A Three-Step Synthesis of Fluoxetine

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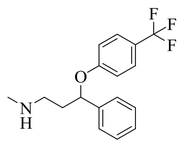
Abstract

Fluoxetine is the active ingredient in the antidepressant Prozac. It works as a selective serotonin reuptake inhibitor to treat conditions including depression and obsessive-compulsive disorder. To assemble this molecule, a three-step synthesis was utilized. Intermediates included 1-propanone, 3-(methylamino)-1-phenyl-(synthesized through an S_N2 reaction between 3-chloropropiophenone and methylamine) and α-[2-(methylamino) ethyl] benzyl alcohol (synthesized through reduction of the first intermediate using $NaBH_4$). The second intermediate was subjected to 4-chlorobenzotrifluoride and sodium hydride to produce the desired molecule, fluoxetine. Over the course of this multi-stage procedure, several synthetic difficulties led to the formation of unexpected products.

Fluoxetine Background



Fluoxetine

A new class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), has emerged within the last few decades. They treat a broad spectrum of conditions including depression, obsessive-compulsive disorder, and bulimia nervosa. This class of medications has been shown to be equally effective compared to older treatments, but contains far fewer adverse side-effects. One of the leading antidepressants of this type is fluoxetine.

Exposure to this medication alters the presynaptic serotonin transporter. Since this presynaptic transporter differs from those of other neurotransmitters such as dopamine and norepinephrine, SSRIs are able to target and alter only the function and uptake of serotonin. SSRIs bind to the serotonin specific enzyme at the end of the transporter, modifying the shape and reducing the binding ability of serotonin. Because of the decreased binding, serotonin accumulates in the presynaptic transporter. Instead of being transported with the enzyme, it is able to be captured, stored, and used later in the cell. This reallocation and redistribution of serotonin facilitates an array of physiological alterations, aiding in the treatment and recovery from many physiological disorders.

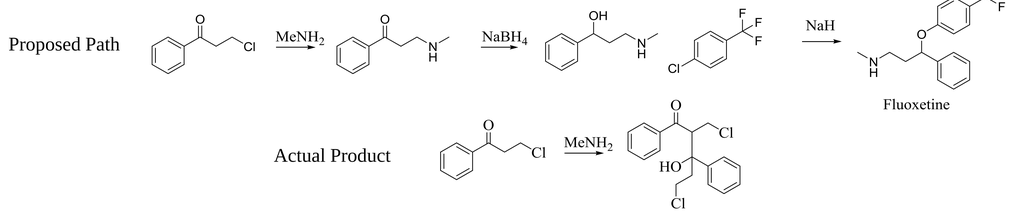
Green Chemistry

Green chemistry strives to improve the sustainability of chemical reactions, making them safer and less hazardous. There are a variety of ways to "green up" a reaction, often focusing on the use of catalysts, improving atom economy, and using less dangerous starting materials and reagents. Practical considerations must also be taken regarding the cost of the "green" alternative and the time required.

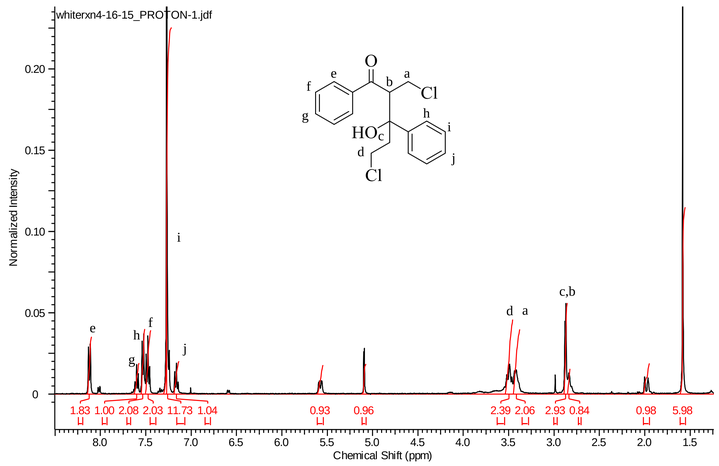
To improve this procedure, we retrosynthetically examined the first reaction and focused on safer solvents. Replacing the solvent of the first reaction, methanol, with water, would reduce the hazards, making the reaction safer while decreasing cost.

