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S_NAr Reactions of 2-Haloarylsulfoxides with Alkoxides Provide a Novel Synthesis of Thiotomoxetine

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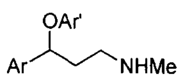
Abstract: A five step synthesis of thiotomoxetine (**2**) is described. Installation of the aryl ether was accomplished using a highly efficient S_NAr fragment coupling between amino alcohol (**4**) and a 1-halo-2-methylsulfinylbenzene (X = F or Cl) followed by a selective reduction of the arylsulfoxide moiety.

Various substituted 3-aryloxy-3-aryl-1-propanamines (**1**) are potent and selective inhibitors of neuronal norepinephrine and serotonin uptake.[1] Many of these compounds are useful therapies for the treatment of a variety of illnesses including depression, obesity, obsessive compulsive disorder, attention deficit disorder, urinary incontinence and alcoholism. The most notable members in this family of compounds are fluoxetine (Ar' = *p*-CF_3Ph) and (*R*)-tomoxetine (Ar' = *o*-MePh). Over the past decade, several methods for the synthesis of these important biological targets have appeared in the literature. Recently, a new member of this class of compounds, (*R*)-thiotomoxetine (**2**), was chosen as a candidate for clinical development. Thiotomoxetine has been prepared on small scale using standard Mitsunobu chemistry, but this route is not amenable to scale-up.[2] We report herein an efficient and scaleable process for the synthesis of optically pure **2**.



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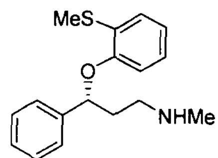

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Nucleophilic aromatic substitution (S_NAr) coupling between an amino alcohol and a suitably activated haloaromatic is one of the most efficient methods for installation of the aryloxy moiety in these compounds.[3,4] For example, (*S*)-fluoxetine has been prepared in 96% yield and >99% ee by coupling (*S*)-N-methyl-3-hydroxy-3-phenylpropanamine and *p*-chloro-trifluoromethyltoluene.[5] However, moderate yields and extensive racemization was observed with less activated substrates (e.g. *o*-fluorotoluene).[6] There is one report in the literature in which 2-fluorothioanisole was coupled with achiral alcohols, but the forcing conditions required were not applicable to a synthesis of optically active thiotomoxetine.[7]

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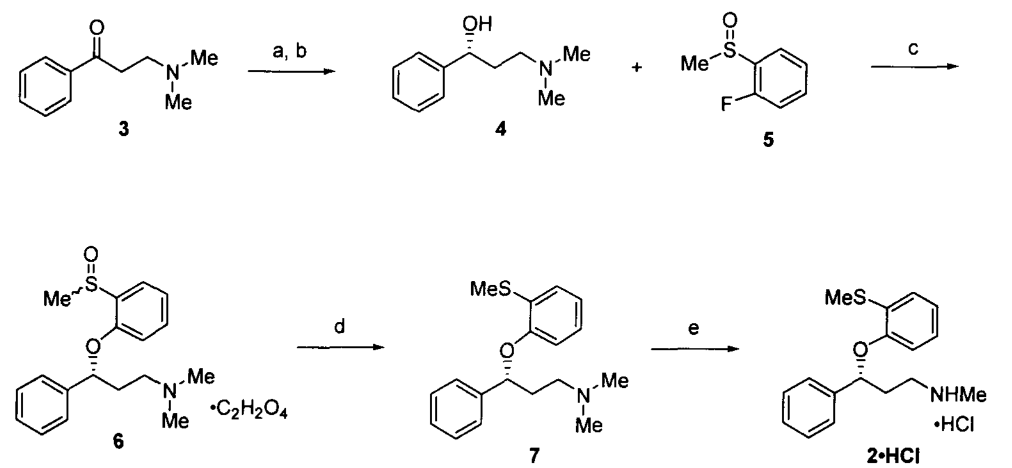
We envisioned that facilitation of the S_NAr process could be accomplished by conversion of the thiomethyl substituent in 2-fluorothioanisole to an electron withdrawing group such as a methylsulfoxide or sulfone. This strategy requires subsequent reduction of the activating group to provide the desired methylsulfide. The difficulty in reduction of aryl sulfones to the corresponding sulfides prompted us to focus on the S_NAr coupling of a 2-haloarylsulfoxide with an optically pure amino alcohol.[8] This strategy is outlined in scheme 1.

