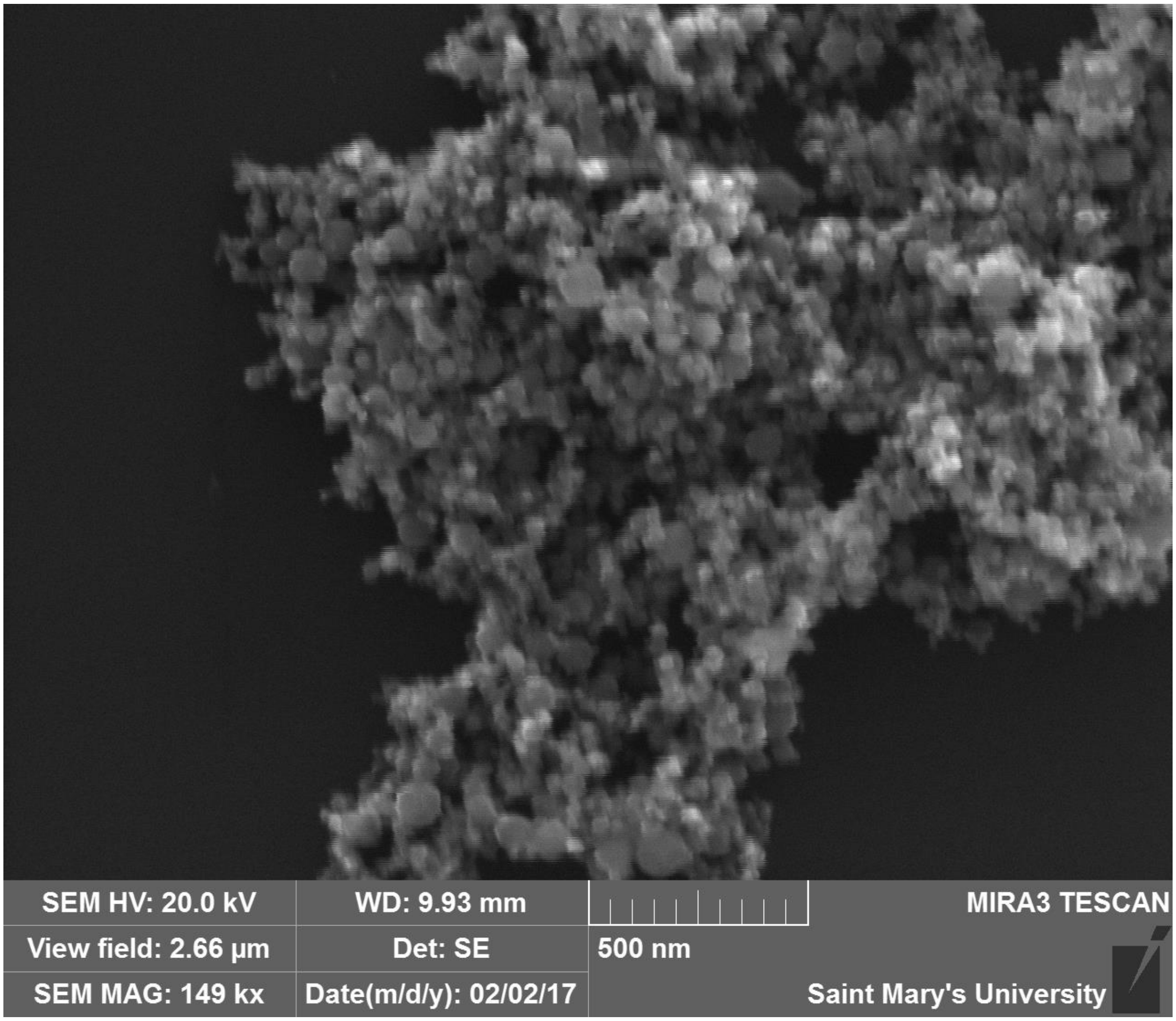


Figure 15.1. SEM image of rust nanoparticles, 500 nm scale.

