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SYNTHESIS OF *R*- AND *S*- FLUOXETINE, NORFLUOXETINE AND RELATED COMPOUNDS FROM STYRENE OXIDE†

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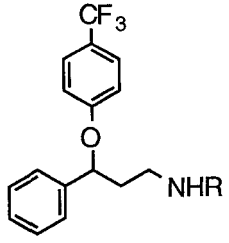
Abstract: A facile, high yield synthesis of *R*-- or *S*--fluoxetine and norfluoxetine is described. This synthetic route utilizes readily available starting materials.

Previously we disclosed a convenient method for preparing the enantiomers of (**1**) and its congeners.[1] That synthetic approach used readily available starting materials and a classical resolution. In connection with our continued efforts to develop new synthetic methods for fluoxetine analogs,[2] we report herein a new synthesis for *R* -or *S* -fluoxetine and one of its metabolites, *S*-norfluoxetine (**2**).



1. R = CH_3, fluoxetine

2. R = H, norfluoxetine

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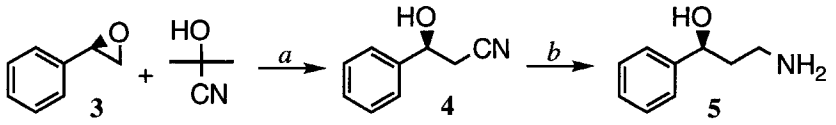
A key feature of our approach is utilization of enantiopure styrene oxide which is a readily available as starting material. Incorporation of the amine functionality early in the synthesis via cyanide addition followed by reduction affords the optically pure penultimate **5**. Arylation by nucleophilic aromatic substitution provides norfluoxetine. *S*-norfluoxetine was then converted to fluoxetine by *N*-methylation.

Regioselective epoxide ring opening with cyanide, a latent amine



3 4 5

a) Et_3N, THF b) $BH_3 \bullet S(CH_3)_2$, THF

functionality, was achieved in 90% yield by simply treating (*R*)-styrene oxide (**3**) with acetone cyanohydrin in the presence of triethylamine (equation).[3] Reduction of nitrile **4** with borane-methyl sulfide complex provided primary amine **5**. This key intermediate was then used to prepare optically active *S*-fluoxetine and *S*-norfluoxetine.

Attempts to arylate 3-phenyl-3-hydroxypropylamine (**5**) with 4-chloro-benzotrifluoride using sodium hydride / *N,N*-dimethylacetamide (DMAC)[4] gave the desired *O*-arylated product along with significant amounts of the *N*-acylated byproduct arising from interaction of the solvent, DMAC and the primary amine. Based on this observation, we conclude that the primary amine reacts much more readily with the solvent than the secondary amine, *N*-methyl-3-phenyl-3-hydroxypropylamine. The acetylation problem was avoided by substituting DMSO for DMAC as solvent.

In addition, the choice of base also had an impact on the optical purity of the final product. During development of this step for large scale preparation, several bases were evaluated using DMSO as solvent at 90 °C (see Table). Based on the survey, when potassium alkoxides were generated, epimerization of the final product was observed. For example, when *S*- 3-phenyl-3-hydroxypropyl-amine with an optical purity >99% was reacted with potassium *t*-butoxide as base in DMSO and 4-chlorobenzotrifluoride as acylating agent, the resulting product had an optical purity of only 16.6% ee. Very little, if any, epimerization

