KBTX12 Master's Thesis in Chemistry and Chemical Engineering

Azetidinium salts: Preparation, reactivity and their adaptation to stereoselective synthesis

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CHALMERS

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Introduction

Today's society is becoming increasingly aware of the environmental impact of plastic materials and the negative connotations attached to their use. The demand for these plastics to be replaced with bio-based materials has been steadily increasing in recent times. Recently, cellulose-based biomaterials have garnered a lot of attention due to their biodegradability and the abundance of source material.[1,2] However, cellulose based materials aren't easy to chemically manipulate for different applications and hence, research is required in this area to help make them mainstream.[3]

Recently, azetidinium salts have emerged as viable reagents to functionalize cellulose. Azetidinium salts possess ring strain owing to their four membered ring structure and hence easily open up on reacting with soft nucleophiles such as the carboxyl and sulfonate groups in cellulose and modified cellulose.[4] Therefore, it would be possible to use azetidinium salts as scaffolds to introduce various functional groups into the cellulose microstructure.

Azetidinium salts have also found their niche in the pharmaceutical industry, being used as intermediates in the synthesis of various drugs.[5]

Structure and Synthesis of Azetidinium Salts

Azetidinium salts are generally prepared by reacting equimolar quantities of epichlorohydrin and secondary amine or by reacting equimolar quantities of epichlorohydrin and primary amine followed by subsequent quarternization with alkyl halide in a suitable solvent. [6] This results in the formation of a heterocylic four membered ring with nitrogen and a hydroxyl group attached to the 3 position. [7]

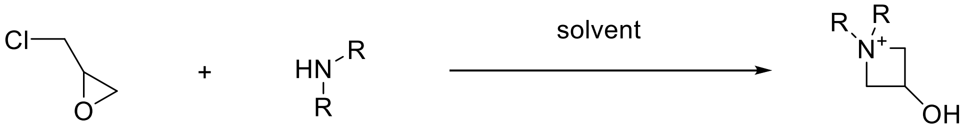


Figure 1: Synthesis of Azetidinium Salts using epichlorohydrin and N,N-dialkylamine

Theoretically, the hydroxyl group can occur at both the axial and equatorial positions of the ring but this has never been spectroscopically evaluated.

This project

This master thesis will be split into two phases:

Phase I: Synthesis and Characterization of Azetidinium Salts

In this phase, azetidinium salts will be prepared either by reacting equimolar amounts of epichlorohydrin and various dialkyl amines to yield aminochlorohydrins, which on heating in a suitable solvent will yield azetidinium salts.

A subproject is included within this phase wherein effective ways of alkylating the hydroxyl group are investigated. Another point of investigation would be to see whether this reaction is better effected on the aminochlorohydrin followed by ring closure or directly on the azetidinium salt.

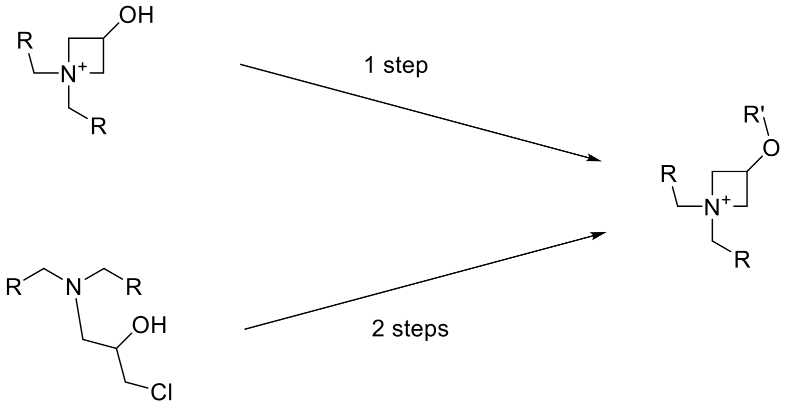


Figure 2: The two ways by which alkylation of hydroxyl group on the azetidinium salts can be effected.

Phase II: Investigation of nucleophilic attack of azetidinium salts by chiral carboxylic acids

In this part of the project, the prepared azetidinium salts are reacted with chiral carboxylic acids such as lactic acid, O-silyl protected lactic acid, mandelic acid and methyl-glucaronic acid in water to determine if the azetidinium salts can be used as scaffolds for enantiomeric introduction into larger substrates.

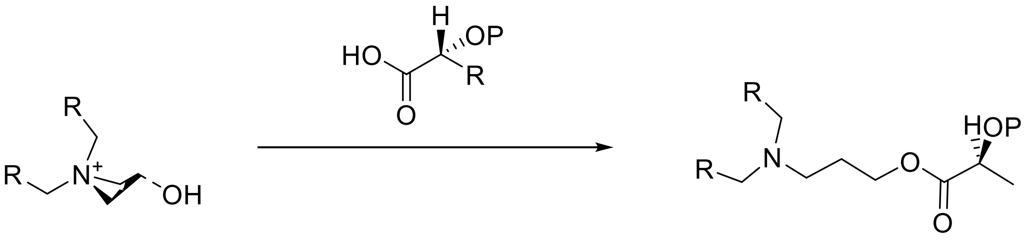
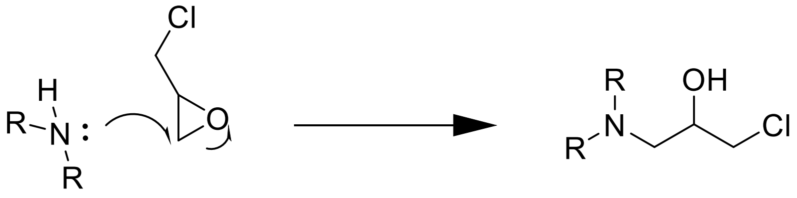


Figure 3: Reaction between azetidinium salt and chiral carboxylic acid

Theory

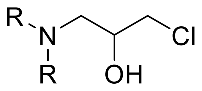
Reaction between Epichlorohydrin and Amines

The reaction between epichlorohydrin and amines proceeds via an S_N2 like mechanism. The lone pair of electrons on the amines attacks the electron deficient epoxide carbon to form a carbon nitrogen bond resulting in the opening of the three membered ring. This results in the formation of an aminochlorohydrin.

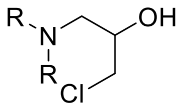


Ring Closing of Aminochlorohydrins

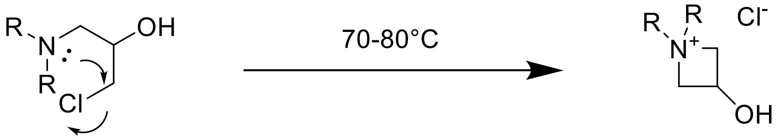
Aminochlorohydrins when taken in a bad solvent behaves similarly to polymers when taken in a bad solvent. The compound starts coiling into itself to increase the entropy of the system. This brings the electron deficient end carbon and electron rich nitrogen closer together which on high temperatures react to give the final azetidinium salt. [8]



In a good solvent



In a bad solvent



Alkylation of hydroxyl group

The alkylation of hydroxyl groups generally employs the use of a base to abstract a proton resulting in the formation of a nucleophile. These nucleophiles on reaction with alkyl halides yield ethers.

$$R{-}OH \xrightarrow{\text{base}} R{-}O^{-}$$

$$R{-}O^{-} \xrightarrow{R'X} R{-}O{-}R'$$

Nucleophilic Attack of Azetidinium Salts

Since azetidinium ions are positively charged they have an affinity towards nucleophiles such as carboxylates, sulphonates etc. This, along with the high ring strain associated with 4 membered rings encourages the nucleophilic attack of Azetidinium salts under mild conditions. These properties enhance their desirability as potential scaffolds for chemically modifying biopolymers with nucleophilic functional groups.

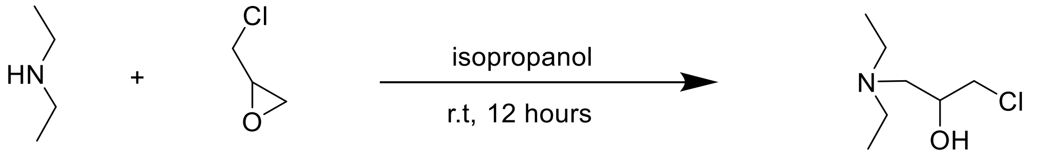
Figure 4: Nucleophilic Ring opening of azetidinium salt by carboxylate ion

Experimental Section

I. Synthesis of Aminochlorohydrins (open forms)

11mmol (1.1 equiv.) of dialkylamine is dissolved in 10ml of isopropanol taken in a vial. Stirring is induced and 0.784ml (10mmol, 1 equiv., 0.9252g) of epichlorohydrin is added dropwise to this mixture. The reaction mixture is stirred overnight at room temperature and excess solvents and unreacted epichlorohydrin are evaporated in a rotary evaporator. Eluent system used: 10% MeOH in DCM.

1. Synthesis of 1-chloro-3-(diethylamino)propan-2-ol



1-chloro-3-(diethylamino)propan-2-ol

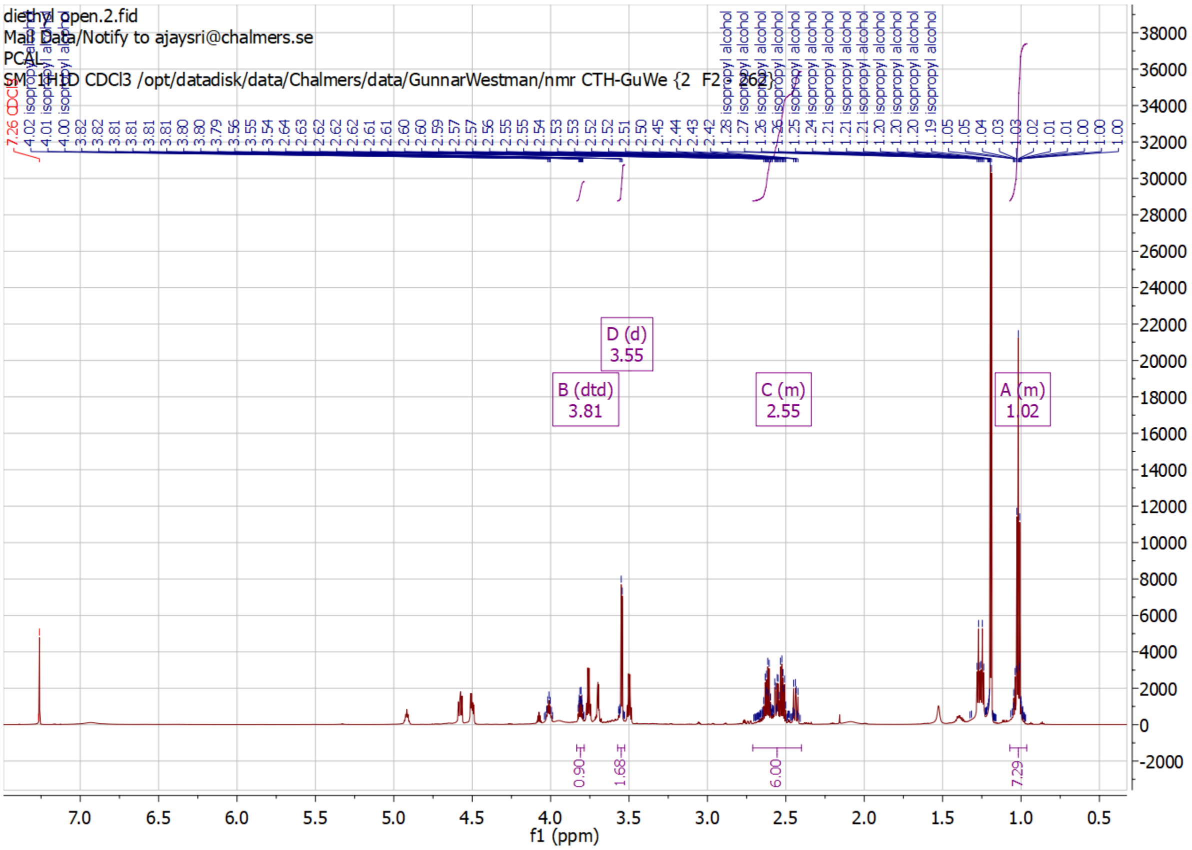
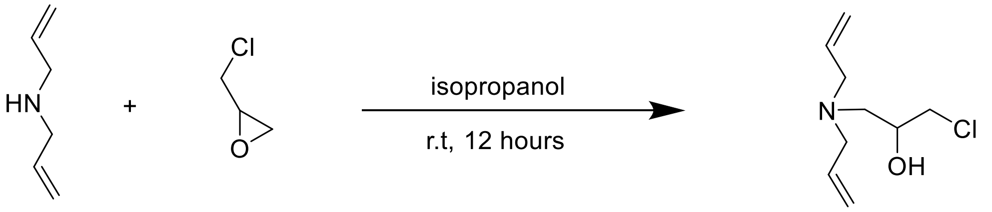


Figure 5: ^{1}H NMR of 1-chloro-3-(diethylamino)propan-2-ol. Slight ring closure is observed.

