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# A Convenient Method for Preparing Enantiomerically Pure Norfluoxetine, Fluoxetine and Tomoxetine

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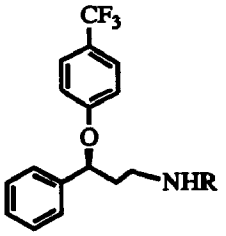
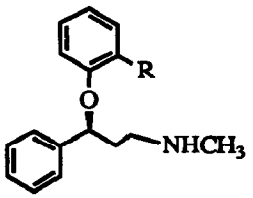
***Abstract***: A convenient synthesis for enantiomers of norfluoxetine, fluoxetine and tomoxetine is described. All final products were derived from a common intermediate, 3-phenyl-3-hydroxypropylamine.

Because of the important biological activity[1] of fluoxetine **1**,[2a-d] nisoxetine **4**,[2c] and tomoxetine **3**,[2a-c] methods for their enantioselective synthesis have received growing interest in recent years. These compounds are regarded as potent antidepressants. In addition, fluoxetine holds potential pharmaceutical applications for the treatment of alcoholism, anxiety, chronic pain and eating disorders.[3] In the course of synthetic studies directed toward the bulk scale preparation of the fluoxetine metabolite, *S*-norfluoxetine **2**, a general synthetic method was developed for preparing several members of this class of molecules.




**1** R = $CH_3$ *S*-fluoxetine
**2** R = H *S*-norfluoxetine




**3** R = $CH_3$ *S*-tomoxetine
**4** R = OMe *S*-nisoxetine

Our approach involves the addition of two common, readily available starting materials: benzaldehyde and acetonitrile. We envisioned a common intermediate, enantiomerically pure 3-phenyl-3-hydroxypropylamine, being derived in a few steps after nucleophilic addition of acetonitrile to benzaldehyde.

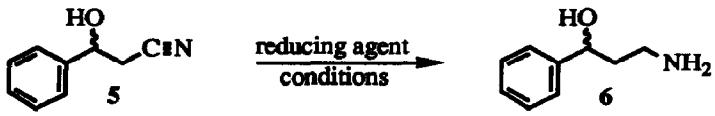
Thus, treatment of acetonitrile with 1.1 equivalent of base in THF followed by the addition of benzaldehyde resulted in clean addition to form hydroxynitrile **5**. Several different bases and reaction conditions were used in the process of optimizing the reaction for multi-gram preparations. Employing potassium *tert*-butoxide as base gave the best results. A brief summary is given in Table 1.

Table 1. Addition of acetonitrile to benzaldehyde


| Base | Conditions | Yield (%) |
|---|---|---|
| a) KO$^t$Bu | THF, -50 - 0°C, 3 h | 98 |
| b) *n*-BuLi | THF, -65°C, 22 h | 72 |
| c) NaOMe | THF, 23°C, 2 h | 66 |

Without further purification, hydroxynitrile **5** was reduced to primary amine **6**. Table 2 summarizes the results of reduction using several reducing agents and conditions. Recrystallization of racemic amino alcohol from 1:1 toluene / heptane provided a colorless crystalline solid, mp 56 °C, in good yield.

Table 2. Reduction of 3-phenyl-3-hydroxypropanenitrile



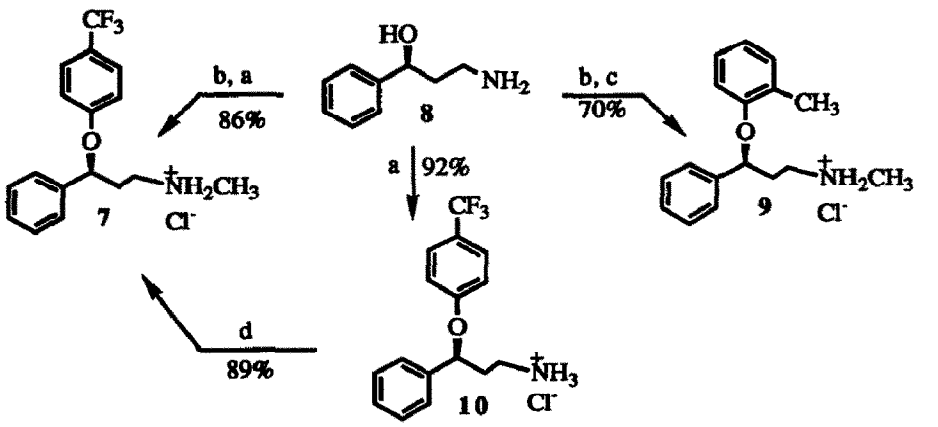

| Reducing agent | Conditions | Yield (%) |
|---|---|---|
| a) LAH | THF, 65°C, 2 h | 90 |
| b) $BH_3$•$SMe_2$ | THF, 65°C, 3 h | 96 |
| c) Raney® Ni | EtOH/$NH_3$ 30 psi, $H_2$ 170 psi, 90°C | 96 |

