A Mechanochemical Approach for Organocatalysis

And

Improved Synthesis of Gemini Surfactants

By
Jacob William Campbell

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Approved: Dr. Robert Singer
Professor

Approved: Dr. Jason Masuda
Chairperson

Date: April 23, 2020

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Abstract

Mechanochemistry and organocatalysis provide green synthetic methods for chemical reactions. Reported herein are Morita-Baylis-Hilman reactions co-catalyzed by 1,4-diazabicyclo[2.2.2]octane, DABCO, and 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)-thioureido)-benzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate using a mechano-chemical approach known as Liquid Assisted Grinding, LAG. These room temperature reactions used methanol as a liquid additive to achieve an 85.7 % conversion and 14.8 % isolated yields, which is a slight improvement over conventional methods.

Gemini cationic surfactants have a lower critical micelle concentration (CMC) when compared to conventional analogues. This led to many improvements in materials such as soaps, detergents, wetting agents and foaming agents. There is a particular interest from a physical and material chemistry standpoint on how gemini cationic surfactants will behave with other surfactants in mixed micellular systems. Previously reported syntheses of quaternary amine gemini surfactants in the literature noted long reaction times, poor yields and large solvent use, making large scale production troublesome. Reported herein is an improved synthesis of mcm type cationic gemini surfactants using microwave irradiation.

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List of Abbreviations.

8-4-8	*N1,N1,N4,N4*-tetramethyl-*N1,N4*-dioctylbutane-1,4-diaminium bromide
12-4-12	*N1,N1,N4,N4*-tetramethyl-*N1,N4*-didodecylbutane-1,4-diaminium bromide
12-4-8	*N1*-octyl-*N1,N1,N4,N4*-tetramethyl-*N4*-dodecylbutane-1,4-diaminium bromide
14-4-14	*N1,N1,N4,N4*-tetramethyl-*N1,N4*-ditetradecylbutane-1,4-diaminium bromide
14-4-12	*N1*-dodecyl-*N1,N1,N4,N4*-tetramethyl-*N4*-tetradecylbutane-1,4-diaminium bromide
14-4-8	*N1*-octyl-*N1,N1,N4,N4*-tetramethyl-*N4*-tetradecylbutane-1,4-diaminium bromide
2D	Two dimensional
[BMIM][PF_6]	1-Butyl-3-methylimidazolium hexafluorophosphate
[BMPyr][$N(Tf)_2$]	1-Butyl-1-methylpyrrolidinium bis(trifluoromethanesulfonyl)imide
CMC	Critical micelle concentration
COSY	Correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEPT	Distortionless enhancement by polarization transfer spectroscopy
DLS	Dynamic light scattering
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DTAB	Dodecyltrimethylammonium bromide
ESI-HRMS	Electrospray ionization high resolution mass spectrometry
ESI-MS	Electrospray ionization mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
ILs	Ionic liquids
IR	Infrared spectroscopy

IUPAC	International Union of Pure and Applied Chemistry
LA	Liquid additive
LAG	Liquid assisted grinding
MBH	Morita-Baylis-Hillman
NMR	Nuclear magnetic resonance
NOESY	Two-dimensional nuclear magnetic resonance spectroscopy
RT	Room temperature
SDS	Sodium dodecyl sulfate
TSILs	Task specific ionic liquids
TUD	Thiourea dioxides
$C_{10}E_8$	3,6,9,12,15,18,21,24-Octaoxatetratriacontan-1-ol
Tan δ	Dissipation factor
zw3-12	*N*-dodecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate

1.0.0 A Mechanochemical Approach for Organocatalysis

1.1.0 Introduction

1.1.1 Green Chemistry

Since the introduction of Green Chemistry in the early 1990s, there has been large adoption of this field on an international scale.[1,2] The success of the Green Chemistry area of interest has been highlighted over the last 30 years, even sparking its own Royal Society of Chemistry journal in 1999[3] Many review articles have been published in *Green Chemistry* to highlight these successes, but perhaps the most comprehensive review is the one that outlined the principle and practices that many chemists follow today. The book, "Green Chemistry, Theory and Practice" by Paul Anastas and John Warner outlines the purpose and meaning of Green Chemistry. Green Chemistry is defined therein using "The Twelve Principles of Green Chemistry", which advises chemists on how they can better design their syntheses for the goal of sustainability.[4] These principles help to guide the current research, and are as follows:

1. Waste prevention, rather than cleaning or treating waste once created; 2. Atom economy, reducing the atoms used that are not incorporated in the final product; 3. Less hazardous chemical synthesis, in order to protect handlers and the environment; 4. Designing safer chemicals, considering the toxicity and volatility of products; 5. Safer solvents and auxiliaries, as solvents account for the most of total chemical waste and should be minimized; 6. Design for energy efficiency, avoiding wasteful processes such as heating and cooling; 7. Use of renewable feedstocks; 8. Reduce derivatives, where minimizing reaction steps inherently

reduces waste; 9. Catalysis, focusing on reducing reaction times and energy use; 10. Design for degradation, avoiding anything that can persist or bio accumulate; 11. Real-time analysis for pollution prevention, insuring that reactions are not producing pollutants; 12. Inherently safer chemistry for accident prevention.

This work seeks to apply several of these principles: prevention of waste, atom economy, less hazardous synthesis, benign chemicals, safer solvents, energy efficiency, catalysis and inherently safer chemistry for accident prevention—with heavy focus on energy efficiency and catalysis.

1.1.2 Ionic Liquids

Ionic liquids (ILs) are defined as any salts that melt below 100°C. ILs are relevant in the field of Green Chemistry because they have no measurable vapour pressure, so they are inherently non-volatile chemicals and are often non-toxic and generally non-flammable.[5] Ionic liquids are also praised for their tunable properties because both the cation and anion components can be varied. Ionic liquids have even been called "designer solvents" because they can be tuned for hydrophobicity, viscosity, melting point and density.[6] Drawbacks of ionic liquids are that they are often 5-20 times more expensive than molecular solvents, often have very high viscosity, often very hygroscopic and, depending on design, can be toxic, non-biodegradable and non-sustainable.[7,8]

The most commonly used cations for ionic liquids are pyridinium, pyrrolidinium, imidazolium, sulfonium, ammonium and phosphonium ions, all of which are organic and can be readily functionalized. For instance, hydrocarbon chains can be added to tune for

hydrophobicity of the molecule. Most of the common anions are inorganic, such as tetrafluoroborate, hexafluorophosphate, various halides, bis(fluorosulfonyl)amide and bis((trifluoromethyl)sulfonyl)amide (Figure 1). If halide-free syntheses are desired, then organic anions such as methylsulfonate can be used. ILs commonly feature nitrogen or phosphorous based heteroatoms because they are easily quaternized to generate salts. As of 2008 over 1000 ionic liquids have been reported in the literature and over 300 are commercially available.[9]

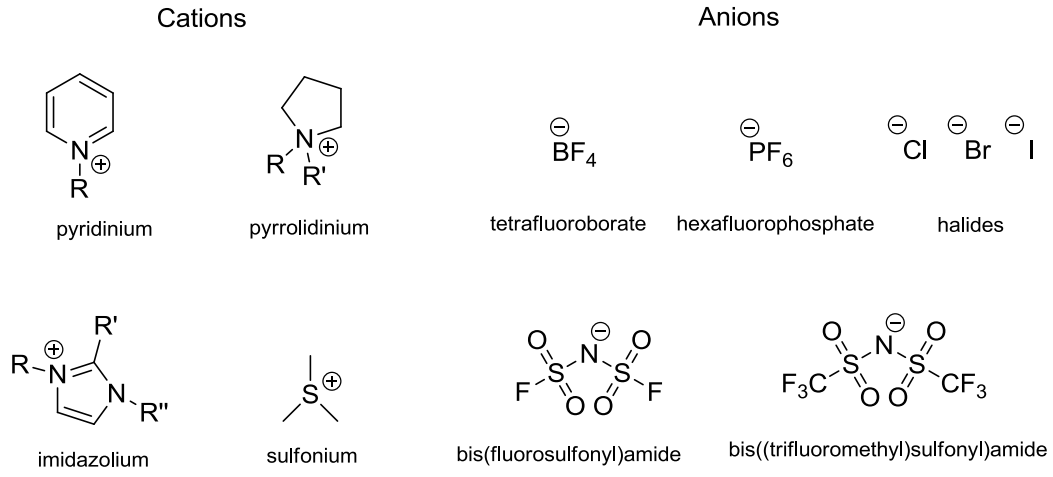


Figure 1: Common Components of Ionic Liquids

1.1.3 Task Specific Ionic Liquids

Task specific ionic liquids (TSILs) are functionalized ionic liquids that are designed with a specific application in mind. The predominant use of TSILs is in catalysis as a way to facilitate the separation and subsequent reuse of catalysts, such as a two-phase or heterogeneous catalysis.

TSILs have been used for extraction of metal ions from an aqueous phase by Rogers *et al.* in 2001.[10,11] This work described a functionalized imidazolium-based cation with thioether, urea and thiourea moieties to coordinate to mercury (II) and cadmium (II) transition metals through the sulfur atom. This designer cation with a hexafluorophosphate anion resulted in a water immiscible ionic liquid. The aim of this work was to have a two-phase system for ease of recycling the TSIL. Since the TSIL described by this report was so expensive, they used mostly 1-butyl-3-methylimidazolium hexafluorophosphate and doped with 10% TSIL.

Some of the above principles of *Green Chemistry* were employed in this thesis. For this thesis the TSIL and reagents are dissolved in a selected IL. When the reaction is complete the reagents and products are extracted with solvent, the IL will retain the TSIL for subsequent reactions. Butylmethypyrrolidinium bistriflimide [BMPyr][$N(Tf)_2$] was selected as the IL because it is hydrophobic, has a low viscosity when compared to other ILs—allowing for ease of mixing and also dissolves most organic molecules, excluding alkanes and aromatics.[5] The TSIL that was designed for this research (also known as an ionic liquid tag) has a pyrrolidinium-based cation for preferential solubility in the chosen IL and a thiourea moiety for catalyzing the MBH reaction. The preferential solubility allows for the TSIL to be retained in the IL, whilst leaving behind the reactants and products in the organic phase, allowing for liquid-liquid extraction.[5] This strategy for separation and recovery was reported by the Singer group with comparable yields after three consecutive reactions.[12] An imidazolium-based cation was not selected for this work because of a known side reaction between imidazolium and aldehydes under mildly basic conditions.[3]

1.1.4 Catalysis

Catalysis is the focus of many chemists in the Green Chemistry field because catalytic systems allow for a better atom economy, have better energy efficiency due to shorter reaction times, and a large majority of pharmaceuticals are made using a catalyst at some stage of the reaction.[14] Catalysts are reagents that are used but not consumed in reactions and lower the activation energy of a reaction by offering an alternative reaction pathway. Since catalysts are not consumed in reactions and can continue to react rapidly, they are often used in sub-stoichiometric amounts.

Commonly catalyzed reactions in the pharmaceutical industry are all carbon-carbon bond forming reactions such as the Diels-Alder reaction,[15] Heck reaction,[16] Wittig reaction,[17] Michael reaction,[18] Suzuki coupling reaction,[19] and the Morita-Baylis-Hillman reaction (MBH).[20,21] The Heck and Suzuki reactions are very unfavourable for green chemistry because they are catalyzed using palladium-based complexes that are both toxic and expensive. The other named reactions are not likely targets for retrofitting with new catalysts because they are already catalyzed using small organic molecules.[22]

1.1.5 Organocatalysis

An organocatalyst shares the same definition as a catalyst except it is an organic compound that does not contain a metal atom.[22] Organocatalysis is used by living organisms in cases such as amino acids L-alanine and L-isovaline catalyzing aldol-type reactions to make sugar derivatives.[22] Using organic molecules as catalysts is as old as Chemistry itself, but it was not widely adopted until the 1990s when Jacobsen and Corey reported that organic Lewis acids can be used for hydrogen-bonding catalysis in Strecker

reactions to activate the imine; beginning the field of organocatalysis that is known today (Figure 2).[14,23]

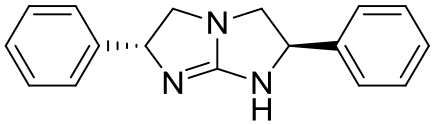


Figure 2. Corey's Catalyst For Strecker Reactions

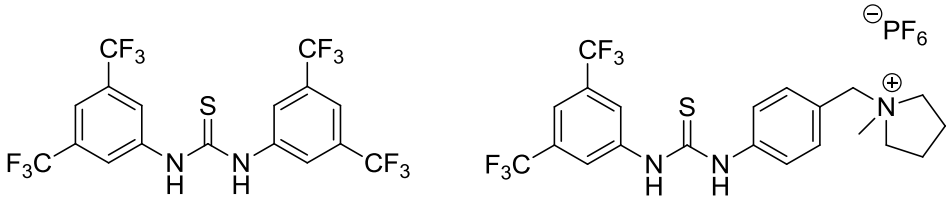
1.1.6 Thioureas in Organocatalysis

The work by Jacobsen and Corey sparked many researchers to study hydrogen-bonding catalysis in other famous reactions such as the Diels-Alder and Friedel-Crafts reactions. With such success demonstrated this showed that the same was possible in the Morita-Baylis-Hillman reactions. In 1996, Roos reported that alcohols such as phenols could significantly increase the rate of Morita-Baylis-Hillman reactions, which indicated that hydrogen-bond catalysis was taking place.[24] Some years later, Schreiner developed a catalyst that was an electron deficient thiourea and it was used as a hydrogen bond donor to activate carbonyls, nitro olefins and imines. These reactions showed that electron deficient thiourea catalysts can act like Lewis acids such as aluminium (III) chloride while the hydrogen atoms in the *ortho* position of the aryl rings help to rigidify the molecule by coordinating to the sulfur atom. Thiourea was selected because it is a stronger acid than urea (pK_a = 21.1 and 29.6 respectively) and ureas have a higher tendency to dimerize due to stronger intramolecular forces.

Later, Sohtome *et al.* showed great results in the Morita-Baylis-Hillman reactions between benzaldehyde and many electrophiles.[25] Schreiner's diarylthiourea showed great

importance of electron-withdrawing groups that are designed to increase the relative acidity of the protons, which was achieved by having bis trifluoromethyl groups in the *meta* position of the arene substituents (Figure 3a).[25,26]

Unfortunately, these reactions are homogenous due to the fact that the thiourea, tertiary amine and reagents all exist in the same phase. A catalyst in a homogenous reaction cannot easily be extracted and is thus not readily recyclable. Recyclability of thiourea organocatalysts can be found in the literature, including thiourea dioxides (TUD) which can be extracted with pyran derivatives[27], thioureas that contain a large hydrophobic chain for preferential solubility[28] and thioureas that can be immobilized using ionic liquids.[12] For this work, bis trifluoromethyl functionality will be used in conjunction with the previously mentioned thiourea and pyrrolidinium moieties (Figure 3b).

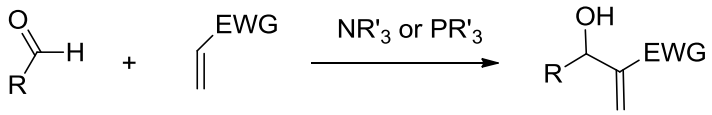


a. Schreiner's Catalyst b. The Target Thiourea Cocatalyst

Figure 3. Thioureas With Bis Trifluoromethyl Moiety For Organocatalysis

1.1.7 Morita-Baylis-Hillman Reaction

The Morita-Baylis-Hillman (MBH) reaction is an addition reaction between the α-position of an activated double bond and an sp^2 electrophilic carbon. [20] This carbon-carbon bond forming reaction creates an allylic alcohol product that is considered a very useful functional group for syntheses. The limitation of MBH reactions is that they are slow, but the rate can be increased through the use of catalysis (Scheme 1).



Scheme 1. General Scheme of Morita-Baylis-Hillman Reactions

Nucleophilic Lewis bases such as tertiary amines and phosphines are known to catalyze the MBH reaction by forming a covalent bond that activates the otherwise electron deficient alkene towards addition.[21] The main catalysts used in MBH reactions are 1,4-diazabicyclo[2.2.2]octane (DABCO**)** , quinuclidine, 4-Dimethylaminopyridine (DMAP), imidazole and triethylamine (Figure 4). Based on reactivity studies, DABCO and DMAP had the best catalytic activity and DABCO slightly outperformed DMAP with less reactive electrophiles because DABCO is a better nucleophile.[29] DABCO was the selected catalyst for this work.