1-chloro-3-(diethylamino)propan-2-ol: white solid; ^{1}H NMR (800 MHz, Chloroform-*d*) δ 3.81 (dtd, *J* = 9.4, 5.2, 4.1 Hz, 1H), 3.55 (d, *J* = 5.2 Hz, 2H), 2.71 – 2.40 (m, 6H), 1.07 – 0.96 (m, 6H). Yield = 1.524g (92%)

2. Synthesis of 1-chloro-3-(diallylamino)propan-2-ol



1-chloro-3-(diallylamino)propan-2-ol

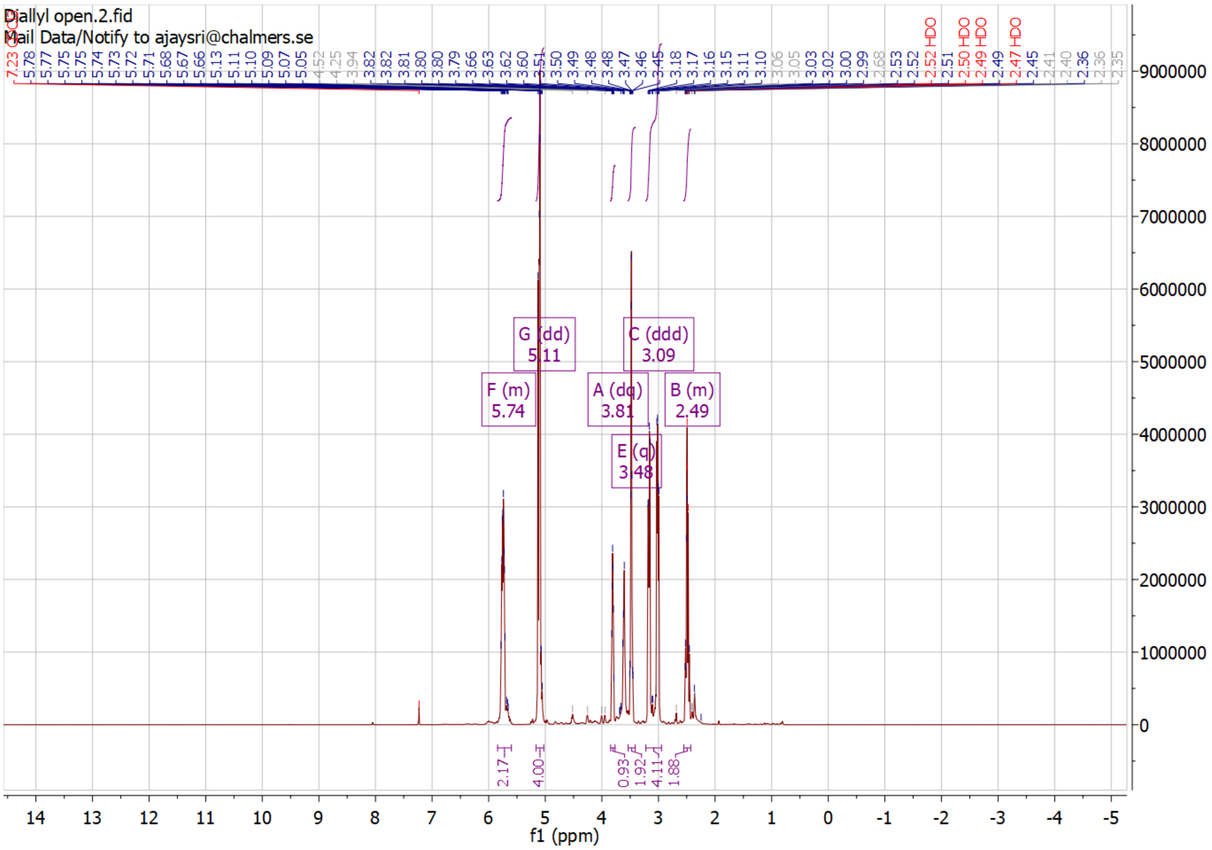
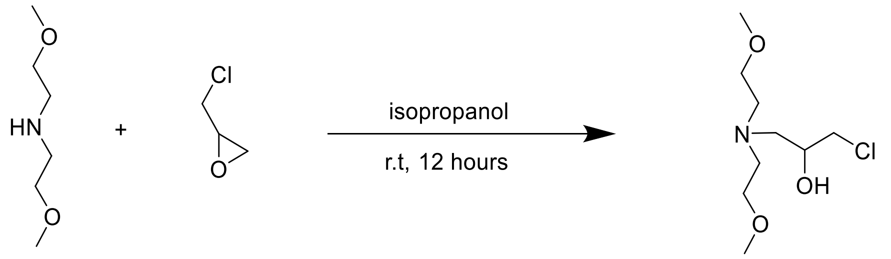


Figure 6: ^{1}H NMR of 1-chloro-3-(diallylamino)propan-2-ol

1-chloro-3-(diallylamino)propan-2-ol: reddish brown oil; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.84 – 5.60 (m, 2H), 5.11 (dd, *J* = 14.3, 7.5 Hz, 4H), 3.81 (dq, *J* = 9.0, 4.8, 4.1 Hz, 1H), 3.48 (q, *J* = 4.4, 3.9 Hz, 2H), 3.09 (ddd, *J* = 94.7, 14.3, 6.4 Hz, 4H), 2.55 – 2.43 (m, 2H). Yield = 0.804g (95.2%)

3. Synthesis of 1-(bis(2-methoxyethyl)amino)-3-chloropropan-2-ol



1-(bis(2-methoxyethyl)amino)-3-chloropropan-2-ol

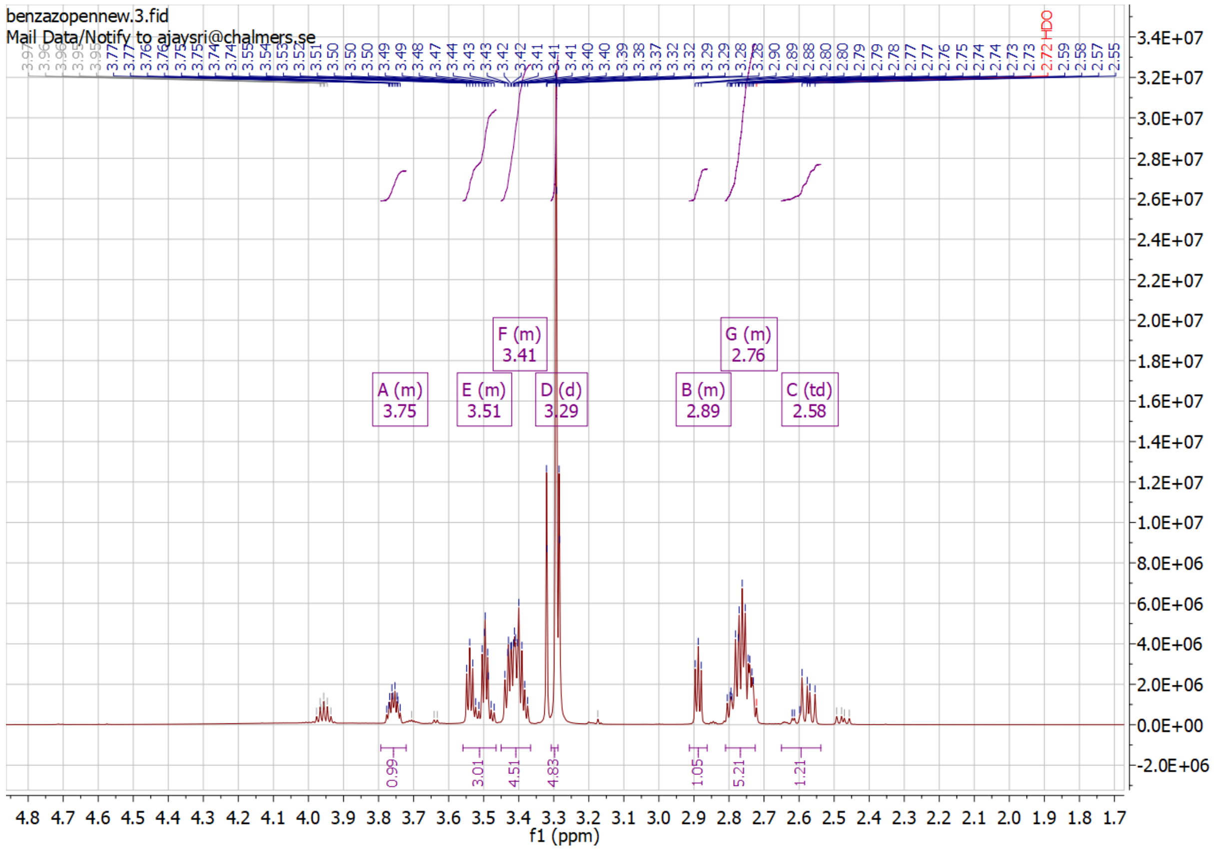
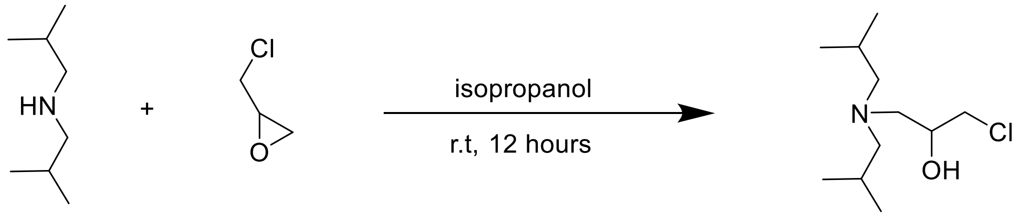


Figure 7: ^{1}H NMR of 1-(bis(2-methoxyethyl)amino)-3-chloropropan-2-ol

1-(bis(2-methoxyethyl)amino)-3-chloropropan-2-ol: yellow oil; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.79 – 3.72 (m, 1H), 3.56 – 3.46 (m, 3H), 3.45 – 3.37 (m, 5H), 3.29 (d, *J* = 1.2 Hz, 4H), 2.91 – 2.86 (m, 1H), 2.81 – 2.73 (m, 4H), 2.58 (td, *J* = 13.2, 9.0 Hz, 1H). Yield = 1.94g (86%)