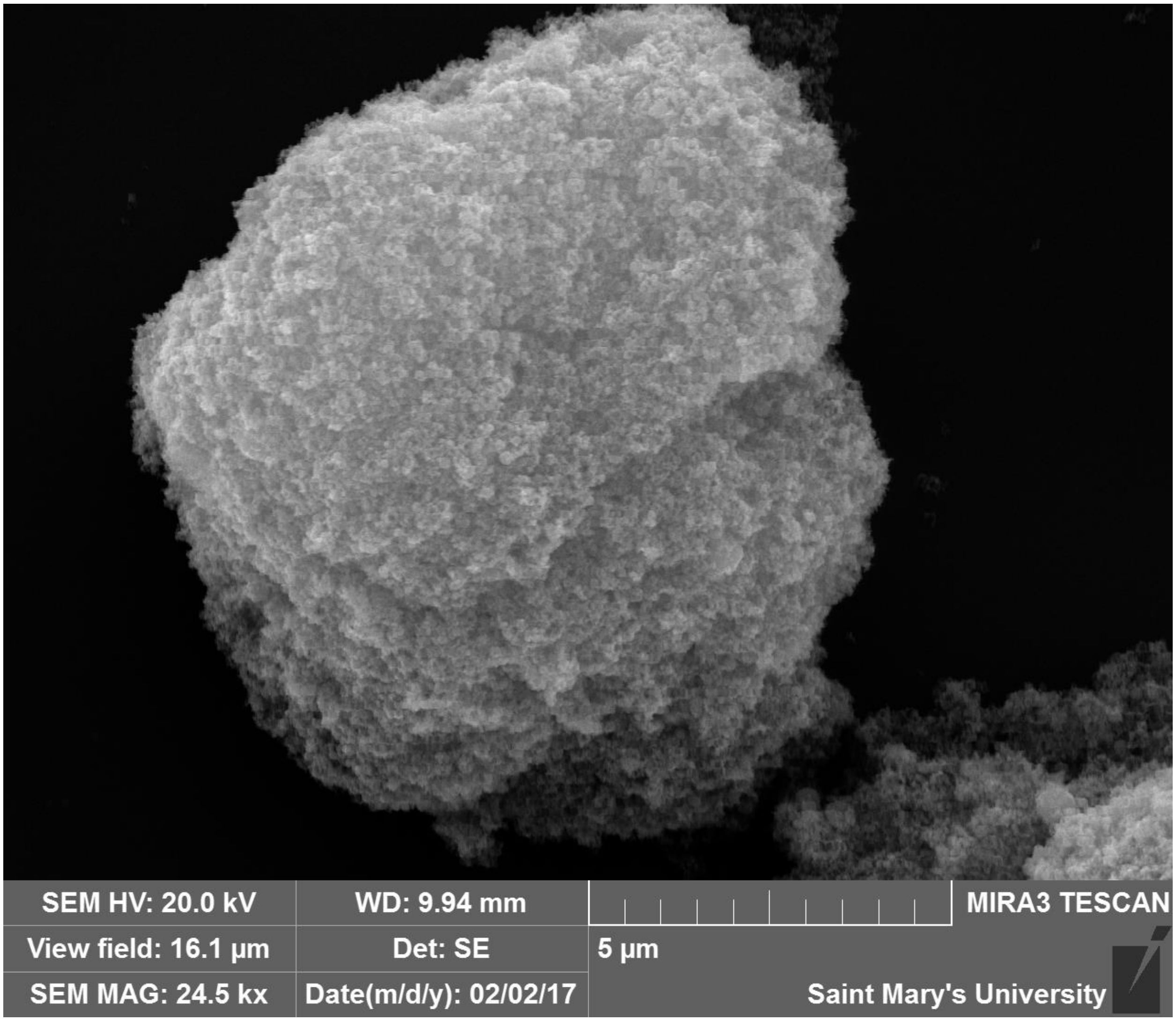


Figure 15.2. SEM image of rust nanoparticles, 5 µm scale.

The rust nanoparticles were approximately 50-100 nm and were all very similar shape and size but the nanoparticles displayed significant agglomeration and when zoomed out to 5µm (Figure 15.2) it is clear that, despite the small size, the nanoparticles may not have enhanced reactivity as an aggregate.

In order to see if the presence of Fe(II) is actually necessary in the reaction, the reaction was conducted in rust and isopropanol only. As expected this reaction had no conversion of

DXM *N*-oxide HCl to norDXM. This lack of conversion supports the proposed mechanism (Figure 7) and the necessity of Fe(II) in the reaction. In order to solve the lack of reactivity, a co-catalyst was used. As shown by Nakano *et al*[34] the use of a co-catalyst (13 mol-%) can decrease the reaction time needed while maintaining conversion. In this case a co-catalyst containing Fe(II) is required and $FeSO_4{\cdot}7H_2O$ was chosen. In this modified reaction 1 equivalent of rust was added to the starting materials along with 13 mol-% of $FeSO_4{\cdot}7H_2O$.