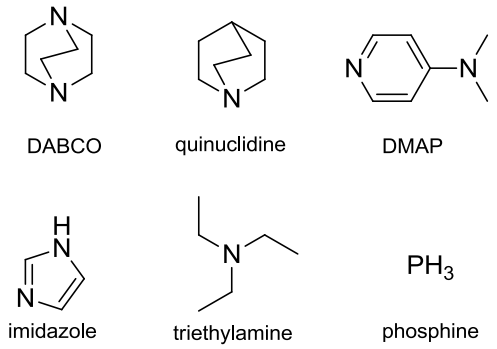
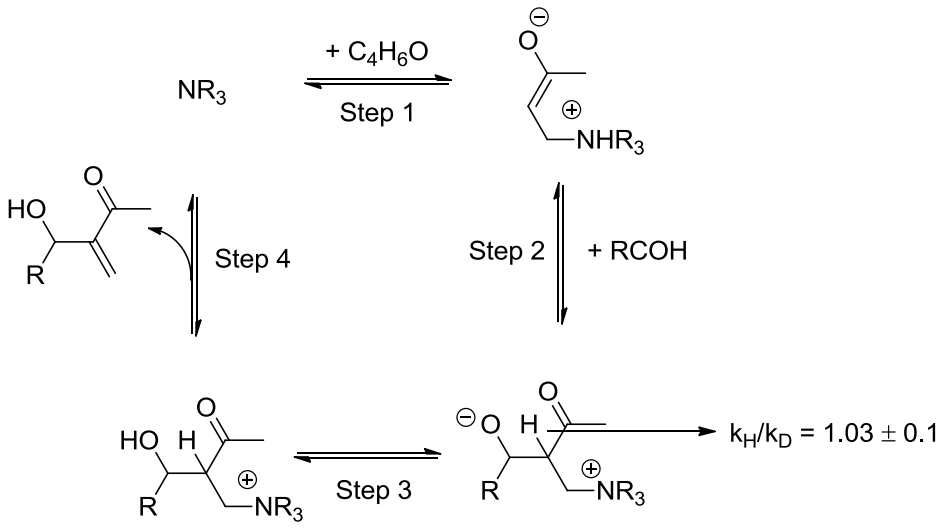


Figure 4. Common Catalysts for MBH Reactions

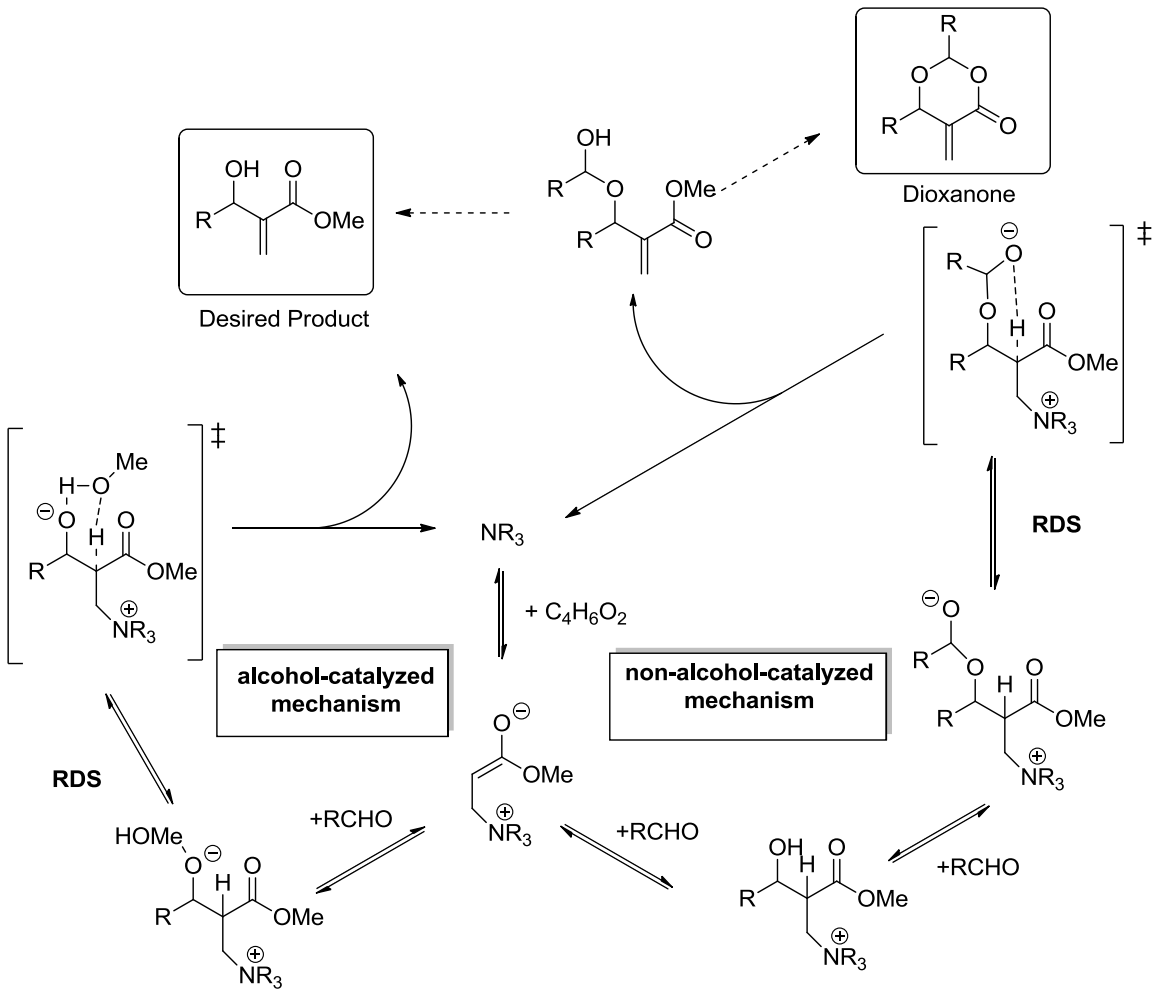
The first mechanism for the MBH reaction was proposed by Hoffmann in the 1980s.[30] Kinetic studies led them to believe that the first step was the addition of the tertiary amine to the activated alkene to generate a zwitterionic intermediate, followed by a second step in which the aldehyde adds to the C2 position of the zwitterion. The third step was an intramolecular proton shift, while the final step was an E2 or E1cb elimination to release the catalyst and form the MBH product (Scheme 2). A low isotope effect of 1.03±0.1 was observed for the second step, which led them to believe this was the rate determining step.[31] The justification was due to an increase of charge separation. The issues with this mechanism and the reason it went out of favour was that it did not explain some stereocontrol issues, and the dioxanone by-product from the MBH reaction between aldehydes with acrylates could not be accounted for.[32]



Scheme 2. Hoffmann Proposed MBH Reaction Mechanism

McQuade *et al.* and Affarwal *et al.* have addressed these issues with particular interest in a proton transfer in a newer, more advanced mechanism that was postulated in 2005.[33,34] These new mechanistic studies showed that the MBH reaction is second order with respect to the aldehyde and shows a primary kinetic isotope effect greater than two in polar protic and polar aprotic solvents, meaning that the proton abstraction is relevant regardless of solvent. Evidence of a second addition of aldehyde was found, this formed a hemiacetal species. The hemiacetal species, if an ester is present, is the source of dioxanone side product. It was also noted that initially the proton transfer will be limiting but later, as the conversion percentage increased, the rate determining step will be the first addition of aldehyde. McQuade and Affarwal proposed that the proton transfer mechanism could proceed one of two ways; the first being a non-alcohol-catalyzed pathway that is similar to Hoffmann's proposed mechanism, except for the formation of the hemiacetal species, and the second is an alcohol-catalyzed, general acid catalysis, pathway which suggests any

present alcohol will perform the proton transfer, herein reported as a proton-shuttle (Scheme 3). Evidence for some of these intermediates have been found using electrospray ionization mass spectrometry, demonstrating evidence for the co-catalysts' role in the mechanism.[35]



Scheme 3. McQuade/Aggarwal Improved MBH Reaction Mechanism

In 2015 it was reported by Singleton and Plata that the mechanism for the alcohol-catalyzed MBH reaction is more mundane than what McQuade and Affarwal had postulated in the previous decade.[36] The evidence that was found supported that the deprotonation/elimination of the α-CH bond simply followed acid-base chemistry and not the proton-shuttle process previous reported. There was a contention surrounding the proton-shuttle process and many articles, both supportive and unsupportive, were published on this topic. Singleton and Plata believed that the downfall of researchers before them was

a heavy reliance on solely computational studies, whereas they had experimental results in conjunction with a wide breadth of computational studies. They synthesized intermediates to obtain the rate law of the elimination step and most notably showed the rate of elimination remained the same when the hydroxyl group was substituted for a methoxy group (Figure 5). Further support was an observed solvent kinetic isotope effect if 0.96 H/D methanol.

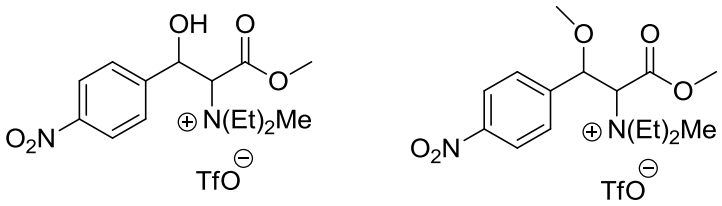


Figure 5. Synthesized Intermediates For Studying The α-CH Elimination Step

1.1.8 Liquid Assisted Grinding and Dry Grinding

Liquid assisted grinding (LAG) and dry grinding both fall under the broad term of mechanochemistry, which simply refers to reactions induced by mechanical energy (i.e., grinding). This type of chemistry is appealing because it can be used to react solid phase reagents and thus avoid solvents entirely.[37] With no solvent present this would be considered dry or neat grinding; however, mechanochemistry is not confined to be strictly solvent or rather *liquid*-free. This is the case with the LAG approach, which is when a small quantity (<1μL/mg) of solvent is added to facilitate the reaction.[38] The distinction between mechanochemical approaches is based on a ratio of total reaction volume of liquids to total mass of solid materials. This value is denoted by the Greek letter eta (η) and is measured in units of micro liters of total liquid materials per milligrams of total solid materials

(μL/mg).[38] A solution phase reaction is considered any $\eta > 20$, while slurry has an η value between 1 and 20, and LAG has $\eta < 1$ while dry grinding must be 0. When in the LAG regime, solvents are referred to as liquid additives.

1.1.9 Objective

Sustainable Chemistry, also known as Green Chemistry, is an area of research that puts emphasis on principles that are used as a guide to minimize harm to human health and the environment. The impetus for this work comes from the environmental and economic impact of using transition metals for catalysis, more specifically metals with low natural abundance and high toxicity. The use of organocatalysis becomes important in this area of interest. Organocatalysis refers to using catalysts that do not contain a metal atom and are predominantly made of C, H, O, S and P. As has been demonstrated by many previous researchers, organocatalysts can be, and have been, used to retrofit problematic transition metals in synthesis. Unfortunately, many organocatalysts lack recyclability as they are used in the same phase as the organic reactants (homogenous catalysts) and cannot be easily separated. Recyclability is a key component of Green Chemistry, which will also be addressed within this work by using ionic liquids. Ionic liquids will be used for preferential partitioning or immobilization of organocatalysts from crude reaction mixtures by designing the organocatalyst to have similar physical properties (i.e., solubility).

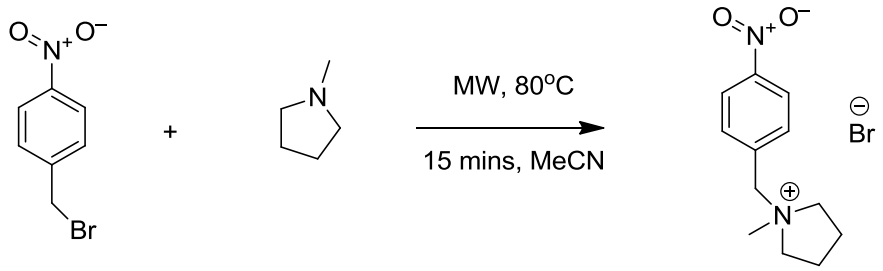
This chapter will focus on adapting the Morita-Baylis-Hillman (MBH) reaction to enhance its green attributes. The MBH reaction can be catalyzed by a tertiary amine and can be cocatalyzed by intermolecular hydrogen bond donation as demonstrated by

Schreiner's work using electron deficient thiourea derivatives. The thiourea moiety was selected for this work because of the Lewis acidic pair of hydrogens that can be tuned by varying substituents on the molecule, making it an excellent choice for a co-catalyst. With this work, the thiourea co-catalyst will be further functionalized by installing an ionic liquid functionality, also known as an ionic liquid tag, which will make it preferentially soluble in ionic liquids. The ionic liquid tag chosen was an *N*-methylpyrrolidium moiety and the selected ionic liquid was butylmethylpyrrolidinium bistriflimide, [BMPyr][$N(Tf)_2$]. This ionic liquid was chosen because it is immiscible in selected organic solvents, and the pyrrolidiuium cation moiety would avert some side reactions that have been reported in the literature observed with other cationic cores such as imidazolium.

Previous Singer group members have studied the MBH reaction using thiourea co-catalysts. McGrath, Watson and Parsons have laid the majority of the ground work for this study, including optimization of stoichiometry, catalyst recycling, catalyst loading, scope of reagents, and even varied the functionality of the thiourea co-catalyst. [39, 40, 41] The objective of this work is to further increase the relative greenness of the MBH reaction by lowering the amount of solvent used and increasing the relative energy efficiency of the reaction. Mechanochemistry was the approach selected to achieve this goal, using methods such as liquid assisted grinding, which uses microliter quantities of solvent, and dry grinding, which is solvent free.

1.2.0 Results and Discussion

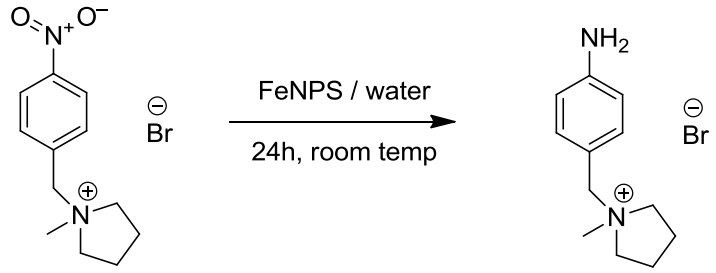
The synthesis of the pyrrolidinium based thiourea co-catalyst was carried out over four optimized steps to give an improved overall percent yield of 68% over the previous syntheses (Scheme 4).[39] The first step follows a previously reported microwave assisted S_N2 reaction between 4-nitrobenzaldehyde and *N*-methylpyrrolidine to give the 4-nitrobenzylpyrrolidinium bromide salt in an 82% yield in only 15 minutes.[39] This product is easily characterized by ^1H NMR spectroscopy by observing a shift in aromatic peaks as the reaction proceeds to product.