Scheme 1



Reagents: (a) $NaBH_4$, H_2O, 0 °C. (b) *i.* (*R*)-(-)-Mandelic acid, EtOAc, 77 °C to -15 °C. *ii.* NaOH, MTBE. (c) *i.* NaH, DMSO, 50 °C. *ii.* oxalic acid, MeOH, 0 °C. (d) TMSCl, DMS, Py, CH_2Cl_2, 23 °C. (e) *i.* Cl_3CH_2OCOCl, Proton-Sponge, toluene, 70 °C. *ii.* 5N NaOH, DMSO, 23 °C. *iii.* HCl, EtOAc, 23 °C.

Preparation of **4**[9] was achieved through a sodium borohydride reduction of commercially available 3-dimethylaminopropiophenone hydrochloride **3** followed by an efficient classical resolution with (*R*)-(-)-mandelic acid in EtOAc (43% yield, 94% ee).[10] The optical purity could be upgraded to >99% ee through recrystallization of the intermediate mandelate salt in acetone/MTBE. However, 94% ee **4** provided thiotomoxetine (**2**) in >99% ee after subsequent isolations and crystallizations. The S_NAr fragment coupling between the sodium alkoxide of **4** and fluorosulfoxide[11] **5** proceeded smoothly at 50 °C in DMSO providing **6** in 90% isolated yield as a 1:1 mixture of diastereomers at the sulfoxide center.[12] Notably, *no racemization* was observed under these mild reaction conditions. The mixture of sulfoxides **6** was reduced using a representative protocol involving trimethylsilylchloride and dimethylsulfide in CH_2Cl_2 at 23 °C to provide the arylsulfide **7** in 95% yield and 99% ee.[13] Other reduction conditions were investigated but led to decomposition (i.e. BH_3•THF) or no reaction (i.e. DIBAL). Dealkylation of the tertiary amine was accomplished by treatment of **7** with 2,2,2-trichloroethyl chloroformate and in situ hydrolysis of the carbamate with NaOH to give **2** which was isolated as its HCl salt in 75% yield and >99.5% ee.

Sulfoxide activation represents a novel method for facilitation of the S_NAr reaction, and we, therefore, sought to establish the scope of its applicability. The results of this study are shown in the Table. Reactions of primary and secondary sodium alkoxides with both the fluoro- and more economical chlorosulfoxides provided high yields (82-97%) of the desired substitution products (entries 1-4). However, the more hindered tertiary alkoxides gave low yields of the desired product (<10%) along with substantial decomposition (entries 5 and 6). Phenoxide was also found to be a poor coupling partner. No reaction was observed even at elevated temperatures (entry 7) .

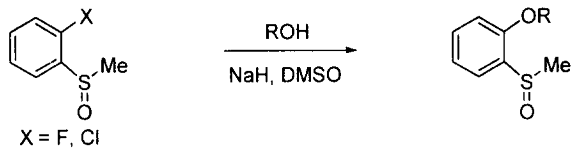


Table: Scope of alkoxy-S_NAr reactions

Entry	ROH	X	Temperature (°C)	Time (h)	Yield (%)
1	MeOH	F	25	10	97
2	MeOH	Cl	75	16	91
3	**4**	F	50	8	90
4	**4**	Cl	75	12	82
5	*t*-BuOH	F	25-50	24	< 10%
6	*t*-BuOH	Cl	75	16	NR
7	PhOH	F	120	48	NR

Sulfoxide activation in aromatic substitution chemistry has been demonstrated in a concise synthesis of thiotomoxetine **2** which eliminates racemization and avoids Mitsunobu chemistry. This synthesis features an efficient reduction/resolution for the installation of the asymmetric center in amino alcohol **4** along with a high yielding S_NAr fragment coupling of this amino alcohol with 2-halosulfoxide **5** with no racemization observed.

