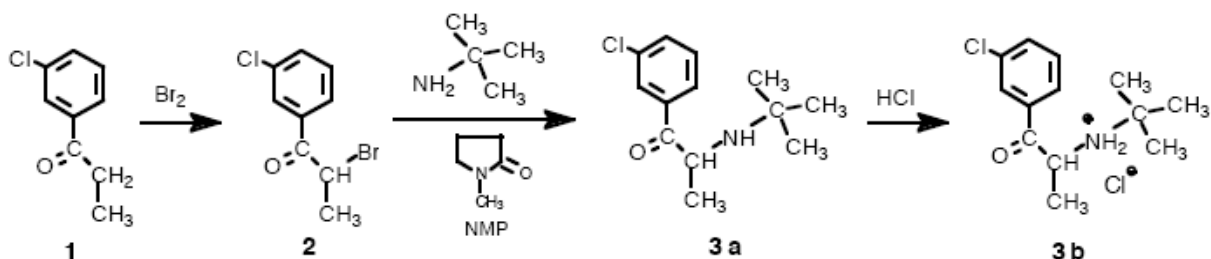


A Short, One-Pot Synthesis of Bupropion (Wellbutrin, Zyban)

Adapted by R. Minard from a procedure by Daniel M. Perrine,* Jason T. Ross, Stephen J. Nervi, and Richard H. Zimmerman, Department of Chemistry, Loyola College, Baltimore, MD, J. Chem. Ed., Nov. 2000, 1479-1481

Introduction:

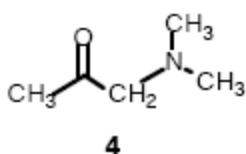
Bupropion, **3b**, the hydrochloride salt of ($\pm$)-2-(*t*-butyl-amino)-3-chloropropiophenone, has a unique pharmacological profile. It was first marketed in 1985 by Burroughs-Wellcome (now Glaxo-Wellcome) as an antidepressant, under the trade name Wellbutrin. Unlike selective serotonin reuptake inhibitors such as Prozac, Zoloft, or Paxil, it does not interfere with sexual performance, is less likely to cause drowsiness, and is as effective as Ritalin in the management of attention-deficit hyperactivity disorder (ADHD)¹. But its most interesting feature was discovered by accident: in early clinical trials, many smokers taking the drug reported that after one or two weeks their craving for tobacco seemed to fade and they were able to quit smoking with few or no withdrawal symptoms (Johnston, J. A., head of Psychiatry Clinical Development, Glaxo Wellcome; personal communication, 14 Dec 1998). When double-blind studies confirmed these anecdotal reports², bupropion was marketed in 1997 with a new name, Zyban, for use as an aid in smoking cessation. This experiment gives you the opportunity to synthesize a well-known pharmaceutical, and an “anti-addiction” drug. Perrine and coworkers investigated various approaches for the synthesis of Zyban. By modifying the published procedures^{3,4}, which require more than 24 hours and give yields below 40%, they developed a short, “one-pot” (really one flask) synthesis that can be carried out in less than two hours and gives material 98% pure in an average overall yield of 80%: The overall synthetic scheme is as follows:



The ketone **1** is α -brominated to bromoketone **2**. $\text{S}_{\text{N}}2$ displacement of Br by *t*-butylamine yields **3a** as a noncrystalline oil. This is converted into the crystalline ammonium hydrochloride salt **3b** by reaction with hydrochloric acid. The greatest improvement in yield came from using N-methylpyrrolidinone (NMP, also called 2-methyl-2-pyrrolidinone) in place of dimethylformamide (DMF) as a solvent for the amination of **2**. In DMF the reaction can take many hours^{3,4}, whereas in NMP it is complete in less than 10 min at 50–60 °C. The short reaction time enhances the yield because the free base of **3** (but not its hydrochloride salt) is significantly liable to decomposition. Additionally, this one-pot procedure skips the isolation of intermediate **2** and prevents exposure to a lachrymatory α -halogenated ketone.

(Tear gas is a lachrymatory compound!) The lab provides a study of α -halogenation and the influence of a non-protic polar solvent on competition between nucleophilic substitution and elimination reactions.