Scheme 4. Synthesis of 1-methyl-1-(4-nitrobenzyl)pyrrolidin-1-ium bromide

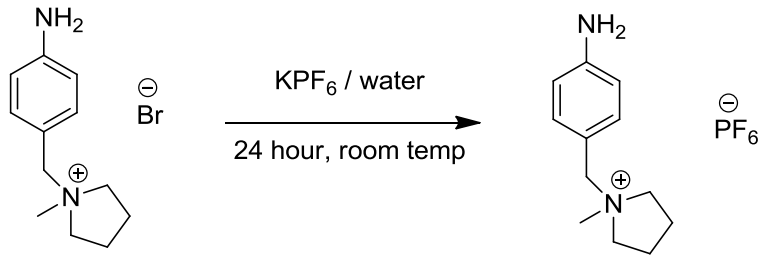
In previous syntheses, the 4-nitrobenzylpyrrolidinium bromide salt was metathesized (i.e., exchange of ions) to an amine using hexafluorophosphoric acid in the next step of this synthetic pathway; however, this results in a water insoluble salt that is more difficult to reduce to the required amine. The optimized synthetic route is to perform the reduction first and then phase-separate the desired product out of water by performing the metathesis in *situ* with potassium hexafluorophosphate. This order of reactions leads to a higher yield after the reduction in less time because the compound and reducing agents are in the same phase, unlike previously reported methods. This approach also aids as a

cleanup method, as the resulting hexafluorophosphate salt crashes out of solution and leaves all water-soluble impurities behind in the aqueous phase. This reaction uses sodium borohydride to reduce iron(II) sulfate heptahydrate to iron(0) which will then be used to reduce the nitro group to the desired amine (Scheme 5). This method also uses sodium citrate as an reducing agent to preserve iron(0) over the long reaction time, and can be performed under an argon atmosphere for the same effect. Yields were not obtained after the reduction because the product remains in aqueous solution; however, the percent conversion can be determined by taking an aliquot of sample and running ^{1}H NMR spectroscopy. The aromatic peaks once again shifted, but the better indication came from the broad singlet around 4.30 ppm from the newly formed amine protons in the *para* position on the aromatic ring. In order to confirm these were the amine N-H peaks, one drop of heavy water was added to the NMR sample and as expected the peaks disappeared because of the protons exchanged with deuterium atoms. The amine peaks are missing in this spectrum because the hydrogen atoms of the amine are rapidly exchanging with the deuterium atoms from heavy water.



Scheme 5. Synthesis of 1-(4-aminobenzyl)-1-methylpyrrolidin-1-ium bromide

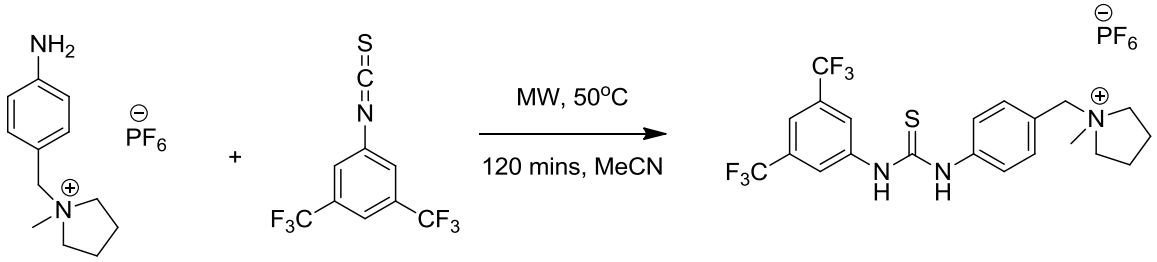
Before the metathesis step, the iron(0) nanoparticles had to be removed. This was accomplished by filtering the reaction mixture through a bed of Celite. Excess potassium hexafluorophosphate was then added and precipitate instantaneously began to form (Scheme 6). After 12 hours of stirring, the reaction mixture was filtered and the solids were collected to yield 95% of the desired hexafluorophosphate salt. A spectroscopic handle for this product is the hexafluorophosphate anion which was confirmed using ^{19}F and ^{31}P NMR spectroscopy which showed the desired doublet and septet respectively. To confirm that no halides are present a silver nitrate test can be performed.



Scheme 6. Synthesis of 1-(4-aminobenzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate

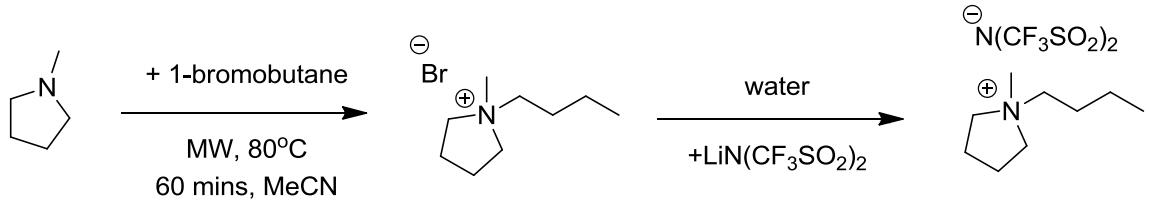
Finally, the isolated amine was dissolved in acetonitrile and reacted with 3,5-bis(trifluoromethyl)phenyl isothiocyanate in a microwave reactor at 50°C for 120 minutes to afford the desired thiourea at 87% yield (Scheme 7). This was a previously reported experimental result where the only variation was in reaction time. It is worth noting that some polymerized isothiocyante could form here; however, given that yields were high for this step of the reaction, no precautions were taken to avoid this undesirable reaction. The best diagnostic peak in the ^{1}H NMR spectrum was the broad singlets above 10 ppm that integrated to two protons, which correlate to the two secondary amine peaks on the thiourea.

These peaks both disappeared when the ^{1}H NMR spectra was rerun with one drop of heavy water due to the previously mentioned exchange with deuterium.



Scheme 7. Synthesis of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate

Two ionic liquids were used as solvents for the Morita-Baylis-Hillman reaction in this work. The first, 1-Butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]), was previously made by past researchers, and ^{1}H NMR spectroscopy was used to confirm both the structure and purity before use. The second ionic liquid, 1-Butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide ([BMPyr][$N(Tf)_2$]), had to be made using a previously reported method designed by Cheng. *et al* (Scheme 8). [42] When comparing ^{1}H NMR spectral data it showed agreement with previous reports in the literature. [42]



Scheme 8. Synthesis of 1-Butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide

The remaining compounds required for this work could all be purchased from the Millipore Sigma chemical supply company. The selected α,β-unsaturated aldehydes, more commonly referred to as enones, were cyclohexenone (2-Cyclohexen-1-one), chromone (1-Benzopyran-4-one) and coumarin (1,2-Benzopyrone). Cyclohexenone was selected due to its prevalence in the MBH literature and use in previous studies in the Singer group. Chromone and coumarin were selected because they are solid enones, which were required to properly examine the MBH reaction in the LAG regime.

Aldehydes selected for this work were benzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde. The para-chloro and para-nitro derivatives were selected not only because they are solids, but also because they are activated towards nucleophilic attack by since the carbonyl carbon in these compounds are more electrophilic. The para-chloro substituent removes electron density both inductively and mesomerically, but is less pronounced than the electron withdrawing capability of para-nitro substituents.

Many nucleophilic amines have been used as tertiary amine catalysts in MBH reactions. One of the most frequently used, 1,4-diazabicyclo[2.2.2]octane (DABCO), has alkyl groups that are tied back *via* covalent bonds, reducing the steric bulk and increasing nucleophilicity and thus reactivity.

The first of the MBH reactions performed in this work was a repeat of previous research as a control to ensure familiarity with the system: the reaction between cyclohexenone and benzaldehyde using a conventional stirring method.[39] Both of these reagents are liquids, so the reaction was under neat conditions. The stoichiometry of this MBH reaction was determined by previous researchers, who showed that the best reactivity is one equivalent of aldehyde, five equivalents of enone, 10 mol% DABCO and 10 mol%

thiourea co-catalyst. This optimized stoichiometry was used throughout this research. This reaction was performed parallel under two catalytic conditions; condition (A) is just 10% DABCO and (B) is 10% DABCO and 10% thiourea. After three hours of stirring, aliquots of the crude reaction mixture were taken and studied using ^{1}H NMR spectroscopy. The spectra were integrated to determine percent conversion to MBH product, where the best spectroscopic handles were the acyl proton of the aldehyde starting material and the methine proton of the final product. Under catalytic conditions (A), the reaction went to 75.9% conversion, whereas under conditions (B), the reaction went to 85.2% conversion with reaction times being identical. This showed an increase in rate for the thiourea co-catalyzed reaction. The conventional stirring MBH reactions are summarized below in Table 1.

4-chlorobenzaldehyde was then used under the same conditions as above to show reactivity differences. This reaction was also performed under two catalytic conditions, neat and with conventional stirring. Again, after three hours aliquots were taken. The percent conversions were based on ^{1}H NMR spectroscopy showed 89.7% conversion under catalytic conditions (A) and 93.0% conversion under conditions (B), demonstrating the increased reactivity mentioned previously.

The MBH reaction was then attempted under conventional stirring with chromone, 4-chlorobenzaldehyde and 10 mL of acetonitrile. This reaction now had the desired solid starting materials, albeit in solution. Unfortunately, after a three-hour reaction under the same conditions as the other MBH reactions, no conversion was found for either catalyst condition (A) or (B). The reaction was repeated but instead with methanol as the solvent. The MBH reaction is known to proceed *via* two reaction mechanisms, the alcohol-catalyzed

and non-alcohol-catalyzed. The substitution from polar aprotic to a polar protic solvent was intended to follow the alcohol-catalyzed mechanism and push the reaction forward. Sadly, the reaction did not proceed.

To further probe reactivity, the reaction was conducted with 4-nitrobenzaldehyde. This time, the methine proton could be observed in the crude ^{1}H NMR spectrum taken from an aliquot. Under catalyst condition (A) the reaction went to 52.0% conversion and under condition (B) to 21.2% conversion. This shows that the addition of 10% thiourea co-catalyst is inhibiting this reaction, which is opposite to what was found for previous reactions. There is no current explanation for this phenomenon and the mechanistic details of which are beyond the scope and limitations of this work.

The substituted chromone was then isolated for the intention of unequivocally assigning the methine proton that was used to calculate the percent conversion. At this stage of the workup the crude reaction mixture had the desired substituted chromone along with unreacted 4-nitrobenzaldehyde and chromone. A trituration method using a one-to-one methanol to acetonitrile ratio (by volume) was designed that selectively crashed the product out of solution that was then simply collected by filtration. The isolated product yields for the chromone and 4-nitrobenzaldehyde reaction was 25.9% under catalyst condition (A) and 3.1% under condition (B). The percent recovery for this method was low, but perhaps re-concentration of the solvent system could lead to further crops of precipitate. This solvent system was time consuming to design, but it avoided the use of column chromatography, which is also time consuming and requires lots of solvent.

Structural assignment of the substituted chromone derivative lead to some interesting nuances in the NMR spectra which were unexpected (Figure 6). ^{1}H, ^{13}C,

Distortionless Enhancement by Polarization Transfer (DEPT), Correlated SpectrocopY (COSY), Heteronuclear Single Quantum Coherence (HSQC) and D_2O NMR spectroscopy experiments were all essential for structural assignment.

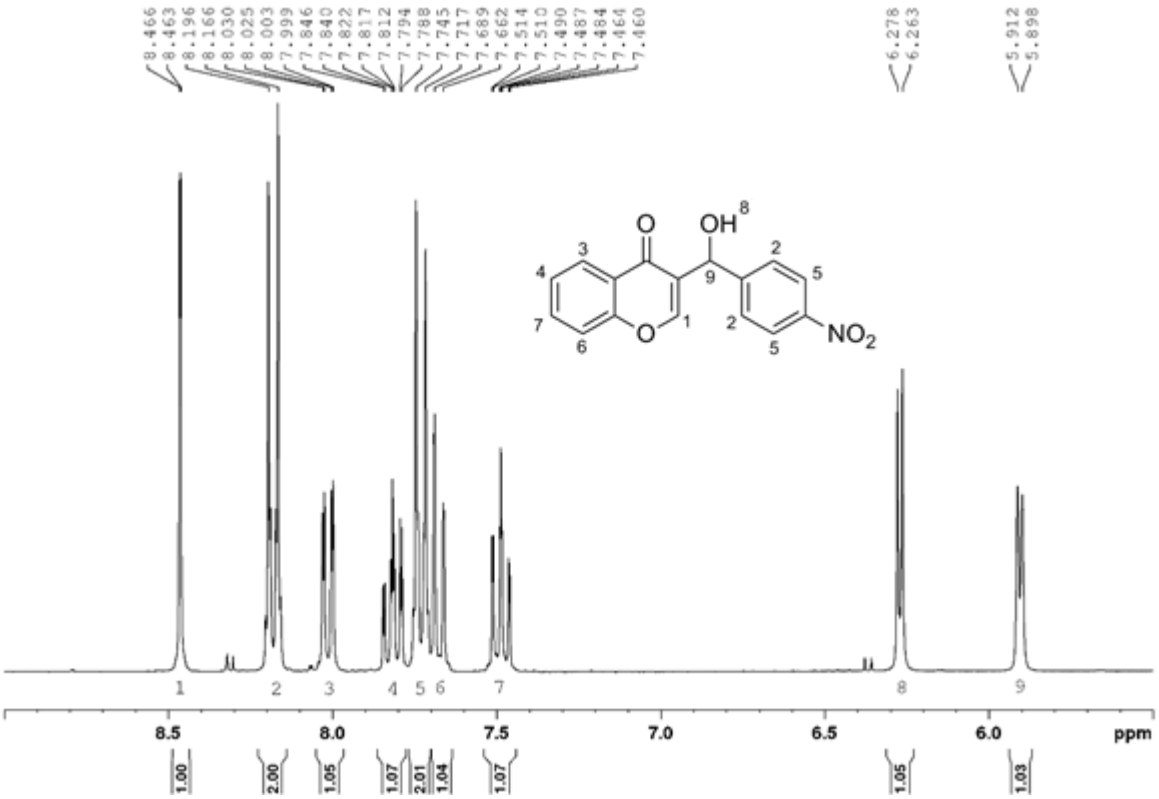


Figure 6. Structure Assignment of Substituted Chromone Derivative

COSY is a commonly used 2D NMR experiment to determine which spin systems in a given molecule are coupled to one another. This tool was helpful to assign the spin system containing protons labeled 3,4,6 and 7 (Figure 7). The spin system containing the protons labeled 1, 8 and 9 is perhaps much more interesting. Disregarding chemical shift, it may be difficult to determine which peak belongs to which proton because the multiplicity of peak labeled 8 and 9. The two options for this coupling are ^4J coupling between protons labeled 1 and 9 or ^3J coupling between protons labeled 8 and 9. The issue

with the first option is that the 4.4 Hz coupling constant is just above what is expected for ^{4}J coupling, while the issue with the latter option is the proton on the alcohol is exchangeable. The answer, which was determined by COSY NMR spectroscopy, was that the proton with the peak labeled 9 is coupled to both. The coupling constant between the methine proton and the alcohol proton is the ^{3}J 4.4 Hz mentioned above. To determine the coupling constant of the ^{4}J allylic coupling, a drop of D_2O was pipetted into the NMR tube (Figure 8). This resulted in the exchangeable proton labeled 8 disappearing in the spectrum and the proton label 9 is now split by 0.94 Hz.