4. Synthesis of 1-chloro-3-(diisobutylamino)propan-2-ol



1-chloro-3-(diisobutylamino)propan-2-ol

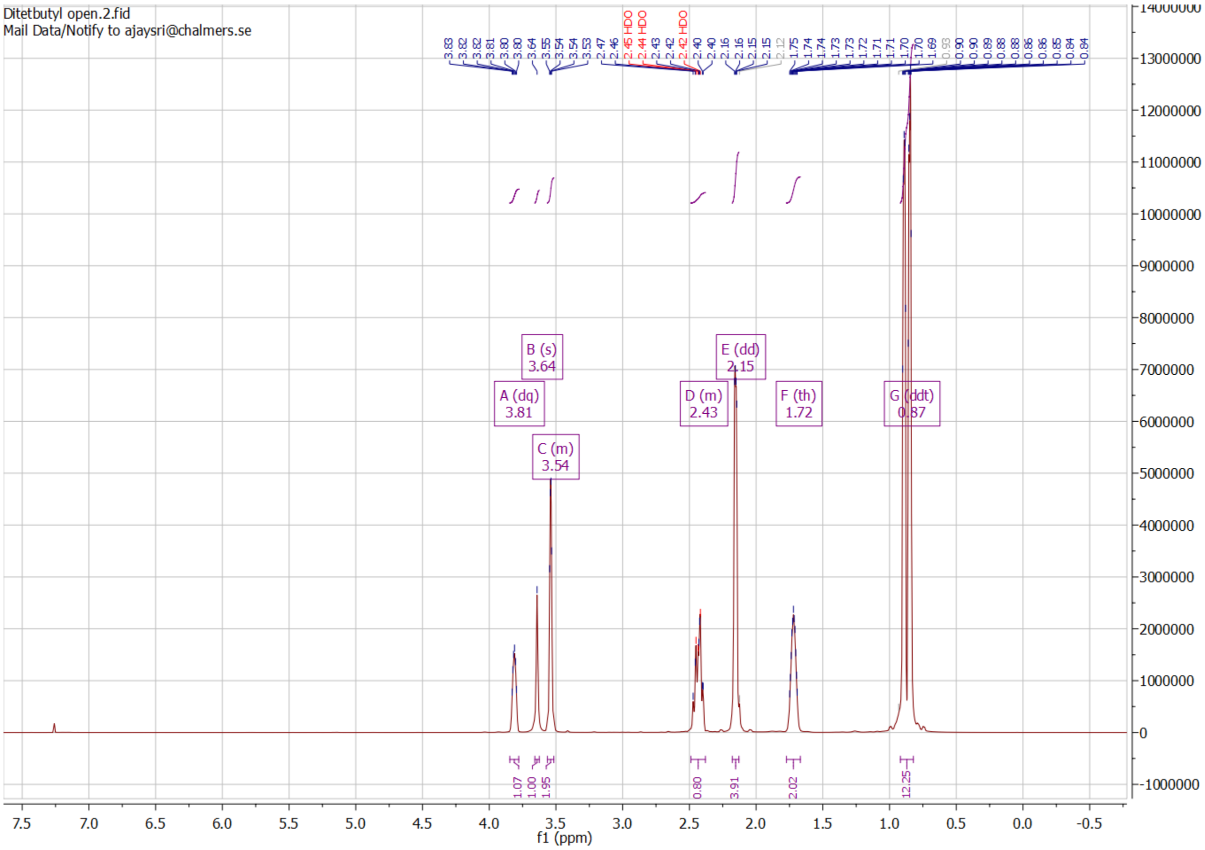
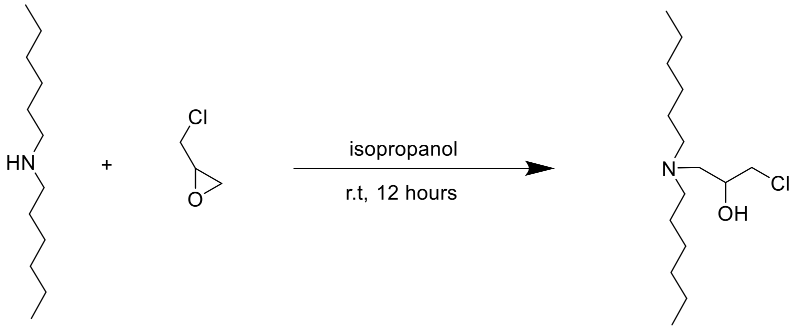


Figure 8: ^{1}H NMR of 1-chloro-3-(diisobutylamino)propan-2-ol

1-chloro-3-(diisobutylamino)propan-2-ol : colourless oil; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.81 (dq, *J* = 9.0, 4.4, 3.9 Hz, 1H), 3.64 (s, 1H), 3.56 – 3.52 (m, 2H), 2.49 – 2.38 (m, 1H), 2.15 (dd, *J* = 6.4, 3.3 Hz, 4H), 1.72 (th, *J* = 10.7, 4.1, 3.5 Hz, 2H), 0.87 (ddt, *J* = 25.2, 6.2, 2.8 Hz, 12H). Yield = 2.169g (97.8%)

5. Synthesis of 1-chloro-3-(dihexylamino)propan-2-ol



1-chloro-3-(dihexylamino)propan-2-ol

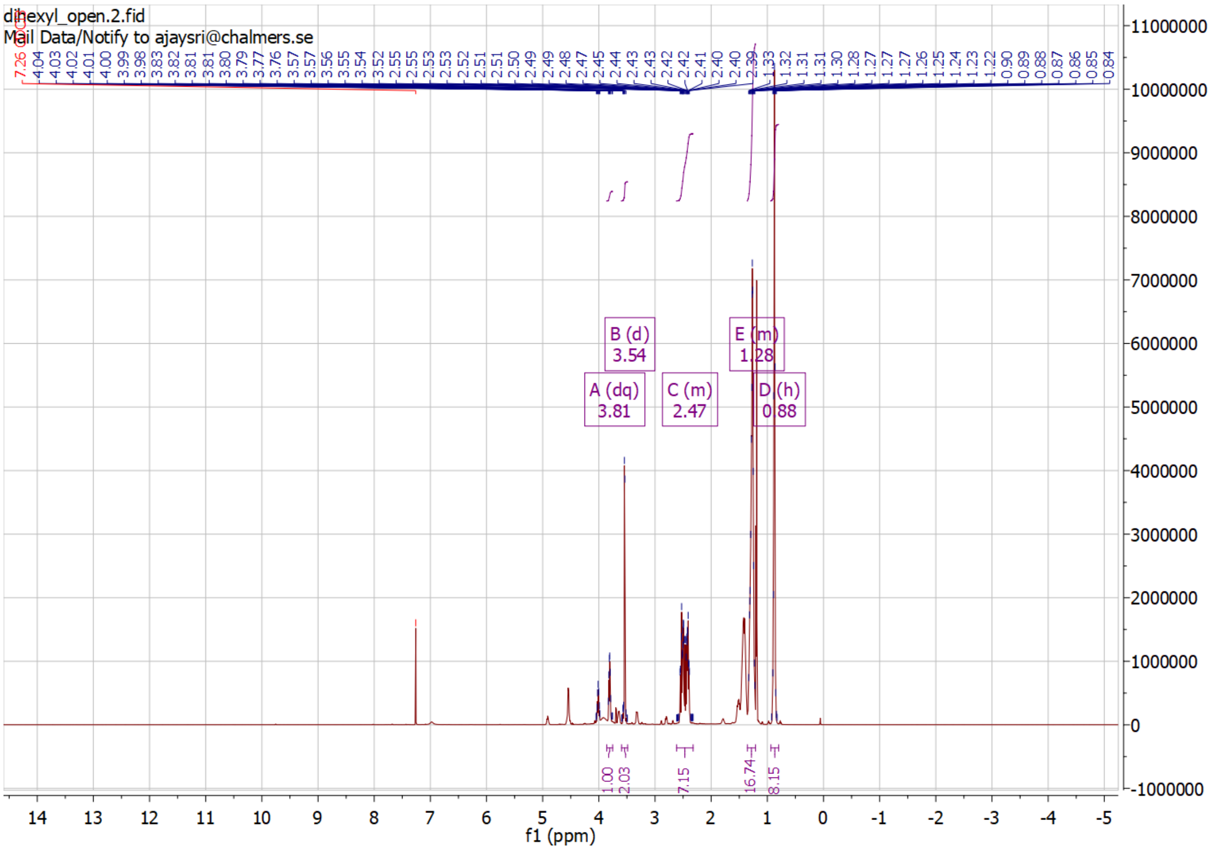
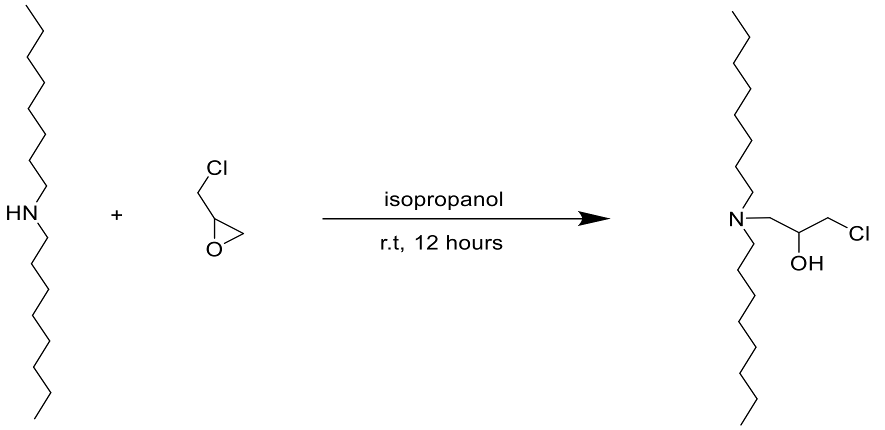


Figure 9: 1H NMR of 1-chloro-3-(dihexylamino)propan-2-ol

1-chloro-3-(dihexylamino)propan-2-ol : yellow oil; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.81 (dq, *J* = 9.6, 4.9 Hz, 1H), 3.54 (d, *J* = 5.2 Hz, 2H), 2.62 – 2.32 (m, 7H), 1.36 – 1.21 (m, 17H), 0.88 (h, *J* = 6.6 Hz, 8H). Yield = 2.35g (84.6%)

6. Synthesis of 1-chloro-3-(dioctylamino)propan-2-ol



1-chloro-3-(dioctylamino)propan-2-ol

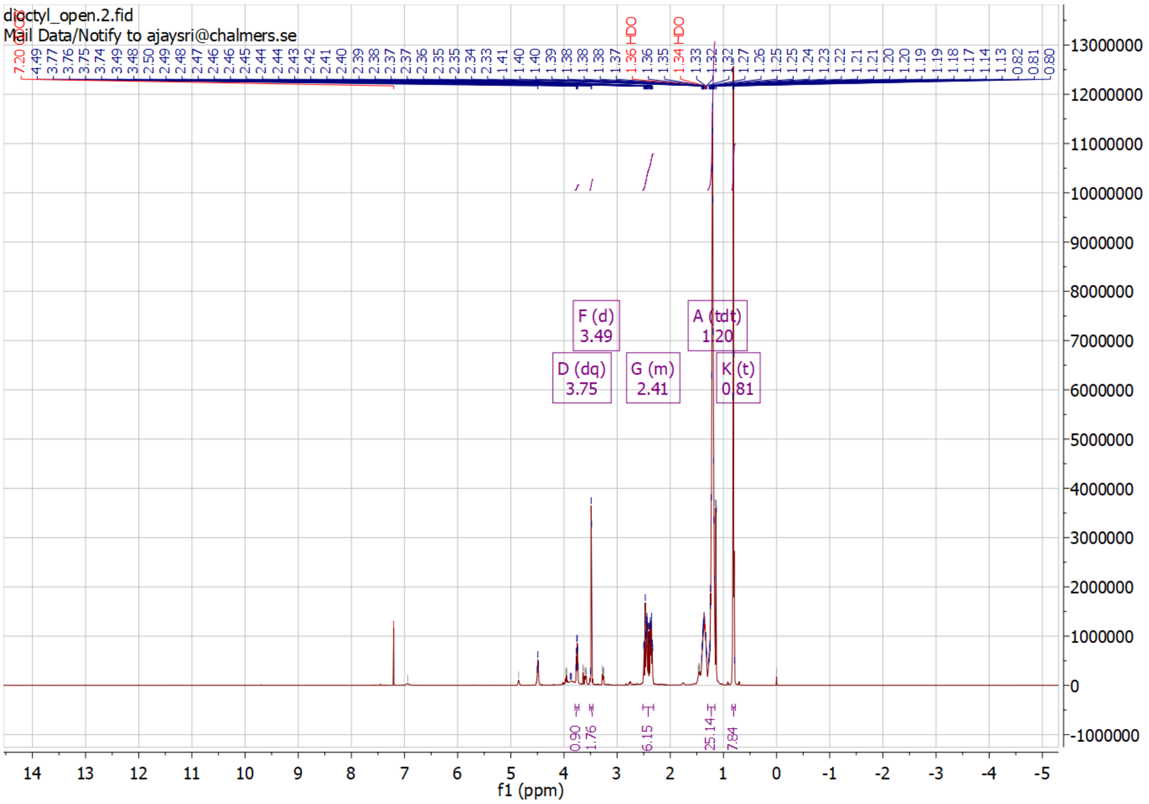
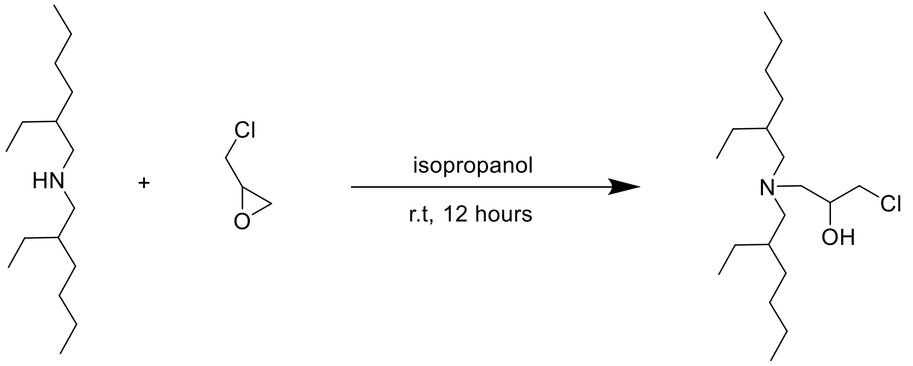


