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An Investigation on Key Parameters that Influence the Synthesis of (*S*)-(+)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine: A Key Intermediate for Duloxetine

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Abstract:

This document highlights the systematic study of influencing factors such as temperature, base, catalyst, and solvent volume in the synthesis of (*S*)-(+)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine oxalate 11a, without affecting the chiral purity.

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Introduction

Duloxetine[1,2] and the related class of compounds such as fluoxetine, tomoxetine, etc. are important for treating psychiatric disorders. Fluoxetine is selective inhibitor of serotonin in serotonergic neurons; tomoxetine and nisoxetine are selective inhibitors of norepinephrine in noradrenergic neurons, while duloxetine is a dual inhibitor[3] of serotonin (5-HT) and norepinephrine (NE) reuptake and thus has a better pharmacological profile as an antidepressant drug.

Serotonin and norepinephrine neurotransmitters are intimately involved in a number of physiological and behavioral processes, suggesting that duloxetine (with the ability to produce robust increases of extracellular serotonin and norepinephrine levels) is not only a highly efficient antidepressant agent for treating psychiatric disorders but also can be used for treating other symptoms such as alcoholism, stress urinary incontinence[4] (SUI), fatigue, stroke, intestinal cystitis, obsessive compulsive disorder, panic disorder, sleep disorder, sexual dysfunction, etc.

Discovery[5] of the synthesis of duloxetine hydrochloride **1** is reported in Scheme 1, in which 2-acetyl thiophene **2** is reacted with *N*,*N*-dimethylamine hydrochloride **3** and paraformaldehyde **4** in the presence of conc. hydrochloric acid to yield 3-(dimethyl amino)-1-(thiophen-2-yl)propan-1-one hydrochloride **5**, which upon reduction with sodium borohydride in the presence of ethanol affords 3-(dimethyl amino)-1-(thiophen-2-yl)propan-1-ol **6**. Resolution of **6** with (*S*)-(+)-mandelic acid affords diastereomeric salt **7**, which on hydrolysis with sodium hydroxide affords (*S*)-alcohol **8**. The key intermediate **11** in the synthesis of duloxetine hydrochloride involves the condensation of **8** with 1-fluoronaphthalene **9** in the presence of sodium hydride/dimethylsulfoxide to yield (*S*)-(+)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine **10**, which on hydrolysis with water affords (*S*)-(+)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propylamine **11**. Demethylation of **11** with phenylchloroformate in the presence of diisopropylethylamine, followed by salt formation with conc. hydrochloric acid[6,7f] in the presence of ethyl acetate afforded duloxetine hydrochloride **1**.

A similar synthetic approach is reported in the literature for the key intermediate **11**, which involves in situ generation using different bases in combination with catalysts. However, the given selectivity could not be reproduced in our laboratory when the reaction was conducted under the literature conditions.[7a−f] The usage of a hazardous base such as NaH in these processes made them commercially nonattractive. In the recent modification[8] of this current process we have conducted the condensation reaction in the presence of a catalytic amount of phase transfer catalyst (PTC) to enhance the enantioselectivity of the desired *S*-isomer **11** to more than 99%.

Now we have taken up a comprehensive study of this condensation reaction on enantioselectivity by employing different types of commercially available bases in the presence of various catalysts in different solvents and at different temperatures.

Results and Discussion

It is known from the literature that there is a significant change in the reactivity of different types of bases towards a particular functional group.[7a−f] During the development of duloxetine, we have screened several types of bases and found that sodium hydroxide in the presence of PTC in dimethylsulfoxide works well in this reaction, resulting in more than 99% enantioselectivity of *S*-isomer **11a.** The formation of desired *S*-isomer **11a** is extremely poor in other solvents such as diglyme, toluene, and a mixture of solvents. The effects of temperature, base, catalyst, and solvent volume on the enantioselectivity of **11a** are shown in Table 1.