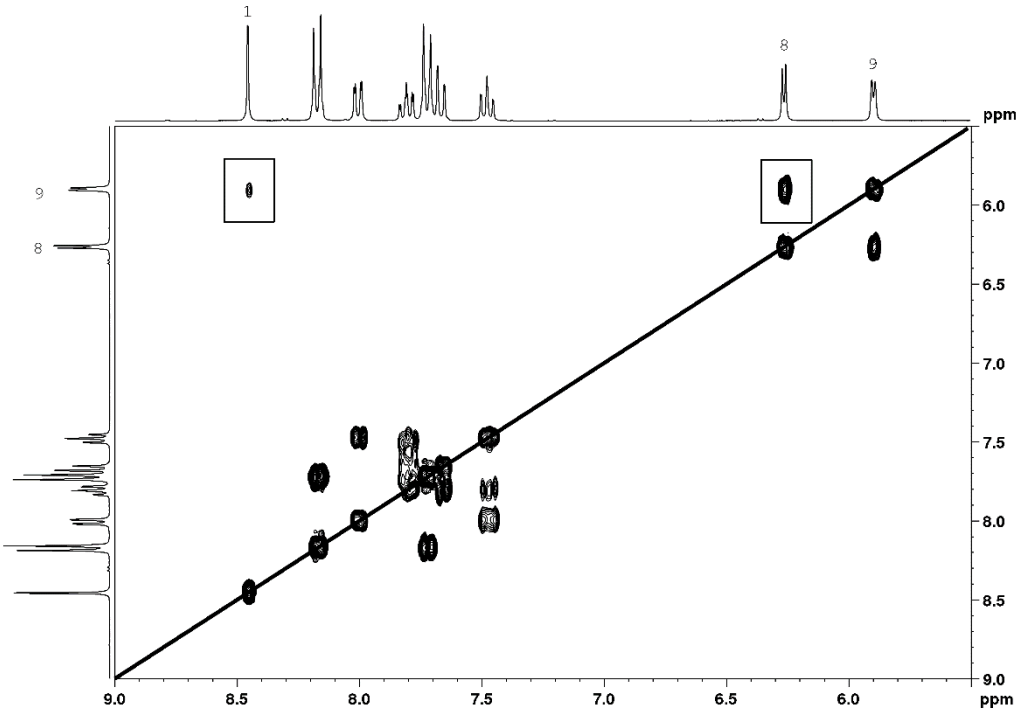


Figure 7. COSY NMR Spectroscopy of Substituted Chromone Derivative

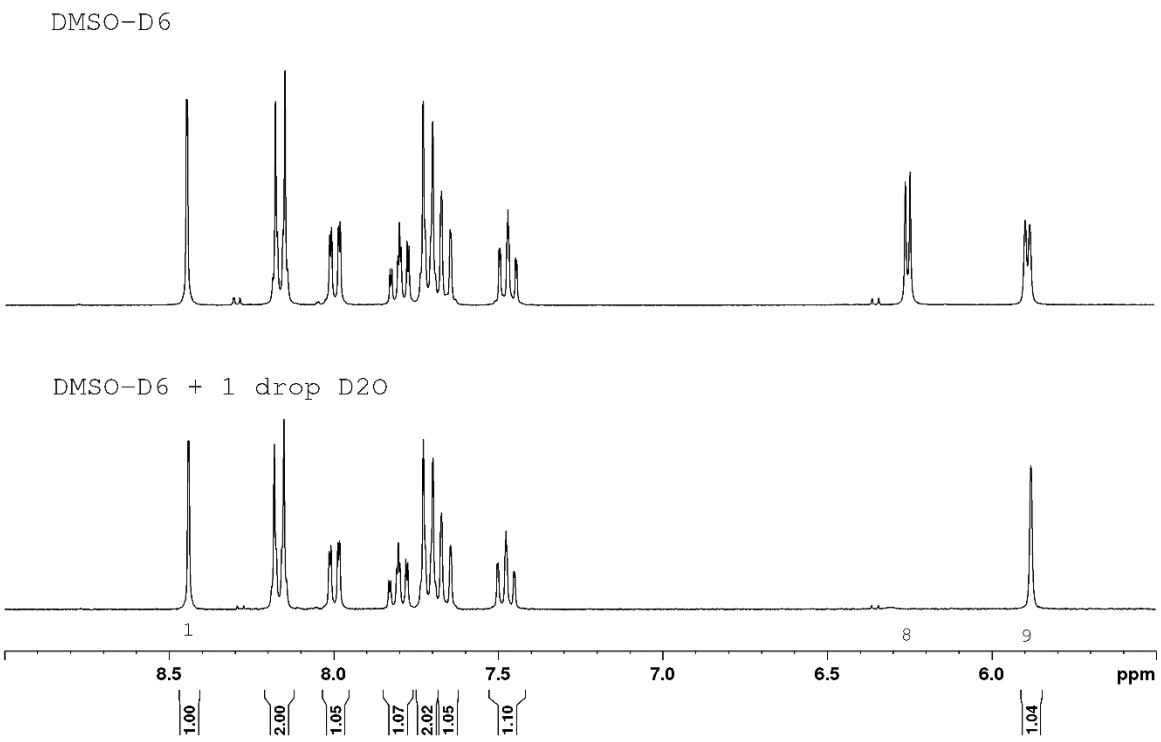


Figure 8. D_2O Drop NMR Spectroscopy Experiment of Substituted Chromone Derivative

The DEPT experiment (Figure 9) is a double resonance pulse program that is used to distinguish between methyl, methylene, methine and quaternary carbons. This information, along with data from HSQC NMR spectroscopy (Figure 10), helped to unequivocally assign the ^{13}C NMR spectrum. HSQC NMR spectroscopy is a two dimensional (2D) experiment that shows coupling between hydrogen and a heteroatom. This is helpful when assigning carbon atoms in a molecule, as the protons have previously been assigned.

The DEPT experiments show that the final product only contains quaternary and methine carbon environments as expected. Quaternary peaks are found because they only seen as positive peak in conventional ^{13}C NMR spectra but disappear in DEPT45, DEPT90 and DEPT 135 experiments. Methine protons persist throughout all for spectra.

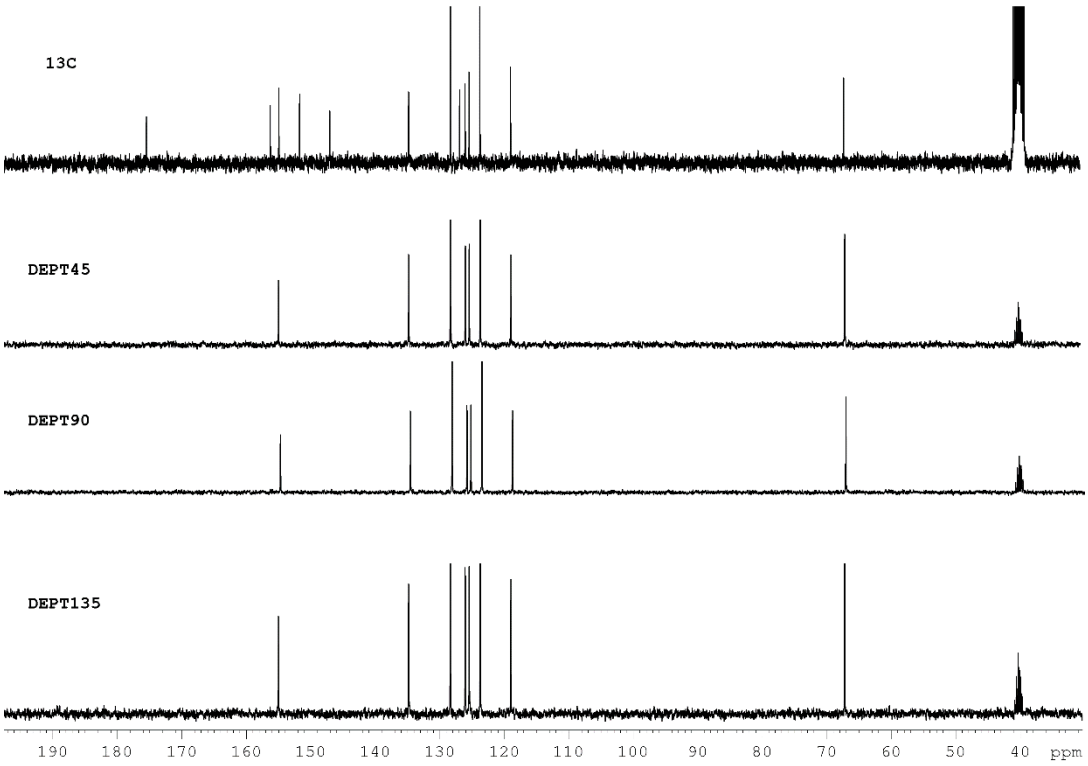


Figure 9. DEPT NMR Experiments For Carbon Assignment

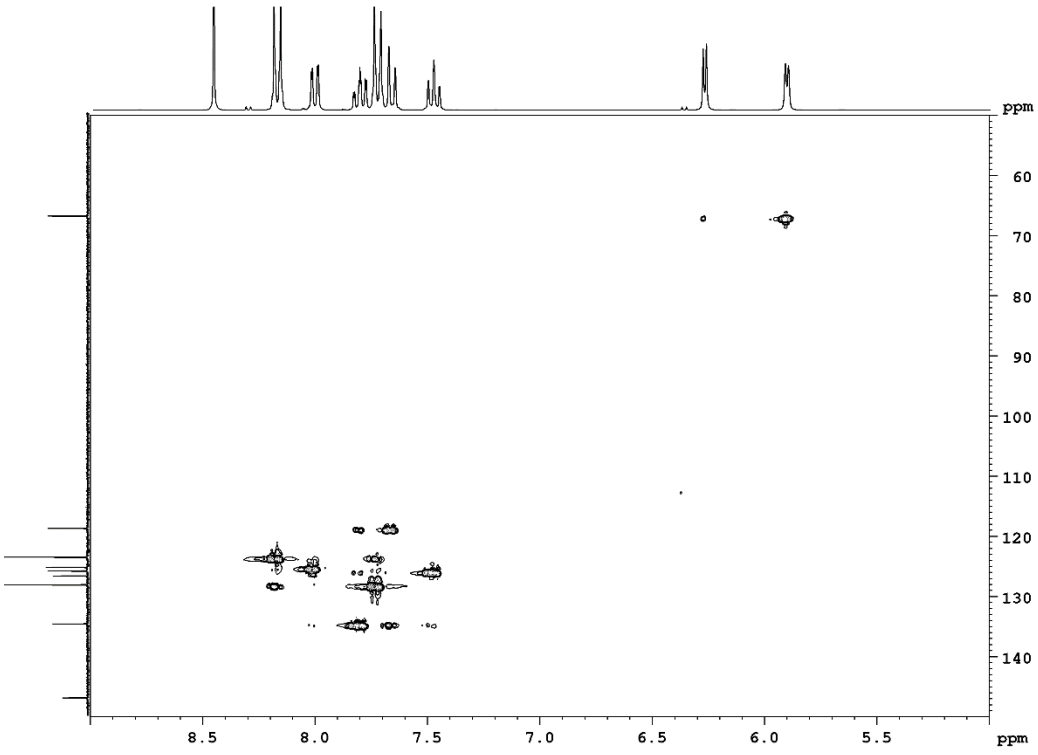


Figure 10. HSQC NMR Experiment For Carbon Assignment

To test the scope of the MBH reaction the enone was then switched to coumarin, a structural isomer of chromone, to test for reactivity difference. The reaction with coumarin did not proceed under identical reaction conditions. The reactivity difference could be due to multiple of reasons, the first being that α,β-unsaturation of coumarin can delocalize into the aromatic ring and make it more stable. Secondly, the addition of DABCO to the β-position would be more sterically hindered for coumarin because of interaction with the aromatic ring. Lastly, after the addition of DABCO and formation of the zwitterionic intermediate compound, the alpha carbon was less nucleophilic for coumarin because of the electron withdrawing inductive effect of the additional oxygen atom (Figure 11).

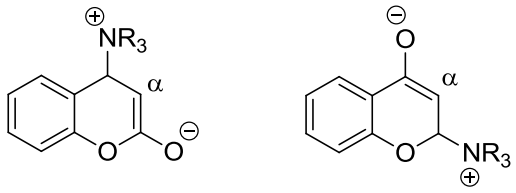


Figure 11. Zwitterionic Coumarin and Chromone Intermediates

Table 1. Summary of MBH Reactions Using Conventional Stirring

Enone	Aldehyde	Catalyst(s)	Solvent or Liquid additive	Amount of Solvent	Conv.[α]	Yield[β]
cyclohexenone	benzaldehyde	A	neat	/	75.9%	/
cyclohexenone	benzaldehyde	B	neat	/	85.2%	/
cyclohexenone	4-chlorobenzaldehyde	A	neat	/	89.7%	/
cyclohexenone	4-chlorobenzaldehyde	B	neat	/	93.0%	/
chromone	4-chlorobenzaldehyde	A	MeCN	10 mL	/	/
chromone	4-chlorobenzaldehyde	B	MeCN	10 mL	/	/
chromone	4-chlorobenzaldehyde	A	MeOH	10 mL	/	/
chromone	4-chlorobenzaldehyde	B	MeOH	10 mL	/	/
coumarin	4-nitrobenzaldehyde	A	MeOH	10 mL	/	/
coumarin	4-nitrobenzaldehyde	B	MeOH	10 mL	/	/
chromone	4-nitrobenzaldehyde	A	MeOH	10 mL	52.0%	25.9%
chromone	4-nitrobenzaldehyde	B	MeOH	10 mL	21.2%	3.1%

A) DABCO; B) DABCO & thiourea; α) Conversion percentage based on ^{1}H NMR spectroscopy; β) Isolated yield

With the success in the MBH reaction using the selected starting materials and with authentic samples of products in hand, the same reactions were attempted in the liquid assisted grinding (LAG) regime. The reaction conditions for LAG are similar to conventional stirring—one equivalent of aldehyde, two equivalents of enone, two catalyst conditions (i.e 10% DABCO with or without 10% thiourea co-catalyst) and a reaction time of three hours. The difference is the addition of two steel milling balls and up to two microliters of a liquid additive. The amount of liquid additive had to be calculated for each reaction based on milligrams of material in the reaction using the previously described η value. An implication of this is less liquid additive is for catalyst condition (A) because there is less total mass. LAG MBH reactions are summarized in Table 2 below.

The first MBH reaction using the ball mill used cyclohexenone and 4-chlorobenzaldehyde under neat conditions. The ^{1}H NMR spectrum of the crude aliquot showed a low percent conversion when compared to the same reaction under conventional stirring. This was not a promising result; however, this reaction was not in the LAG regime and therefore not crucial to the objective of this study.

The remaining MBH reactions discussed herein are all within the LAG regime (i.e. $\eta \leq 1$) and use chromone and 4-nitrobenzaldehyde as the solid reagents. This reaction, which showed previous success under conventional stirring, was first performed with $\eta = 1$ for the liquid additive. When methanol was used as a liquid additive an increase in percent conversion was observed - 85.7% conversion for catalyst condition (A) and 36.9% conversion for condition (B). Unfortunately, isolated yields were still low at 14.8% and 11.3% respectively. These results showed LAG outperformed conventional stirring methods.

Next, ethanol was selected to test the scope of this reaction with other polar protic liquid additives. The conversions were considerably lower than those for methanol at 12.5% conversion for catalyst condition (A) and 2.1% for condition (B). With such low percent conversions, isolated yields were not worth pursuing.

The reaction was then tested with polar aprotic liquid additives such as acetonitrile, 1-Butyl-1-methylpyrrolidinium bis(trifluoromethanesulfonyl)imid, [BMPyr][$N(Tf)_2$] and 1-Butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6], which unsurprisingly all had no conversion to products.

Ionic liquids were chosen for this reaction because they could potentially facilitate the recycle of the thiourea co-catalyst. The ionic thiourea co-catalyst used is preferentially soluble in ionic liquids, whereas the reagents and products of the MBH reaction are preferentially soluble in ether. This allowed for products and unreacted reagents to be extracted, and the thiourea dissolved in the ionic liquid could be reused in subsequent reactions. The thiourea co-catalyst was inhibiting this MBH reaction, meaning that this approach proved to be ineffective. One possible reason for this inhibition could be due to a competition between the two mechanistic pathways (i.e., non-alcohol-catalyzed versus alcohol-catalyzed mechanism (Scheme 3)). Past researchers have shown success with these means, but with more reactive starting materials such as cyclohexenone. [39]

Table 2. Summary of MBH Reactions Using LAG

Enone	Aldehyde	Catalyst(s)	Liquid additive	η – μL/mg	Conv.[α]	Yield[β]
cyclohexenone	4-chlorobenzaldehyde	A	neat	/	15.0%	/
cyclohexenone	4-chlorobenzaldehyde	B	neat	/	64.2%	/
chromone	4-nitrobenzaldehyde	A	MeOH	1	85.7%	14.8%
chromone	4-nitrobenzaldehyde	B	MeOH	1	36.9%	11.3%
chromone	4-nitrobenzaldehyde	A	EtOH	1	12.5%	/
chromone	4-nitrobenzaldehyde	B	EtOH	1	2.1%	/
chromone	4-nitrobenzaldehyde	A	MeCN	1	/	/
chromone	4-nitrobenzaldehyde	B	MeCN	1	/	/
chromone	4-nitrobenzaldehyde	A	$BMPyrN(Tf)_2$	1	/	/
chromone	4-nitrobenzaldehyde	B	$BMPyrN(Tf)_2$	1	/	/
chromone	4-nitrobenzaldehyde	A	$BMIMPF_6$	1	/	/
chromone	4-nitrobenzaldehyde	B	$BMIMPF_6$	1	/	/

A) DABCO; B) DABCO & thiourea; α) Conversion percentage based on ^{1}H NMR spectroscopy; β) Isolated yield

The final study in this chapter investigated the effect of varying the η-value for the liquid assisted grinding MBH reaction of chromone and 4-nitrobenzaldhyde under the two catalyst conditions (i.e 10% DABCO with or without 10% thiourea co-catalyst). As expected, the percent conversions decreased as η decreased (i.e. as the amount of liquid additive was decreased) (Table 3). The ideal case is to have no liquid additive at all and move into the dry grinding regime. Unfortunately, the dry grinding reactions did not proceed to products but this strengthened the understanding that these reactions are proceeding through the alcohol-catalyzed mechanism.