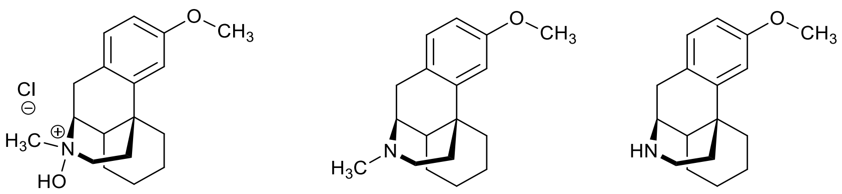
As with magnetite, the reaction was first conducted in isopropanol in order to compare the reaction time and yields with the current benchmark. This reaction should be monitored with the use of an LC to obtain kinetic data, however this has yet to be conducted. In order to obtain the highest yield possible prior to the LC experiments this reaction was stirred under reflux for 8 days. This allowed for a yield of 55%. To further the rust studies, [BMIM] [PF_6] was used as the ionic liquid of choice. After 8 days of stirring the highest yield that could be obtained was 12% norDXM. This is once again much lower than nZVI in isopropanol but is quite similar to magnetite in isopropanol.

Multiple *N*-demethylation reactions using various sources of iron and various solvents were conducted and the results are summarized in Table 1. It can be seen that the benchmark for the modified Polonovski reaction is still nZVI in isopropanol as no reaction using alternate iron sources could exceed 60% yield compared to the known 86% yield using nZVI. The main problem with the magnetite nanoparticles is predicted to be because of the quality of nanoparticles used. Had the nanoparticles been monodisperse and smaller perhaps the reaction would have been more efficient.

Table 1. Results of *N*-demethylation reactions in various solvents with different sources of iron.

Catalyst	Solvent	Isolated yield of norDXM
nZVI	*i*-PrOH	86.1%[12]
nZVI	[BMIM] [PF_6]	46.1%
Magnetite	*i*-PrOH	54.4%
Magnetite	[BMIM] [PF_6]	17.1%
Magnetite	[BMIM] [NTf_2]	N/A
Magnetite	[BMPyr] [NTf_2]	N/A
Rust and $FeSO_4$	*i*-PrOH	55.4%
Rust and $FeSO_4$	[BMIM] [PF_6]	11.6%

The norDXM and DXM isolated from all the above *N*-demethylation reaction was characterized using ^1H NMR, ^{13}C NMR and mass spectrometry. All three compounds (Figure 16) contain the methoxy group present in the ^1H NMR around 3.8 ppm.



12 13 14

Figure 16. Starting material, **12**, and isolated products (DXM, **13**, and norDXM, **14**) from *N*-demethylation reactions.

The key structural differences between the two products and starting material is clearly shown in the ^1H NMRs of each compound (Figure 17). The starting material contains an additional methyl peak, that of the *N*-methyl that is also present in DXM. This peak is absent in the spectrum of norDXM meaning that the reaction has been successful in removing the methyl group from the nitrogen.