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References and Notes

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8. For use of 1-fluoro-4-methylsulfinylbenzene in a S_NAr coupling see: UK Patent Application GB 2 060 622.
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10. A representative procedure: To a well stirred solution of 3-dimethylaminopropiophenone hydrochloride (21.4 g, 0.100 mol) in 600 mL of H_2O at 0 °C was added sodium borohydride (4.80 g, 0.127 mol) in small portions. The solution was warmed to 23 °C over 2 h and was treated sequentially with acetone, concentrated HCl (25 mL) and 5N NaOH (50 mL). The aqueous solution was extracted with CH_2Cl_2 (3X500 mL). The combined organics were dried over 3A molecular sieves, filtered and concentrated to a volume of 40 mL. This mixture was solvent exchanged into EtOAc (final volume of 40 mL) and treated with a solution of (*R*)-(-)-mandelic acid (7.40 g, 0.048 mol) in 140 mL of EtOAc. The reaction mixture was heated to reflux for 1 h and cooled to -15 °C over 1 h. The solvent was removed via cannula and this process was repeated three times with 100 mL of EtOAc. The product was filtered and dried *in vacuo* at 40 °C to provide 14.19 g (43%, 94% ee) of the mandelic acid salt. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48-7.19 (m, 10H), 4.94 (s, 1H), 4.74 (dd, J = 7.2, 5.4 Hz, 1H), 3.10-2.95 (m, 2H), 2.60 (s, 6H), 1.99-1.94 (m, 2H). ^{13}C NMR (d_6-DMSO, 62 MHz) δ 175.4, 145.5, 142.7, 128.1, 127.6, 126.9, 126.6, 126.5, 125.7, 73.3, 70.2, 54.8, 42.8, 34.2; IR ($CHCl_3$) 3400, 3010, 1604, 1494, 1453, 1352, 1087, 1059 cm^{-1}; Anal. Calcd. for $C_{19}H_{25}NO_4$: C 68.86; H, 7.60; N, 4.23. Found: C 68.58; H, 7.34; N, 4.38.
11. Sulfoxide **5** was prepared by mono-oxidation of 2-fluorothioanisole with *m*-CPBA in CH_2Cl_2.
12. A representative procedure: To a stirred suspension of NaH (60 % oil dispersion, 0.811 g, 20.27 mmol) in DMSO (7.2 mL) was added a solution **4** (3.63 g, 20.27 mmol) in 1.8 mL DMSO over 15 min. The resulting mixture stirred for 10 min and a solution of sulfoxide **5** (3.52 g, 22.29 mmol) in 1.8 mL of DMSO was added. The reaction mixture was heated to 50 °C and stirred for 8 h. The reaction was then cooled to RT and added to a quench solution consisting of H_2O (32 mL) and EtOAc (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (10 mL). The combined EtOAc layers were washed with 20 mL each of H_2O and saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in 50 mL of MeOH and was treated with a solution of oxalic acid (1.83 g, 20.27 mmol). The solution was concentrated to approximately 10 mL and 20 mL of MTBE was added. The white precipitate was collected by filtration, washed with 10 mL of MTBE and dried *in vacuo* at 40 °C to give 7.43 g (90%) of sulfoxides **6** as a 1:1 mixture of diastereomers. ^{1}H NMR (d_6-DMSO), 300 MHz): δ 7.70-6.70 (m, 7H), 5.75 (m, 0.5H), 5.52 (m, 0.5H), 3.20-3.10 (m, 2H), 2.84 (s, 1.5H), 2.79 (s, 1.5H), 2.73 (s, 6H), 2.45-2.15 (m, 2H). ^{13}C NMR (d_6-DMSO, 62 MHz) δ 164.7, 152.6, 152.3, 139.8, 139.4, 134.0, 133.9, 131.8, 131.7, 128.9, 128.7, 128.3, 128.2, 128.1, 126.1, 125.9, 125.6, 124.9, 124.0, 121.7, 121.6, 114.0, 113.4, 77.8, 76.7, 53.6, 53.4, 42.2, 41.6, 41.1, 32.2, 32.0; Anal. Calcd. for $C_{20}H_{25}NO_6S$: C 58.95; H, 6.18; N, 3.44. Found: C 58.82; H, 6.34; N, 3.26.
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