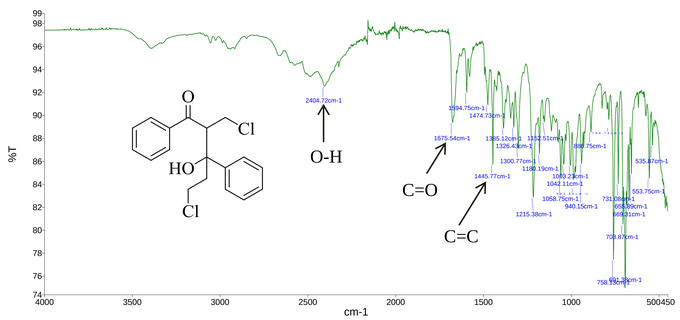
Minnesota Pollution Control Agency

Synthetic Schemes



NMR and IR Data





Extraction Set-Up Using brine and CH_2Cl_2

Crude Reaction Product

Green Chemistry Calculations

Comparison Parameters	Methanol	Water
Hazards	Flammable, acute toxicity, organ toxicity	None
Cost	$0.07/mL	$0.02/mL
Percent Yield	Not Determined	Not Determined
E Factor	Not Determined	Not Determined
Reaction Time, Temp	15 minuntes, Room Temperature	Not Determined
Product Purity, byproducts	Minimal Impurities	Not Determined
Waste produced	≈ 20 mL methanol Hydrochloric acid (0.17g) Methylamine (8.6g)	Hydrochloric acid (0.17g) Methylamine (8.6g)

Discussion

This three-step procedure encountered several synthetic difficulties, preventing completion of the reaction scheme. Instead of assembling fluoxetine, the final molecule synthesized was the product of an Aldol reaction. Although the first reaction was supposed to proceed as a simple S_N2 replacement, the chlorine atom leaving and being replaced with an amine, the data collected conclusively proved this was not what happened. Instead, the methylamine deprotonated the α carbon of 3-chloropropiophenone, facilitating the attack of a second 3-chloropropiophenone molecule. This proceeded as an Aldol reaction, with the with final product being reprotonated. Although the reaction was heated, suggesting the possibility of an Aldol condensation, the data from both NMR and IR suggest the final condensation did not occur. No alkene functionality was present in the data.

The NMR data shows the appropriate peaks, splitting, and integration to account for all of the protons expected in the Aldol product. The IR data requires more interpretation due to the expected OH stretch. Although this stretch is supposed to occur around 3500 cm^{-1}, this data shows a stretch in the 2400-2500 cm^{-1} region. Although this is uncommon, it is not unprecedented, and, due to the heavy conjugation of the molecule, this down-shifted peak may represent the expected OH stretch. Therefore, both data sets support the formation of an Aldol product.

Conclusion

This synthetic scheme resulted in an unsuccessful attempt to synthesize fluoxetine. Although the first reaction was supposed to proceed through an S_N2 mechanism, the weak base favored deprotonation at the α carbon. This, in combination with the poor leaving group ability of chlorine, led to an Aldol reaction. In order to assemble the desired molecule, alterations will need to be made to the procedure, or a new synthetic scheme will need to be derived. Retrosynthetically, the first solvent could be replaced with water to "green up" the reaction. However, since the desired synthesis did not occur in the optimized solvents, this green alternative may not be the best way to assemble the molecule. The current procedure, without alterations, is not a good synthetic path to follow in an undergraduate laboratory for fluoxetine synthesis.

Future Directions

- Repeat synthetic scheme using a protecting group on ketone
- Utilize a starting material with bromine instead of chlorine (improved leaving group)
- Use X-ray crystallography to verify formation of Aldol product
- Design a new synthetic scheme using different reactions and starting materials

References

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