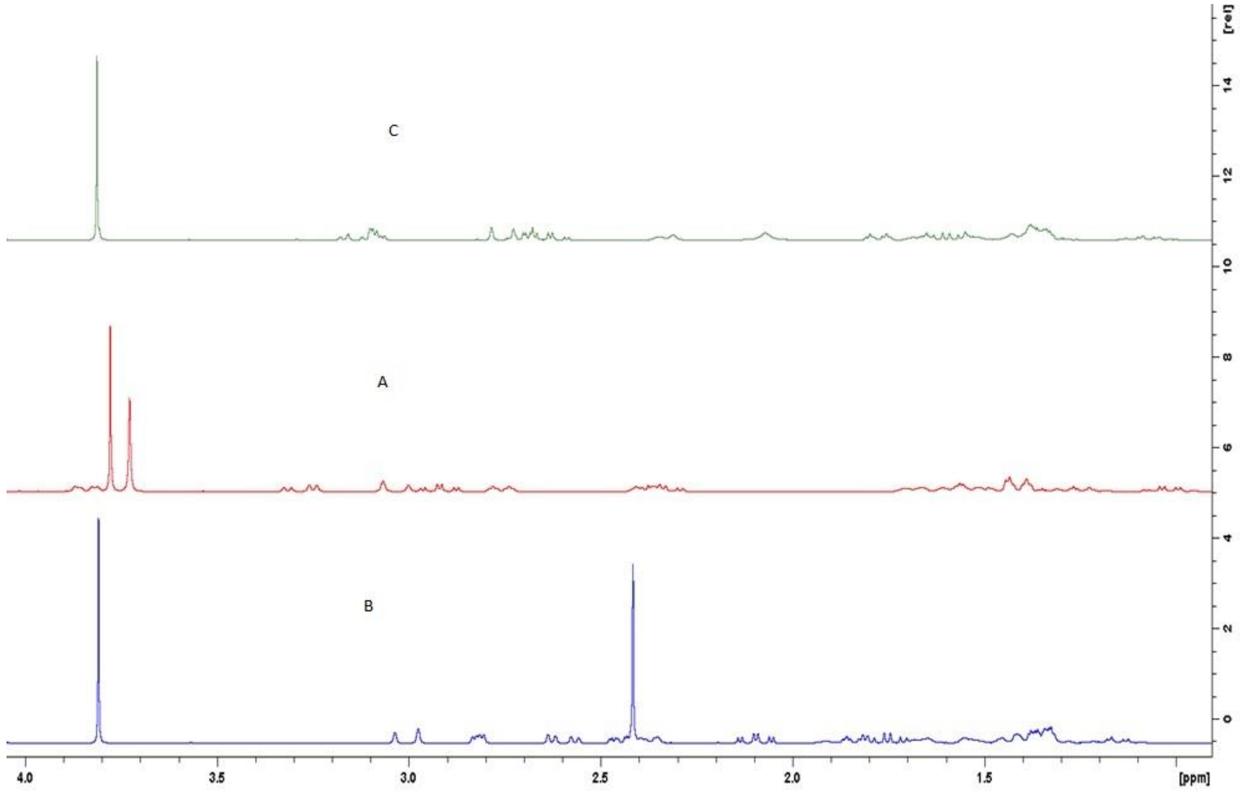


Figure 17. ^{1}H NMR of DXMNOHCl starting material, A, DXM, B, and norDXM, C. Aromatic region was removed for clarity.

3. Conclusion

The *N*-demethylation of DXM was performed using three different iron sources in solvents ranging from isopropanol to ionic liquids. It was discovered that the highest yielding reactions used nanoscale zero valent iron (nZVI) and isopropanol with an isolated yield of 86%. Solvent effects are very prominent in this reaction and it was shown that using the ionic liquid [BMIM] [PF_6] with nZVI allowed for a 46% yield of *N*-demethylated product.

The use of green iron sources as alternatives to synthesized nZVI lead to poor yields in all solvents. Magnetite nanoparticles were characterized with SEM and were shown to have a large size distribution and yielded 54% when reacted in isopropanol and only 17% when reacted in [BMIM] [PF_6]. Additional ionic liquids were chosen to further investigate the efficiency of the magnetite nanoparticles; however unexpected decomposition occurred in all ionic liquids containing bis(trifluoromethylsulfonyl)imide as an anion. [BMIM] [NTf_2] was allowed to stir under the reaction conditions with no substrate as well as with no magnetite and both trials lead to decomposition. This decomposition is unexplained and warrents further studies to investigate the strange findings. Lastly, rust nanoparticles were utilized. The rust nanoparticles were characterized by SEM and significant agglomeration was observed. As rust does not contain any source of Fe(II) the initial reactions of just rust nanoparticles lead to no conversion. Therefore a co-catalyst of $FeSO_4 \cdot 7H_2O$ was used and yielded 30% *N*-demethylated product in isopropanol and 12% when in [BMIM] [PF_6].

4. Future Work

The current work demonstrates that when using magnetite and rust, moderate yields can be achieved while using isopropanol, however, no conclusive kinetic data has been collected for these reactions. In order to fully compare the different iron sources, the time needed for 100% conversion must be known. Therefore further liquid chromatography trials should be undertaken to obtain this data.

