The Synthesis of NMP, a Fluoxetine (Prozac®) Precursor, in the Introductory Organic Laboratory

Daniel M. Perrine,[1] Nathan R. Sabanayagam, and Kristy J. Reynolds
Department of Chemistry, Loyola College in Maryland, 4501 N. Charles St., Baltimore, MD 21210-2699

Background

The principal synthetic pathways we considered to prepare this lab are sketched above. We first attempted to simplify Corey's (*1*) enantioselective synthesis of fluoxetine, which starts from commercially available **8**, by dispensing with the chiral catalyst and substituting $NaBH_4$ for BH_3, which we felt was unsuitably hazardous for an introductory laboratory setting.

A question that may arise from the students or which can be posed to them is why in a period of only a few years several enantioselective syntheses of fluoxetine were published by such preeminent chemists as Brown(*2*), a Nobel laureate; Corey, a Nobel laureate-to-be; and Sharpless (*3*). The answer lies in the fact that the activity of most drugs marketed as racemates actually likes predominately or exclusively with one of the enantiomers. Ibuprofen (Advil ®, Nuprin®, etc.) is the most common example. While marketed as the racemate, it is known that the *S*-(+) form is the only active form, and in Europe, this form is marketed as dexibuprofen (Seractil®). A contrasting example is found in the over-the-counter cough suppressant dextromethorphan (the DM of Robitussin DM®). This is the exclusively dextrorotatory form, and has no analgesic or narcotic properties; while the antitussive properties are found equally in its enantiomer, levomethorphan, the levorotatory form is an opioid narcotic and a Schedule II drug (*4*).

It was consequently expected that studies of the activity of the *R* versus the *S* form of fluoxetine would reveal significant differences in their respective activities. At the same time that the enantioselective syntheses of Sharpless, Brown, and Corey were being developed and published, workers at Eli Lilly Research Laboratories were testing this hypothesis. To their surprise, they found only a slight difference in activity between the enantiomers: "regardless of the species or pharmacological test, there is little enantiospecificity regarding interactions of fluoxetine with the serotonin-uptake carrier," and ". . . all the in vitro and in vivo data . . . indicate that the eudismic ratio of the fluoxetine enantiomers is near unity"(*5*). (The eudismic ratio is the ratio of affinities or activities of two enantiomers.)

In any case, we were quite satisfied to be able to find a route to the racemic material, and it seemed an obvious thing to substitute the much safer and convenient $NaBH_4$ for BH_3 in the reduction of **8**. But when we carried out this reaction, we were surprised to find that GC-MS showed that over 10% of our starting material **8** was converted to **12** and **14**, with displacement of chlorine by hydride. Several variations of concentration, temperature, and solvent did nothing to eliminate this undesirable side reaction. This complication, plus the drawback that **8** is in any case fairly expensive, led us to direct our attention to the patent procedure of Molloy and Schmiegel (*6*). This begins with **1**, which is quite inexpensive or can be made in a classic Mannich reaction (*7*) of acetophenone, **15**, with formaldehyde and dimethylamine. [Unfortunately for the goal of synthesizing Prozac itself, Mannich reactions using primary amines usually form a mixture of products, and this was the case when Mannich himself (*8*) and, later, Blicke and Burckhalter (*9*) attempted to synthesize 3-monomethylaminopropiophenone from methylamine and acetophenone.] As summarized in the *Journal* article, for reasons of safety and economy we have modified the patent procedure in several ways. Reduction of **1** to **2** by use of $NaBH_4$ instead of borane was simpler, safer, and quicker. By coupling with **3** (which is very cheap) instead of **7** (which is very expensive) we were able to eliminate one step in the patent procedure while avoiding the

[1]Corresponding author.

use of $SOCl_2$, which is as disagreeable as it is toxic. Additionally, the lab now exemplified nucleophilic aromatic substitution, which we thought was more interesting than the more ordinary Williamson ether synthesis.