Enantiomerically pure amino alcohol **8**[4] was obtained by classical resolution with mandelic acid in the following manner. First, an absolute ethanol solution (four volumes) containing the racemic alcohol **6** was heated to 50 °C. An absolute ethanolic solution of mandelic acid [(*S*)-(+)-mandelic acid for isolating the *R* amino alcohol and (*R*)-(-)-mandelic acid for isolating the *S* amino alcohol] also at 50 °C was added to the amino alcohol solution. The mixture was stirred at 50 °C for 1.0 h then cooled to room temperature before refrigerating for 1 to 5 days for crystallization of the salt. To increase enantiomeric purity, the resulting mandelate salt was recrystallized twice using 10 volumes of absolute ethanol. Recovery of the free amine was accomplished by dissolving the mandelate salt in 5 N sodium hydroxide and extracting with dichloromethane. On average, an overall chemical yield of 24 % with enantiomeric purity [5] >96 % ee was obtained from this

classical resolution.

*S*-Norfluoxetine hydrochloride **10** (see Scheme 1) was prepared by first generating the sodium alkoxide of **8** with sodium hydride in DMSO[6] at 50 °C for 20 min. Next, 4-chlorobenzotrifluoride was added and the reaction mixture heated to 90 °C for 40 min. After cooling to room temperature, the solution was diluted with 2 N sodium hydroxide and extracted into toluene. An equal volume of heptane was added to the toluene/free base solution followed by 1 equivalent of gaseous hydrogen chloride to obtain *S*-norfluoxetine hydrochloride **10** as white needles in 92% overall yield.

**Scheme 1.**




a) NaH, DMSO, 4-chlorobenzotrifluoride, HCl. b) THF, methyl chloroformate, $NaHCO_3$, LAH. c) NaH, DMSO, 2-fluorotoluene, HCl d) 5 N NaOH, THF, methyl chloroformate, LAH, HCl.

In the preparation of fluoxetine and tomoxetine (Scheme 1), the amino alcohol **8** was monomethylated by first forming the carbamate followed by reduction with lithium aluminum hydride in refluxing THF to obtain the *N*-methyl amino alcohol in excellent yield.[7] Following the procedure used for arylating the *S*-norfluoxetine intermediate and salt formation, *S*-fluoxetine hydrochloride **7** was obtained as a colorless crystalline solid in >90% from (*S*)-*N*-methyl-3-phenyl-3-hydroxypropylamine. Alternatively, *S*-fluoxetine hydrochloride **7** was obtained in 89% from the monomethylation of *S*-norfluoxetine free base using similar conditions used for methylating amino alcohol **8**. Although tomoxetine **3** has been prepared from *N*-methyl-3-phenyl-3-hydroxypropylamine and *o*-cresol using Mitsunobu conditions,[8] this method was not desirable for large-scale synthesis. Instead we chose to circumvent the Mitsunobu procedure by using an arylation similar to the one used in the fluoxetine and norfluoxetine syntheses. Treatment of the alkoxide of (*S*)-*N*-methyl-3-phenyl-3-hydroxypropylamine with 2-fluorotoluene and subsequent salt formation gave modest chemical yields of *S*-tomoxetine hydrochloride **9**, however, epimerization of the chiral center was observed. This unusual racemization is currently being investigated. The *R* isomers of norfluoxetine, fluoxetine, and tomoxetine can also be prepared starting from (*R*)-3-phenyl-3-hydroxypropylamine.[9]

A convenient method for preparing the *R* or *S* isomers of fluoxetine, norfluoxetine and tomoxetine has been demonstrated. This practical, inexpensive synthetic method is considered to be significant in the preparation of fluoxetine and its congeners.

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4. A future publication will address the asymmetric synthesis of this intermediate.
5. Enantiomeric purity was determined by direct HPLC using a Chiralcel OB cellulose based column from Daicel Industries. The amino alcohol **8** was acylated with acetyl chloride under Schotten Baumann conditions with saturated sodium bicarbonate and methylene chloride prior to analysis. Chromatographic conditions were 10% isopropyl alcohol in hexane at flow rate of 1.5 mL/min. A column temperature of 40 °C was used and eluent was monitored at a wavelength of 215 nm.
6. Unlike similar reactions ( see reference 1), *N,N*-dimethylacetamide (DMAC) was not an appropriate solvent for this reaction since the primary amine was acylated during the arylation. Ten to 15% of the acetamide by-product was isolated. The problem was eliminated by switching to methyl sulfoxide (DMSO).
7. The Eschweiler-Clarke procedure and related methylation of amines are generally either ineffective in amine monomethylation or they afford very poor yields. For a review see Moore, M. L. *Org. React.* **1949**, *5*, 301.
8. Mitsunobu, O. *Synthesis.* **1981**, 1. See also reference 1.
9. Satisfactory analytical and spectral data were obtained for all compounds reported.

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