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Scheme 1. **Precedented synthetic approach**

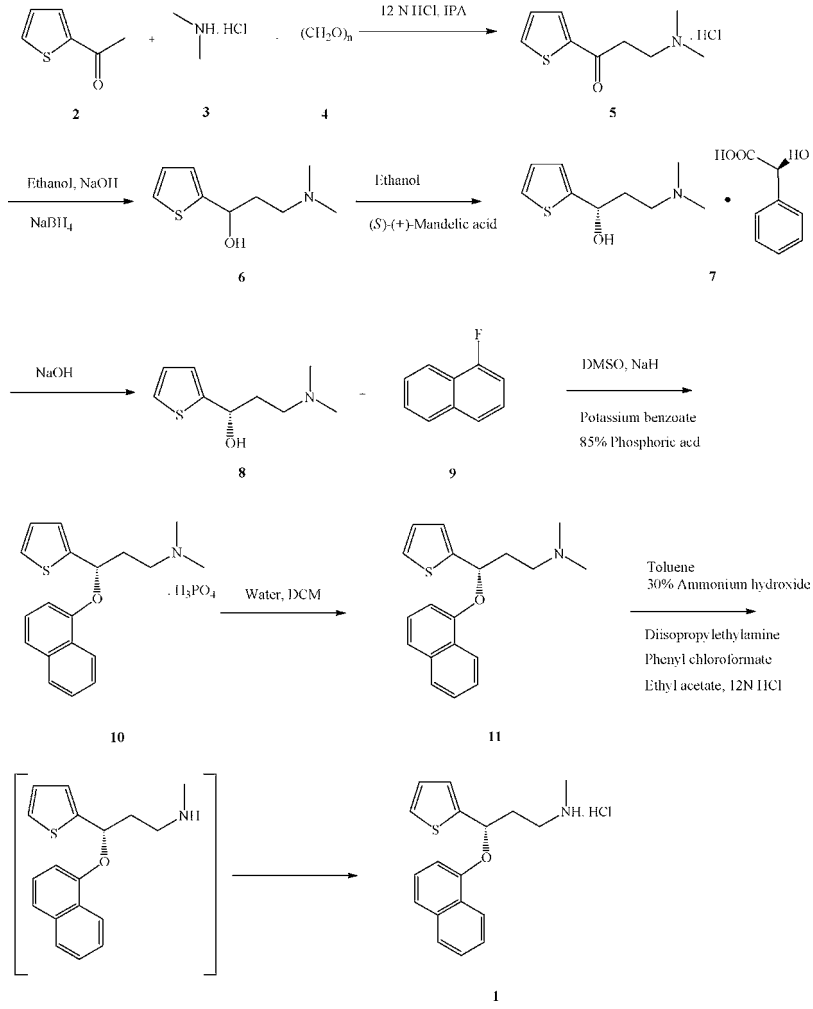

Table 1. **Effect of base, solvent, catalyst and temperature**

								ratio by HPLC		ratio by chiral HPLC	
entry	solvent mixture	solvent (v)	base	catalyst	time (h)	temp (°C)	yield (%)	**11a**	**10**	**11a**	**11b**
1	DMSO	3	KOBt	TBAB	8−9	90	72.0	98.9	ND	57.1	42.9
2	Toluene: DMSO	15:1	KOBt	TBAB	48−50	60−65	39.8	45.2	48.2	39.3	60.7
3	Toluene: DMSO	5:5	NaOH	TBAB	50−55	60−65	25.0	68.2	25.8	52.8	47.2
4	Diglyme	11	KOH	−	3−6	115−120	42.6	89.7	8.7	99.6	0.4
5	DMSO	5	NaH	KI	3−5	60−65	39.7	89.5	6.6	98.9	1.1
6	DMSO	10	NaOH	KI	50−55	60−65	77.3	97.6	ND	91.9	8.1
7	DMSO	10	NaOH	TBAB	50	60−65	66.9	96.6	ND	95.9	4.1
8	DMSO	10	NaOH	KI	50−55	60	65.5	97.0	0.6	94.8	5.2
9	DMSO	10	NaOH	PhCOOK	40−45	60−65	73.8	99.0	ND	86.1	13.9
10	DMSO	5	NaOH	KI	65−70	50−55	49.1	83.7	3.6	99.7	0.3
11	DMSO	5	NaOH	KI	60−65	55−60	48.9	86.7	3.7	99.2	0.8
12	DMSO	5	NaOH	KI	60−65	60	58.6	93.6	1.2	98.1	1.9
13	DMSO	5	NaOH	KI	50−55	60−65	78.9	97.4	ND	96.5	3.5
14	DMSO	5	NaOH	KI	40−45	65−70	68.3	96.4	ND	96.2	3.8
15	DMSO	5	NaOH	TBAB	50−55	60−65	55.8	99.2	ND	99.7	0.3