Figure 10: ^{1}H NMR of 1-chloro-3-(dioctylamino)propan-2-ol. Some unreacted amine left in the product.

1-chloro-3-(dioctylamino)propan-2-ol: yellow oil; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.75 (dq, *J* = 9.6, 4.9 Hz, 1H), 3.49 (d, *J* = 5.1 Hz, 2H), 2.52 – 2.31 (m, 6H), 1.20 (tdt, *J* = 13.8, 9.3, 6.0 Hz, 25H), 0.81 (t, *J* = 7.0 Hz, 6H). Yield = 3.274g (98%)

7. Synthesis of 1-(bis(2-ethylhexyl)amino)-3-chloropropan-2-ol



1-(bis(2-ethylhexyl)amino)-3-chloropropan-2-ol

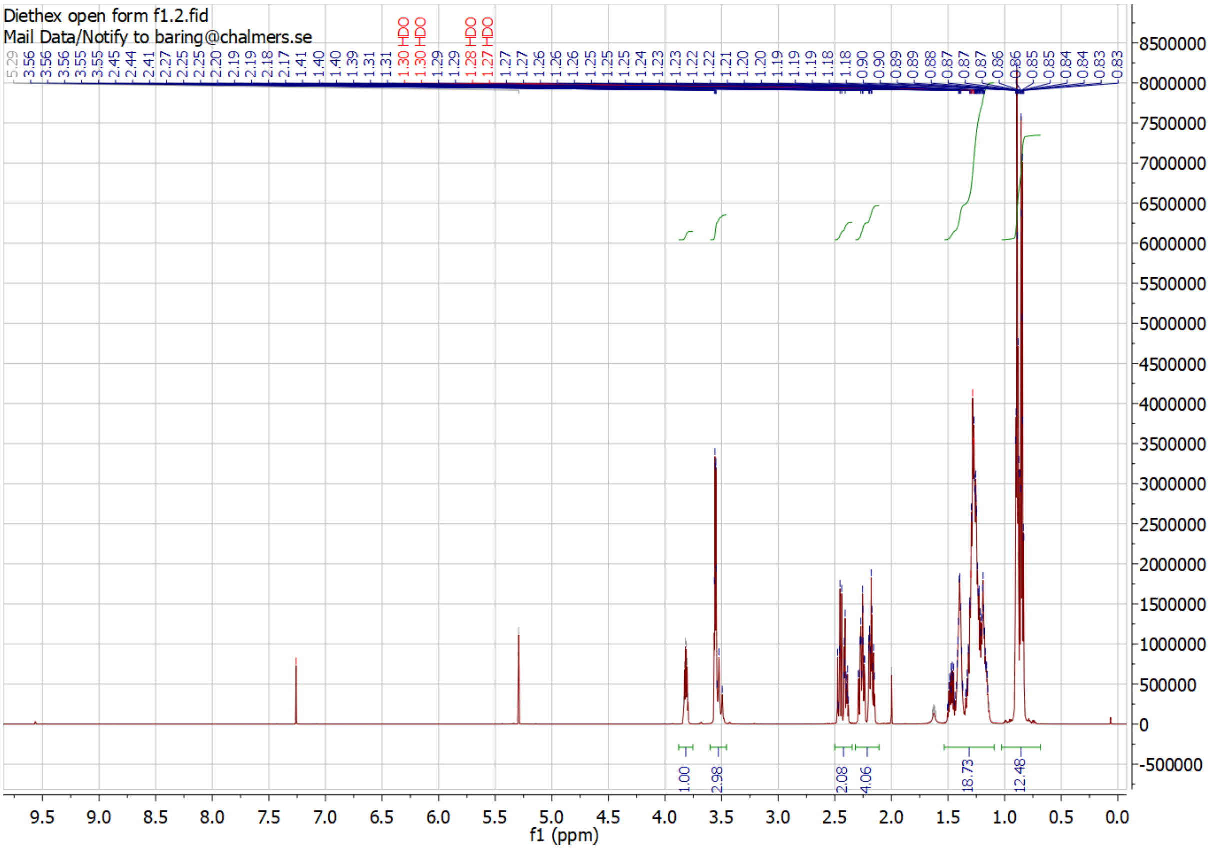
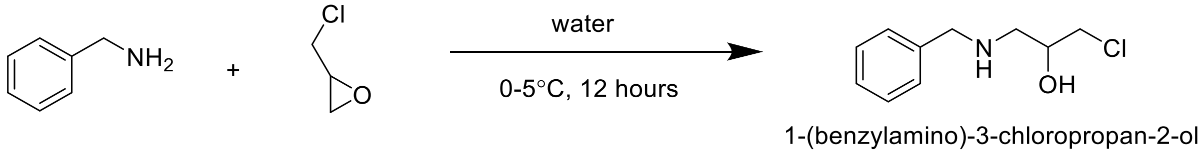


Figure 11: ^{1}H NMR of 1-(bis(2-ethylhexyl)amino)-3-chloropropan-2-ol

1-(bis(2-ethylhexyl)amino)-3-chloropropan-2-ol : yellow oil; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.82 (dq, *J* = 9.7, 4.9 Hz, 1H), 3.60 – 3.45 (m, 3H), 2.49 – 2.36 (m, 2H), 2.30 – 2.22 (m, 2H), 2.22 – 2.13 (m, 2H), 1.52 – 1.12 (m, 18H), 0.91 – 0.81 (m, 12H). Yield = 2.756g (82.5%)

8. Synthesis of 1-(benzylamino)-3-chloropropan-2-ol



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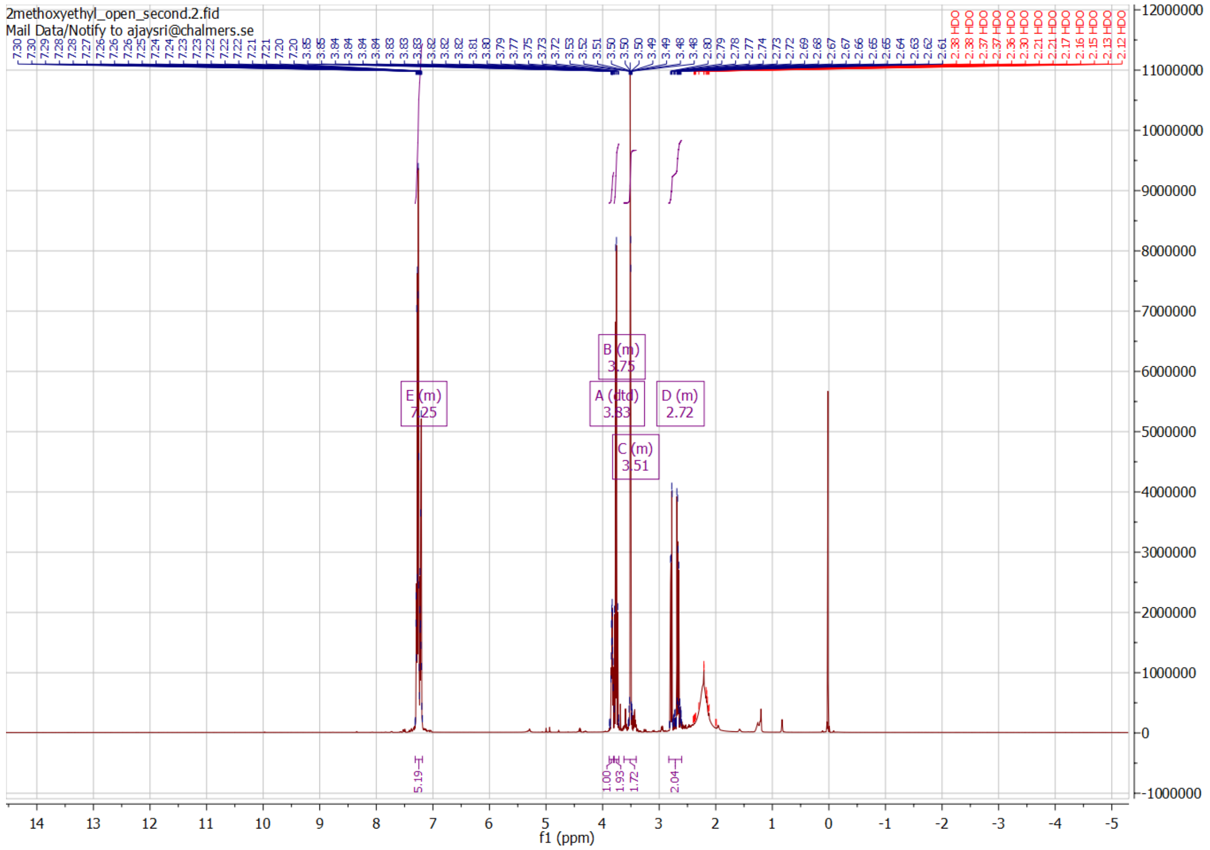


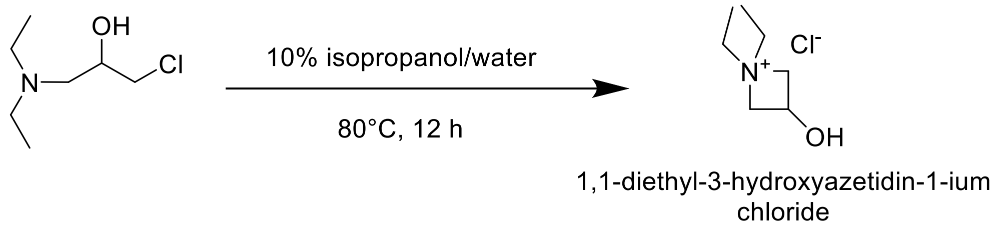
Figure 12: 1H NMR of 1-(benzylamino)-3-chloropropan-2-ol

1-(benzylamino)-3-chloropropan-2-ol : white solid; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.31 – 7.18 (m, 5H), 3.83 (dtd, *J* = 7.8, 5.5, 4.0 Hz, 1H), 3.80 – 3.71 (m, 2H), 3.62 – 3.41 (m, 2H), 2.83 – 2.60 (m, 2H). Yield = 1.915g (95.9%)

II. Synthesis of Azetidinium salts from Aminochlorohydrins

5mmol of aminochlorohydrin is taken in a vial with 5ml of 10% v/v isopropanol/water mixture and stirred at 80°C overnight. The mixture is then taken and extracted with 5ml dichloromethane twice to remove any amine or aminochlorohydrin remaining and the aqueous layer is then evaporated in a rotary evaporator to remove excess solvents. Eluent system used: 10% MeOH in DCM.

