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

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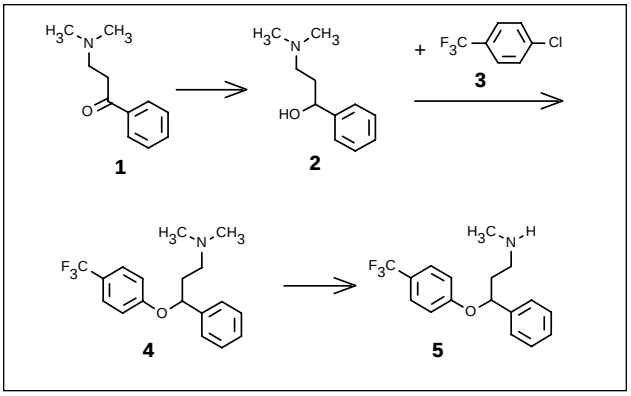
The majority of our organic chemistry students have as their goal a career in the health sciences, and they become more engaged in a laboratory experiment when it involves structures with a potential pharmacological application. With this in mind, we have devised a synthesis of **4** (see scheme), the immediate precursor of one of the most widely used (and most profitable) drugs of all time: (±)-*N*-methyl-3-(*p*-trifluoromethylphenoxy)-3-phenylpropylamine (**5**), an antidepressant with the nonproprietary name of fluoxetine and marketed by Eli Lilly under the trade name Prozac (*1*, *2*).

Prozac was introduced in 1986 as the first in a new class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), which are much less toxic than drugs in earlier antidepressant classes such as the tricyclics. There are a number of syntheses of Prozac reported in the literature, including enantioselective syntheses by Corey (*3*) and Sharpless (*4*). Our modified procedure relies on these methods and on Molloy's original patent (*5*), in which Prozac was formed from **4**, "*N*-methyl-Prozac" (NMP), using the von Braun demethylation reaction. NMP is of interest in itself because it is nearly as active an SSRI as fluoxetine (*5*), is the subject of an Eli Lilly patent in its own right (*6*), and is almost certainly a prodrug for Prozac, being metabolized to it in vivo.

The synthesis of **4** summarized here is used in the second semester of our introductory organic chemistry course. It requires two periods. In the first, shorter period, students reduce 3-dimethylaminopropiophenone, **1**, with $NaBH_4$ to form the alcohol **2**; in the second, longer session, this product is coupled in an S_NAr reaction with 4-chlorobenzotrifluoride, **3**, to form **4**, which is isolated as the oxalate salt.

In the literature procedures, the reduction of **1** is carried out using diborane. We use $NaBH_4$, which is much safer and equally effective. The patent procedure converts **2** to the alkyl chloride using $SOCl_2$ and couples this in a Williamson synthesis with *p*-trifluoromethylphenol. Since thionyl chloride is caustic and *p*-trifluoromethylphenol quite costly, we turned to the S_NAr reaction used by later workers (*3, 7*), which employs inexpensive **3**. Unfortunately, the best yields in this coupling required the use of sodium hydride. Substituting a solution of potassium *t*-butoxide in *t*-butyl alcohol lowered the yield but considerably increased the margin of safety. This and several other modifications finally resulted in a process that employs equipment and materials that are all readily available, relatively inexpensive, and reasonably safe.



This experiment naturally leads to a discussion of such topics as Mannich bases, of which **1** is a classic example (*8*); the mechanism for the S_NAr reaction (*9*); the cost-effectiveness of alternate routes to pharmaceuticals; the effect of chirality on pharmacological activity; and even the broader issue of whether antidepressant drugs are over- or underutilized in our society (*1*). It has been carried out by two classes of sophomores of about 20 students each. Student surveys at the end of the course indicated that the students found it intriguing and exciting to be practicing "real" pharmaceutical chemistry.

Literature Cited

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[W]Detailed procedures for this laboratory are available in *JCE Online* at *http://jchemed.chem.wisc.edu/Journal/issues/1998/Oct/abs1266.html.*