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An Efficient Racemization Process of Tolterodine using Potassium *tert*-Butoxide in DMSO

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A novel racemization process was developed for the conversion of (*S*)-tolterodine, obtained as a byproduct during the resolution of racemic tolterodine, into racemic (*R*,*S*)-tolterodine. The process involves protection of the phenolic hydroxyl group with benzyl chloride, followed by racemization using potassium tert-butoxide in DMSO at 60-65 ºC. Subsequent debenzylation with Raney nickel afforded racemic tolterodine, which was resolved with L-(+)-tartaric acid to obtain tolterodine tartrate. The racemization of the undesired (*S*)-enantiomer enables its recycling into the resolution process, thereby reducing material loss and providing a practical approach for improving the yield of the desired (*R*)-tolterodine.

Keywords: Tolterodine, Racemization, DMSO, Potassium *tert*-butoxide.

INTRODUCTION

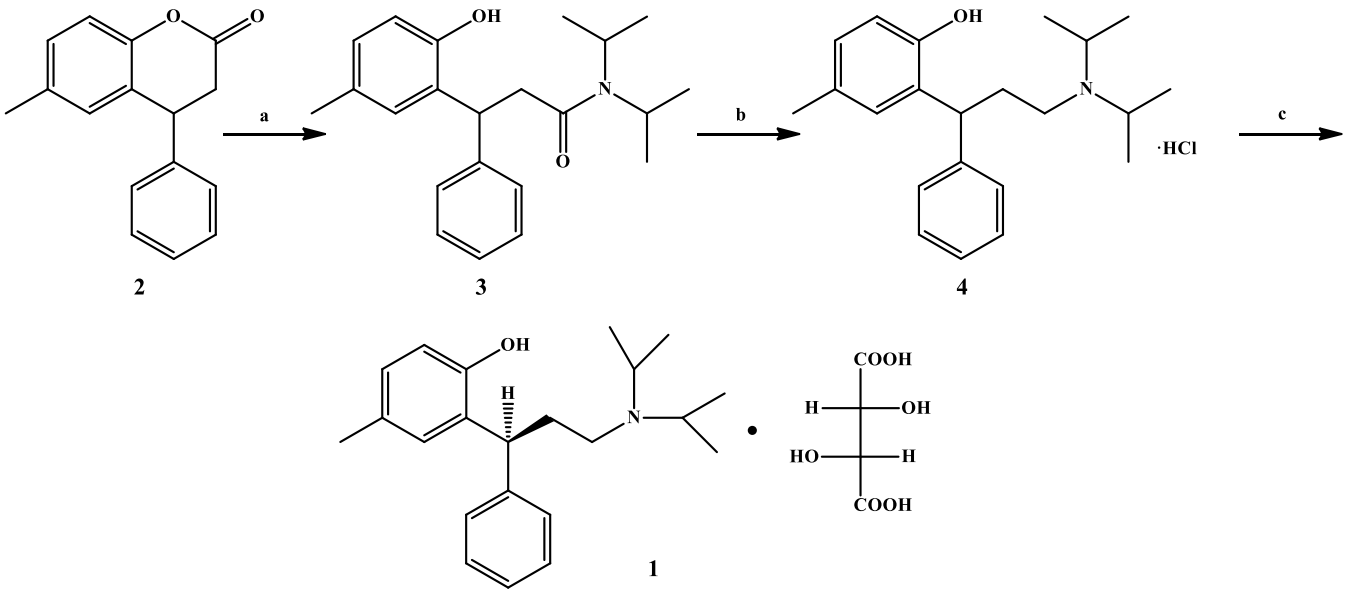
The generic name tolterodine refers to the *R*-enantiomer of the drug, chemically designated as R-(+)-*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine. Tolterodine, particularly (+)-(*R*)-tolterodine L-tartrate, is used in the treatment of urinary bladder hyperactivity in patients with urinary incontinence. The drug produces a spasmolytic effect on bladder smooth muscle by inhibiting the action of acetylcholine at muscarinic receptors [1,2].

R-Tolterodine exhibits better selectivity for muscarinic receptors than for nicotinic receptors and consequently, does not produce significant blocking effects at skeletal neuromuscular junctions. *R*-Tolterodine is administered in the form of its tartrate salt and is marketed as Detrusitol and Detsel in Europe and under the brand name Detrol in the USA. Several synthetic approaches for the preparation of racemic tolterodine have been reported [3-13]. A representative synthetic approach for the preparation of tolterodine is shown in **Scheme-I**. A major limitation of these processes is the lack of recovery of (*S*)-tolterodine during the resolution of racemic (*R*,*S*)-tolterodine, resulting in material loss and increased production cost. In addition, some of the reported methods involve low overall yields, hazardous reagents that require careful handling and chiral auxiliaries that need to be recovered and recycled.