1. Synthesis of 1,1-diethyl-3-hydroxyazetidin-1-ium chloride



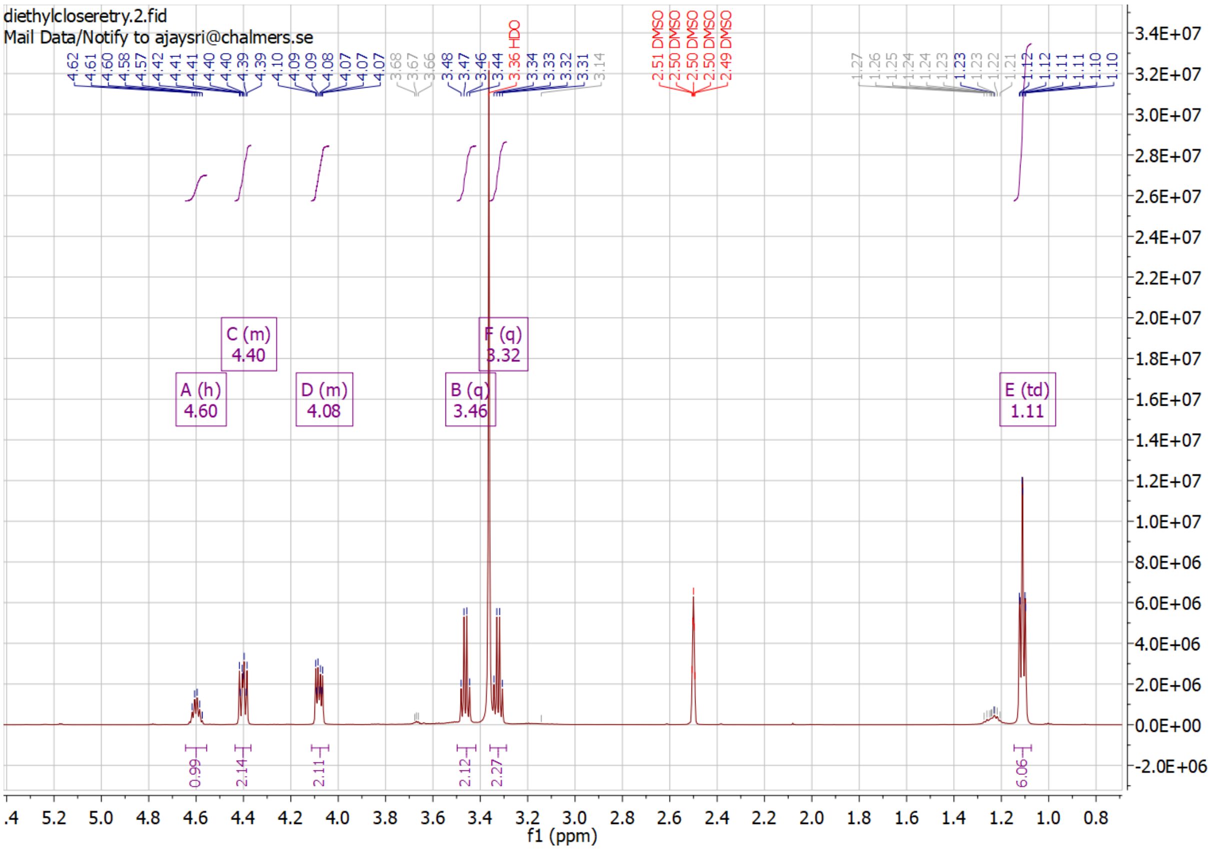
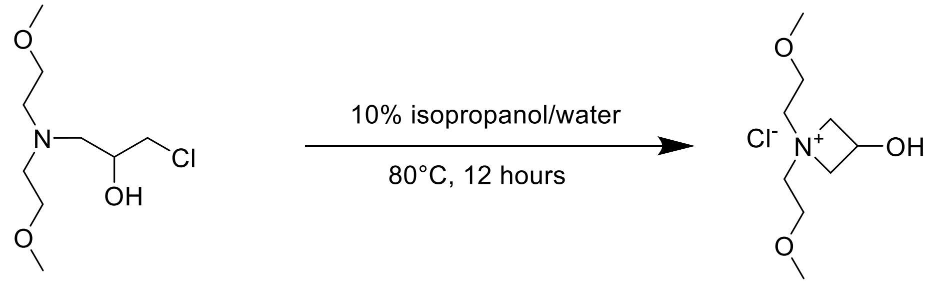


Figure 13: ^{1}H NMR of 1,1-diethyl-3-hydroxyazetidin-1-ium chloride

1,1-diethyl-3-hydroxyazetidin-1-ium chloride: colourless oil; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.60 (h, *J* = 6.4 Hz, 1H), 4.44 – 4.37 (m, 2H), 4.11 – 4.04 (m, 2H), 3.46 (q, *J* = 7.2 Hz, 2H), 3.32 (q, *J* = 7.1 Hz, 2H), 1.11 (td, *J* = 7.2, 1.7 Hz, 6H). Yield = 1.32g (86.6%)

2. Synthesis of 3-hydroxy-1,1-bis(2-methoxyethyl)azetidin-1-ium chloride



3-hydroxy-1,1-bis(2-methoxyethyl)azetidin-1-ium chloride

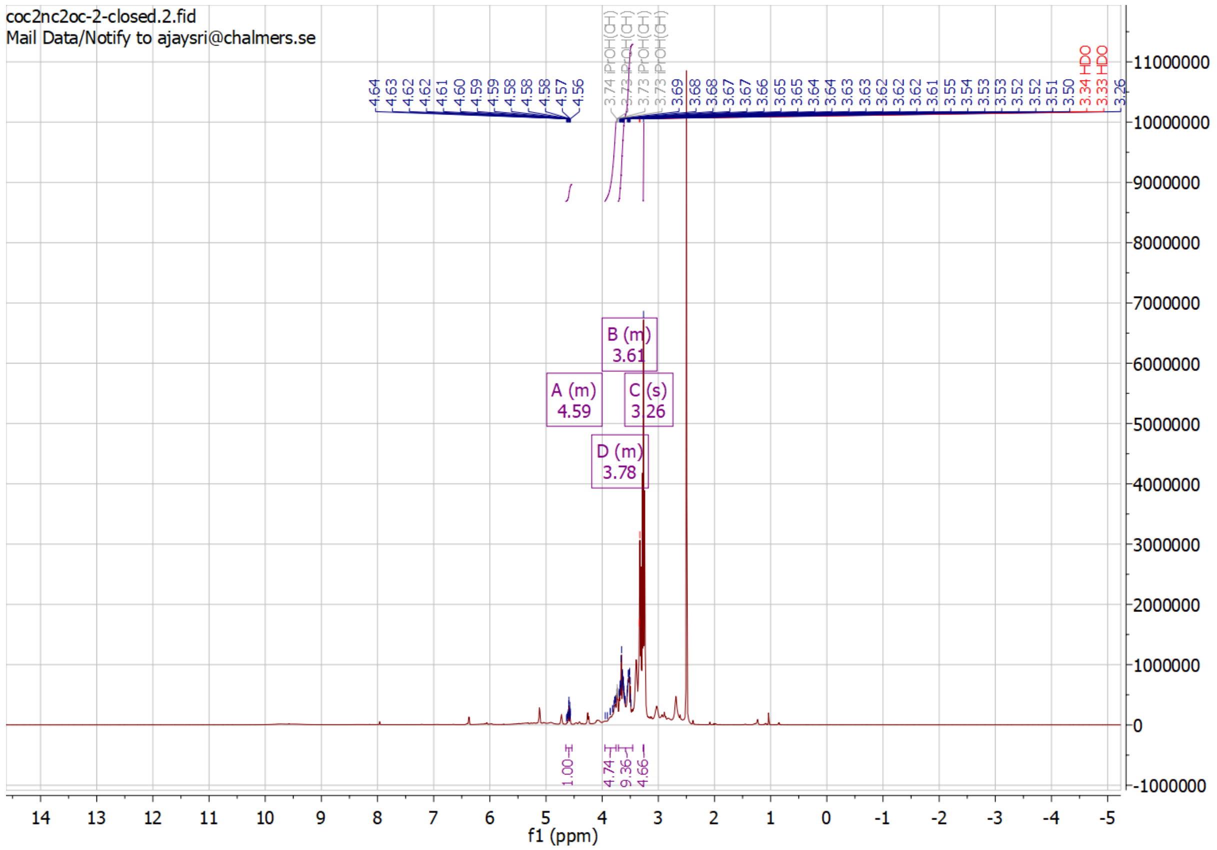
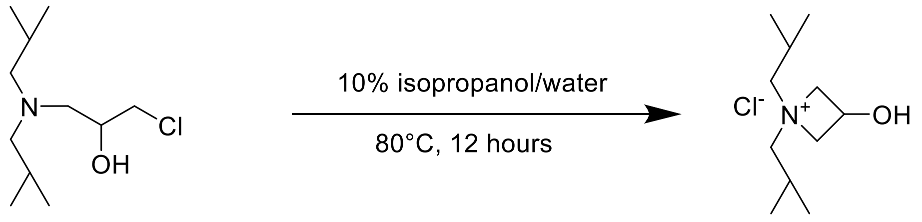


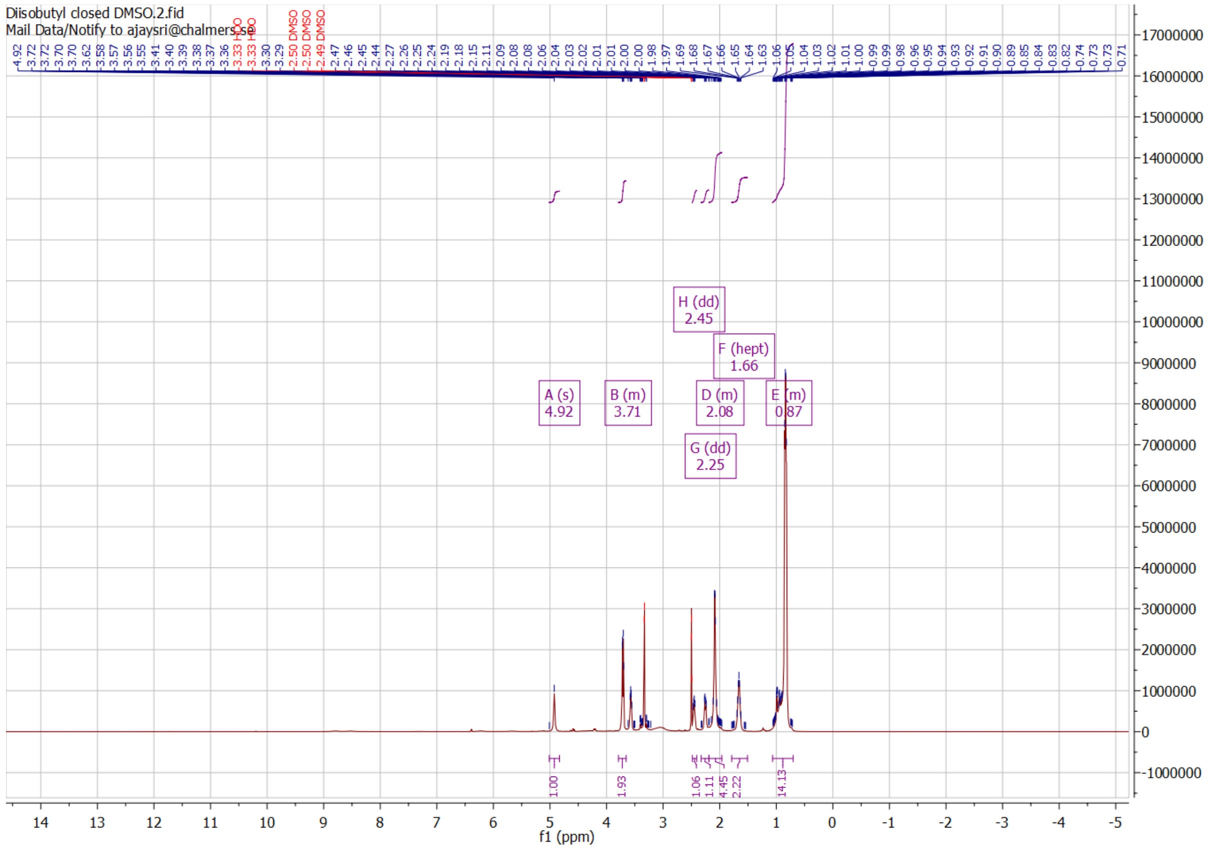
Figure 14: 1H NMR of 3-hydroxy-1,1-bis(2-methoxyethyl)azetidin-1-ium chloride