Table 3. Summary of MBH Reactions Varying η - Value

Catalyst(s)	η - value	Conversion Percentage[α]	Yield[β]
A	0	/	/
B	0	/	/
A	0.5	60.9%	16.4%
B	0.5	43.0%	6.6%
A	0.75	68.1%	12.9%
B	0.75	45.1%	9.1%
A	1	85.7%	14.8%
B	1	36.9%	11.3%

A) DABCO; B) DABCO & thiourea; α) Conversion percentage based on ^{1}H NMR spectroscopy; β) Isolated yield

1.3.0 Conclusion

A thiourea co-catalyst was synthesized using an optimized method that led to a relatively higher overall yield of 68.0 percent. The purity of this compound, >95%, was determined using nuclear magnetic resonance spectroscopy. The co-catalyst had a rate inhibiting effect on the MBH reaction under methanolic conditions.

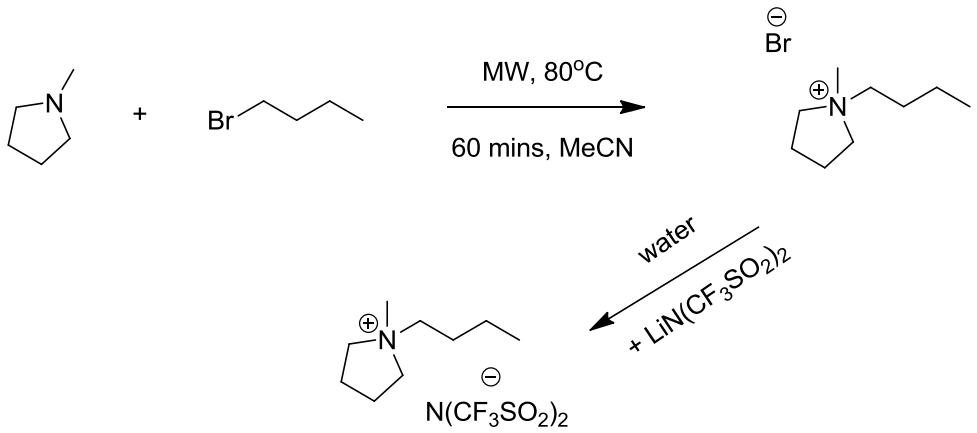
The Morita-Baylis-Hillman was successfully performed in the liquid assisted grinding regime using chromone, 4-nitrobenzaldehyde and DABCO under alcohol-catalyzed conditions at 85.7 percent conversion to the desired substituted chromone derivative. Methanol was found to be the best liquid additive for this reaction, with the highest conversion percentage of 85.7 achieved when $\eta = 1$. Liquid assisted grinding outperformed conventional stirring in this study. The desired product was isolated by a simple trituration process and fully characterized by nuclear magnetic resonance spectroscopy, electrospray ionization mass spectrometry, electrospray ionization high resolution mass spectrometry, melting point and attenuated total reflectance infrared spectroscopy.

1.4.0 Future Work

The future work for this project should include broadening the scope of the MBH reaction under LAG conditions. This would include varying the solid aldehyde and enone substrates along as well as the liquid additive. Phenol is a great choice for a liquid additive because it is about 106 times more acidic than methanol. Perhaps phenol will catalyze the MBH well enough to switch the enone to coumarin, the structural isomer of chromone.

1.5.0 Experimental

1.5.1 Synthesis of butylmethylpyrolidinum (trifluoromethylsulfonyl)imide [BMPyr][N(Tf)$_2$]

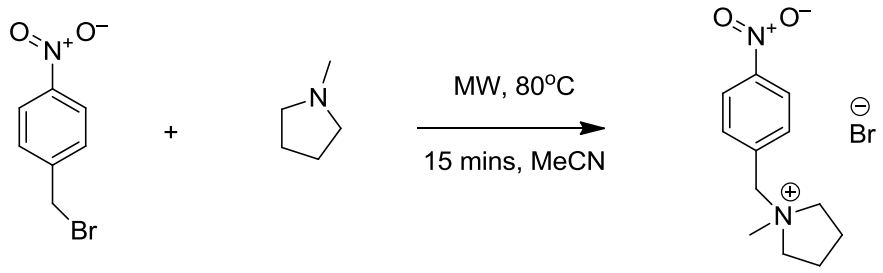


The synthesis of butylmethylpyrrolidinum (trifluoromethylsulfonyl)imide was adapted from Cheng. *et al,* who described a one-pot microwave synthesis of this ionic liquid.[42] 0.52 mL (5 mmol) *N*-methylpyrrolidine, 0.67 mL (6.25 mmol) 1-bromobutane and 10 mL MeCN was added to a 35 mL CEM microwave reaction tube. The reaction tube was placed in a CEM microwave reactor at 40 W power at 80 °C for 60 minutes. The crude reaction mixture was poured into a beaker and acetonitrile was added until the solid precipitate was fully dissolved. Then enough ethyl acetate was added until a 1:1 acetonitrile

to ethyl acetate solution was obtained, which crashes the product back out of solution. The solid was isolated *via* gravity filtration and fully dried under vacuum. The solid was dissolved in minimal water and 1.43 g (5 mmol) of bis(trifluoromethane)sulfonamide lithium salt was first dissolved in water and then added to the reaction. The solution was stirred for 48 hours. The ionic liquid separates from the aqueous fraction and aggregates on the bottom. Wash the ionic liquid with water in a separatory funnel until it passes the silver nitrate test. The resulting halide-free product weighed 1.94 g (92% yield) and the structure was confirmed using ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53-3.35 (m, 4H), 3.34-3.20 (m, 2H), 2.98 (s, 3H), 2.01 (m, 4H), 1.69 (m, 2H), 1.32 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H).

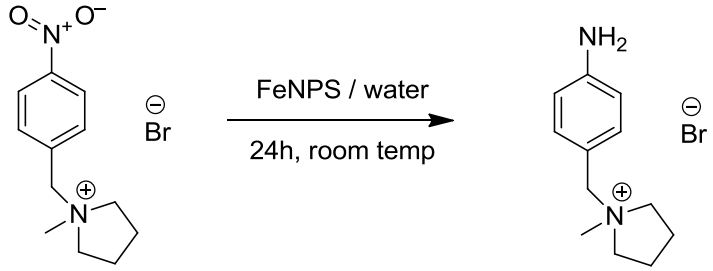
1.5.2 Synthesis of *N*-Methylpyrrolidinium Tagged Thiourea

1-methyl-1-(4-nitrobenzyl)pyrrolidin-1-ium bromide



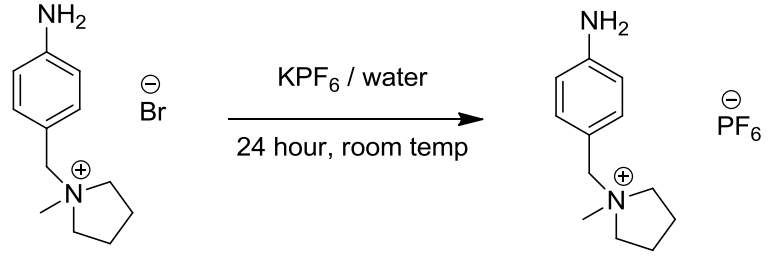
Then 2.16 g (10 mmol) of 4-nitrobenzyl bromide, 1.14 mL (11 mmol) of 1-methylpyrrolidine and 10 mL of acetonitrile was added to a 35 mL CEM microwave reaction tube. The reaction tube was placed in a CEM microwave reactor at 40 W power at 80 °C for 15 minutes. Take off the acetonitrile with a rotary evaporator to receive 2.47 g (8.2 mmol, 82 % yield) of solid material. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.16 (d, J = 9.36 Hz, 2H), 6.61 (d, J = 9.36 Hz, 2H), 5.50 (s, 2H), 3.54-3.41 (m, 2H), 3.40-3.22 (m, 2H), 2.84 (s, 3H), 2.22-2.01 (m, 4H).

1-(4-aminobenzyl)-1-methylpyrrolidin-1-ium bromide



5.75 g (20.69 mmol) of iron(II) sulfate heptahydrate and 0.44 g (1.72 mmol) sodium citrate were added to a tall-form beaker along with 100 mL of water. 1.30 g (34.49 mmol) of sodium borohydride was then added slowly to reduce the iron(II) sulfate to iron (0) nanoscale particles. The 50 mL of water was added and decanted off in triplicate. 1-methyl-1-(4-nitrobenzyl)pyrrolidin-1-ium bromide was added to the decanted iron nanoparticles and stirred at room temperature for 24 hours. With an effort to use minimal water, the crude reaction mixture was passed through 2 cm celite bed on a 150 mL frit. The product was left in water for the subsequent reaction. ^{1}H NMR (300 MHz, DMSO-D6) δ 7.16 (d, J = 9.42 Hz, 2H), 6.58 (d, J = 9.42 Hz, 2H), 5.48 (s, 2H), 4.30 (s, 2H), 3.52-3.39 (m, 2H), 3.40-3.22 (m, 2H), 2.84 (s, 3H), 2.22-2.01 (m, 4H).

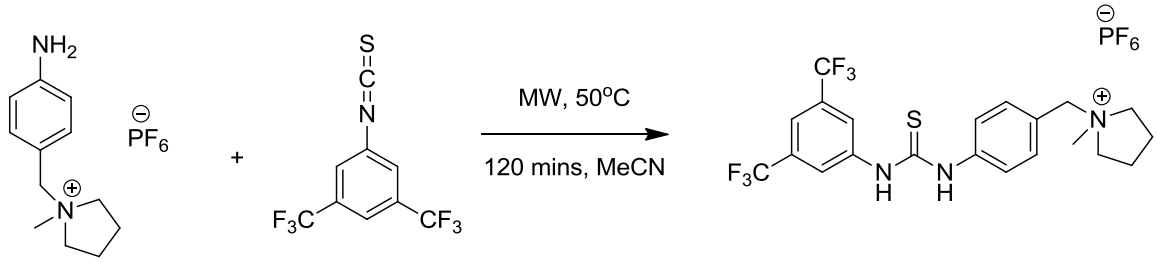
1-(4-aminobenzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate



2.30 g (12.5 mmol) of potassium hexafluorophosphate was dissolved in minimal water and then added to the previously made aqueous reaction mixture. The product

immediately began to precipitate, after 3 hours the reaction mixture could be cooled and then vacuum filtered to yield 2.11 g (7.79 mmol, 95 % yield). ^{1}H NMR spectra data match the previously made bromine salt. ^{31}P NMR (121.5 MHz, DMSO-D6) δ -126.6, -132.5, -138.3, -144.2, -150.0, -155.9, -161.7. ^{19}F NMR (282.5 MHz, DMSO-D6) δ -68.9, -71.4.

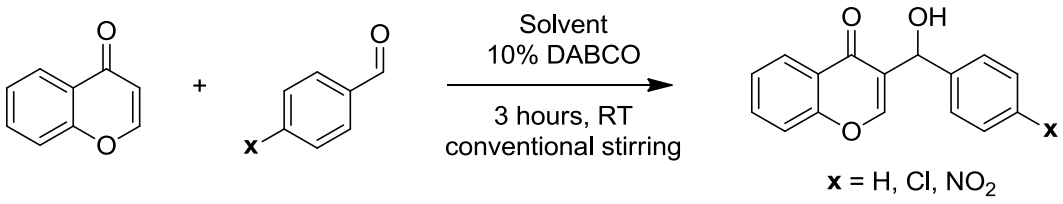
1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate



2.11 g (7.79 mmol) of the previously made 1-(4-aminobenzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate was placed in a 35 mL CEM microwave reaction tube along with 5 mL of acetonitrile and 1.42 mL (7.79 mmol) 3,5-bis(trifluoromethyl)phenyl isothiocyanate and heated to 50°C for 120 minutes. Solvent was removed with a rotary evaporator and the solid yellow product was dried under vacuum to yield 4.12 g (87% yield, 68% overall reaction yield). ^{1}H NMR (300 MHz, DMSO-D6) δ 10.46 (bs, 1H), 10.35 (bs, 1H), 8.25 (bs, 2H), 7.83 (bs, 1H), 7.66 (d, J = 8.74 Hz, 2H), 7.56 (d, J = 8.74 Hz, 2H), 4.53 (s, 2H), 3.65-3.47 (m, 2H), 3.46-3.33 (m, 2H), 2.91 (s, 3H), 2.24-2.08 (m, 4H).

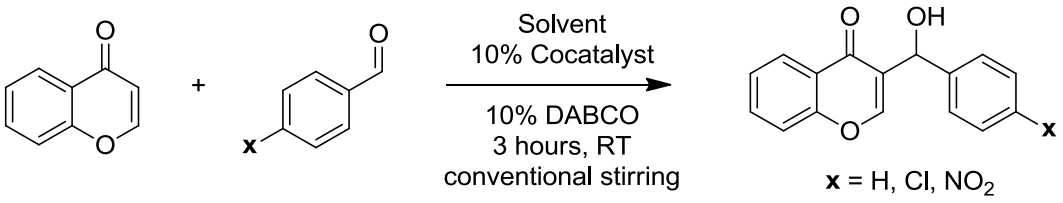
1.5.3 Morita-Baylis-Hillman Reactions

Solution Phase Morita-Baylis-Hillman Reaction with Chromone



0.7306 g (5 mmol) of 1,4-benzopyrone (chromone), 1 mmol of the desired aldehyde and 0.0568 g (0.1 mmol) of 1,4-diazabicyclo[2.2.2]octane were added to a 25 mL round bottom flask and dissolved in 10 mL of the desired solvent. After 3 hours a crude ^{1}H NMR spectroscopy sample in DMSO-D6 was taken to give a % conversion of the desired substituted chromone. If product could not be observed in the crude ^{1}H NMR spectroscopy then no further workup was required.

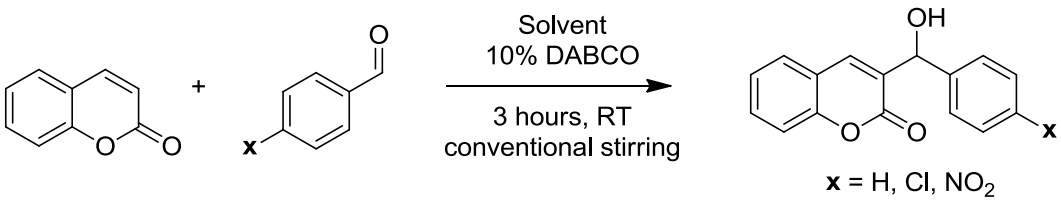
Solution Phase Morita-Baylis-Hillman Reaction with Chromone (Co-catalyzed)



0.7306 g (5 mmol) of 1,4-benzopyrone (chromone), 1 mmol of the desired aldehyde, 0.0568 g (0.1 mmol) of 1,4-diazabicyclo[2.2.2]octane and 0.3038 g (0.1 mmol) of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate co-catalyst were added to a 25 mL round bottom flask and dissolved in 10 mL of the desired solvent. After 3 hours a crude ^{1}H NMR spectroscopy sample in

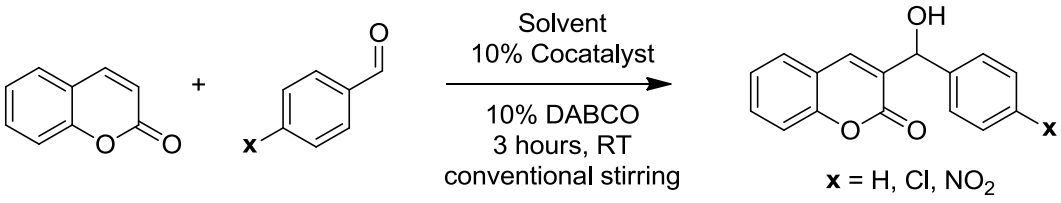
DMSO-D6 was taken to give a yield of the desired substituted chromone. If product could not be observed in the crude ^{1}H NMR spectroscopy then no further workup was required.