The yield of the desired (*R*)-isomer can be improved by racemization of the undesired (*S*)-isomer, followed by resolution of the resulting racemic mixture. This approach allows the undesired enantiomer to be converted back into the racemate and subsequently used for the production of the desired (*R*)-isomer. In view of these limitations associated with the preparation of tolterodine tartrate, we aimed to develop an efficient method for the racemization of tolterodine. In the present work, we report a simple racemization process for the conversion of (*S*)-tolterodine into racemic (*R*,*S*)-tolterodine using commercially available starting materials.

EXPERIMENTAL

The solvents and reagents were obtained from commercial sources and used without further purifications. ^{1}H NMR spectra were obtained using a Bruker-Avance 300 MHz, 500 MHz and 125 MHz spectrometer in $CDCl_3$ and DMSO-d_6 solvents and chemical shifts were recorded in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr pellets on a varian FTs 1000 FT-IR Spectrometer. Chiral HPLC chromatographic conditions, Column: Chiral pak-AD-H, 5 µm (250 × 4.6 mm), pump mode: isocratic, flow rate:1.0 mL/min, detection: UV, 220 nm, column oven temp.: 25 ºC, injection volume: 20 µL, data acquisition time: 40 min.



Scheme-I: Reported synthetic route for tolterodine tartrate (1) [Reagents and conditions: (a) diisopropylamine, acetic acid, diisopropyl ether, 25-30 ºC, (b) vitride, toluene, 60 ºC, (c) *L*-(+) tartaric acid, acetone, methanol, 45-50 ºC]

The mass spectra were recorded on API 2000 Perkin Elmer PE-Sciex mass spectrometer. HPLC were recorded on a Shimadzu 2010 instrument. Specific optical rotations were determined in a 1 dm cell using 1 mL capacity using a Perkin-Elmer 241 polarimeter.

Synthesis of *N,N*-diisopropyl-3-[2-benzyloxy-5-methyl-phenyl]-3-phenyl propylamine (6): The solvent was distilled from the mother liquor of compound **1**, obtained during the resolution of racemic tolterodine, under reduced pressure to obtain an oily mass. Dichloromethane (900 mL) and water (500 mL) were added to the oily mass and the pH was adjusted to 10-11 using 5% w/w aqueous NaOH solution (325 mL) at 25-30 ºC. The reaction mass was stirred at 25-30 ºC for 20 min and the layers were separated. The aqueous layer was extracted with dichloromethane (100 mL) and the combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford N,N-diisopropyl-3-[2-hydroxy-5-methylphenyl]-3-phenylpropylamine (**5**) (50 g, 153.84 mmol). Acetone (100 mL), sodium iodide (3.5 g, 23.5 mmol), potassium carbonate (42.5 g, 307.5 mmol) and benzyl chloride (23.4 g, 184.86 mmol) were added to compound **5** and the reaction mixture was heated at reflux for ~ 29 h. The reaction mixture was cooled to 25-30 ºC and filtered. The salts were washed with acetone (50 mL) and the combined filtrate was concentrated under reduced pressure to obtain a gummy residue. *n*-Hexane (125 mL) was added to the residue and the mixture was stirred for 15 min at 25-30 ºC. The light-yellow sticky material formed was filtered and then portion of the *n*-hexane (50 mL) was removed from the filtrate under reduced pressure. Water (400 mL) was added to the remaining organic layer and the pH was adjusted to 4.0-4.5 with 5 N HCl (23 mL). The aqueous phase containing the product was separated and dichloromethane (200 mL) was added. The pH was then adjusted to 9.0-9.5 using 2 N NaOH solution (70 mL). The organic layer was washed with demineralized water (200 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford compound **6** as an oily mass (Yield: 51 g, 80%, SOR: -14.5º, C=1% in methanol). HPLC purity: 98.39%. HRMS for $C_{29}H_{37}NO$ $(M + H)^+$ calcd: 415.6, found: 416.2. IR (KBr, ν_{max}, cm^{-1}): 3436, 3061, 2961, 2929, 2865, 1608, 1599, 1587, 1455, 1397, 1291, 1065, 777, 736; ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 6.85-7.37 (m, 13H, ArH), 5.02 (s, 2H, OCH_2), 4.42 (m, 1H, CH), 2.90 (m, 2H, CH_2), 2.28 (m, 2H, NCH_2), 2.21 (s, 3H, CH_3), 2.03 (m, 2H, CH_2), 0.82 (d, 12H, isopropyl CH_3).