Prelaboratory Exercise: Write the mechanism for the alpha bromination of acetone and the conversion of the α -bromoacetone to the compound shown **4**.



Cautions:

Wear gloves when handling reactive materials and carry out all steps in a well-functioning hood.

Bromine liquid and vapor are extremely caustic to skin and lungs, and should be used only in the hood. Avoid breathing dichloromethane vapors, which are a probable carcinogen; keep this solvent and all mixtures containing it in the hood at all times. Ether vapors are extremely flammable; any open flame or spark can cause a violent explosion. If you spill the contents of the reaction after the addition of the bromine but before the addition of the amine (during **2** $\rightarrow$ **3a**), do not try to clean up the spill, but tell your instructor immediately; the reaction mixture at this stage contains intermediate **2**, which is a lachrymator (irritates eyes and causes tears like onions).

Step 1: 1 $\rightarrow$ 2

Synthesis of 2: From your drawer, obtain a 50 mL round-bottom (RB) flask and an addition funnel. In a good hood, put 1.0 g (5.9 mmol) m-chloropropiophenone, **1**, into the 50 mL round-bottom (RB) flask clamped above a magnetic stirrer, add 5 mL dichloromethane, CH_2Cl_2 , and a magnetic stir-bar and stir until the solid is dissolved. Place the addition funnel on the flask. Put 6.0 mL (6.0 mmol) of a 1.0 M solution of Br_2 in CH_2Cl_2 in the funnel and add a few drops to the flask. If the reaction does not begin immediately (as judged by the disappearance of the color of the bromine), warm the flask briefly with your hand or a warm-water bath. **Once the reaction begins, the color of the bromine will slowly lighten, and the flask should be placed in an ice bath.** The bromine solution **can now be added dropwise to the flask with stirring**; add the bromine solution just rapidly enough so that the color of the bromine has disappeared before the next drop is added.

Isolation of 2: After all the bromine has been added, remove the dropping funnel (**and the color of bromine has lightened**), add two boiling chips and set up a simple distillation apparatus by replacing the addition funnel with a distillation head/thermometer adapter/condenser. Insert the thermometer with the thermometer adapter and connect the condenser to the water aspirator. Distill the solvent (CH_2Cl_2) from the reaction mixture by placing the stirred flask (from before) in a beaker of warm water kept at about 55-70°C

by a heating mantle. When all the CH_2Cl_2 has distilled over (a little less than 10 mL will be collected due to evaporative losses; the temperature of the distillate should rise to 40°C , the boiling point of CH_2Cl_2 and then fall when the CH_2Cl_2 stops distilling. **Don't keep heating after this happens.**), remove the distillation apparatus.

Step 2: 2 -> 3a

Synthesis of 3a: The small amount of dense liquid remaining in the round bottom flask at this stage is **2 (2-bromo-3'-chloropropiophenone)**, which is a mild lachrymator (see Cautions above). Using a funnel, add to this flask, 10 mL of a 50:50 mixture of 5 mL t-butylamine and 5 mL of N-methylpyrrolidinone (NMP), and heat the flask in a $55\text{--}60^\circ\text{C}$ water bath with stirring for 10 minutes.

Isolation of an ether solution of 3a: The flask now contains **3a**, the free base form of bupropion. (**Although most of the lachrymatory 2 has been consumed in forming 3a, you should continue to work in the hood.**) There are two other substances besides **3a** in the flask: the excess t-butylamine and the NMP solvent. All three substances are soluble in ether, but the last two are also soluble in water, while **3a** as the free base is not soluble in water. We will take advantage of these solubility differences to isolate our product in pure form.

