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Preparation of Venlafaxine-Antidepressant Drug

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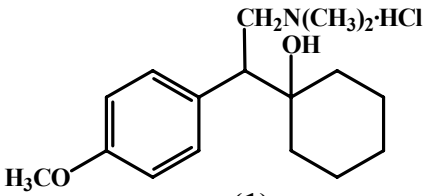
Venlafaxine (**1**) is an antidepressant and an alternative for tricyclic antidepressants or MAO inhibitor. Its synthesis generally suffers from low yields, tedious workup and high cost. To over-come these drawbacks, a simple, facile, cost effective and friendly process at industrial scale is reported.

Key Words: Venlafaxine, Antidepressant Drug.

INTRODUCTION

Venlafaxine, (±)-1-[2-(dimethylamino)-1-(4-ethoxyphenyl)ethyl]cyclo hexanol hydrochloride (**1**) an antidepressant which does not structurally resemble any of the earlier reported antidepressants of the class[1]. It serves as an alternative tricyclic antidepressant or an MAO inhibitor[2-5] and is free from any side effects associated with the SSRIs [fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil) and fluvoxamine (Luvox)][6] and the impact on both serotonin and norepinephrine associated with the tricyclic antidepressants [amitriptyline (Elavil), imipramine (Tofranil), *etc.*].

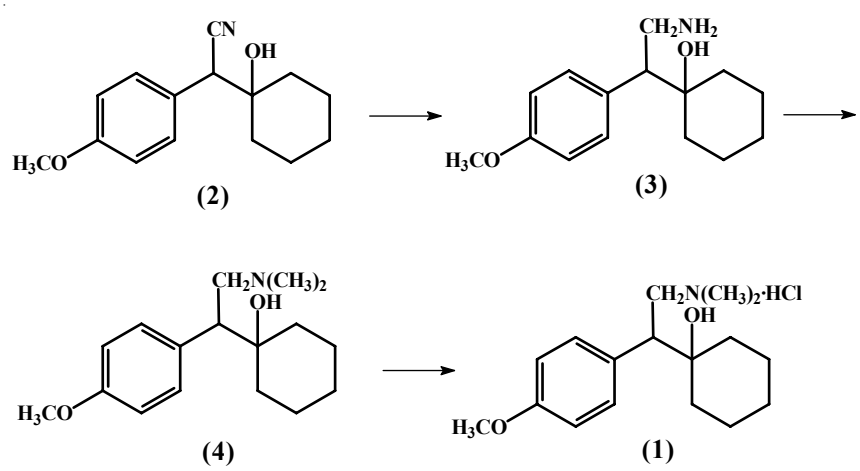


(1)

Structure of venlafaxine (**1**)

The patented process for the synthesis of venlafaxine (**1**)[7] involves reduction of 1-[cyano(*p*-methoxyphenyl)methyl]cyclohexone (**2**) with 5% rhodium on alumina to yield 1-[2-amino-1-(*p*-methoxyphenyl) ethyl] cyclohexanol (**3**). This on treatment with a mixture of formaldehyde and formic acid furnished 1-[2-(dimethylamino-1-(4-methoxyphenyl)] ethylcyclohexanol (**4**) in 35 % yield, which on subsequent acidification generated **1** (**Scheme-I**).

The method described in **Scheme-I**, is not suitable for the preparation of venlafaxine in large quantities. Keeping in view of the above set backs, in present communication, a cost effective, commercially viable and industrially scalable process for the preparation of venlafaxine.



Scheme-I

Apparently, the above reaction suffers from few drawbacks: (i) reduction of compound **2** to **3** involves the use of highly expensive reagents like rhodium on alumina in a mixture of ammonia-ethanol (20 % v/v), which is less accessible in terms of usage and storage, (ii) very low yields of venlafaxine base **4**, (iii) isolation of **4**, by column chromatography which is not viable in large scale.

EXPERIMENTAL

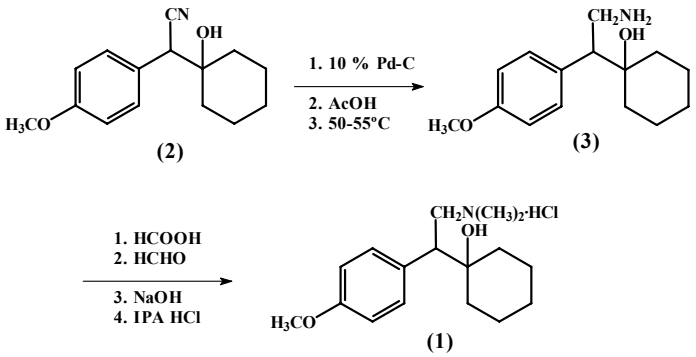
^{1}H and ^{13}C NMR spectra were measured on Varian mercury plus 400 MHz FT-NMR spectrometer in $CDCl_3$, the chemical shifts are reported in ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. Mass spectrum (70 eV) was recorded on Shimadzu LC-MS QP-8000a spectrometer. The solvents and reagents were used without further purification.