Synthesis of (±)-*N,N*-diisopropyl-3-[2-benzyloxy-5-methyl phenyl]-3-phenyl propylamine (7, racemic benzyloxy amine tolterodine): To a solution of compound **6** (41 g, 98.79 mmol, SOR: -14.5º, C = 1% in methanol] in DMSO (123 mL), potassium *tert*-butoxide (22.15 g, 197.39 mmol) was added. The reaction mass was stirred for 6 h at 60-65 ºC and then cooled to 25-30 ºC. The reaction mass quenched into water (738 mL) and extracted with diisopropyl ether (615 mL). The organic layer was washed with water (369 mL) and concentrated under reduced pressure to afford compound **7** as oily mass [(yield :39 g, 95%, SOR: -0.43º (C=1% in methanol)]. HPLC purity: 97.82%. HRMS for $C_{29}H_{37}NO$ $(M + H)^+$ calcd: 415.6, found: 416.2. IR (KBr, ν_{max}, cm^{-1}): 3436, 3061, 2961, 2929, 2865, 1608, 1599, 1587, 1455, 1397, 1291, 1065, 777, 736. ^1H NMR (300 MHz, DMSO-d_6, δ ppm): 6.85-7.37 (m, 13H, ArH), 5.02 (s, 2H, OCH_2), 4.42 (m,1H, CH), 2.90 (m, 2H, CH_2), 2.28 (m, 2H, NCH_2), 2.21 (s, 3H, CH_3), 2.03 (m, 2H, CH_2), 0.82 (d, 12H, isopropyl CH_3).

Synthesis of (±)-*N,N*-diisopropyl-3-[2-hydroxy-5-methyl phenyl]-3-phenylpropyl amine hydrochloride (4): To a solution of compound **7** (39 g, 93.97mmol in methanol (250 mL) placed in an autoclave, Raney nickel (15 g) was added. Applied hydrogen pressure 5-6 kg/cm^2 and stirred for 6 h at 25-35 ºC. The reaction mass cooled to 25-30 ºC. The catalyst was removed by hyflow bed filtration and washed the bed with methanol (50 mL). The pH of the filtrate was adjusted to 1.0-1.5 with conc. HCl (15 mL, 35% w/w). The solvent was distilled off from the filtrate under reduced pressure at