The literature method for effecting this S_NAr reaction (*10*) is to deprotonate **2** by heating it at 90 °C for several hours with NaH in *N*,*N*-dimethylacetamide (DMAA). We found that bringing the reaction to reflux for 30 minutes allowed the reaction time to be considerably shortened with no significant loss in yield, and this can provide an interesting laboratory exercise for an advanced synthesis class. But we felt that sodium hydride was too hazardous for a beginning lab, even when used in an oil dispersion. After exploring a few other combinations of solvents and bases (*11*), we settled on the use of Aldrich's 1.0 *M* solution of potassium *tert*-butoxide in *t*-butyl alcohol, which is reasonably safe to use and can be dispensed from an automatic pippetor directly into the student flasks. We tried using *t*-butyl alcohol as the reaction solvent, but found that an aprotic polar solvent like DMAA was indispensable. Additionally, DMAA is inexpensive and partitions cleanly into the aqueous phase of a water-ether workup. We then considered making our own solutions of K *t*-butoxide in DMAA for student use but decided this was too inconvenient. Our present procedure, which represents a manageable compromise of the many factors involved, is to distill off the *t*-butyl alcohol, thereby raising the temperature to the boiling point of the DMAA and shortening the reaction time (while, admittedly, lowering the yield).

Notes for the Instructor

These Notes are keyed to (**Ins #**) *within the "Instructions to the Student" document.*

Ins 1 The toxicity of **2** and **4** is not known, but is likely to be quite low. While oxalic acid is poisonous in large quantities, it occurs in the leaves of many edible plants, particularly rhubarb. It is probably a good idea (in order to disabuse any student adventurers who might imagine that consuming their product would give them some sort of a "high") to emphasize that antidepressants are *not* euphorigenic, i.e., they will not make you "feel good" if you are not already depressed any more than aspirin will make you feel better if you don't have a headache. (Even if a person is psychologically depressed, antidepressant drugs begin to help only after they have been taken daily at their regular dosage—which for fluoxetine is about 20-60 mg—for a minimum of two weeks; a one-time dose has no effect.)

Ins 2 The patent uses the von Braun reaction to remove the methyl group. This procedure involves reacting **4** with cyanogen bromide, CNBr, to eliminate MeBr and replace the *N*-methyl group with an *N*-cyano group (a cyanamide) which can then be easily hydrolyzed to the carbamate and eliminated. (See March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 436-437.) Other, less hazardous reagents for removing one of the methyl groups, such as ethyl chloroformate, could be used in an advanced laboratory for the synthesis of Prozac from NMP.

Ins 3 It is easy to monitor the course of this reaction by noting the disappearance of the ketone stretch in the IR at 1676 cm^{-1}. We found it was invariably over in 10 minutes.

Ins 4 If students have access to a rotary evaporator, the ether can be removed from a tared flask and the yield for this stage of the reaction calculated.

Ins 5 A sample recrystallized once from MeOH/HOH had a melting point of 40-42 °C; the one reference we were able to find to the *racemic* material, like ours, was recrystallized from pentane, mp 46-47 °C (*12*). For the purpose of this experiment, using the crude oil for the next step is perfectly satisfactory.

Ins 6 The purest product by mp and GC-MS seemed to come from the students who distilled the reaction mixture fairly slowly, perhaps allowing time for the reaction. (Better results might be obtained by stopping the distillation when the distillate is above 100 °C and refluxing 5-

10 minutes.)

Ins 7 The desired product is usually contaminated by unreacted **2**, as well as the excess of **3**. (All the literature methods upon which we modeled this step used an excess of **3**. When we attempted to run the reaction with a molar equivalent, the reaction failed to reach completion.) The presence of **3** is not a great problem, since it will not form an oxalate salt in the final step and is thus easily separated from the product **4ox**. However, **2** can form an oxalate salt which will make purification and isolation of **4ox** much more difficult. Fortunately, **2**, which is both an alcohol and an amine, is much more soluble in water than is **4**, an ether and an amine. We found that adequate washing of an ether solution of **4** contaminated with **2** resulted in complete elimination of **2** with no significant loss of **4**.