The recyclability of the ionic liquids has not yet been tested. It is proposed that since the nanoparticles form a suspension in the ionic liquid both the solvent and the catalyst should be recyclable. This hypothesis should be tested using [BMIM] [PF_6] as it does not decompose under the reaction conditions. Magnetite should be investigated for this purpose. Since rust requires doping with $FeSO_4 \cdot 7H_2O$ it is expected that some replenishing will have to occur to replace the Fe (II) source.

5. Experimental:

5.1. General Methods

Magnetite nanoparticles, rust nanoparticles, iron (II) sulfate heptahydrate, and dextromethorphan hydrobromide were purchased from Sigma Aldrich and stored under atmospheric conditions. All other reagents and solvents were purchased from various chemical suppliers and used as received. Synthesis of dextromethorphan *N*-oxide hydrochloride and subsequent *N*-demethylation reactions were performed in glassware that was cleaned using a Mandel Lancer dishwasher followed by drying in an oven at 110 °C for a minimum of one hour.

Nuclear Magnetic Resonance spectra were obtained from a Bruker 300 MHz Ultrashield spectrometer. All ^{1}H and ^{13}C experiments were conducted at 300 and 75 MHz, respectively. Spectra were processed using Topspin. Chemical shifts (δ ppm) were referenced with solvent residual peaks. Deuterated NMR solvents DMSO-d6 and chloroform-d were purchased from Cambridge Isotope Laboratories. Melting point data was determined using an Electrothermal Mel-Temp 3.0 apparatus. IR spectra were obtained from a Bruker ALPHA Infrared Spectrometer by use of the attenuated total reflection (ATR) sampling technique. Electrospray ionization mass spectrometry experiments were conducted by Patricia Granados at the Saint Mary’s University Center for Environmental Analysis and Remediation (CEAR). ESI-MS was performed using an Agilent 1100 LC/MSD Trap.

5.2. Preparation of Nanoscale Zero Valent Iron:

168mg (0.62 mmol) of iron (III) chloride hexahydrate was dissolved in 5 mL of water and 5 mL of ionic liquid, [BMIM] [PF_6], and stirred at 300 RPM for 30 minutes before a 0.12 M aqueous solution of sodium borohydride was added dropwise. The solution was stirred for 30 minutes, after which a black precipitate formed and then transferred evenly into two centrifuge tubes. Next followed the washing process which consisted of water washings (3 x 5 mL) with repetitions of centrifugation and removal of water. The iron was then dried under vacuum.

5.3. Synthesis of dextromethorphan *N*-oxide hydrochloride[2]:

2.59g (7.0 mmol) of DXM HBr was dissolved in 80 mL of chloroform and washed with concentrated ammonium hydroxide (pH 10). The organic layer was then cooled to -20 °C and 1.2 molar equivalents of mCPBA was added to the solution all in one portion. The mixture was stirred at -20 °C and gravity filtered to afford DXM *N*-oxide in solution. The solution was then washed successively with NaOH/brine (3 x 15 mL), followed by brine (2 x 15 mL) and finally with 6 M HCl (pH 2). The resulting organic layer was concentrated to dryness to afford DXM *N*-oxide hydrochloride as a white foam. IR (ATR): 3018.8 (w), 2923.5 (m-br) 2427.8 (s, OH stretch), 2379.0 (s-br), 1494.3 (s), 1443.3 (s), 1277.7 (s), 1035.3 (s), 799.5 (vs, OH bend). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (d, 1H), 6.84 (d, 1H), 6.79 (m, 1H), 4.28 (s, 1H, broad), 2.92 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.40-3.25 (m, 1H), 3.16-2.87 (m, 2H), 2.80 (m, 1H), 2.35-2.25 (m, 2H), 1.75-1.64 (m, 1H), 1.68-1.53 (m, 2H), 1.50-1.32 (m, 3H), 1.32-1.20 (m, 1H), 1.17-0.97 (m, 38 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.69, 138.81, 129.27, 123.28, 112.49, 111.46, 72.85, 59.56, 55.34, 37.30, 36.55, 35.65, 35.09, 27.13, 25.77, 21.67. ESI-MS (+): Calcd for $C_{18}H_{26}NO_2$ m/z: 288.20. Found m/z: 288.3.