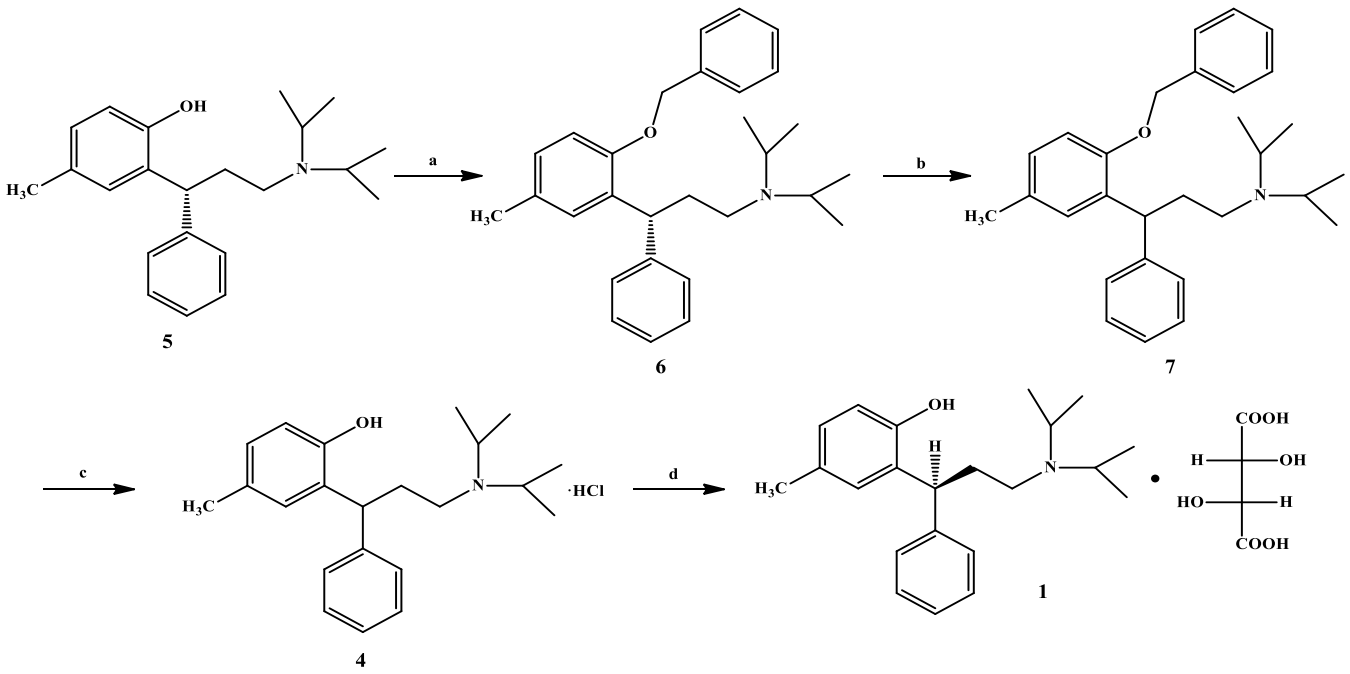
35-40 ºC. The resultant residue was crystallized from acetone (200 mL), filtered, washed with acetone (50 mL) to obtain compound **4** as a white crystalline solid (yield:26.5 g, 78%). HPLC purity: 97.63%. Mass: molecular formula HCl salt: $C_{22}H_{32}ClNO$, molecular weight: 361.95 [obtained value: 325.9]. IR (KBr, ν_{max}, cm^{-1}): 3200-3500, 3050-3000, 2970-2870, 1600-1580, 1510-1450, 1380-1360, 1260-1200, 1170-1050, 830-700; ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 8.5-11.5 (Br, 1H, HCl), 6.7-7.4 (m, 8H, ArH), 4.5-5.2 (m, 1H, CH), 2.8-3.2 (m, 2H, CH_2), 1.0-1.3 (d, 12H, isopropyl CH_3).

Synthesis of (+)-*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine hydrogen tartrate (1): To a suspension of (±)*N*,*N*-diisopropyl-3-[2-hydroxy-5-methylphenyl]-3-phenyl propylamine hydrochloride (40 g, 110.65 mmol) in a mixture of dichloromethane (410 mL) and water (205 mL) aqueous ammonia (18% w/w, 21 mL) was added to adjust the pH of the reaction mass to 9.5 ± 0.2. The mixture was stirred for 20 min at 25-30 ºC. The organic layer was separated and washed with water (2 × 132 mL). The organic layer was concentrated under reduced pressure at below 40 ºC to obtain a viscous mass. To the residue acetone (400 mL) was added. The reaction mass was warmed to 45-50 ºC and *L*-(+)-tartaric acid (19.85 g, 132.3 mmol) solution in methanol (100 mL) was added at 45-50 ºC for about 1 h. The reaction mass was stirred for 1 h at 45-50 ºC. Further, the reaction mass was cooled to 0-5 ºC and stirred for 1 h. The precipitated product was filtered, washed with pre-cooled acetone (2 × 80 mL) (**Scheme-II**). The solid was dried at 45-50 ºC under reduced pressure to provide **1** [Yield: 22 g, 84%) white solid with purity 99.92% by HPLC, Chiral purity: 99.84% by HPLC. Mass: molecular formula tartrate salt $C_{30}H_{41}NO_7$, molecular weight: 527.65 [obtained value:325.6]. IR (KBr, ν_{max}, cm^{-1}): 3869, 3321, 3000, 2863,1509, 1401, 1249, 1173, 1069, 774, 708. NMR (300 MHz, DMSO-d_6, δ ppm): 6.649-7.32 (m, 8H, ArH), 4.323 (t, 1H, CH), 3.973 (s, 2H, CH_2), 3.384-3.365 (d, 2H, CH_2), 2.719-2.602 (m, 2H, CH_2), 2.307-2.283 (d, 2H, CH_2), 2.258-2.167 (s, 3H, CH_3), 1.089-1.068 (d, 12H, isopropyl CH_3).

