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Simple and an efficient method for the synthesis of 1-[2-dimethylamino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol hydrochloride: (±) venlafaxine racemic mixtures

Basappa, C. V. Kavitha and K. S. Rangappa*

Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570006, India

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Abstract—A novel synthetic method was developed for the synthesis of venlafaxine using inexpensive reagents. An improvement in the method, in the yield was achieved for the conversion of the venlafaxine. This is an improved version, simple and efficient method for the large-scale synthesis of venlafaxine.

1. Introduction

Depression is a common psychiatric disorder and one of the most frequent illnesses in world, affecting people of all gender, ages, and backgrounds. The causes of depression are complex and differ widely among individuals, but they are thought to involve brain biochemistry, inherited genes, social environment, and upbringing. In studying the brain, the dysfunction of the norepinephrine (NE), serotin (5-HT), and dopamine (DA) neurotransmitter systems known as monoamine hypothesis[1,2] is the most widely accepted basis for depression.

A large number of chemical structures have been found to exhibit antidepressant activity with diminished cardiovascular and anticholinergic liability. That is (*S*)-fluoxetine (SSRI), nisoxetine (NARI), mirtazapine (NSSA), (*R*,*S*)-paroxetine (SSRI), reboxetene (NARI), nebiolol (NEB), respiridone (RP), and venlafaxine (VNF) are reported to exhibit significant inhibitory effect against depression.

Among these nebiolol, respiridone (RP) and venlafaxine (VNF) have been proven to be the most potent antidepressent agents and are approved by the drug authorities of many countries for the treatment of depression. One of them, venlafaxine[3–6] shows a faster onset of action and increased efficiency and simple molecule.

2. Chemistry

Although a few methods are available in the literature, they are tedious, give poor yields, usually require expensive reagents, and are not feasible for large-scale synthesis. Venlafaxine was first synthesized by J. P. Yarderli and co-workers[7–9] and then by different groups by different methods.[10] The first route involves the conversion of 4-methoxyphenyl acetonitrile **1** to venlafaxine by condensation[9] reactions of **1** with cyclohexanone followed by catalytic hydrogenation[11–13] and N-methylation. The earlier methods suffer from very low temperature −78 °C, particularly unattainable in tropical conditions and expensive Rh/alumina catalyst is used for reduction, which makes the process economically enviable. The use of highly toxic and pyrophoric reagents like LDA, butylithium, $NaNH_2$, NaH makes the process industrially unattractive. Reduction of amide group by costly reagents like KBH_3/BF_3 etherate AlH_3/THF is involved. More over the amine 1-[2-amino-1-(4-methoxyphenyl ethyl)]cyclohexanol, has been found to be highly unstable and need to be processed to the next stage.

Here, we report a synthetic method involving improved version, inexpensive reagents, nonhazordous solvents,

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* Corresponding author. Tel.: +91-0821-2412191; fax: +91-0821-251-6133/2421263; e-mail: rangappaks@yahoo.com

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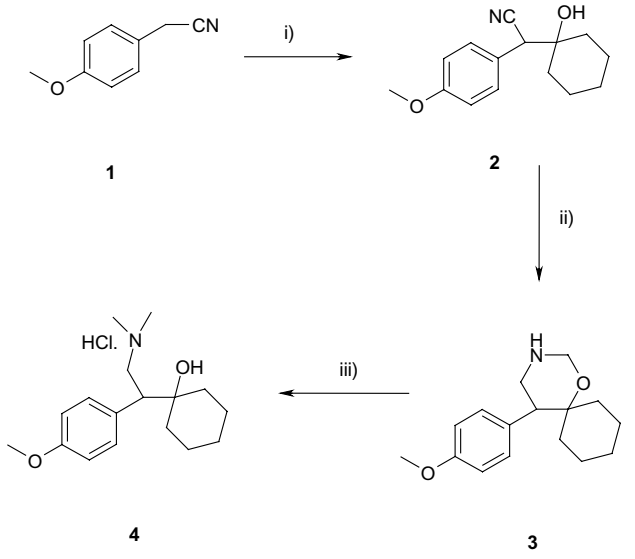
which can be conveniently applied for industrial scale synthesis.

In the first step 4-methoxyphenyl acetonitrile **1** was converted to 1-(cyano-(4-methoxyphenyl) methyl) cyclohexanol **2** by reacting with cyclohexanone in presence of sodium hydroxide at 25–30 °C in aqueous methanolic media. The condensed product was subjected to catalytic transfer hydrogenation method by using Raney-nickel/hydrogen at 10-atm pressure in presence of anhydrous ammonia and a methanol as a solvent. After reduction was completed, 5 equiv of 37–40% formaldehyde solution was added and the reaction mixture was stirred for 3 h. After completion of the reaction, the catalyst was filtered, methanol was distilled, precipitate was washed with water (200 mL) and hexane (100 mL) to get 80% of **3** (Scheme 1).

The oxazine **3** thus obtained is suitable as an intermediate for conversion to venlafaxine and extensive purification is avoided at this stage. More over, the oxazine being solid, handling is easier and preferred in industry in large scale. Further more, the oxazine **3** is found to be stable for long periods of time from heat, air, and light.