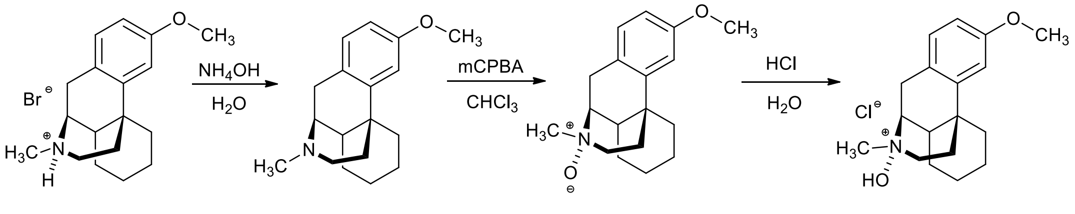


Figure 18. Scheme of synthesis of DXM N-oxide hydrochloride

5.4. *N*-demethylation of dextromethorphan *N*-oxide hydrochloride[2]:

161.9 mg (0.5 mmol) of DXM *N*-oxide hydrochloride was dissolved in the appropriate volume of appropriate solvent (20 mL of isopropanol or 5 mL of ionic liquid) and stirred at 900 RPM. 0.5 mmol of the appropriate iron source was added and the solution was stirred for the specified length of time at 95°C. The reaction mixture was then gravity filtered and the filter paper was washed with chloroform. The norDXM was extracted from the ionic liquid with chloroform and concentrated ammonia in brine (5 mL in 20 mL of chloroform). The solution was then concentrated to dryness. The residue was then purified *via* column chromatography on SiO2 (pore size 60 Å, particle size 220-440 mesh) using a $CHCl_3$/MeOH/NH_4OH gradient (85:15:1) which isolated the *N*-demethylated product as a yellow oil. IR (ATR): 2922.0 (s), 2853.7 (m), 1608.3 (m), 1573.2 (w), 1495.1 (s), 1454.3 (m), 1400.3 (m), 1322.2 (w), 1269.8 (m), 1236.0 (vs), 1187.7 (w), 1158.7 (w), 1118.8 (w), 1066.6 (w), 1038.8 (s), 986.7 (w), 858.0 (m), 796.0 (m). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (d, 1H), 6.81 (d, 1H), 6.74 (m, 1H), 4.90 (s, 1H), 3.76 (s, 3H), 3.18-2.98 (m, 2H), 2.87-2.43 (m, 3H), 2.41-2.23 (m, 1H), 1.82-1.72 (m, 1H), 1.72-1.43 (m, 3H), 1.43-1.22 (m, 5H), 1.18-0.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.31, 141.23, 129.35, 128.68, 111.21, 110.85, 55.20, 51.13, 45.05, 41.96, 38.88, 38.02, 36.78, 32.55, 26.66, 26.57, 22.05. ESI-MS (+): Calcd for $C_{17}H_{23}NO$ m/z: 258.18 [M + H]+. Found m/z: 258.1 [M + H]+.

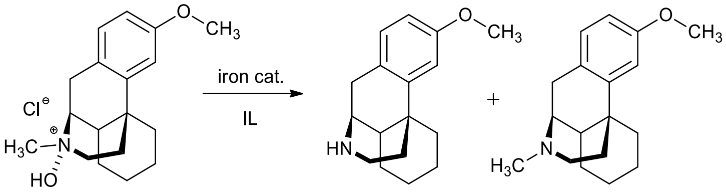


Figure 19. Scheme of synthesis of norDXM

5.5. Synthesis of 1-butyl-3-methylimidazolium chloride:

32 mL (0.4 mol) of 1-methyl imidazole was dissolved in 25 mL acetonitrile. 55 mL (0.52 mol) of chlorobutane was added dropwise and the solution was refluxed for 48 hours at 80°C. The obtained [BMIM] [Cl] was dried under vacuum. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 10.31 (s, 1H), 7.59 (m, 1H), 7.44 (m, 1H), 4.29 (t, 2H), 4.09 (s, 3H), 1.85 (m, 2H), 1.33 (m, 2H), 0.91 (t, 3H).