RESULTS AND DISCUSSION

The synthetic approach to convert (*S*)-tolterodine to (*R*,*S*)-tolterodine proposed is depicted in **Scheme-II**. Epimerization of enriched (*S*)-tolterodine obtained from mother liquor during the resolution of (*R*,*S*)-tolterodine involves protection of phenolic-OH **5** with benzyl chloride in acetone to afford compound **6**, which was racemized with potassium *tert*-butoxide in DMSO to give compound **7**. Thereafter, debenzylation of compound **7** by using Raney nickel in methanol afforded the desired (*R*,*S*)-tolterodine (**4**). Further, this racemic tolterodine was resolved with *L*-(+)-tartaric acid to get the optically pure tolterodine tartrate (**1**).

Initially, compound **5** was subjected to racemization under various conditions using different bases including sodium bicarbonate, potassium bicarbonate, sodium hydroxide, sodium carbonate, potassium carbonate, potassium hydroxide, sodium *tert*.-butoxide and potassium *tert*.-butoxide, in different solvents such as toluene, dimethylformamide, dimethylacetamide, DMSO, diglyme, monoglyme, ethylene glycol, xylene and acetonitrile. However, the results obtained were not satisfactory. Subsequently, the phenolic hydroxyl group of compound **5** was protected with benzyl chloride in the presence of potassium carbonate in acetone, as shown in **Scheme-II**. The racemization of the resulting protected compound was then investigated under various reaction conditions and the results are summarized in Table-1. The racemization proceeded



Scheme-II: Racemization of tolterodine [Reagents and conditions: (a) benzyl chloride, K_2CO_3, NaI, acetone, reflux, (b) DMSO, potassium *tert*-butoxide, 60-65 ºC, (c) H_2, Raney nickel, methanol, 25-30 ºC, (d) aqueous NH_3, DCM/H_2O, pH 9.5 ± 0.2, 25-30 ºC; acetone, L-(+)-tartaric acid/MeOH, 45-50 ºC, then 0-5 ºC]

TABLE-1
SCREENING OF BASE FOR RACEMIZATION OF *N,N*-DIISOPROPYL-3[2-BENZYLOXY-5-METHYLPHENYL]-3-PHENYL PROPYLAMINE (**6**)

Entry	Base	Mole equivalents	Solvent	Temp. (ºC)	Time (h)	SOR* (º)	Yield (%)
1	Sodium *tert*-butoxide	2.5	DMSO	60-65	12	-9	89
2	Sodium *tert*-butoxide	3.0	DMAc	60-65	15	-10.5	92
3	Potassium hydroxide	3.0	Toluene	105-110	10	-12	94
4	Potassium *tert*-butoxide	4.0	Toluene	105-110	8	-11.5	95
5	Potassium *tert*-butoxide	1.0	DMSO	60-65	6	-4.0	93
6	Potassium *tert*-butoxide	2.0	DMSO	60-65	6	-2.0	94
7	Potassium *tert*-butoxide	2.5	DMSO	60-65	6	+0.1	95
8	Potassium *tert*-butoxide	3.0	DMF	60-65	8	-6.0	93

*$[\alpha]_D^{25}$ C = 1% in methanol

effectively using potassium *tert*.-butoxide in DMSO at 60-65 ºC (Table-1, entry 7). To the best of our knowledge, racemization of tolterodine under these conditions has not been previously reported.

The racemization of compound **6** was therefore carried out using potassium *tert*.-butoxide in DMSO. This process is potentially useful for large-scale production because the undesired (S)-tolterodine generated during the resolution of racemic tolterodine can be racemized and recycled into the resolution process. Thus, the process provides a cyclic approach that can improve the overall yield of the desired (R)-tolterodine.

Conclusion

A practical racemization process has been developed for the conversion of (*S*)-tolterodine into racemic (*R*,*S*)-tolterodine. Protection of the phenolic hydroxyl group followed by treatment with potassium *tert*.-butoxide in DMSO at 60-65 ºC resulted in effective racemization. Subsequent debenzylation and resolution with L-(+)-tartaric acid afforded tolterodine tartrate. The process provides a means of recycling the undesired (*S*)-tolterodine generated during resolution and can therefore reduce material loss and improve the efficiency of tolterodine production. The use of readily available reagents and relatively mild reaction conditions makes this approach suitable for further evaluation on a larger scale.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language and no data, results or scientific conclusions were generated by AI. All analyses, interpretations and conclusions are the authors' own. The authors reviewed and edited the content and take full responsibility for the published work.

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