Ins 8 0.85 g of anhydrous oxalic acid is a rounded equivalent of the amount calculated on the basis of a 100% conversion of the 2.0 g of starting 3-dimethylaminopropiophenone hydrochloride into NMP free base (a most unlikely event). The anhydrous acid is preferable to the dihydrate. Isopropyl alcohol would probably be an acceptable substitute for absolute ethanol. Methanol is not a good choice, since the product is too soluble in it. Generally, amine salts are best formed under anhydrous conditions, hence the use of the anhydrous oxalic acid and the absolute ethanol. It is better to add the ether solution to the acid rather than the other way around: on reverse addition it forms a material which filters very poorly. This may be because a mixture of the dibasic and the monobasic salt is formed when excess base is present or because the product is so insoluble in ether that a microcrystalline solid is formed which clogs the filter paper.

Ins 9 The oxalate salt takes some time to dry to constant mass. It appears very bulky and copious when first collected, but shrinks considerably on drying. The highest yield our students obtained by this procedure was about 2.5 g (64% based on the initial Mannich base hydrochloride).

Ins 10 The actual melting point is 143.5-145.0 °C, but most student samples will melt from 115-130 °C. A sample which was twice recrystallized from an EtOH/EtOEt solvent mixture melted at the 143.5-145.0 °C (with no decomposition noted up to 150 °C), and was sent to Quantitative Technologies Inc for analysis. *Calc:* C 58.11, H 5.36, N 3.39, F 13.79 %. *Found:* C 58.02, H 5.41, N 3.46, F 13.52%. The only literature data on this compound are the mp and % elemental analysis which appear in the Eli Lilly patents, and both (mp "117-119 with decomposition," "calc. ... H 3.36. . . Found . . . H 3.49") seem to contain errors or typos (*2*). I (DMP) called Eli Lilly and spoke to Dr. Bryan Molloy as we were developing this laboratory exercise, which he found to be pedagogically interesting. But when the issue of this melting point and percent composition came up, he apologized, saying he had to discontinue the conversation because he was under orders from the company's lawyers not to discuss the matter due to pending litigation. A subsequent search of the Web disclosed that Barr Laboratories is challenging Lilly's Prozac patents (http://www.barr-labs.com/prozac.htm); I had not been aware of this.

The recrystallized material with melting point noted above was transformed to the free base and had the following spectral data: FTIR: 1616, 1510, 1460, 1330, 1110, 1060, 836 cm^{-1}; HNMR (60 MHz, $CDCl_3$) δ 1.9-2.2 [10H, m, N-(CH_3)$_2$, N-CH_2-CH_2], 5.2 (1H, t, J = 7.5 Hz), 6.8-7.4 (9H, m, Ar*H*). MS *m/e* 324 ($M + 1^+$, 1.2%), 323 (M^+, 6.5%), 58 ($Me_2NCH_2^+$, 100%). A sample was sent to Spectral Data Services for ^{13}C DEPT NMR analysis: ^{13}C NMR (91 MHz, $CDCl_3$) δ 160.5 (C), 141.0 (C), 128.6 (CH), 127.6 (CH), 126.5 (CH), 125.7 (CH), 122.8 (C), 124.3 (q, CF_3, J = 267 Hz), 122.5 (q, C-CF_3, J = 30 Hz), 115.7 (CH), 78.5 (CH), 55.7 (CH_2), 45.5 (CH_3), 36.8 (CH_2).

Approximate Quantities of Chemicals Needed for Each 10 Students

Week One

25 g 3-dimethylaminopropiophenone Hcl
100 mL 95% ethanol
100 mL 6.0 *M* hydrochloric acid
25 g anhydrous magnesium sulfate
300 mL 10% NaOH solution
5 g sodium borohydride
350 mL diethyl ether

Week Two

40 mL 4-chlorobenzotrifluoride
300 mL dimethylacetamide
300 mL 1.0 *M* potassium *t*-butoxide
250 mL abs EtOH
600 mL diethyl ether
25 g anhydrous magnesium sulfate
10 g anhydrous oxalic acid

Literature Cited

1. Corey, E. J.; Reichard, G A. *Tetrahedron Lett.* **1989**, *30*, 5207-5210.

2. Srebnik, M.; Ramachandran, P.V.; Brown, H.C. *Abstracts of Papers*, 193rd National Meeting of the American Chemical Society, Denver, CO; American Chemical Society: Washington, D.C., 1987; ORGN 110.

3. Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081-4084.

4. See Perrine, D. M., *The Chemistry of Mind-Altering Drugs: History, Pharmacology, and Cultural Context,* American Chemical Society: Washington, DC, 1996); pp 71-74.

5. Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412-1417 (quoted material from pp 1415-1416). These workers propose an explanation for the near equivalence of the fluoxetine enantiomers.

6. (a) Molloy, et al. U.S. Patent 4 314 081, 1982; (b) Molloy , et al. U.S. Patent 4 584 404, 1986; (c) Molloy , et al. U.S. Patent 4 626 549, 1986

7. Maxwell, C. E. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 305-306.

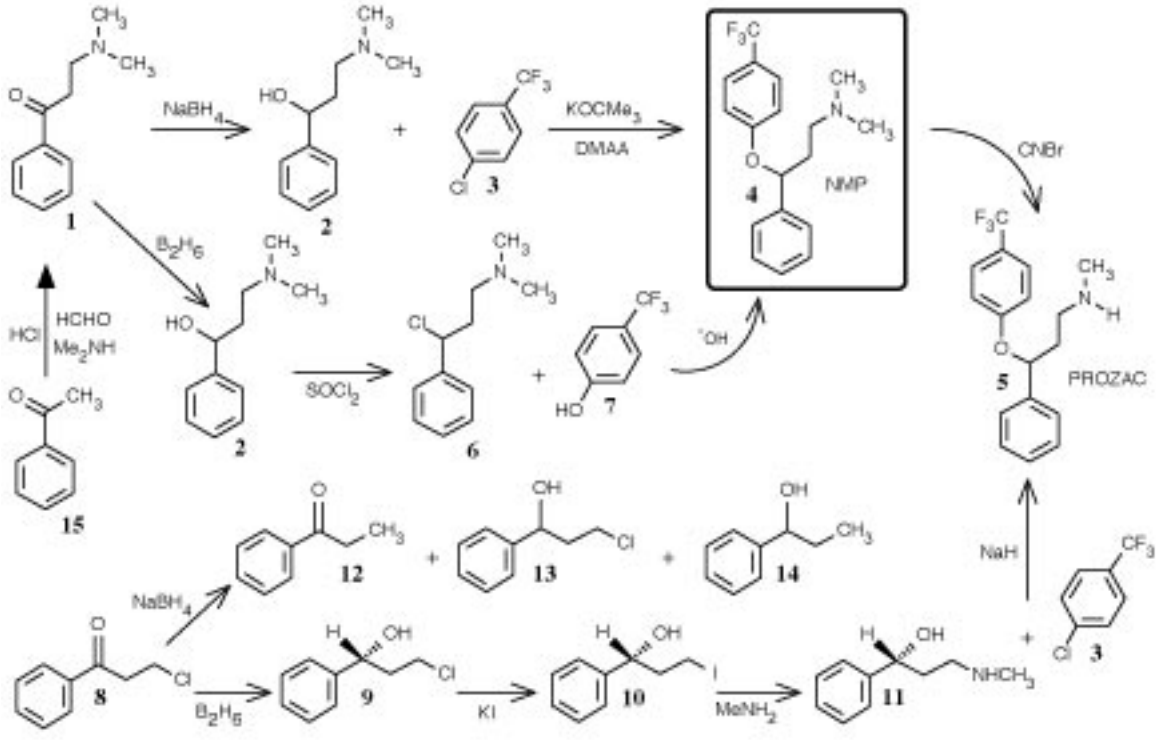
8. Mannich, C.; Heilner, G. *Ber.* **1922**, *55*, 356.

