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

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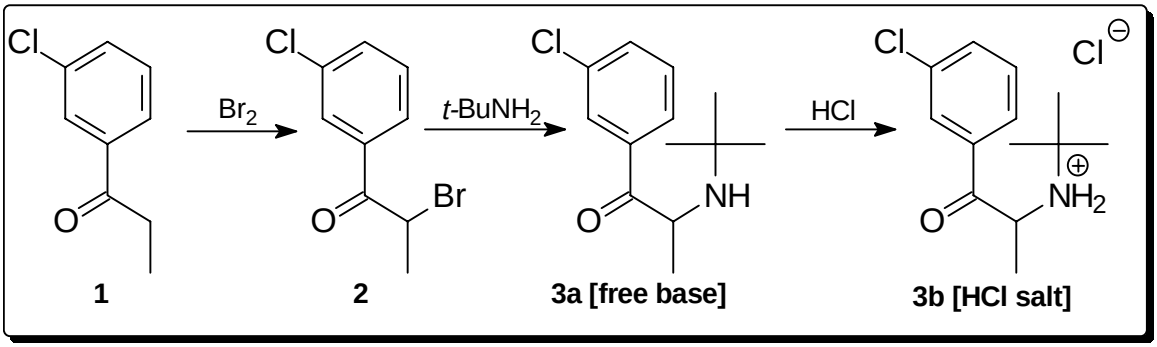
[The following document consists of two parts: the Student Instructions, pp. 1-3, and the Guide for the Instructor, pp. 4-22. Notes in the Student Instructions which are preceded by "Ins" are notes for the Instructor and can be found at the end of the Guide for the Instructor, on pp. 20-21. Those notes preceded by "Student Notes" are for the student and can be found at the end of the Student Instructions on p. 3.]

Student Instructions

Precautions: *Wear gloves 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 ➜ 3a**), do not try to clean the spill but tell your instructor immediately (Ins 1); the reaction mixture at this stage contains intermediate* **2**, *which is a lachrymator (irritates eyes and causes tears like*



onions) .

[1 ➜ 2] Put 1.0 g (5.9 mmol) *m*-chloropropiophenone, **1**, in a 50 mL round-bottom (RB) flask, add 5.0 mL dichloromethane, CH_2Cl_2, and a magnetic stirbar and stir until the solid is dissolved. Clamp the flask in the hood and attach a 50 mL pressure-equalizing dropping funnel. 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 RB. 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 rapidly disappear, and the RB 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

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so that the color of the bromine has disappeared before the next drop is added *(Student Note 1; Ins 2)*.

After all the bromine has been added, remove the dropping funnel and insert a simple distillation apparatus. Distill the solvent from the reaction mixture by placing the stirred RB in a heated (55-60 °C) water bath. When all the dichloromethane has distilled over (a little less than 10 mL will be collected due to evaporative loses; the temperature of the distillate should rise to 40 °C, the bp of dichloromethane), remove the distillation apparatus *(Ins 3)*.

[2 ➜ 3a] The small amount of dense liquid remaining in the flask at this stage is **2** (2-bromo-3′-chloropropiophenone), which is a mild lachrymator (see *Precautions* above). Using a funnel, add to the flask 10 mL of a 50:50 mixture of *t*-butylamine and *N*-methylpyrrolidinone (NMP), and heat the (unstoppered) flask in a 55-60 °C water bath with stirring for 10 minutes *(Student Note 2)*.

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. 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 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 tap water, and return the combined ether extracts to the separatory funnel. Shake the ether solution five times with 25 mL portions of water, 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 by stirring it in the beaker with anhydrous K_2CO_3. You should add K_2CO_3 until new material swirls freely in the solvent without clumping.

[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.

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, K_2CO_3. Stir this powder 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 K_2CO_3 desiccant.

Using a Pasteur pipet, add a 20:100 v:v 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 *(Ins 4)*. A few pipets-full will be needed; test the pH by touching a stirring rod moistened with the solution to a small piece of pH paper moistened with water *(Student Note 3)*.

About half way to the equivalence point, sparkling white crystals of bupropion hydrochloride, **3b**, will begin to form in the beaker. When the pH of the beaker is < 3 enough acid has been added. 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 a rapid stream of air through the crystals during vacuum filtration; if you do, they may develop a static electric charge, and when approached with a spatula will leap around the bench like Mexican jumping beans.)

When the crystals are dry, determine the mass and calculate the percent yield. Your instructor may wish you to determine the mp and/or run a TLC of your product *(Ins 5)*.

Student Notes

Note 1. You should be able to see small bubbles forming where the bromine solution falls into the flask; what do you think these are? 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 is this? Alpha halogenations are acid-catalyzed; does this explain why this reaction is often slow at first but then proceeds rapidly?

Note 2. The displacement of a bromine atom by an amine is usually an S_N2 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? What other reactions would be expected to compete with the S_N2 reaction which forms bupropion? The choice of solvent in these reactions can be very significant. Try to find a discussion of solvent effects in S_N2 reactions in your textbook, in the library, or the Web.)

Note 3. The HCl solution was made by mixing 20 mL concentrated HCl (12.0 M) with 100 mL isopropyl alcohol. Assuming there is no contraction or expansion of volume on mixing, what is the molarity of the resulting solution? How many mL should you need if all your starting material (5.9 mmol **1**) has been converted to **3a**?)