Preparation of 1-[2-Amino-l-(*p*-methoxy phenyl)ethyl]cyclohexanol (3): A suspension of 1-[cyano-(*p*-methoxy phenyl)methyl]cyclohexanol (**2**, 60 g, 0.245 mol) in acetic acid (350 mL) was hydrogenated in an autoclave at a pressure of 10-15 kg/cm^2 in the presence of 10 % palladium on charcoal (1.8 g) at a temperature of 50-55ºC. The same temperature and pressure was maintained till the starting material disappeared in TLC,

after which the catalyst was filtered. The filtrates were combined and evaporated under reduced pressure. To the residue *o*-xylene (3 × 60 mL) was added and traces of acetic acid was removed azotropically. The resultant solid obtained was suspended in ethyl acetate (120 mL) and stirred for 0.5 h at ambient temperature. Upon completion of this step, the suspension was filtered accompanied by ethyl acetate washing (20 mL). The solid thus obtained was dried at 55-60ºC to afford compound **3** (Yield: 57 g).

Preparation of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol hydrochloride (1): A stirred mixture of 1-[2-amino-l-(*p*-methoxy phenyl)ethyl]cyclohexanol (**3**, 55.0 g, 0.22 mol), formic acid (25 mL), 40 % formaldehyde solution (92 mL) and water (275 mL) was heated at 90-98ºC for 19 h. The reaction mass was cooled and washed with chloroform (4 × 55 mL). The washings were discarded. The aqueous layer was then cooled to 5ºC and basified with 48 % sodium hydroxide solution (25 mL). The product was extracted from the alkaline aqueous layer with chloroform (3 × 100 mL). The organic layer was then evaporated under reduced pressure to yield an oily residue, which was dissolved in isopropyl alcohol (225 mL). The resultant solution was acidified with isopropyl alcohol hydrochloride till pH of *ca.* 2 was achieved. The precipitated solid was filtered and washed with isopropyl alcohol (25 mL). It was then dried at 55-60ºC to yield the compound **1** (Yield: 44.0 g) (**Scheme-II**).

Mass: Protonated molecular ion at m/z = 278; IR (ν_{max}, cm^{-1}): 3352 (OH), 3017 (aromatic C-H), 2936 (aliphatic C-H), 1614 & 1514 (Ar C=C), 1248 & 1043 (aryl alkyl ether -C-O-C-), 1180 (-C-N-); ^{1}H NMR: 0.89-1.70 (m, 10H, aliphatic C-H); 2.69 (br, 6H, 2 × N-CH_3); 3.19-3.31 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3); 3.93 (dd, 1H, *J* = 12.4 Hz, CH); 6.85 (d, 2H, *J* = 8.6 Hz, CH), 7.14 (d, 2H, *J* = 8.6 Hz, CH); ^{13}C NMR: 21.0, 21.4, 25.2, 31.2, 36.4, 42.5, 44.8, 52.2, 55.1, 59.9, 73.4, 113.9, 130.1, 131.1, 158.7. $[\alpha]_D^{25}$ = + 0.4º (c = 1.1 in 95 % ethanol).



Scheme-II

RESULTS AND DISCUSSION

In present approach, we have identified 1-[cyano-(*p*-methoxy phenyl)-methyl]cyclohexanol (**2**), a readily accessible and commercially available compound, as an apt starting material. Reduction of **2** by 10 % palladium on carbon in acetic acid in an autoclave at a pressure of 10-15 kg/cm^2 yield 1-[2-amino-1-(*p*-methoxy phenyl)ethyl]cyclohexanol (**3**). Reaction of **3** with a mixture of formaldehyde and formic acid and subsequent acidification with isopropyl alcohol hydrochloride yielded the required venlafaxine hydrochloride in 60 % yield (**Scheme-II**). The reaction thus avoids the formation and isolation of venlafaxine freebase, which in turn improving the yields of venlafaxine hydrochloride to 60 %.

In conclusion, the improved process for venlafaxine hydrochloride offers distinctive advantages over the reported procedures. It is noteworthy that the present process provides high yielding, commercially viable and plant friendly process and hence renders the method superior.

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