3-hydroxy-1,1-bis(2-methoxyethyl)azetidin-1-ium chloride: yellow oil; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.65 – 4.54 (m, 1H), 3.95 – 3.75 (m, 5H), 3.71 – 3.46 (m, 9H), 3.26 (s, 5H). Yield = 1.86g (95.9%)

3. Synthesis of 3-hydroxy-1,1-diisobutylazetidin-1-ium chloride

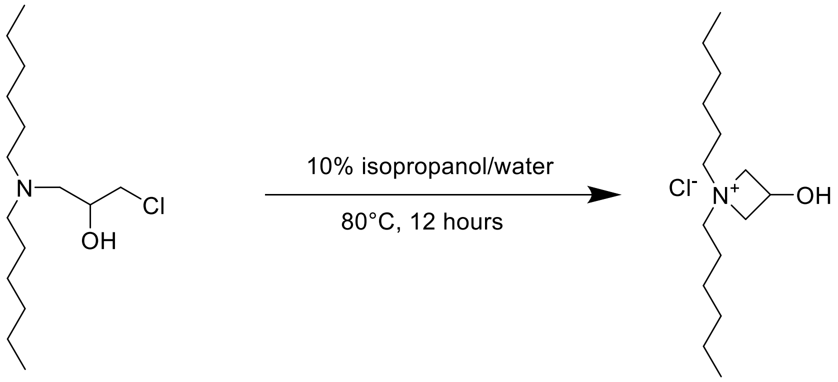


3-hydroxy-1,1-diisobutylazetidin-1-ium chloride

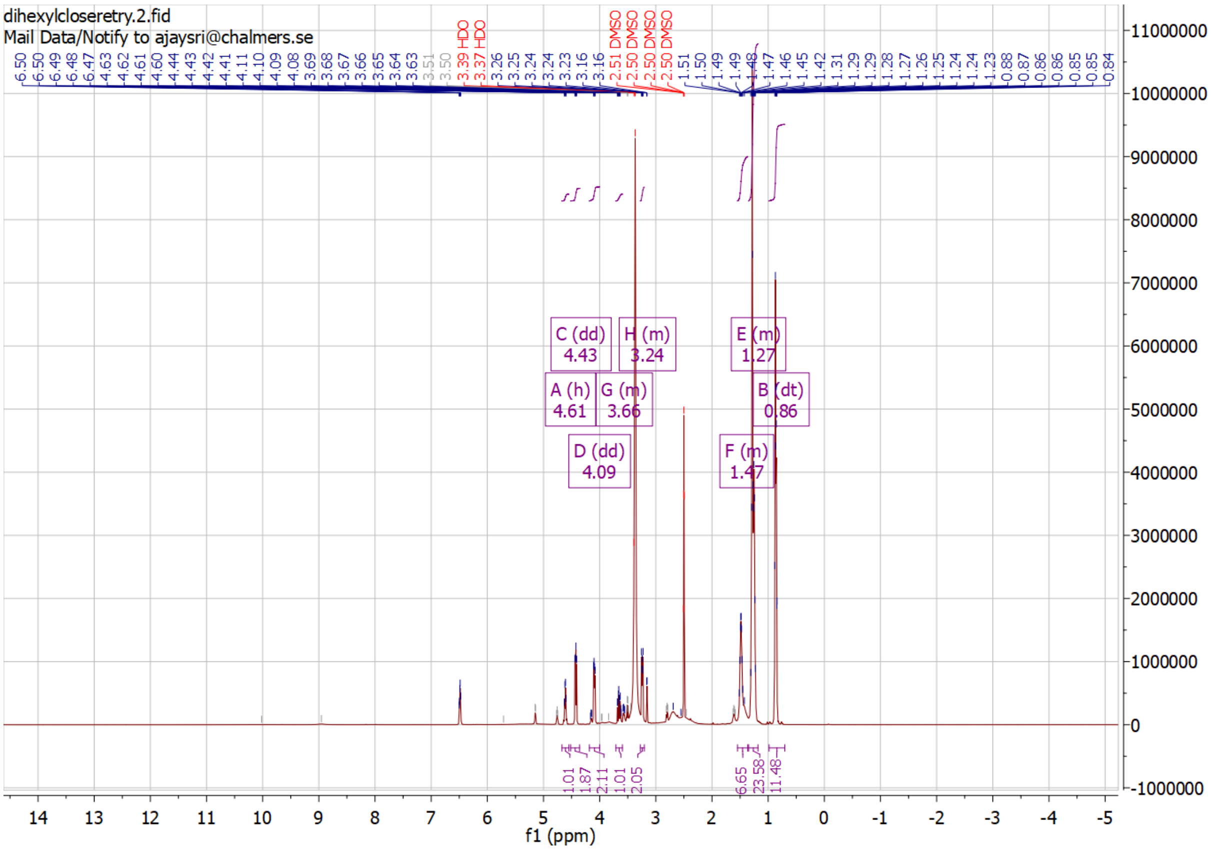


^{1}H NMR (600 MHz, DMSO-d_6) δ 4.92 (s, 1H), 3.79 – 3.65 (m, 2H), 2.45 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.25 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.19 – 1.96 (m, 4H), 1.66 (hept, *J* = 6.7 Hz, 2H), 1.07 – 0.70 (m, 14H). Yield = 2.16g (99.7%)

4. Synthesis of 1,1-dihexyl-3-hydroxyazetidin-1-ium chloride

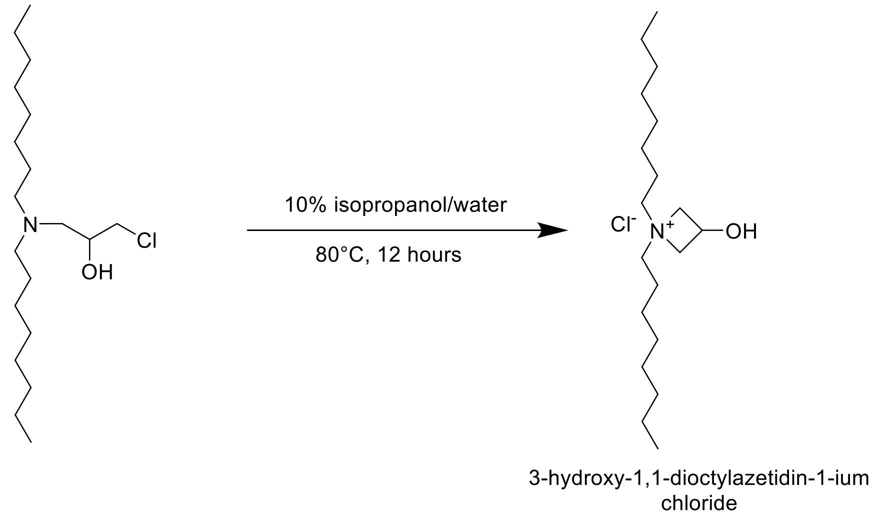


1,1-dihexyl-3-hydroxyazetidin-1-ium chloride



^{1}H NMR (600 MHz, DMSO-d_6) δ 4.61 (h, *J* = 6.4 Hz, 1H), 4.43 (dd, *J* = 11.7, 7.3 Hz, 2H), 4.09 (dd, *J* = 11.6, 5.5 Hz, 2H), 3.71 – 3.60 (m, 1H), 3.28 – 3.20 (m, 2H), 1.55 – 1.36 (m, 7H), 1.35 – 1.18 (m, 24H), 0.86 (dt, *J* = 9.3, 6.7 Hz, 11H). Yield = 2.28g (96.7%)

5. Synthesis of 3-hydroxy-1,1-dioctylazetidin-1-ium chloride



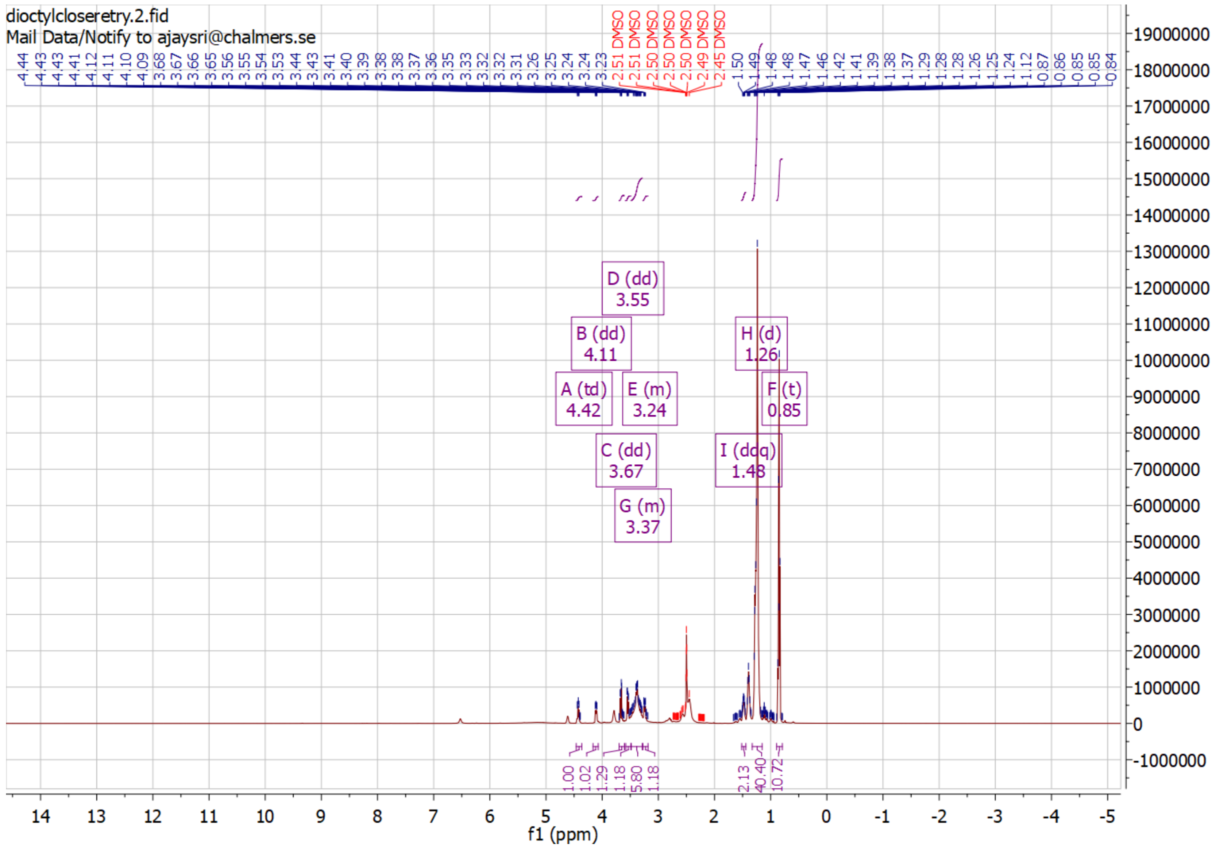
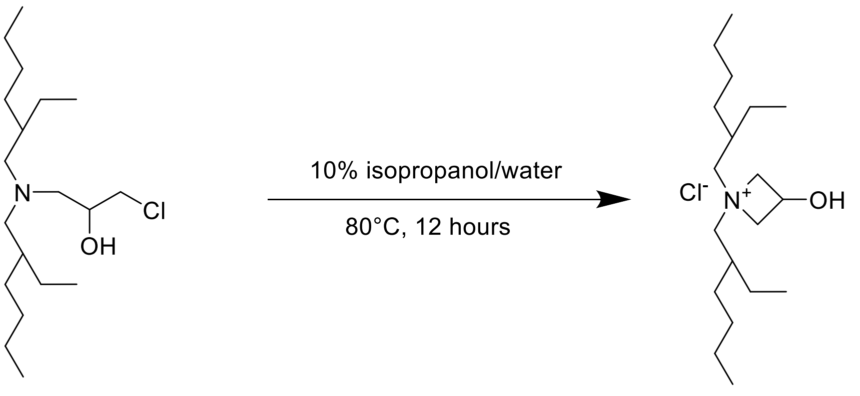