Solution Phase Morita-Baylis-Hillman Reaction with Coumarin



0.7306 g (5 mmol) of 1,2-benzopyrone (coumarin), 1 mmol of the desired aldehyde and 0.0568 g (0.1 mmol) of 1,4-diazabicyclo[2.2.2]octane were added to a 25 mL round bottom flask and dissolved in 10 mL of the desired solvent. After 3 hours a crude ^{1}H NMR spectroscopy sample in DMSO-D6 was taken to give a yield of the desired substituted coumarin. If product could not be observed in the crude ^{1}H NMR spectroscopy then no further workup was required.

Solution Phase Morita-Baylis-Hillman Reaction with Coumarin (Cocatalyzed)



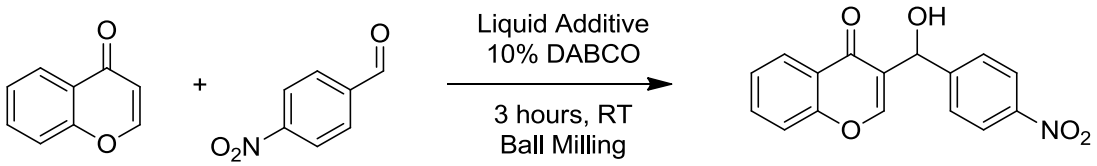
0.7306 g (5 mmol) of 1,2-benzopyrone (coumarin), 1 mmol of the desired aldehyde, 0.0568 g (0.1 mmol) of 1,4-diazabicyclo[2.2.2]octane and 0.3038 g (0.1 mmol) of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate co-catalyst were added to a 25 mL round bottom flask and dissolved in 10 mL of the desired solvent. After 3 hours a crude ^{1}H NMR spectroscopy sample in

DMSO-D6 was taken to give a yield of the desired substituted coumarin. If product could not be observed in the crude ^{1}H NMR spectroscopy then no further workup was required.

Solution Phase Workup for Morita-Baylis-Hillman Reactions

The reaction between 1,4-benzopyrone (chromone) and 4-nitrobenzaldehyde was the only reaction that proceeded and the desired substituted chromone was observed *via* ^{1}H NMR spectroscopy. In order to isolate this product, the solvent was first taken off on a rotary evaporator. The solids are then dissolved in 5 mL of chloroform (thiourea co-catalyst is insoluble) and gravity filtered to leave behind the thiourea. Next, the solvent is once again removed on a rotary evaporator and then dissolved in 5 mL of 1:1 by volume methanol/acetonitrile solution and left in the freezer overnight. The next morning the yellow/white solids were gravity filtered and washed with chilled 1:1 by volume methanol/acetonitrile solution. The solids were dried and weighed, melting point 198.5-200.6°C. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.47 (s, 1H), 8.18 (d, J = 9.32 Hz, 2H), 8.01 (dd, J = 7.86 & 1.60 Hz, 1H), 7.82 (tt, J = 7.96 & 1.60 Hz, 1H), 7.73 (d, J = 8.51 Hz, 2H), 7.68 (d, J = 8.51 Hz, 1H), 7.49 (tt, J = 7.86, 1.13 Hz, 1H), 6.27 (d, J = 4.22 Hz, 1H), 5.90 (d, J = 4.22 Hz, 1H). ^{13}C NMR (75.5, $CDCl_3$) δ 175.6, 156.3, 155.0, 152.0, 147.0, 134.8, 128.3, 126.7, 126.0, 125.4, 123.7, 123.7, 119.0, 67.2. ESI-HRMS m/z: $[M+Na]^+$ Calcd for $C_{16}H_{11}NO_5$ 320.0535; Found 320.0527. $[2M+Na]^+$ Calcd for $C_{16}H_{11}NO_5$ 617.1172; Found 617.1151.

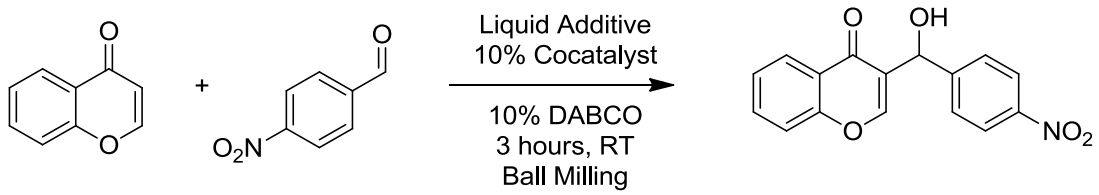
Liquid Assisted Grinding Morita-Baylis-Hillman Reaction for Chromone Derivatives



0.7306 g (5 mmol) of 1,4-benzopyrone (chromone), 1 mmol of the desired aldehyde, 0.0568 g (0.1 mmol) of 1,4-diazabicyclo[2.2.2]octane, two steel milling balls, and 939 μL of liquid additive (1η) were added to a PTFE milling jar and shook at 25 Hz for 3 hours in a MM400 Retsch ball mill. After the milling the contents of the billing jars were transferred to a 1 dram scintillation vial and the liquid additive was taken off with a rotary evaporator. The dried crude product was dissolved in chloroform. The cloudy solution was filtered through a 2 cm celite plug in a 25 mL syringe, leaving behind the milling balls and suspended paramagnetic iron. An aliquot of the clear solution was taken for a crude ^{1}H NMR yield in DMSO-D6. If there was substituted chromone product in the crude ^{1}H NMR then the rest of the clear solution was rotary evaporated to dryness, then redissolved in 5 mL of 1:1 by volume methanol/acetonitrile solution and left overnight in a freezer to precipitate. The yellow/white solids were gravity filtered and washed with chilled 1:1 by volume methanol/acetonitrile solution. The solids were dried and weighed, melting point 199-200.8°C. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.46 (s, 1H), 8.19 (d, J = 9.32 Hz, 2H), 8.01 (dd, J = 7.86 & 1.60 Hz, 1H), 7.81 (tt, J = 7.96 & 1.60 Hz, 1H), 7.73 (d, J = 8.51 Hz, 2H), 7.69 (d, J = 8.50 Hz, 1H), 7.50 (tt, J = 7.86, 1.13 Hz, 1H), 6.27 (d, J = 4.22 Hz, 1H), 5.91 (d, J = 4.22 Hz, 1H). ^{13}C NMR (75.5, $CDCl_3$) δ 175.5, 156.3, 154.9, 152.1, 147.0, 134.8, 128.3, 126.7, 126.0, 125.4, 123.7, 123.7, 119.0, 67.2. ESI-HRMS m/z:

$[M+Na]^+$ Calcd for $C_{16}H_{11}NO_5$ 320.0535; Found 320.0510. $[2M+Na]^+$ Calcd for $C_{16}H_{11}NO_5$ 617.1172; Found 617.1158.

Liquid Assisted Grinding Morita-Baylis-Hillman Reaction for Chromone Derivatives (Cocatlyzed)



0.7306 g (5 mmol) of 1,4-benzopyrone (chromone), 1 mmol of the desired aldehyde, 0.0568 g (0.1 mmol) of 1,4-diazabicyclo[2.2.2]octane, 0.3038 g (0.1 mmol) of 1-(4-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)benzyl)-1-methylpyrrolidin-1-ium hexafluorophosphate co-catalyst, two steel milling balls, and 1242 μL of liquid additive (1η) were added to a PTFE milling jar and shook at 25 Hz for 3 hours in a MM400 Retsch ball mill. After the milling the contents of the billing jars were transferred to a 1 dram scintillation vial and the liquid additive was taken off with a rotary evaporator. The dried crude product was dissolved in chloroform. The cloudy solution was filtered through a 2 cm celite plug in a 25 mL syringe, leaving behind the insoluble thiourea, the milling balls and suspended paramagnetic iron. An aliquot of the clear solution was taken for a crude ^1H NMR yield in DMSO-D6. If there was substituted chromone product in the crude ^1H NMR then the rest of the clear solution was rotary evaporated to dryness then redissolved in 5 mL of 1:1 by volume methanol/acetonitrile solution and left overnight in a freezer to precipitate. The yellow/white solids were gravity filtered and washed with chilled 1:1 by

volume methanol/acetonitrile solution. The solids were dried and weighed, melting point 198.7-201.1°C. ^{1}H NMR (300 MHz, DMSO-D6) δ 8.46 (s, 1H), 8.19 (d, J = 9.32 Hz, 2H), 8.01 (dd, J = 7.86 & 1.60 Hz, 1H), 7.81 (tt, J = 7.96 & 1.60 Hz, 1H), 7.73 (d, J = 8.51 Hz, 2H), 7.69 (d, J = 8.50 Hz, 1H), 7.50 (tt, J = 7.86, 1.13 Hz, 1H), 6.27 (d, J = 4.22 Hz, 1H), 5.91 (d, J = 4.22 Hz, 1H). ^{13}C NMR (75.5, $CDCl_3$) δ 175.5, 156.3, 154.9, 152.1, 147.0, 134.8, 128.3, 126.7, 126.0, 125.4, 123.7, 123.7, 119.0, 67.2. ESI-HRMS m/z: $[M+Na]^+$ Calcd for $C_{16}H_{11}NO_5$ 320.0535; Found 320.0522. $[2M+Na]^+$ Calcd for $C_{16}H_{11}NO_5$ 617.1172; Found 617.1155.

2.0.0 Improved Synthesis of Gemini Surfactants

2.1.0 Introduction

2.1.1 Surfactants

The focus of this project is to improve the synthesis of a class of surfactants called gemini surfactants. Surfactants, or surface-active agents, are any compound that lowers the surface tension or interfacial tension of an aqueous system. Surfactants have applications in detergency, lubrication, wetting agents, emulsifiers, foaming agents and dispersants. Generally, surfactants are organic compounds that contain both hydrophobic and hydrophilic groups, also known as amphiphilic in nature. Surfactants are further classified as anionic (e.g., alkyl sulfates such as sodium dodecylsulfate, SDS),[43] cationic (e.g., quaternary ammonium salts such as dodecyltrimethylammonium bromide, DTAB),[44] non-ionic (e.g., polyoxyethylene surfactants such as $C_{10}E_8$)[45] and zwitterionic (e.g., ammonium alkylsulfonates such as ammoniopropanesulfonate, Zw3-12)[46] (Figure 12).

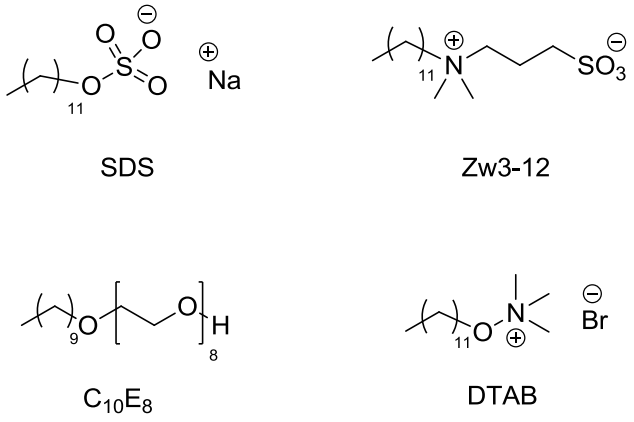


Figure 12. Common Surfactants

When surfactants are added to an aqueous solution they aggregate at the air-water or oil-water interface, lowering the surface tension or the interfacial tension. Once a certain monomer concentration is achieved, known as the critical micelle concentration, the interface is fully saturated with monomers and surfactant molecules to form supramolecular structures known as micelles.[47] In general, micelles are spherical in shape; however, ellipsoids, cylinders and bilayers are also possible (Figure 13).[48]

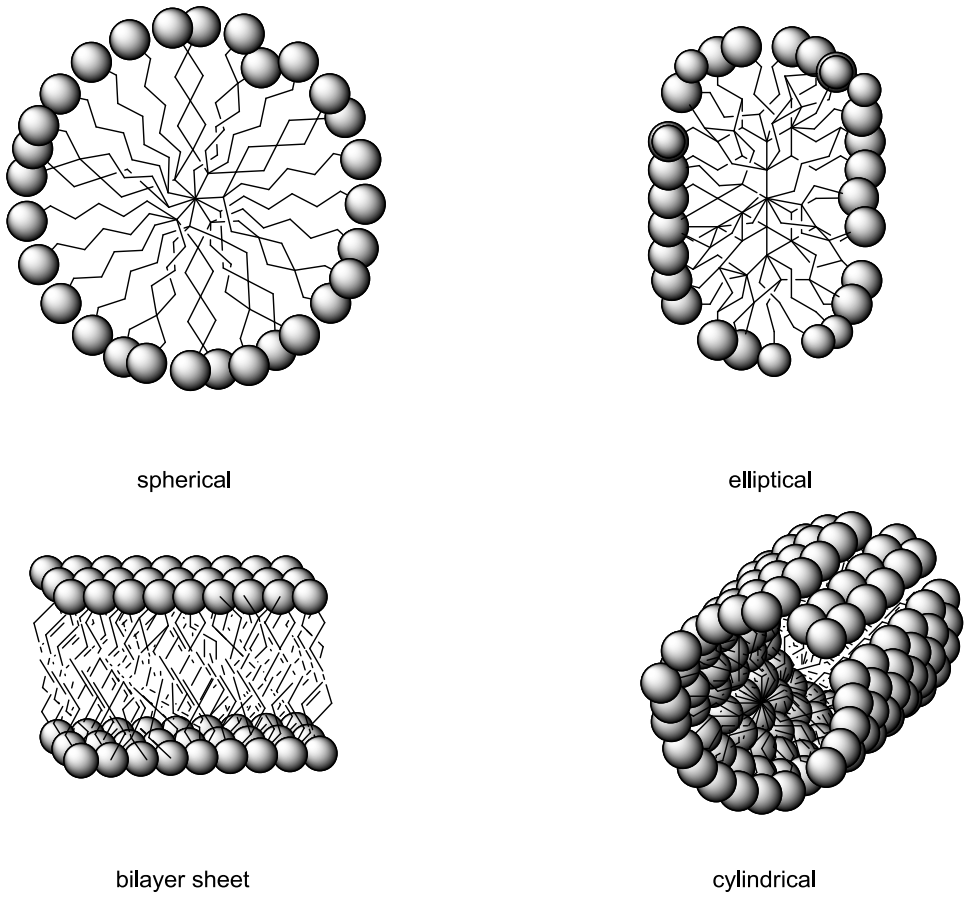


Figure 13. Cross-section View Of Common Micelle Shapes

2.1.2 Mixed Micellular Systems

It is well known in the literature that surfactants of differing types (e.g., cationic and non-ionic) have synergistic effects and often outperform individual surfactants. Mixed micellular systems are simply when a mixture of two (or more) surfactants reach their critical micelle concentrations and form micelles that have monomer units of both surfactants within the same micelle. It is also possible to have a system of two or more surfactants that form micelles but have no mixture of monomers, these too have synergistic effects but not to the same extent.[46]

The interactions of mixed micellular systems can be seen using a two-dimensional nuclear magnetic resonance technique called Nuclear Overhauser Effect, spectroscopy (NOESY). The cross peaks in a NOESY NMR spectrum show resonances from nuclei that are spatially close (within five angstroms), but not necessarily coupled to one another. When a micelle consists of only one type of monomer the cross peaks will be very minimal, but when there is two different types of monomers within the micelle the interactions are directly observed by the abundance of cross-peaks. This technique can be used to find concentrations that optimize these mixed micellular interactions.[46]

2.1.3 Gemini Surfactants

Gemini surfactants, unlike the general structure of surfactants, have two matching head groups, a linking chain and either two hydrophobic tails the same length (symmetric gemini surfactants) or different in length (nonsymmetric gemini surfactants). Gemini surfactants require a lower concentration of surfactant in order to reach CMC when compared to conventional surfactants (0.0055 wt% and 0.5 wt% respectively). [46] This is

important because the desired effect of a micellar system is obtained with less compound. This substantial decrease in CMC can be attributed to the relative increase of hydrophobic effects thanks to the second alkyl chain.[49] This chapter focuses on the syntheses of cationic quaternary ammonium salts as cationic gemini surfactants, in particular nonsymmetric or unsymmetric gemini surfactants, that will later be used in conjunction with the zwitterionic surfactants to form a mixed micellar system.