Transfer the contents of the flask to a separatory funnel, add 25 mL water and **10 mL of diethyl ether** and extract the mixture 3 times with 25 mL portions of ether, collecting and combining the ether extracts in a beaker. Remember to shake the separatory funnel well during each extraction and to wait for the layers to fully separate (**Caution! Ether is very volatile and pressure will develop!**). The ether layer(s) will be on top and contain your product, **3a**, while the aqueous layer will be at the bottom. The water layer contains the NMP solvent and excess t-butylamine; discard this layer, rinse the funnel with water, and return the combined ether extracts to the separatory funnel. Shake the ether solution five times with new 25 mL portions of water each time, allowing the layers to separate each time and then discarding the water layer. Transfer the ether solution to a clean, dry Erlenmeyer flask and remove any remaining water with anhydrous Na_2SO_4 . **You should add Na_2SO_4 until some of Na_2SO_4 is seen to swirl freely in the solvent without clumping.**

Step 3: 3a -> 3b

At this point your beaker contains a solution of the free base of bupropion, **3a**, in ether. Like most amines, the free base of this compound is soluble in ether and insoluble in water. But when **3a** is reacted with an acid, it will form a salt which will have opposite solubility properties, being insoluble in ether but soluble in water. Most pharmaceuticals are amines like bupropion, and they are nearly always marketed and administered in their salt form, usually the chloride. Following an ancient convention, amine chlorides in pharmacy and medicine are referred to as the "hydrochloride": e.g., morphine hydrochloride, fluoxetine (Prozac) hydrochloride. We will form the hydrochloride salt in a solvent mixture consisting mostly of ether, so that it will precipitate out in crystalline form.

Synthesis of 3b: Decant the ether solution through a funnel loosely plugged with cotton into a dry beaker chilled in an ice bath. The white powder remaining behind is the drying agent, Na_2SO_4 . Wash any residual **3a** from this powder by stirring it with enough fresh ether to cover it, allow it to settle, and decant the ether through the same cotton-plugged funnel into the beaker in the ice bath. You can then discard the cotton plug and the Na_2SO_4 desiccant. Using a Pasteur pipet, add a 2:10 vol:vol solution of conc. HCl: isopropyl alcohol dropwise with manual stirring to the chilled ether solution until the contents of the beaker are acid to pH paper (You will need ~10-12 ml of the HCl: isopropyl alcohol solution for this part). Test the pH by touching a stirring rod moistened with the solution to a small piece of pH paper. About half way to the equivalence point, sparkling white crystals of bupropion hydrochloride (white crystals), **3b**, will begin to form in the beaker. When the pH of the beaker is less than pH 3 enough acid has been added to your reaction.

Isolation of 3b: Cover the beaker loosely with a watch glass, and allow it to chill thoroughly for 5-10 minutes in the ice bath. Collect the crystals by gentle vacuum filtration, wash them twice with small portions of ether, and let them air dry. (**Do not force rapid stream of air through the crystals during vacuum filtration; if you do, they may develop a static electric charge**)

1. When the crystals are dry, determine the mass, calculate the percent yield, and determine the melting point of your product (3b).

Post Lab Questions

1. a) You should be able to see small bubbles forming when the bromine solution falls into the flask. If the humidity is high enough, you may notice a fog or fumes coming from the mouth of the flask as the reaction takes place. What fumes are being formed in this process?
- b) Alpha halogenations are acid-catalyzed; does this explain why this reaction (bromination step) is often slow at first but then proceeds rapidly? Explain your answer
2. a) The displacement of a bromine atom by an amine is usually an $\text{S}_{\text{N}}2$ process. Why would you expect that the reaction you are carrying out, using t-BuNH_2 , might be much slower than the same reaction using methyl amine?
- b) What other reactions would be expected to compete with the $\text{S}_{\text{N}}2$ reaction which forms bupropion?
- c) The choice of solvent in these $\text{S}_{\text{N}}2$ reactions can be very significant. Try to find a discussion of solvent effects in $\text{S}_{\text{N}}2$ reactions in your textbook, in the library, or the Web and explain what type of solvents are used in $\text{S}_{\text{N}}2$ reactions.

3. The HCl solution was made by mixing 2 mL concentrated HCl (12.0 M) with 10 mL isopropyl alcohol. Assuming there is no contraction or expansion of volume on mixing, what is the molarity of the resulting solution?

For Post-Lab Discussion:

Interpret your IR Spectrum by drawing the structure of your product on the spectrum and assigning the key features of the spectrum to functional groups in the molecule.

Cleaning Up:

The aqueous extracts can be washed down the drain with lots of COLD water. Discard the ether filtrate in the appropriate waste container in the hood.

Literature Cited

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