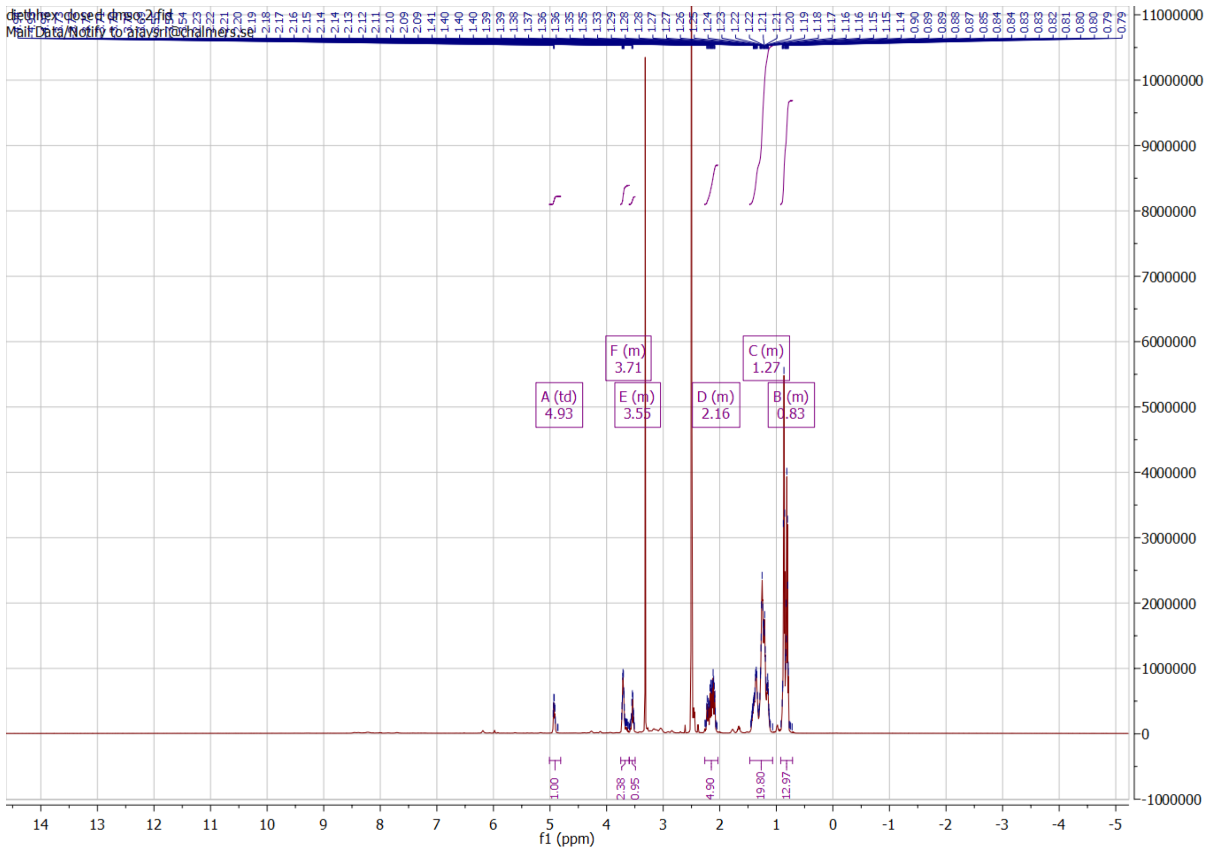
Figure 15: 1H NMR of 3-hydroxy-1,1-dioctylazetidin-1-ium chloride

3-hydroxy-1,1-dioctylazetidin-1-ium chloride: yellow oil; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.42 (td, *J* = 14.3, 12.9, 7.1 Hz, 1H), 4.11 (dd, *J* = 11.7, 5.6 Hz, 1H), 3.67 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.55 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.48 – 3.29 (m, 6H), 3.27 – 3.18 (m, 1H), 1.48 (ddq, *J* = 15.3, 11.3, 5.8, 5.2 Hz, 2H), 1.26 (d, *J* = 25.7 Hz, 40H), 0.85 (t, *J* = 7.1 Hz, 11H). Yield = 2.245g (98.7%)

6. Synthesis of 1,1-bis(2-ethylhexyl)-3-hydroxyazetidin-1-ium chloride

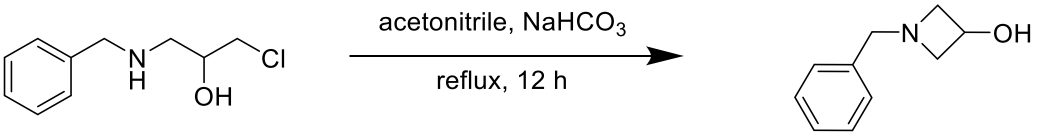


1,1-bis(2-ethylhexyl)-3-hydroxyazetidin-1-ium chloride



^{1}H NMR (600 MHz, DMSO-d_6) δ 4.93 (td, J = 7.1, 4.7 Hz, 1H), 3.75 – 3.60 (m, 2H), 3.60 – 3.50 (m, 1H), 2.26 – 2.03 (m, 5H), 1.47 – 1.07 (m, 20H), 0.92 – 0.71 (m, 12H). Yield = 2.654g (96.3%)

7. Synthesis of 1-benzylazetidin-3-ol



1-benzylazetidin-3-ol

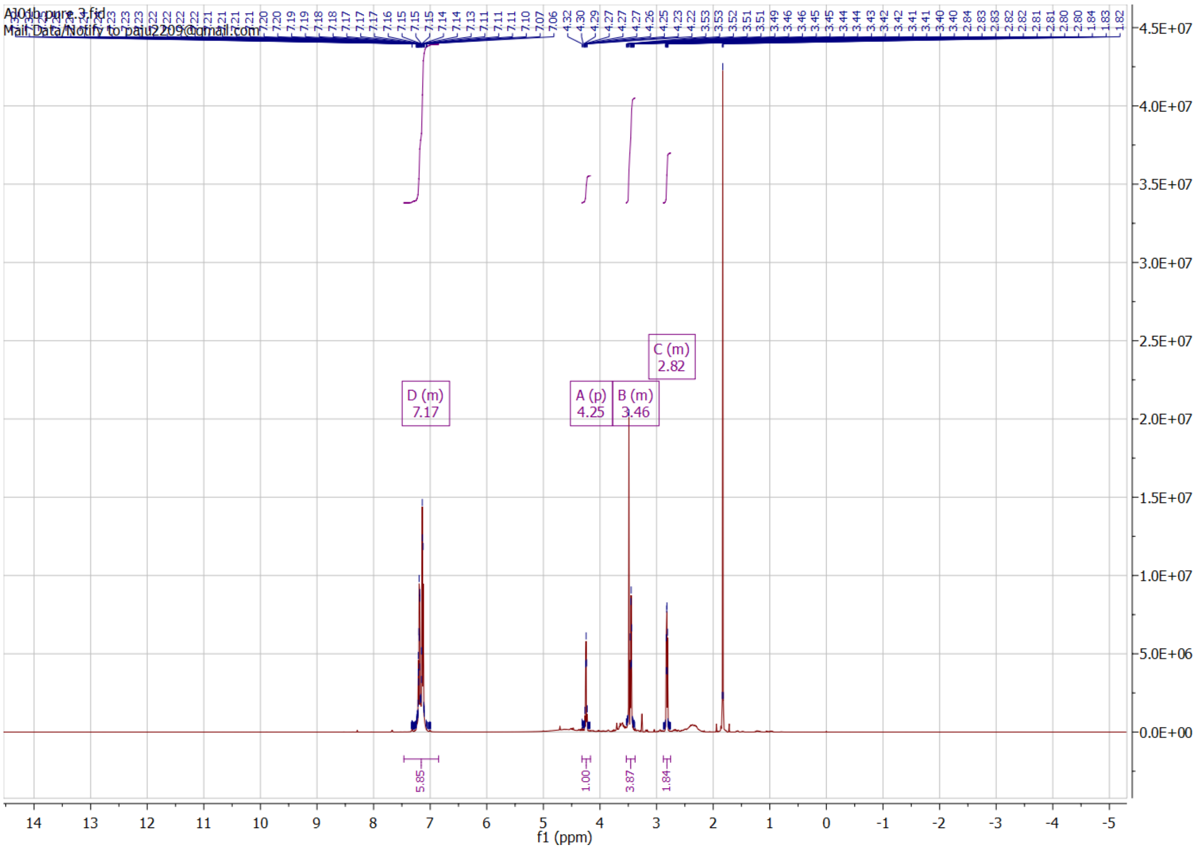


Figure 16: 1H NMR of 1-benzylazetidin-3-ol

1-benzylazetidin-3-ol : colourless oil; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.47 – 6.85 (m, 6H), 4.25 (p, *J* = 6.0 Hz, 1H), 3.53 – 3.38 (m, 4H), 2.88 – 2.75 (m, 2H). Yield = 1.62g (99.3%)

III. Alkylation of alcohols

For the alkylation of alcohols, two different bases were tested in two different solvent systems, namely triethylamine in acetonitrile and potassium tert-butoxide in 50% v/v THF/acetonitrile mixture. 1.5 mmol of the base along with 1mmol of the azetidinium salt/aminochlorohydrin was taken in a vial containing 5ml of the respective solvent system and allowed to stir for 20 minutes. To this, 0.07mL (1.1mmol, 0.156g, 1.1equiv.) of methyl iodide was added and allowed to stir for 3 hours at 40°C. The reaction was monitored with thin layer chromatography.

IV. Reaction of Azetidinium salts with chiral carboxylic acids

Two different carboxylic acids were used for these reactions, namely lactic acid and mandelic acid. 1mmol of azetdinium salt was mixed into a 20% v/v methanol/water mixture and allowed to stir till completely dissolved. To this, 1.2mmol of chiral carboxylic acid was added slowly and allowed to stir overnight. The reactions were monitored with thin layer chromatography.

Results and Discussion

I. Synthesis of aminochlorohydrins

The synthesis of aminochlorohydrins was successful for 8 different amines on reaction with epichlorohydrin. The yields ranged from 72% to 91%. For some of the compounds such as 1-chloro-3-(dioctylamino)propan-2-ol and 1-chloro-3-(dihexylamino)propan-2-ol, there were significant amounts of unreacted amines which were difficult to separate. Hence, the reaction mixture was used for further steps as they were. Some compounds like 1-chloro-3-(dihexylamino)propan-2-ol seemed to ring close even before heating in the water-isopropanol mixture.

A characteristic feature of the proton NMRs of aminochlorohydrins is a multiplet at a chemical shift around 2.5 indicating the protons in the vicinity of the nitrogen. Another characteristic of these NMRs is the appearance of a prominent pentet between chemical shifts 3.6 and 3.9 indicating the proton attached to the hydroxyl carbon.