2.1.4 Measuring Critical Micelle Concentration

There are many ways in which critical micelle concentration (CMC) can be studied, including drop-shape analysis,[50] fluorescence using pyrene,[51] surface tension measurements,[52] NMR spectroscopy,[53] dynamic light scattering (DLS) and calorimetry measurements.[46] The latter two will be the methods used to determine the CMC of these compounds in the future.

DLS is a relatively new method used to obtain particle size in colloidal systems. When light, usually a monochromatic light source (e.g., a laser) is scattered on a suspension, there is a certain intensity and fluctuations at which light is scattered. These fluctuations are due to the motion of a local concentration of particles. When the critical micelle concentration is reached there is a great increase in intensity due to the formation of micelles.[54]

The second method that will be used is a relatively simple calorimetry experiment. The thermodynamics of micellular formation is fairly well understood and it is well known that the CMC plays a factor in the Gibbs free energy of micellization. When the surfactant is precipitated out in the form micelles the free energy of the system is decreased, this

means that the aggregation process is thermodynamically favoured and spontaneous. Calorimetry is a process that measures the heat released (exothermic) or absorbed (endothermic) during a reaction. Using highly sensitive calorimetry the Gibbs energy change, entropy change and the heat capacity can be calculated. The heats of micelle formation can be plotted against concentration to determine the CMC.[55]

2.1.5 Microwave Heating

The improved synthesis of these gemini surfactants employs the use of a microwave reactor. Many books and other reviews have been written on the usefulness of microwave heating in synthesis, with many of them highlighting short reaction times, increased product yield and even reduced impurities by avoiding side reactions.[56, 57, 58] It is important to study how microwave radiation can be used to induce chemical reactions to understand how it is beneficial over conventional heating methods.

Microwave electromagnetic radiation is not powerful enough to break bonds by direct absorption (i.e., photochemistry) because the photon energy from a microwave source is not high enough.[58] It is instead dielectric heating, as molecules absorb the energy and convert it to heat. In dielectric heating the diploe moment of the molecules will tend to orient and reorient under the influence of the microwaves electric field. This method does not rely on the convection of a system like conventional heating, which is very energy inefficient due to the temperature of the reaction vessel being higher than the reaction mixture and temperature gradients through the reaction vessel.[58] This phenomenon allows for an entire solution to be heated simultaneously and more efficiently because the reaction

vessel will not be heated first. One issue, and the reason domestic microwave ovens are not used, is inhomogeneity of the microwave field, commonly referred to as hot spots and cold spots, which can lead to irreproducibility.[57]

The ability for a molecule to be heated by microwave irradiation relies heavily on its dielectric constant. The dielectric constant, Ɛ', is the polarizability of the solvent in an applied electric field and the storage of that energy. In other words dielectric constant simply refers to the macroscopic properties of a solvent, whereas dipole moment refers to a given molecule. Similarly the dielectric loss factor, Ɛ", is the ability that a molecule can release that stored energy as heat. Together these terms are known as the dissipation factor, tan δ (Figure 14), which is the ability of molecules to turn microwaves to heat and changes with frequency. High values of tan δ are molecules that absorb microwaves very well which should only be used for reagents or solvents and low values of tan δ should be used for the reaction vessel.

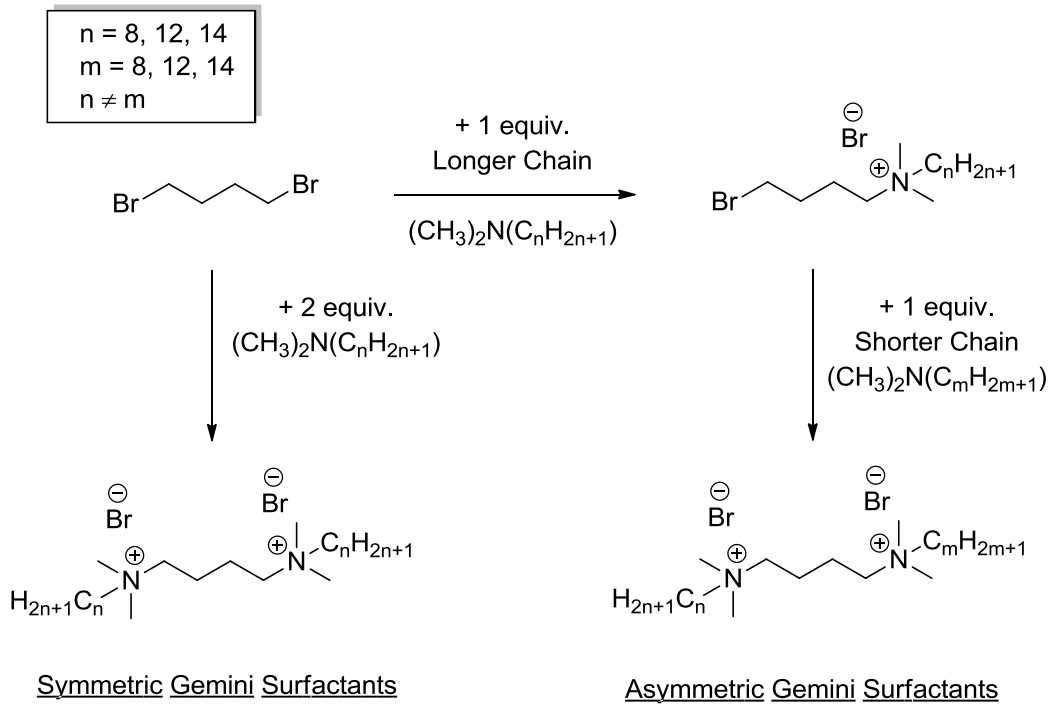
$$\tan\delta = {}^{\varepsilon''}\!/_{\varepsilon'}$$

Figure 14. Dissipation Factor Relationship

2.2.0 Results and Discussion

This chapter focused on six homologues as target cationic gemini surfactants for an improved synthesis. These targets all follow the general IUPAC configuration *N*-alkyl-1-*N*'-alkyl-2-*N,N,N',N'*-tetramethyldiammonium dibromide and vary in chain length of the alkyl groups and physical properties (Scheme 9). The six target surfactants are further classified as symmetrical (mcm type), which have two equally long alkyl chains, or as non-

symmetrical (or asymmetrical) (mcn type), which have two alkyl chains of different lengths. These gemini surfactants are summarized below (Table 4). All products were characterized by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, ESI-MS and ESI-HRMS.



Scheme 9. Symmetric and Asymmetric N-alkyl-1-N'-alkyl-2-N,N,N',N'-tetramethyldiammonium Dibromide

Tables 4. Summary of Reactions for the Improved Synthesis of Gemini Surfactants

Surfactant Number	Length of Chain 1	Length of Chain 2	Abbreviation	Yield (%)
1	tetradecyl ($C_{14}H_{29}$)	tetradecyl ($C_{14}H_{29}$)	14-4-14	92.0
2	dodecyl ($C_{12}H_{25}$)	dodecyl ($C_{12}H_{25}$)	12-4-12	87.6
3	octyl (C_8H_{17})	octyl (C_8H_{17})	8-4-8	84.1
4	dodecyl ($C_{12}H_{25}$)	octyl (C_8H_{17})	12-4-8	27.0
5	tetradecyl($C_{14}H_{29}$)	dodecyl ($C_{12}H_{25}$)	14-4-12	30.5
6	tetradecyl ($C_{14}H_{29}$)	octyl (C_8H_{17})	14-4-8	24.9

The percent yields of the symmetrical gemini surfactants reported are comparable to previous methods. The significant improvement of the improved method comes from the use of a CEM microwave reactor, which greatly decreased reaction times. Unfortunately, the previously reported syntheses suffered from the requirement of long reaction times of 24-48 hours, high energy requirement to maintain reflux temperature and a lot of chlorinated solvent. [59] In the reported improved synthesis the reaction is complete in 30 minutes and used a more energy efficient heat source and only required a fraction of the solvent (<5%) used in previous methods. The workup and isolation of compounds in these reported syntheses is comparable to previously reported reactions. It is worth taking into consideration that previously reported method was performed in dichloromethane at reflux (40°C) and the reported improved syntheses were performed at 60°C. In the original syntheses, dichloromethane was used because it solubilizes the starting materials but not the tertiary amine intermediate, this could be the source of the improved reaction times but likely not. It is more reasonable that the improvements are result of the efficiency in which the solvent and reagents are being heated.

Yields for the reported asymmetric gemini surfactants did not improve over those previously reported; however, the reported yields were achieved in under 90 minutes and a higher purity (based on NMR), which is much more efficient than the previously reported multiday syntheses. The high purities of this method suggest that this method can be further optimized to outperform previous methods. NMR spectroscopy of crude reaction mixtures after each step of the reported synthesis could provide insight as to how these reactions can be improved.

There are four areas of focus when optimizing these reactions. The first issue is that when dibromobutane is left *in situ* after the first reaction, the addition of the shorter alkyl chain dimethylamine will lead to more monosubstituted product. This can be addressed by exploiting the low boiling point of dibromobutane and removing it *in vacuo*. The second optimization is promoting the monosubstituted isolable intermediate and reduce the formation of disubstitution after the first step, which is directly addressed by performing the reaction in excess dibromobutane. The third optimization regards solvent and temperature effects of the system. Solvents can behave differently when subjected to microwave irradiation because of their diverse ranges of polar and ionic properties. Dichloromethane (tan δ 0.042) was the selected solvent for previously reported methods but for the improved synthesis acetonitrile (tan δ 0.062) was selected because it has the highest heating rate of 2.36°Cs^{-1} at 50W power, and would thus be the most energy efficient way of heating this system. Acetonitrile also has higher dielectric constant compared to dichloromethane, 37 and 9.1 respectively. The more polar solvent can better free the nucleophile in S_N1 chemistry and thus increases the rate of reaction. Optimization of temperature and reaction times were not performed due to time constraints; caution must be taken during the first step of this reaction to ensure conversion to monosubstitution and but not disubstitution. This final optimization is derived from high hygroscopicity of these materials, which causes issues when trying to obtain an accurate mass of the final materials rewrite. This issue is very apparent when characterizing the materials *via* ^{1}H NMR spectroscopy because due to large water peaks in the spectra. To combat this issue, the materials were placed in a vacuum desiccator for 24 hours, but despite these efforts the materials still contained some water. This method has not been optimized further; however,

the azeotropic removal of water using a Dean-Stark apparatus and toluene may prove effective.

This work also demonstrated an increase in relative greenness when switching from conventional to microwave heating. Not only did this method improve energy efficiency, but it also used a small fraction of solvent (<5%), had much higher purity (based on NMR) and performed in a fraction of the time when compared to previously reported methods.

The proton and carbon NMR spectra were the essential characterization techniques used to determine full conversion to products. The spectra for the symmetric gemini surfactants were relatively simple (Figure 15 and 16). The proton NMR spectra showed the correct proton count as well as the correct multiplicity for the given compounds. The spectra for the asymmetric gemini surfactants were no more complex than the symmetric and mostly just used for purity and proton count of the integrations (Figure 17 and 18).