9. Blicke, F. F.; Burckhalter, J. H. *J. Am. Chem. Soc.* **1942**, *64*, 451-454.

10. (a) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412-1417. (b) Koenig, T. M.; Mitchell, D. *Tetrahedron Letters* **1994**, *35*, 1339-1342.

11. Mitchell, D.; Koenig, T. M. *Synthetic Communications* **1995**, *25*, 1231-1238.

12. *J. Am. Pharm. Assoc.* **1955**, *44*, 766.


NaBH4
KOCMe3
DMAA
NMP
CNBr
B2H6
SOCl2
HCl
HCHO
Me2NH
PROZAC
NaBH4
B2H6
KI
MeNH2
NaH

The Synthesis of NMP, a Fluoxetine (Prozac®) Precursor, in the Introductory Organic Laboratory

Daniel M. Perrine, Nathan R. Sabanayagam, and Kristy J. Reynolds
Department of Chemistry, Loyola College in Maryland, 4501 N. Charles St., Baltimore, MD 21210-2699

In the following document, notes preceded by "Ins" are notes for the Instructor and can be found in the "Notes for the Instructor" document; "Notes for the Student" are found at the end of this document.

> *CAUTION!* 3-Dimethlyaminopropiophenone (**1**) is a toxic irritant. Sodium borohydride is a flammable solid and corrosive. Ethyl alcohol and 4-chlorobenzotrifloride (**3**) are flammable liquids and irritants. Sodium hydroxide, hydrochloric acid, and oxalic acid are corrosive and toxic. Potassium *tert*-butoxide is corrosive. *N*,*N*-Dimethlyacetamide is an irritant. Ether is a flammable liquid and toxic. Oxalic acid is toxic. The toxicity of **2, 4,** and **4ox** are unknown (**Ins 1**).

Introduction. Fluoxetine, **5**, is the international nonproprietary, or generic name for Eli Lilly's Prozac, an antidepressant drug which was introduced in 1986 as the first in the class of selective serotonin reuptake inhibitors (SSRIs). Other more recent drugs in this class include Zoloft and Paxil. SSRIs are notable for having a much wider margin of safety and lower incidence of side effects than earlier antidepressants like the tricyclics (Tofranil, Anafranil). Fluoxetine (Prozac) is one of the most widely used (and most profitable) drugs of all time. In the original patent of Molloy et al. (1982), Prozac was synthesized by removing a methyl group from **4** (**Ins 2**).

We will synthesize **4**, which is *N*-methyl-Prozac (NMP)—i.e., Prozac with an extra methyl group on the amine nitrogen. NMP is of interest in itself, since it is nearly as active an SSRI as fluoxetine and is probably a prodrug for fluoxetine—i.e., it is metabolized in vivo to fluoxetine by *N*-demethylation. In our experimental procedure we will synthesize **2** the first week and use it the second week to synthesize NMP, which we will isolate as the oxalate salt, **4ox**.

WEEK ONE

Synthesis of* 2: *(±)-3-(dimethylamino)-1-phenylpropanol. Weigh 2.00 g of 3-dimethylamino-propiophenone hydrochloride (the amine salt of the free base **1**) into a 100 mL beaker. Place the beaker on a magnetic stirrer, add a ½-in magnetic stir bar and 10 mL of water to the beaker, and stir to dissolve. Then add (with stirring) sufficient 10% NaOH (about 5-6 mL) to bring the solution to pH > 10. The free base of **1** will form and come out of solution as a milky oil. With continued stirring, add enough 95% EtOH (about 9-10 mL) to dissolve the free base of **1** and to form a clear solution again.