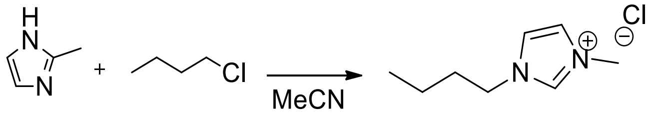


Figure 20. Scheme of synthesis of [BMIM] [Cl]

5.6. Synthesis of 1-butyl-3-methylimidazolium hexafluorophosphate:

3.5 g (20 mmol) of synthesized [BMIM] [Cl] was dissolved in 15 mL of water in an icebath. 3.6 mL (24 mmol) of hexafluorophosphoric acid was added dropwise and the solution was stirred overnight. The solution was washed with water (5 x 5 mL) before being dissolved in dichloromethane and run through a silica plug. ^{1}H NMR (DMSO, 300 MHz) δ 9.08 (s, 1H), 7.75 (t, 1H), 7.68 (t, 1H), 4.16 (t, 2H), 3.86 (s, 3H), 1.79 (m, 2H), 1.28 (m, 2H), 0.91 (t, 3H). ^{13}C NMR (DMSO, 75 MHz) δ 136.50, 123.59, 122.24, 48.56, 35.70, 31.34, 18.77, 13.21.

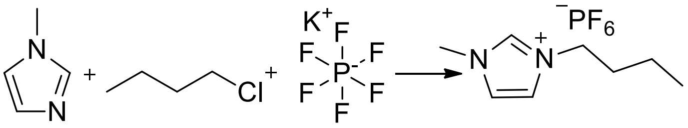


Figure 21. Scheme of synthesis of [BMIM] [PF$_6$]

5.7.Synthesis of 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl) imide:

Synthesized [BMIM] [Cl] was dissolved in water and combine with $LiNTf_2$ dissolved in water. The solutions were combined and dichoromethane was added. The organic phase was washed with water and then the aqueous phase was tested with $AgNO_3$. The aqueous phase was then concentrated to dryness to afford the desired ionic liquid. ^{1}H NMR(($(CD_3)_2CO$), 300 MHz) δ 9.00 (s, 1H), 7.75 (t, 1H), 7.69 (t, 1H), 4.14 (t, 2H), 3.92 (s, 3H), 1.84 (m, 2H), 1.35 (m, 2H), 0.95 (t, 3H).^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.16, 123.81, 122.39, 50.05, 36.40, 32.00, 19.41, 13.27.

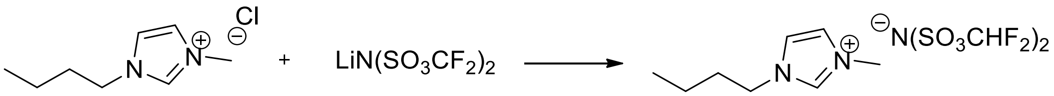


Figure 22. Scheme of synthesis of [BMIM] [NTf_2]

5.8.Synthesis of 1-butyl-1-methylpyrrolidinium bis(trifluoromethanesulfonyl) imide[35]:

10 mL of ethyl pyrrolidine, 20 mL of acetonitrile, and 10.1 mL of 1- bromobutane were added to a 100 mL long neck round bottom flask and attached to a condenser. The reaction flask was placed in the microwave reactor at 40 W power and stirred at 80 °C for 1 hour. The reaction mixture was then placed in a beaker and the solid precipitate was dissolved in acetonitrile. An equal volume of ethyl acetate was added and solid product crashed out of solution. The resulting mixture was passed through a frit and washed with ethyl acetate. After drying under vacuum, the solid was dissolved in 100 mL of water and combined with 19.1 g (68 mmol) LiNTf2 dissolved in water. The combined solution was stirred at room temperature for 48 hours. The resulting viscous liquid was washed in the round bottom with water. The washings were repeated until no more bromine remained in solution, indicated by negative results from a silver nitrate test. ^{1}H

NMR (($CD_3)_2CO$), 300 MHz) δ 3.72 (3, 4H), 3.54 (t, 2H), 3.25 (s, 3H), 2.32 (m, 4H), 1.91 (m, 2H), 1.44 (m, 2H), 0.99 (t, 3H). ^{13}C NMR (($CD_3)_2CO$), 75 MHz) δ 122.97, 118.72, 65.06, 64.89, 48.82, 26.12, 22.18, 20.23, 13.60.

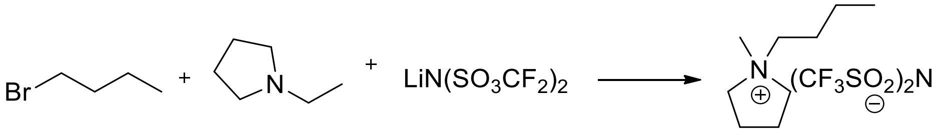


Figure 23. Scheme of synthesis of [BMPry] [NTf_2]

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