**Title**

Synthesis of NMP from 3-dimethylaminopropiophenone hydrochloride

**Introduction**

The synthesis of NMP is prepared in a two-step synthesis, starting from 3-dimethylaminopropiophenone hydrochloride. The first reaction combines 3-dimethylaminopropiophenone hydrochloride with sodium borohydride to convert the carbonyl into an alcohol. In the second reaction, the alcohol is deprotonated and 4-chlorobenzotrifluoride is added, which reacts with the electron-rich oxygen and expels the Cl-, giving the final product, NMP. One more step can be added to create the oxalic salt of NMP, in which case, oxalic acid is added to NMP to form the said salt.

The first reaction occurs by carbonyl reduction using NaBH4. The B-H bond attacks the carbon, detaching itself and forming NaBH3-. As a result of this attack, the oxygen breaks one of its bonds, and therefore needs something (preferably a hydrogen atom) to become stable again. When HCl is added, oxygen grabs the hydrogen, protonating itself, thereby resulting in a secondary alcohol.

Carbonyl Reduction



The second reaction occurs by nucleophilic aromatic substitution. After the alcohol has been deprotonated via the use of potassium t-butoxide, 4-chlorobenzotrifluoride is added, which results in nucleophilic aromatic substitution occurring. The alkoxide ion of the reduced carbonyl group, formed by deprotonation using K t-butoxide, can displace the Cl from the benzene ring only because of the presence of the electron withdrawing CF group. The deprotonated oxygen attacks the carbon with the halogen, which results in a Meisenheimer complex. Eventually, one of the resonance structures in the Meisenheimer complex allows for the reaction to continue, kicking off the Cl- and resulting in, this case, NMP.

Nucleophilic aromatic substitution



The expected product, NMP, was characterized by melting point and IR spectroscopy.

**Experimental**

*A – Synthesis of 3-(dimethylamino)-1-phenylpropanol*

3-dimethylaminopropiophenone hydrochloride (2.08 g, 9.73 mmol) was stirred with water (10 mL). Then, 10% sodium hydroxide (6 mL) was added in order to bring the pH below 10. The product changed to a milky oil, which then changed back to a clear solution once 95% ethanol (10 mL) was added. In a separate beaker, water (10 mL), 10% sodium hydroxide (4 drops), and sodium borohydride (0.41 g, 10.8 mmol) were mixed and dissolved together. The two beakers were then added together, stirred for ~15 minutes, and hydrochloric acid (5 mL) was added until the reaction was complete, i.e., fizzing stopped. Sodium hydroxide (20 mL) was added to make the solution basic, and then the solution was added into a separatory funnel alongside diethyl ether (20 mL). The two were then separated, and then the same process was repeated again with more diethyl ether (10 mL). The ether layers were mixed together, dried with magnesium sulfate, and then RotaVapped. An IR was taken for characterization, and then the crude oil was then left for a week.

*B – Synthesis of NMP*

The oil compound was mixed with 4-chlorobenzotrifluoride (4 mL), dimethylacetamide (30 mL), and potassium t-butoxide (30 mL). Slow distillation was done for an hour and ten minutes to collect ~50mL of the t-butyl alcohol. Water (40 mL) and tetrahydrofuran (30 mL) were mixed together in a separatory funnel, and then mixed with saturated sodium chloride (20 mL) to achieve the “ether” solution, since diethyl ether was not available. The solution was dried with magnesium sulfate. An IR was taken for characterization.

*C – Synthesis of the oxalate salt of NMP*

Oxalic acid (0.85 g, 9.44 mmol) was mixed with absolute ethanol (15 mL), and then the NMP ether solution was added drop-wise. No precipitate formed until ~5 minutes after all the NMP had been added. The crystals were collected by vacuum filtration using a Buchner funnel, then left to dry. The mass was recorded, one final IR spectrum was taken, and melting point was recorded, which were all used for characterization.

**Results**

**Table 1.** Synthesis of NMP oxalate salt (4ox):

|  |  |
| --- | --- |
| Compound identity | N-methyl-Prozac (NMP) |
| Theoretical yield | 3.03 g |
| Mass recovered | .845 g |
| Percent recovery | 27.9% |
| Melting point (literature) | 143.5–145.0 (°C) |
| Melting point (experimental) | 139.5 – 140.0 (°C) |

**Table 2.** IR Data of 3-(dimethylamino)-1-phenylpropanol (2):

|  |  |  |
| --- | --- | --- |
| Peak position (cm-1) | Peak shape | Functional Group |
| 3364.65 | Strong, broad | -OH group |
| 2972.58 | Strong | C-H sp3 |
| 1660.07, 1650.63 | Strong | Benzene ring C-C |
| 1537.26, 1556.68 | Strong | Aromatic C=C |
| 1038.14 | Strong | C-N (amine) |

**Table 3.** IR Data of NMP (4):

|  |  |  |
| --- | --- | --- |
| Peak position (cm-1) | Peak shape | Functional Group |
| 3399.47 | Strong, broad | -OH group |
| 2947.86 | Medium | C-H sp3 |
| 1621.10 | Strong | Benzene ring C-C |
| 1263.56 | Weak | C-O (ether) |
| 1196.62 | Weak | C-F or C-N (amine) |