In a vial or small beaker make 10 mL of water basic with 3 drops of 10% NaOH; add 0.40 g of $NaBH_4$ and stir to dissolve (Student Note 1). Add this $NaBH_4$ solution with stirring to the beaker containing **1**. Allow the reaction to stir for 15 min to ensure a complete reaction (**Ins 3**). Cautiously *(vigorous evolution of hydrogen gas!),* with continued stirring, make the mixture acidic by dropwise addition of 6.0 *M* hydrochloric acid. (This destroys the excess $NaBH_4$. About 5 mL will be needed; add the acid until the "fizzing" stops.) You now have an aqueous solution of the hydrochloride salt of **2**. We will need **2** in its free base form in order to couple it with **3**; to form the free base, make the solution basic again to pH > 10 with 10% NaOH. (About 15 mL will be needed to make the solution neutral, and a further 5-7 mL will be needed to bring the pH to >10.) Stir in a few chips of ice to cool the mixture to room temperature, and transfer the solution to a separatory funnel. Add 20 mL of diethyl ether, shake well *(pressure can develop!)* allow the layers to settle, and separate them. Reserve the upper ether layer in a beaker and extract the lower aqueous layer with an additional 10 mL portion of ether; add the second ether extract to the beaker containing the first ether extract. Discard the aqueous layer and dry the

combined ether extracts over anhydrous $MgSO_4$ and (to ensure no $MgSO_4$ is transferred) filter the ether solution through a loose cotton plug in a funnel into a 250 mL RB flask containing a ½-inch stirbar. Use a simple distillation apparatus (Claisen adaptor, thermometer, condenser; *flammable vapors!*) with magnetic stirring to remove the ether (**Ins 4**). Most of the ether will distill over near its bp of 36 °C; continue the distillation until the temperature of the distilling solvent is about 55-60 °C, at which point about 30 mL of ether should have been collected. The colorless oil which remains behind in the RB is ***(±)-3-(dimethylamino)-1-phenylpropanol,* 2**, along with some residual ether. Leave the stirbar in the flask, stopper it with a ground-glass stopper, and keep it in your drawer for use in the next lab. Depending on the amount of residual ether, on standing for a few days at cool temperatures, **2** may solidify to a waxy white solid with a mp slightly above room temperature, but whether this occurs or not will not affect the next step in your synthesis of NMP (**Ins 5**).

WEEK TWO

Synthesis of* 4 (NMP): *(±)-N,N-dimethyl-3-phenyl-3-(4-trifluoromethylphenoxy)propanamine.
(Student Note 2) To the 100 mL RB containing **2** and a ½-in stir bar, add 4 mL of 4-chlorobenzotrifluoride, **3**, and 30 mL of dimethylacetamide (Student Note 3). With stirring, add to this mixture 30 mL of 1.0 *M* potassium *tert*-butoxide *(caustic alkali!)* in *tert*-butyl alcohol (Student Note 4). Using a simple distillation apparatus, distill the mixture slowly, with stirring, over a 15-20 min period, until the temperature of the refluxing solvent mixture reaches 150 °C (**Ins 6**).

Remove the heating mantle and disconnect the RB (*hot! use a towel!*) from the distillation apparatus. Cool the RB by briefly immersing it in a cold water bath or a stream of running water. Add 40 mL water and 30 mL ether to the RB, swirl to dissolve, remove the stirbar, and pour the contents of the RB into a 250-mL separatory funnel. Shake well, allow the layers to separate, and drain the lower, aqueous layer into a 100 mL beaker. Transfer the upper, ether layer into a separate 100 mL beaker. Return the water layer to the separatory funnel, add 10 mL fresh ether, shake and separate, again reserving the lower layer but combining the ether layer with the previous 30 mL extract. Return the water layer to the separatory funnel and extract it a third time with 10 mL fresh ether. Discard the aqueous layer. Pour the ether extracts back into the separatory funnel and add 25 mL water. Shake well, allow the layers to settle, and discard the lower, aqueous layer. Add a final 25 mL water to the separatory funnel, and again shake well, allow the layers to settle, and discard the lower, aqueous layer. (If the aqueous washings are still cloudy at this point, add another 25 mL water to the ether solution in the separatory funnel, and once again shake well, allow the layers to settle, and discard the lower, aqueous layer. Repeat this process until the lower, aqueous layer is completely clear.) Dry the ether solution with anhydrous $MgSO_4$, and filter it through a funnel containing a cotton plug (to exclude any residual $MgSO_4$) into a dry dropping funnel (**Ins 7**).