In the course of synthetic development, it becomes necessary to investigate parameters such as temperature, base, catalyst and solvent volume on the aromatic substitution reaction in duloxetine between a chiral secondary alkoxide and 1-fluoronaphthalene. From the standpoint of large-scale manufacturability, high enantioselectivity is necessary with complete reaction conversion. Initially, the reaction was conducted in dimethylsulfoxide in the presence of potassium tertiary butoxide at 90 °C (entry 1, Table 1), the complete conversion was observed in 8−9 h, but 42.9% of the undesired isomer **11b** was observed (i.e., racemization occurred). Reaction was also conducted in a mixture of solvents (toluene/dimethylsulfoxide) at 60−65 °C with different ratios (entries 2 and 3, Table 1), and the expected selectivity was not achieved. To increase the nucleophilicity of the alkoxide ion, potassium hydroxide was used in the presence of diglyme medium. The accelerated reaction rates were

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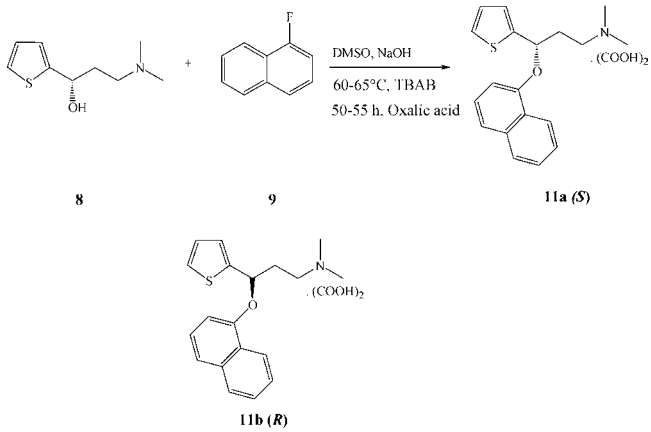
Table 2. **Screening of various amounts of TBAB**

entry	TBAB (v)	yield (%)	ratio by HPLC		ratio by chiral HPLC	
			11a	**10**	**11a**	**11b**
1	0.10	53.2	95.3	2.6	99.6	0.4
2	0.12	55.8	99.6	ND	99.7	0.3
3	0.14	56.4	99.4	ND	98.8	1.2

Scheme 2. **Synthesis of enantiomerically pure 11a**



8 **9** **11a (*S*)**

11b (*R*)

observed in these conditions, but the unreacted alcohol remained nearly 9% (entry 4, Table 1), which proved difficult to remove by crystallization.

However, literature reports have noted that, in substitution reactions of the electronically activated aromatic substrate reactions with either lithium, sodium or potassium methoxide, the addition of 1.0−4.0 molar equiv of either potassium iodide or potassium acetate accelerated the reaction rates.[9,10] Due to these interesting results, reactions were conducted in the presence of sodium hydroxide with potassium iodide at different temperatures but desired selectivity was not observed (entries 10−14, Table 1). By increasing solvent volume, did reduce the reaction times, production of the **11b** was ∼ 5−8% (entries 6 and 8, Table 1). Reaction with potassium benzoate instead of potassium iodide (entry 9, Table 1) afforded excellent yields and observed complete conversion of alcohol **10**, but undesired isomer **11b** was enhanced relative to the use of other catalysts.