**Table 4.** IR Data of NMP oxalate salt (4ox):

|  |  |  |
| --- | --- | --- |
| Peak position (cm-1) | Peak shape | Functional Group |
| 2993.78 | Medium | C-H sp3 |
| 1768.91, 1757.89 | Strong | Contamination |
| 1246.05 | Strong | C-O (ether) |
| 1057.02 | Medium | C-F or C-N (amine) |

**Table 5.** H NMR Data of NMP (4):

|  |  |  |  |
| --- | --- | --- | --- |
| **ppm** | **multiplicity** | **integration** | **assignment** |
| 1.9-2.2 | Multiplet | 10H | a |
| 5.2 | Triplet | 1H | b |
| 6.8-7.4 | Multiplet | 9H | c |

**Discussion**

The purpose of this experiment was to synthesize and characterize the oxalate salt of NMP, a precursor to Prozac. The first step was a reduction of the carbonyl group using sodium borohydride. The solution needed to be basic in the addition of sodium borohydride, which is why sodium hydroxide was used. This prevents an accidental protonation of the electronegative oxygen. The product of that reaction then needed to be made acidic to destroy any excess sodium borohydride, then was made basic again—to the solution’s free-base form—in order for coupling with 4-chlorobenzotrifluoride to occur. The temperature of the coupling reaction between the two is suggested to be around 155 °C in order to ensure the rapid coupling can be achieved, and also to remove as much ether, t-butyl alcohol, and excess 4-chlorobenztrifluoride, since their boiling points are all lower than that of dimethylacetamide. The product, 3-(dimethylamino)-1-phenylpropanol, was isolated and used in the succeeding step.

The second step was a nucleophilic aromatic substitution reaction between the formed crude product—after its deprotonation via using potassium t-butoxide—and 4-chlorobenzotrifluoride. Deprotonation was necessary because an electron-rich oxygen was needed in order for nucleophilic aromatic substitution to occur.

In making the NMP salt, using anhydrous oxalic acid and absolute ethanol is preferable because amine salts are best formed under anhydrous conditions. The final product was synthesized in a low-to-moderate yield after recrystallization and was characterized by melting point and multiple IR spectra. H NMR from a reference article was also included. The experimental melting point was well within the range of what was expected from this experiment (120-150 °C), and was only slightly lower than that of the specific “goal” melting point. This helps to confirm the presence of NMP, but is not specific enough by itself to efficiently confirm the identity of the product.

The IR spectra was much more efficient at confirming the identity of NMP as the final product. The most important peaks in the IR of 3-(dimethylamino)-phenylpropanol is the OH peak. This confirms that the carbonyl was successfully reduced. Although the peak at 1660.07 or 1650.63 could be unreacted carbonyl group, this seems extremely unlikely because excess sodium borohydride was used to ensure the reaction and also because a ketone group, even a conjugated one, usually has a wavenumber between 1750-1680. Therefore, it seems more likely that these peaks are accounted for by the conjugated C-C and aromatic C=C bonds of the benzene ring. The peak at 1038.14 could account for the C-N group of the amine, but is unspecific, as this peak can be overlapped with other groups fairly easily.

The IR spectrum of NMP shows contamination, which isn’t unexpected. The contamination at 3399.47 is unreacted 3-(dimethylamino)-phenylpropanol. Again, the peak at 1621.10 is unlikely to be unreacted carbonyl, so it is more likely to be C-C bonds of the benzene ring. The peak at 1196.62 could be the C-N group of the amine, but could also be the C-F bond of the trifluromethyl group. The peak at 1263.56 seems is the C-O ether bond.

The IR spectrum of the NMP oxalic salt is not very soluble in ethyl acetate, so this spectrum has the potential to be contaminated or otherwise wrong. The spectrum shows a lack of any OH peak, which suggests that the unreacted 3-(dimethylamino)-phenylpropanol also became its oxalic salt, which is hard to isolate from the desired product. However, the strong peak at 1246.04 could appropriately be the C-O ether bond. Similarly, the peak at 1057.02 could be either the amine or the trifluoromethyl group. The peaks at 1768.91 and 1757.89 are extremely hard to identify because their wavenumbers are too high to suggest a ketone, but could be explained by the contaminating oxalate salt of 3-(dimethylamino)-phenylpropanol. Overall, the oxalate salt IR is very unspecific and generally unhelpful in characterization. However, the previous IR suggests the successful synthesis of NMP.

HNMR

While this experiment was executed successfully, there were several areas that could use improvement. It is imperative that directions are read correctly and that amounts of starting material be correct. If the amount of 3-dimethylaminopropiophenone hydrochloride is too small, e.g., 0.2 g instead of the recommended 2.0 g, no crystals will be synthesized at the end of the experiment. The yield of the final product could have been improved upon by distilling for a longer time, and longer distillation could also decrease chances of contamination in the synthesis of NMP. It would also be beneficial for a H NMR to be done to further confirm the identity of the product.

**Conclusion**

NMP was successfully prepared and characterized via a two-step synthesis with minimum error. This experiment allowed students the chance to synthesize a compound in an intriguing and exciting way, similar to practicing “real” pharmaceutical chemistry.

**References**

(1) Perrine, D.M.; Sabanayagam, N. R.; Reynolds, K. J. *J. Chem. Ed.* **1998**, 1266.