Synthesis of* 4ox, *the oxalate salt of NMP. Dissolve 0.85 g of anhydrous oxalic acid (**Ins 8**) in 15 mL absolute ethanol in a 100-mL beaker. Place a magnetic stirbar in the solution and put the beaker on a stirring apparatus beneath the dropping funnel. With good stirring, allow the ether solution of NMP to drop into the acid solution in the beaker until the first permanent insoluble precipitate forms (Student Note 5). Usually this is a flocculent white material. Stop the addition of NMP at this point and stir the contents of the beaker for a few minutes. The precipitate will slowly grow in bulk; when formation of new precipitate has stopped, continue adding the NMP-ether solution from the dropping funnel with stirring. If necessary to maintain stirring, add additional 5-mL aliquots of absolute alcohol to the beaker. When all the NMP solution has been added, remove the stir bar from the beaker and allow the product to digest for 5 minutes in an ice bath.

Collect the crystals of **4ox** by vacuum filtration using a Büchner funnel. Wash them with ether and allow them to air dry in your drawer overnight (**Ins 9**). Report the mass and the melting point. This

material *sinters* (softens) a few degrees before its actual melting point, which is between 120 and 150 °C (**Ins 10**).

Notes for the Student

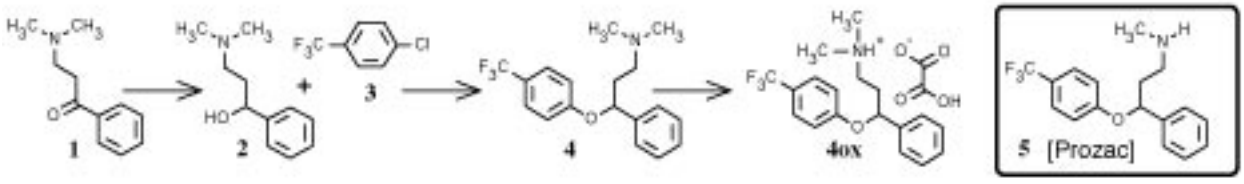
Note 1. If the water is neutral or acidic, the sodium borohydride will rapidly react with it forming hydrogen gas. Note that the product of this borohydride reduction is the ± or racemic form (hydride is delivered to the ketone randomly from either side), and consequently the final NMP (and Prozac® itself) are likewise racemates.

Note 2. This coupling reaction of **2** with **3** is an example of a *nucleophilic aromatic substitution* (also known as the S_NAr mechanism, see pp. 519-521 of your Fessenden text). The alkoxide ion of **2**, formed by deprotonation of **2** by the strong (and strongly hindered) base K *t*-butoxide, can displace the Cl from the benzene ring only because of the presence of the electron withdrawing CF_3 group. (The trifluoromethyl group functions like the nitro group in the discussion in Fessenden on pp 520-521.)

Note 3. The dimethylacetamide (DMAA) has a bp of 165 °C. Ether boils at 34.6 °C, *t*-butyl alcohol at 83.0 °C, and 4-chlorobenzotrifluoride (**3**) at 137 °C. The coupling reaction of **2** with **3** probably occurs in DMAA as solvent at a temperature > 100 °C. The purpose of the distillation to 155 °C is twofold: to ensure that a high enough temperature is achieved for (rapid) coupling and to remove as much ether, *t*-butyl alcohol, and excess **3** as possible, simplifying the workup.

Note 4. The potassium *t*-butoxide is in about 2.5 molar excess to ensure complete deprotonation of alcohol **2**. Try to make the addition of this base as rapid as possible, avoiding exposure to moisture or air; if too much water is present, the coupling of **2** and **3** will not take place. On the other hand, a *slower* distillation of the reaction mixture, particularly in the range from 100-150 °C, seems to favor a more complete reaction and a purer product.

Note 5. The free base of **4** and oxalic acid are both soluble in ethanol and in ether; the oxalate salt **4ox** is soluble in alcohol but very insoluble in ether. Without addition of the alcohol, the crystallization will occur too rapidly, and very fine crystals are formed which clog the filter paper.


1
2
4
3
4
40x
5 [Prozac]