Thin layer chromatography was rather ineffective in monitoring the reactions due to the tendency of the compounds to streak throughout the TLC plate. A better way to separate the aminochlorohydrins from the amines needs to be determined.

II. Synthesis of Azetidinium Salts from aminochlorohydrins

The synthesis of azetidinium salts from aminochlorohydrins was successful for all the aminochlorohydrins except 1-chloro-3-(diallylamino)propan-2-ol. Yields ranged from between 84-95% from the previous step.

Initially, the NMRs for these salts were performed in deuterated chloroform, in which they seemed to degrade and hence, d6-DMSO was used henceforth. A comparison of 1,1-bis(2-ethylhexyl)-3-hydroxyazetidin-1-ium chloride in deuterated chloroform and d6-DMSO is shown below:

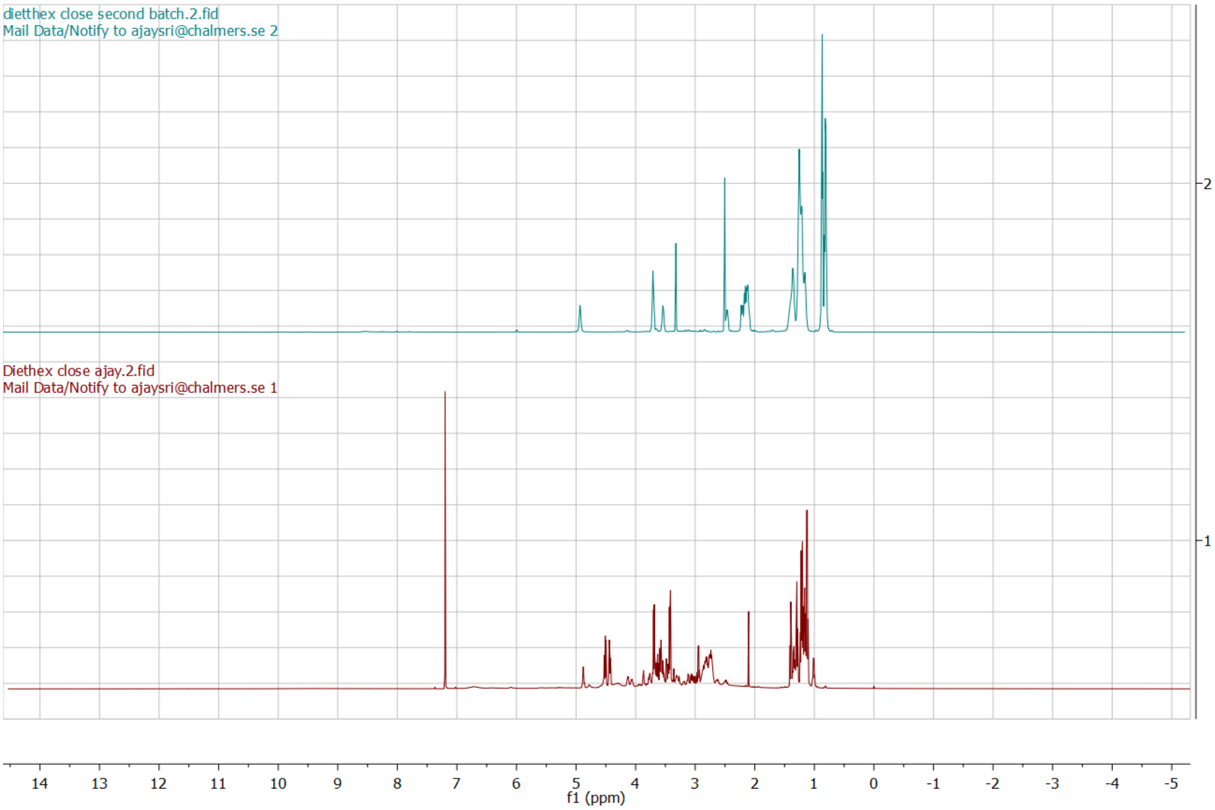


Figure 17: Scheme showing the NMR of 1,1-bis(2-ethylhexyl)-3-hydroxyazetidin-1-ium chloride in d6 DMSO (top) and deuterated chloroform (bottom).

When compared to the open form, the multiplet around chemical shift 2.5 will disappear as the reaction goes along to give rise to new peaks between chemical shift 3.5 and 4.5. The characteristic pentet of aminochlorohydrins will also be replaced by another characteristic pentet, this time between 4.5 and 5.

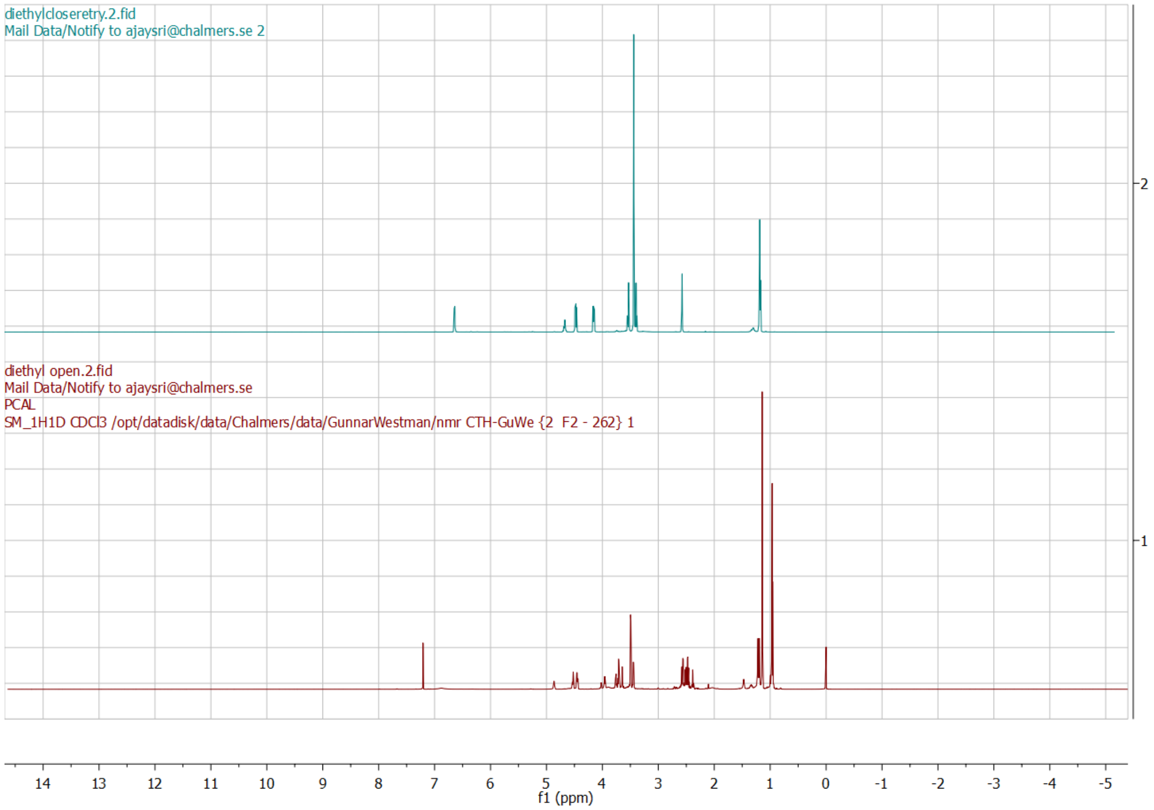


Figure 18: Scheme comparing 1H NMR of Synthesis of 1,1-diethyl-3-hydroxyazetidin-1-ium chloride and 1-chloro-3-(diethylamino)propan-2-ol . The multiplet around 2.5 can be seen disappearing and a new peak arises around 4.9.

The extraction step proved to not be very effective in the removal of excess amine as the amine signals are still present even in the final salt.

III. Alkylation of hydroxyl group

The alkylation of –OH group was ineffective both in the case of the azetidinium salts and the aminochlorohydrins. A new signal was observed in the thin layer chromatography in the case of the potassium *tert*-butoxide in THF/acetonitrile system however this ended up just being unreacted potassium *tert*-butoxide. One again, thin layer chromatography proved to be ineffective as all the compounds tended to streak leading to inconclusive results. Different bases such as sodium hydride and different solvents such as pyridine and dioxane could be explored in the future.

IV. Reaction with chiral carboxylic acids

Once again, both lactic and mandelic acid didn't react with the azetidinium salts. The TLC in the case of lactic acid showed streaks throughout the TLC plate whereas mandelic acid also streaked a bit. It had seemed as though mandelic acid had reacted with 1,1-bis(2-ethylhexyl)-3-hydroxyazetidin-1-ium due to the fattening of a streak under UV light. However, on purifying via column chromatography. It was seen that the fattening was just a continuation of the mandelic acid spot. Different temperatures of 20°C, 40°C and 60°C were attempted to no end. Different solvent systems could be used such as methanol in acetonitrile.

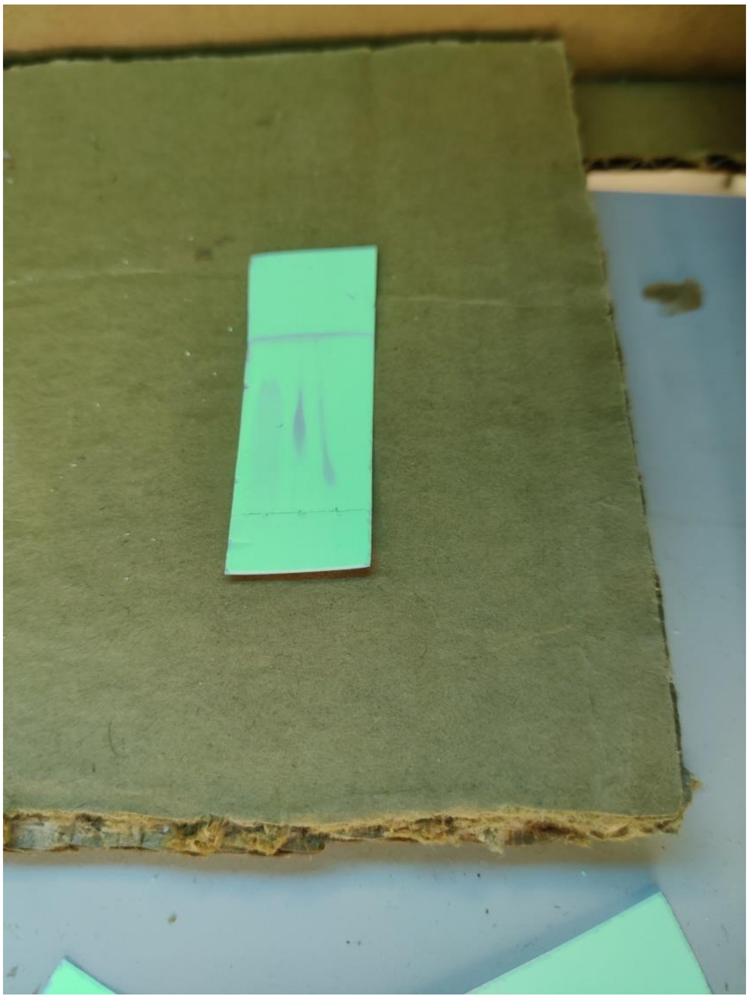


Figure 19: TLC plate showing mandelic acid on the left, reaction mixture with mandelic acid and 3-hydroxy-1,1-bis(2-methoxyethyl)azetidin-1-ium chloride in the center and reaction mixture with mandelic acid and 1,1-bis(2-ethylhexyl)-3-hydroxyazetidin-1-ium in the right.

Conclusion

In total, 6 azetidinium salts and 1 azetidine were synthesized during the course of this project. The alkylation of alcohols and the reaction with chiral carboxylic acids did not work as anticipated and therefore it is important to come up with a new way of reaction monitoring before reattempting this project. Different solvent systems can also be used to see solvent effects on the reactivity.

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