The isolated oxazine **3**, which is treated with 10 equiv of formic acid, 5 equiv of 37–40% formaldehyde solution in presence of water. After completion of the reaction, basify the reaction mass with 30% NaOH solution (pH = 12) and extract the venlafaxine by heptane. The basic solution is extracted to remove venlafaxine using solvents like toluene, xylene, heptane, ethylene dichloride, and methylenedichoride, etc., the preferred solvents being heptane. This solvent is of special importance as they can be distilled off azeotropically to remove water. Removal of water is atmost in this case as the final product venlafexine hydrochloride is highly soluble in water (hygroscopic). The base 1-[2-dimethylamino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol, thus obtained is converted to hydrochloride salt **4** using isopropyl alcohol (IPA) hydrochloride, which is a pure white crystalline compound with purity 99.7% (by HPLC).



Scheme 1. Reagents and conditions: (i) cyclohexanone, NaOH, Bu_4NBr, water–MeOH, rt, 15 h, 96%; (ii) Raney-Ni, H_2 (10 atm), anhydrous NH_3, MeOH, 35–40 °C, 3 h, then aqueous formaldehyde solution, 25–30 °C, 3 h, 83%; (iii) formic acid, aqueous formaldehyde solution, reflux (100 °C), 25–30 h, then HCl in *i*-PrOH (pH = 2), 85% (99.7% purity by HPLC).

In summary, we report an inexpensive, simple, two step, easy to operate, nonhazordous, effluent free, which can be conveniently applied to the large-scale synthesis.

3. Typical procedure

3.1. Synthesis of 1-(cyano-(4-methoxyphenyl)methyl)-cyclohexanol 2

The dissolved sodium hydroxide (20 g, 0.5 mol) and tetra butyl ammonium bromide (5 g) in methanolic water (500 mL each) were slowly added to a stirred solution of 4-methoxyphenyl acetonitrile (50 g, 0.340 mol) in cyclohexanol (49.9 g, 0.515 mol). The reaction mass was stirred for 15 h at room temperature (25–30 °C) and filtered, the residue was thoroughly washed with water (500 mL) and hexane (200 mL) to obtain a compound **2** (80 g, 96%). Mp: 122–124 °C (Ref. 7).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, Ar–H); 6.91 (d, 2H, Ar–H), 3.81 (s, 3H, OCH_3); 3.75 (s, 1H, OH); 1.55 (m, 10H, cyclohexyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 130.8, 123.8, 120, 114.1, 72.9, 55.56, 49.5, 34.9, 25.3, 21.6.

3.2. 5-(4-Methoxyphenyl)-3-aza-1-oxaspiro[5,5] undecane 3

The nitrile **2** (50 g, 0.204 mol) was dissolved in 1000 mL methanol containing 20 g of ammonia and 20 g of Raney nickel. An autoclave equipped with hydrogen inlet and gas induction stirring system was charged with two solutions. The reactor was inhertilzed with nitrogen. The reactor was pressurized with hydrogen so as to reach hydrogen pressure 10 kg. The hydrogenation was continued at 35–40 °C for 3 h until no more of hydrogen gas consumption was found. After the completion of the reaction, 250 mL of 37–40% formaldehyde solution was added and stirred for 3 h. The catalyst was filtered. Distilled the methanol upto three volumes and the precipitate was filtered at cooled condition (10–15 °C) and washed with chilled hexane to obtain **3** (45 g, 83.3%) mp: 121–123 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, 2H, $J = 7.9$, Ar–H); 6.81 (d, 2H, $J = 7.4$ Hz, Ar–H), 4.52 (q, 2H, O–CH_2–NH), 3.78 (s, 3H, OCH_3); 3.41 (t, 1H, CH–CH_2); 2.91 (d, 2H, CH_2–NH), 2.34 (d, 2H, CH_2–NH) 0.9–1.55 (m, 10H, cyclohexyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 130.8, 123.8, 120, 114.1, 72.9, 55.56, 49.5, 34.9, 25.3, 21.6.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.526; H, 8.871; N, 5.359. Found: C, 73.452; H, 8.861; N, 5.41.

3.3. 1-[2-Dimethylamino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol hydrochloride 4

Oxazine **3** (10 g, 0.0381 mol), 10 equiv of formic acid (15 mL), 5 equiv of 37–40% formaldehyde solution (7.1 g, 0.190) and 50 mL of water were added and refluxed for 15 h at 90–100 °C. Cool the reaction mixture for 25 °C, basified the product by the costic solution (maintained 12 pH). Extracted the product by heptane, distilled the heptane completely and dissolved the residue in IPA·HCl (pH = 2). The reaction mass was stirred for 12 h at 20–25 °C. Filtered the precipitate, washed with hexane to obtain the white solid **4**. Purity 99.7% (by HPLC); Yield: 85%; mp: 215–218 °C.

^{1}H NMR (300 MHz, D_2O): δ 7.12 (d, 2H, $J = 8.1$ Hz, Ar–H), 6.76 (d, 2H, $J = 7.8$ Hz, Ar–H), 3.56 (s, 3H, OMe), 3.51 (t, 1H, Ph–CH–CH_2), 3.32 (dd, 2H, CH_2), 2.53 (s, 6H, $(NCH_3)_2$), 0.9–1.3 (m, 10H, cyclohexyl).

^{13}C NMR (100 MHz, D_2O): δ 158.8, 128.3, 114.5, 73.4, 58.5, 56.5, 50.4, 35.1, 34.0, 24.9, 21.3, and 21.11.

Anal. Calcd for $C_{17}H_{27}NO_2Cl$: C, 65.265; H, 8.698; N, 4.477. Found: C, 65.46; H, 8.56; N, 4.521.

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