Table: Effect of Bases on Optical Purity During Arylation

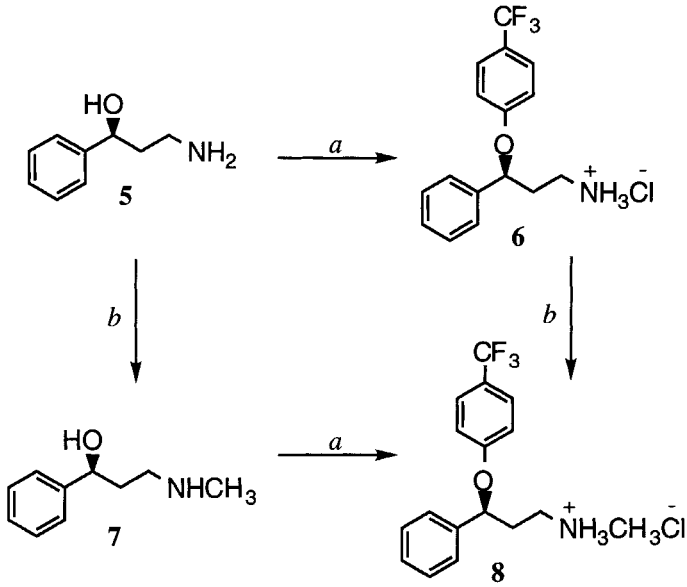
Base	Conditions	Yield	Chiral Purity (%ee)
NaH	1 hr, 90°C	>90	99
NaOH	20 h, 90°C	71	98.4
KOH	8 h, 90°C	78	88.4
KOBu	1 h, 90°C	84	16.6

was observed when sodium alkoxides were generated. The effect of acids on racemization of dissimilar systems have been well documented;[5] however, no formal evaluation of base induced epimerization has been undertaken to our knowledge.

Thus, *S*-norfluoxetine was prepared in 90% yield by alkoxide formation of **5** with sodium hydride/DMSO and arylation with 4-chlorobenzotrifluoride. Treatment of the free base with hydrochloric acid afforded the amine hydrochloride salt as a white crystalline solid (**Scheme**). To obtain fluoxetine, **5** was first methylated by carbamate formation with methyl chloroformate followed by reduction with LAH. Following similar arylating and salt forming conditions of

S-norfluoxetine, *S*-fluoxetine hydrochloride was obtained in 90% yield. Alternatively, fluoxetine was obtained in 90% yield by methylating *S*-norfluoxetine after first forming the methyl carbamate followed by subsequent reduction with LAH.

Scheme



a) NaH/DMSO, 4-ClC$_6$H$_4$CF$_3$, HCl; b) ClCO$_2$Me, LAH

This novel approach to either *R*-or *S*-fluoxetine and its analogs compliments existing methods. However, unlike previous routes, our method takes advantage of readily available, enantiomerically pure starting material.

EXPERIMENTAL

(*S*)-3-phenyl-3-hydroxy propanenitrile (4). To a stirred solution of (*R*)-styrene oxide (10.0 g, 83.0 mmol) in THF (70 mL) was added acetone cyanohydrin (7.78

g , 91.5 mmol) followed by triethylamine (9.3 g, 91.5 mmol). The resulting reaction mixture was heated to reflux for 18 h while monitoring by TLC (silica, 1:1 ethyl ether/petroleum ether, UV). After refluxing, the reaction mixture was cooled to room temperature and the solution concentrated to a residue. The residue was dissolved in KOH (100 mL) and extracted with ethyl ether (2X100 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Flash column chromatography (silica, 1:1 ethyl ether/petroleum ether) gave purified (*S*)-3-phenyl-3-hydroxypropanenitrile (10.4 g, 85.2%) as a colorless oil: IR (CH_2Cl_2) 3605, 3023, 2270, 1603, 1495, 1455, 1414, 1224, 1085, 1057 $^{-1}$cm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.35 (m, 5H), 4.9 (t, J = 6.16 Hz, 2H), 3.3 (br s, 1H), 2.6 (d, J = 6.22 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 27.9, 69.8, 117.5, 125.4, 128.7, 141.12, 176.3; mass spectrum *m/z* (relative intensity) 147(M^+, 100), 138, 129, 107, 79, 51, 39; Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; O, 10.87. Found: C, 73.18; H, 5.88; N, 9.78.