On the basis of these experimental results, we found that entry **15** was good for reaction condition and also screened different amounts of TBAB (Table 2) to obtain the required enantioselectivity. We opted for the following ideal conditions for this process (Scheme 2): (i) DMSO is the ideal reaction medium, (ii) 5.0 equiv of NaOH, (iii) temperature at 60−65 °C, (iv) 0.12 volumes of TBAB, and (v) making oxalate salt. Further, a robust purification method was developed to purge the undesired *R*-isomer **11b**. The detailed purification procedure is mentioned in the Experimental Section.

In conclusion, we have studied the effects of temperature, base, catalyst and solvent volume on stereoselectivity of aromatic substitution in duloxetine. TBAB-catalyzed condensation of (*S*)-(−)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol **8** with 1-fluoronaphthalene **9** in the presence of sodium hydroxide/dimethylsulfoxide selectively furnished (*S*)-(+)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine as oxalate salt **11a**, a key intermediate used in duloxetine hydrochloride **1**.

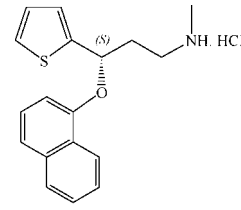


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Figure 1. **APIs structural framework.**

Experimental Section

The ^{1}H was recorded in DMSO at 300 MHz on a Varian Gemini 300 MHz FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on a HP-5989a LC−MS spectrometer. The solvents and reagents were used without any purification.

(*S*)-(+)-*N*,*N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propylamine Oxalate 11a. A mixture of sodium hydroxide (43.2 g, 1.08 mol) in DMSO (200 mL) was heated to 50−55 °C, stirred for 45 min and added (*S*)-(−)-3-dimethylamino-1-thiophen-2-yl-propan-1-ol (**8,** 40 g, 0.216 mol), TBAB (4.8 g, 0.015 mol) respectively. To this solution was added a mixture of 1-fluoronaphthalene (**9**, 47.35 g, 0.324 mol) in DMSO (40 mL) at 50−55 °C and heated about 65 °C, and stirred for 50−55 h. On completion of reaction (vide TLC), the solution was cooled to 15−20 °C and quenched with DM water (400 mL) followed by toluene (400 mL), and the mixture was stirred about 15 min. The organic layer was separated, and the aqueous layer was extracted with toluene (20 mL); the total organic layer was washed with saturated sodium chloride solution (2 × 80 mL). A mixture of separated organic layer and oxalic acid (21.39 g, 0.238 mol) was stirred for 1 h at 55−60 °C, cooled, and stirred about 1 h at 25−35 °C. The separated solid was filtered and washed with toluene (40 mL). The above wet solid and mixture of isopropyl alcohol/DM water (51.2 mL:12.8 mL) was stirred for 45 min at 25−35 °C, cooled, and stirred about 30 min at 10−15 °C. The solid was filtered and washed with chilled isopropyl alcohol (64 mL) and dried at 60 °C under high vacuum to constant weight to afford (*S*)-(+)-*N*,*N*-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propylamine as oxalate (**11a,** 52 g, 59.9%). MS (DIP) *m*/*z* 312.3 (free base, M + 1); Purity by HPLC 99.6%; Chiral HPLC 99.7% (**11b** 0.3%); IR (cm^{-1}) 3445, 2955, 1702, 1596, 1462, 1397, 1095, 720; ^{1}H NMR (300 MHz, DMSO) (δ): 2.08(m, 1H), 2.11 (s, 6H), 2.33 (m, 3H), 5.91 (dd, 1H), 6.96 (dd, 1H), 7.02 (d, 1H), 7.20 (dd, 1H), 7.31 (t, 1H), 7.41 (m, 2H), 7.50 (m, 2H), 7.82 (m, 1H), 8.24 (m, 1H).

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