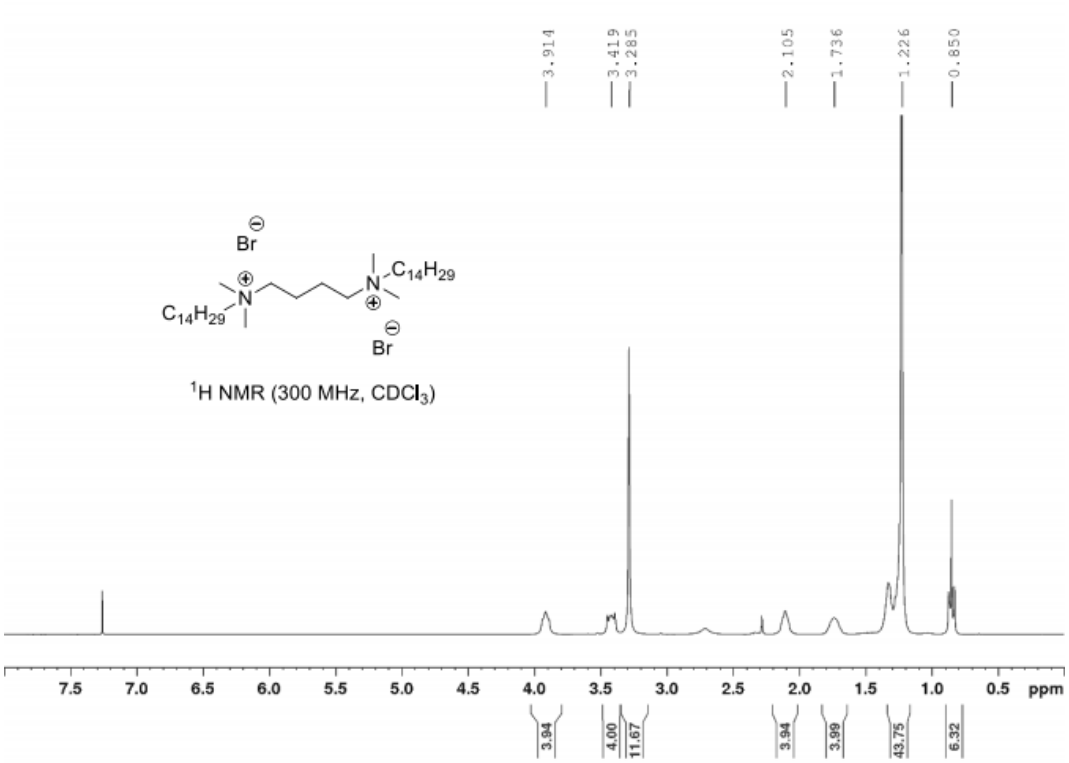


Figure 15. Example Proton Spectra For Symmetric Gemini Surfactant 14-4-14

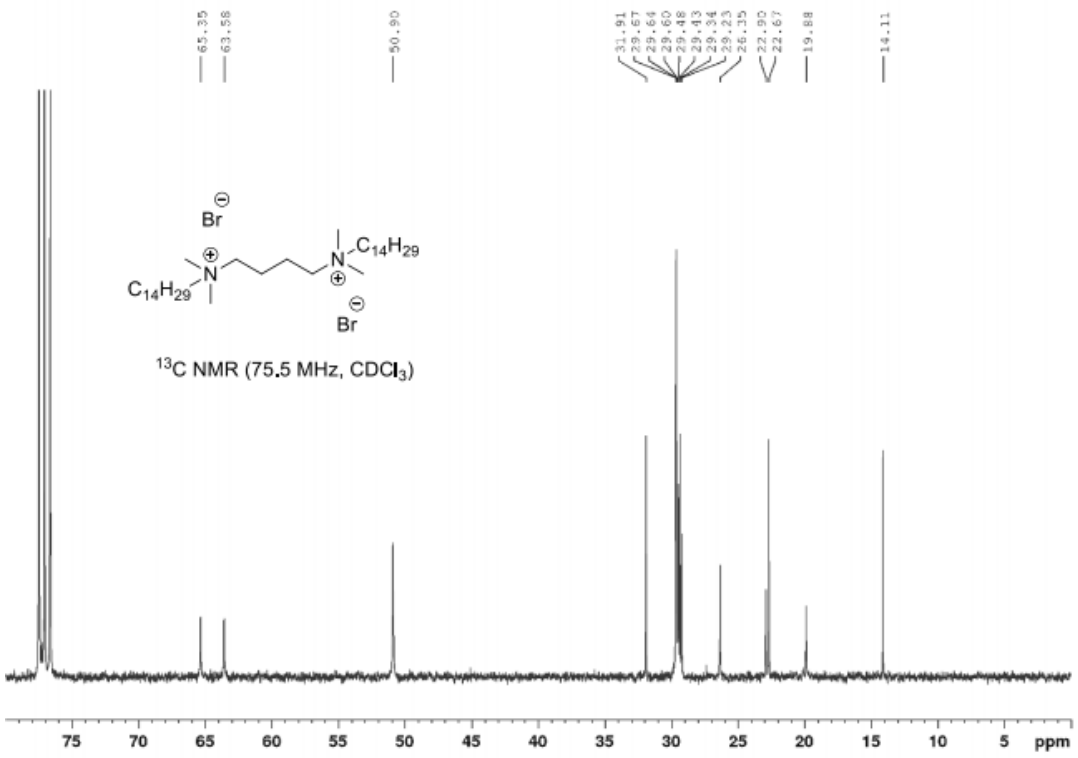


Figure 16. Example Carbon Spectra For Symmetric Gemini Surfactant 14-4-14

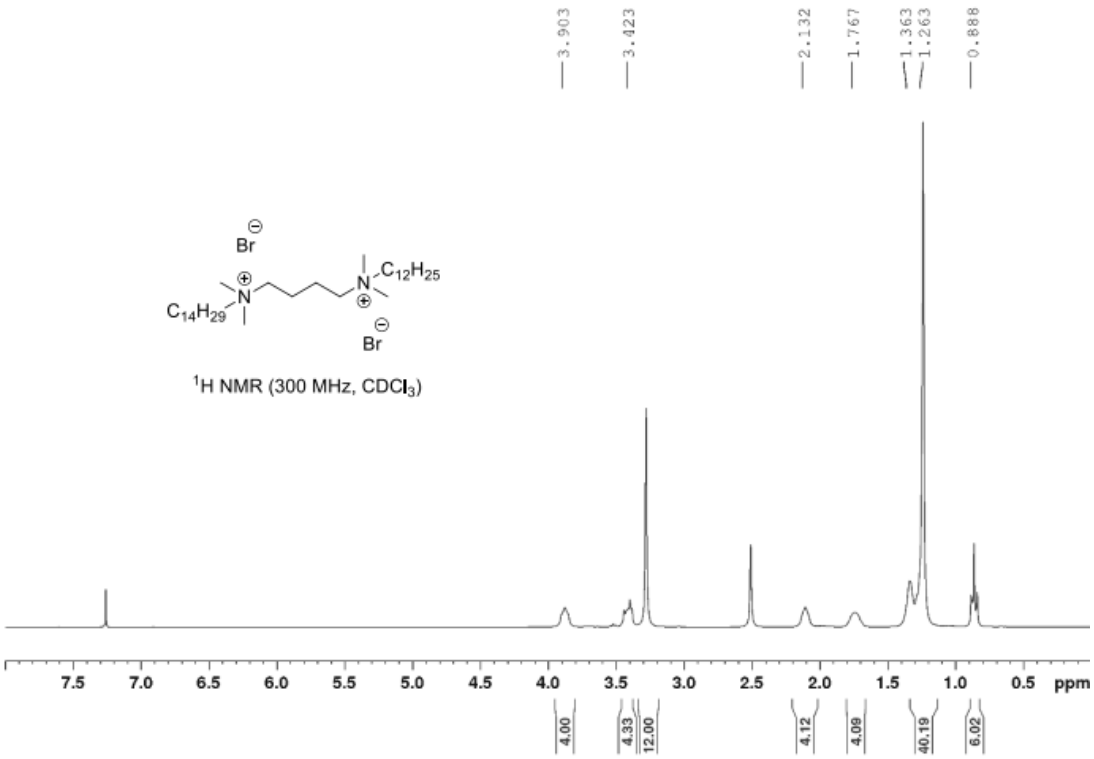


Figure 17. Example Proton Spectra For Asymmetric Gemini Surfactant 14-4-12

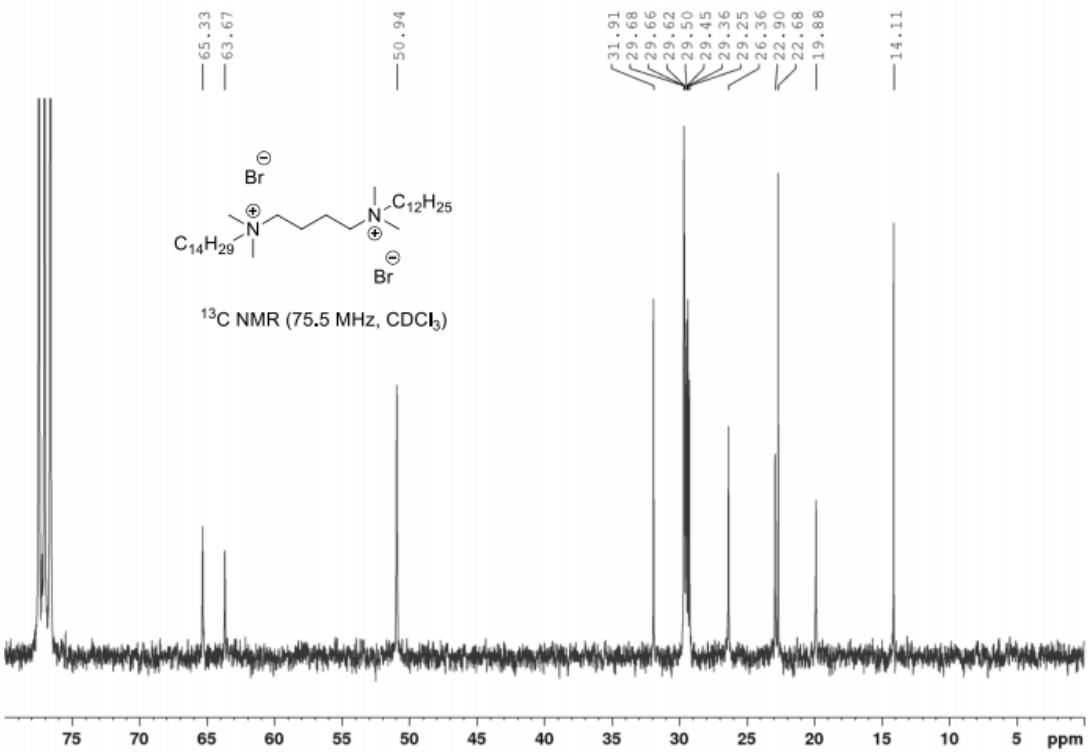


Figure 18. Example Carbon Spectra For Asymmetric Gemini Surfactant 14-4-12

2.3.0 Conclusion

The syntheses of three symmetric and three asymmetric gemini surfactants were improved by designing a highly optimized method that employs a CEM microwave reactor. The characterization of all six desired surfactants was completed using NMR, ESI-MS and ESI-HRMS. The compounds have been sent to Dr. Gerrard Marangoni at St. Francis Xavier University, who will study these compounds critical micelle concentrations and various other physical properties in mixed micellular systems.

2.4.0 Future Work

Future directions of this project include optimization of conditions by closely monitoring the reaction, azeotropically drying the final products—utilizing a Dean-Stark apparatus, and although the main focus of this project was to demonstrate the improved synthesis of these surfactants the physical properties will also be studied. The CMC will be studied by both dynamic light scattering and calorimetry measurements.

2.5.0 Experimental

2.5.1 General Procedures

Syntheses of surfactants were performed in 35 mL CEM microwave reaction tubes with Teflon lids. All glassware was clean in a highly concentrated isopropanol and potassium hydroxide bath, then rinsed with tap water and left to air dry.

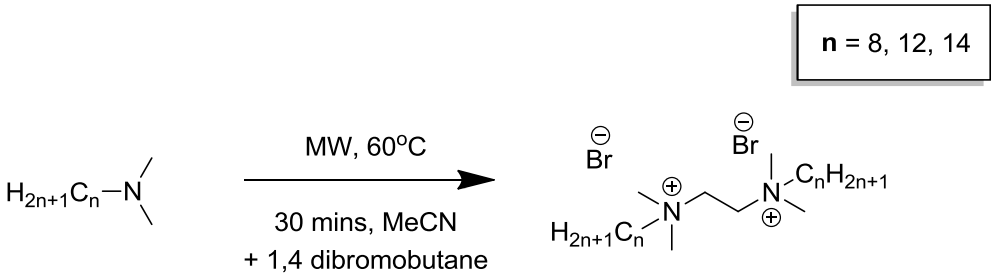
1,4-dibromobutane, *N*,*N*-dimethyltetradecylamine, *N*,*N*-dimethyldodecylamine and *N*,*N*-dimethyloctylamine were purchased from MilliporeSigma chemical supply company

and used without purification. Solvents, such as acetonitrile, ethyl acetate and acetone were purchased from Fisher Scientific chemical supply company and used without purification.

Electrospray ionization mass spectrometry was performed at DalChem Mass Spectrometry Laboratories by Xiao Feng, instrumentation unknown. Samples of 1mg were dissolved in 1mL of ACS grade acetonitrile.

Nuclear Magnetic Resonance Spectroscopy was performed at Saint Mary's University of a Bruker 300 MHz Ultrashield spectrometer and processed using Bruker TopSpin 4.0.6 software. Samples were made up of 10mg of compound dissolvent in deuterated chloroform purchased from Cambridge Isotope Laboratories. Trace impurities and residual solvent peaks were determined using tables developed by Nudelam *et al.*[60]

2.5.2 Symmetric Gemini Surfactants



N1,N1,N4,N4-tetramethyl-*N1,N4*-ditetradecylbutane-1,4-diaminium bromide, **1** (14-4-14), was prepared by dissolving 1 equiv. 1,4-dibromobutane (1.079 g, 5 mmol) and 2.1 equiv. *N,N*-dimethyltetradecylamine (2.535 g, 10.5 mmol) in 10.0 mL of acetonitrile in a 35 mL microwave reaction vessel. The reaction vessel was then placed in a CEM microwave reactor set at 60°C, with pressure tolerance of 15 psi, max power of 15W, and stirred for 30 minutes. After microwave irradiation, the reaction vessel was set in a freezer overnight. The resulting precipitate was vacuum filtered and rinsed with ethyl acetate. The

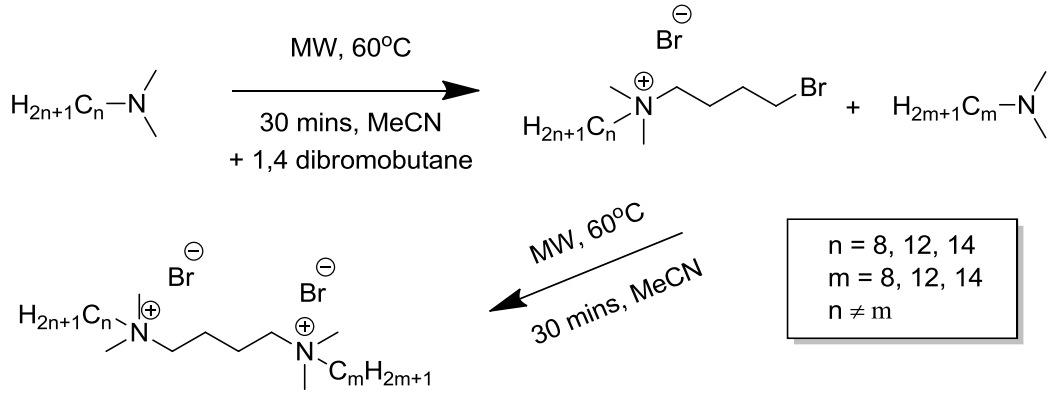
hygroscopic product was then placed into a vacuum desiccator for 24 hours to afford 3.21 g (92.0% yield) of white solid.

1 (14-4-14) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01-3.80 (m, 4H), 6.49-3.35 (m, 4H), 3.28 (s, 12H), 2.19-2.01 (m, 4H), 1.84-1.64 (m, 4H), 1.23 (s, 44H), 0.85 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75.5, $CDCl_3$) δ 65.3, 63.58, 50.9, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 26.3, 22.9, 22.7, 19.9, 14.1. ESI-HRMS m/z: $[M\text{-}Br]^+$ Calcd for $C_{36}H_{78}Br_2N_2$ 617.5348, 618.5382, 619.5329, 620.5361; Found 617.5348, 618.5379, 619.5335, 620.5357.

2 (12-4-12) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01-3.86 (m, 4H), 3.51-3.38 (m, 4H), 3.28 (s, 12H), 2.18-2.23 (m, 4H), 1.82-1.63 (m, 4H), 1.22 (s, 38H), 0.85 (t, J = 7.0 Hz, 6H). ^{13}C NMR (75.5, $CDCl_3$) δ 65.2, 63.6, 50.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 26.3, 22.9, 22.7, 19.9, 14.1. ESI-HRMS m/z: $[M\text{-}Br]^+$ Calcd for $C_{32}H_{70}Br_2N_2$ 561.4722, 562.4756, 563.4702, 564.4735; Found 561.4705, 562.4731, 563.4690, 564.4713.

3 (8-4-8) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85-3.71 (m, 4H), 3.47-3.34 (m, 4H), 3.27 (s, 12H), 2.12-1.99 (m, 4H), 1.82-1.65 (m, 4H), 1.25 (s, 20H), 0.86 (t, J = 7.0 Hz, 6H). ^{13}C NMR (75.5, $CDCl_3$) δ 65.3, 63.5, 50.9, 31.6, 29.1, 29.0, 26.3, 22.6, 19.9, 14.0. ESI-HRMS m/z: $[M\text{-}Br]^+$ Calcd for $C_{24}H_{54}N_2Br_2$ 449.3470, 450.3504, 451.3450, 452.3483; Found 449.3447, 450.3475, 451.3429, 452.3450.

2.5.3 Asymmetric Gemini Surfactants



N1-dodecyl-*N1*,*N1*,*N4*,*N4*-tetramethyl-*N4*-tetradecylbutane-1,4-diaminium bromide, **5** (14-4-12), was prepared by dissolving 4 equiv. 1,4-dibromobutane (0.864 g, 4 mmol) and 1 equiv. of the longer chain dimethylamine (*N*,*N*-dimethyltetradecylamine, (0.241 g, 1 mmol) in 10.0 mL of acetonitrile. Microwave irradiation was performed using the same conditions as the symmetric molecules. A rotary evaporator and high capacity vacuum pump were used to remove solvent and ensure the removal of all unreacted 1,4-dibromobutane. The reaction mixture was then taken back up in acetonitrile and 1 equiv. *N*,*N*-dimethyldodecylamine (0.213 g, 1 mmol) was added. Microwave irradiation was repeated with the same conditions as above. After microwave irradiation, the reaction vessel was set in a freezer overnight. The resulting hygroscopic product was then put through the same workup process as the symmetric molecules to afford 0.205 g (30.5% yield) of white solid.

4 (14-4-8) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94-3.78 (m, 4H), 3.48-3.35 (m, 4H), 3.28 (s, 12H), 2.16-2.03 (m, 4H), 1.82-1.64 (m, 4H), 1.23 (s, 32H), 0.86 (t, J = 7.0 Hz, 6H). ^{13}C NMR (75.5, $CDCl_3$) δ 65.3, 63.6, 50.9, 31.9, 31.6, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 26.4, 22.9, 22.7, 22.6, 19.9, 14.1, 14.0. ESI-HRMS m/z: $[M-Br]^+$ Calcd for $C_{30}H_{66}Br_2N_2$ 533.4409, 534.4443, 535.4389, 536.4422; Found 533.4391, 534.4446, 535.4367, 536.4416.

5 (14-4-12) ^{1}H NMR (300 MHz, CDCl3) δ 3.95-3.80 (m, 4H), 3.48-3.35 (m, 4H), 3.28 (s, 12H), 2.19-2.03 (m, 12H), 1.83-1.65 (m, 4H), 1.24 (s, 40H), 0.86 (t, J = 7.16 Hz, 6H). ^{13}C NMR (75.5, $CDCl_3$) δ 65.3, 63.7, 50.9, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 26.4, 22.9, 22.7, 19.9, 14.1. ESI-HRMS m/z: $[M-Br]^+$ Calcd for $C_{34}H_{74}Br_2N_2$ 589.5035, 590.5069, 591.5015, 592.5048; Found 589.5018, 590.5042, 591.4999, 592.5021.

6 (12-4-8) ^{1}H NMR (300 MHz, CDCl3) δ 3.97-3.84 (m, 4H), 3.46-3.35 (m, 4H), 3.27 (s, 12H), 2.20-2.07 (m, 1.84-1.67 (m, 4H), 1.25 (s, 28H), 0.87 (t, J = 7.16 Hz, 6H). ^{13}C NMR (75.5, $CDCl_3$) δ 65.5, 63.7, 50.9, 31.9, 31.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 26.3, 22.9, 22.7, 22.6, 22.5, 19.9, 14.1. ESI-HRMS m/z: $[M-Br]^+$ Calcd for $C_{28}H_{62}Br_2N_2$ 505.4096, 506.4130, 507.4076, 508.4109; Found 505.4082, 506.4113, 507.4065, 508.4091.

3.0.0 References

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