(*S*) (-) -3-phenyl-3-hydroxypropylamine (5). Borane-methyl sulfide complex (10.0 M, 17.6 mL, 176.8 mmol) was slowly added to a THF (120 mL) solution of 3-phenyl-3-hydroxypropanenitrile (20.0 g, 136 mol) at room temperature. Methyl sulfide was then distilled from the reaction vessel and the resulting THF solution refluxed for 2.5 hr. After cooling to room temperature, methanolic hydrogen chloride (100 mL, 1.0 M) was added to the reaction mixture. Methanol and methylborate were removed by distillation and the reaction mixture neutralized with sodium hydroxide (20 mL, 5 N). At this stage, the reaction was concentrated to a residue and the residue dissolved in sodium hydroxide (50 mL, 5 N).

Extraction of the mixture with methylene chloride followed by concentration provided the crystalline product. Analytically pure material was obtained by recrystallization from toluene: mp = 56 °C; $[\alpha]^{25}_D$ -43.65° (c = 1, MeOH); IR ($CHCl_3$) 3715, 3610, 3397, 3236, 3010, 2926, 2873, 1469, 1435, 1220, 1087, 1062, 839 $^{-1}$cm; ^{1}HNMR ($CDCl_3$) δ 7.45-7.25 (m, 5H), 4.90 (dd, J = 3.6Hz, 1H), 3.08-2.78 (m, 5H), 1.65-1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 145.27, 128.26, 127.00, 125.70, 74.91, 40.31, 40.27; mass spectrum *m/z* (relative intensity) 152 (M^+, 100), 151, 132, 115, 106, 84, 77; Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26; O, 10.58. Found: C, 71.78; H, 8.97; N, 9.31.

(*S*) (+) -Norfluoxetine Hydrochloride (6). The alkoxide of (*S*)-3-phenyl-3-hydroxypropylamine (10.24 g, 67.8 mmol) was generated with sodium hydride (60% in mineral oil, 4.0 g, 101.7 mmol) in DMSO (30 mL) at 55 °C for 30 min under a nitrogen atmosphere. 4-Chlorobenzotrifluoride (18.3 g, 101.7 mmol) was then added to the reaction mixture and the resulting solution heated to 90 °C for 1 h. The reaction mixture was cooled to room temperature and diluted with sodium hydroxide (2 N, 100 mL). Toluene (2X40 mL) was used to extract the product from the hydroxide solution. Heptane (110 mL) was then added to the combined extracts before gasing with HCl (2.35 g, 64.4 mmol) to form the hydrochloride salt (excess HCl gas leads to decomposition)[6]: mp 131 °C; $[\alpha]^{25}_D$ = +36.3° (c = 2, MeOH); IR (KBr) 2972, 2884, 1613, 1517, 1454, 1333, 1312, 1253, 1179, 1161, 1068, 1059, 1010, 928, 837, 701 cm^{-1}; ^{1}H NMR (300 MHz, DMSO D-6) δ 8.28 (br s, 3H), 7.51 (d, J = 8.54 Hz, 2H), 7.45-7.38 (m, 5H), 7.03 (d, J = 8.51 Hz, 2H), 5.70 (dd, 7.26 Hz, 5.4 Hz, 1H), 2.90(t, J = 7.29 Hz, 2H), 2.4-2.1 (m, 2H); ^{13}C NMR (300 MHz, DMSO-d6) δ 35.4, 35.6, 76.4, 116.3, 125.9,

126.7, 126.75, 128.0, 128.7, 140.1, 160.2; mass spectrum, *m/z* (relative intensity) 296 (M^+, 100), 251, 183, 136, 135, 134, 118; Anal. Calcd for $C_{16}H_{17}ClF_3NO$: C, 57.93; H, 5.16; Cl, 10.69; F, 17.18; N, 4.22. Found: C, 58.20; H,, 4.91; Cl, 10.59; F, 16.94; N, 4.15.

References and Notes

†)Part of this work was presented at the 204th American Chemical Society National Meeting, ORGN 81 on "Regioselective Ring Opening of Epoxides with Acetone Cyanohydrin. Application to the Synthesis of (*S*)-Norfluoxetine," August 23-28, **1992**, Washington, DC.

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