Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 19 Nov 2007.

To cite this article: Subhash P. Chavan , Dushant A. Khobragade , Mahesh Thakkar & Uttam R. Kalkote (2007): Practical Synthesis of (±)-Venlafaxine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:22, 3901-3906

To link to this article: http://dx.doi.org/10.1080/00397910701572266

Synthetic Communications®, 37: 3901–3906, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701572266

Practical Synthesis of (±)-Venlafaxine

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Abstract: A practical total synthesis of antidepressant (±)-venlafaxine is disclosed.

Keywords: antidepressant, Grignard reaction, Michael addition

INTRODUCTION

In connection with an ongoing program on the synthesis of antidepressants paroxetine **1** and venlafaxine **2** (Fig. 1), a technically and economically viable protocol[1] for the synthesis of antidepressant drug venlafaxine **2** was developed (Fig. 1, Scheme 1), which was followed by a similar synthesis by Rangappa et al.[2]

Venlafaxine **2** is a new generation, cost-effective antidepression drug,[3,4] quite different from other antidepressants because it has an unique structure and morphological effects. It offers potential pharmacological benefits including early onset of action, dose flexibility, broad range of activity, improved tolerance, and improved efficacy. An earlier response can be particularly beneficial in more severely depressed patients.[5]

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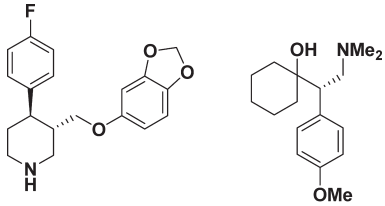
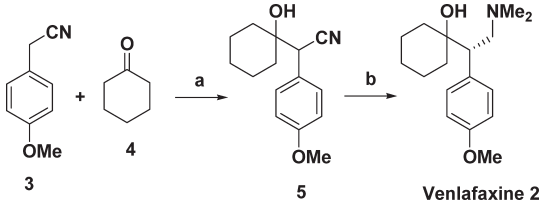


Figure 1. Two of the most important antidepressants, paroxetine **1** and venlafaxine **2**.

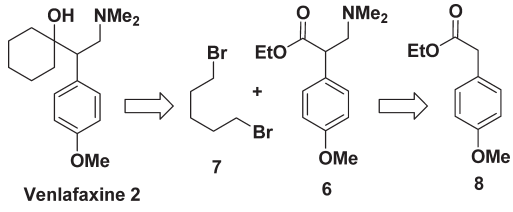


Scheme 1. Reagents and conditions: (a) 10% aqueous NaOH, $TBAHSO_4$, 0–15°C, 30 min–1 h, quantitative yield; (b) H_2, 280 psi, formalin, MeOH, 100°C, 30% (60% cycloalkanol **5** is recovered).

RESULTS AND DISCUSSION

Reported methods[6–14] for the synthesis of venlafaxine **2** involve the use of expensive reagents, strong and hazardous bases such as BuLi and LDA, for coupling *p*-methoxyphenylacetonitrile **3** with cyclohexanone **4** under cryogenic conditions and anhydrous organic solvents to give 1-[cyano (4-methoxyphenyl)methyl]cycloalkanol **5**. The yields are low, and the conditions are not suitable for industrial synthesis.

In this communication, we disclose the synthesis of venlafaxine **2** by a modified procedure employing the aminoester **6**. Retrosynthetic analysis (Scheme 2) reveals that target molecule **2** could be obtained from aminoester **6** and 1,5-dibromopentane **7**. Grignard reaction of 1,5-dibromopentane **7** with



Scheme 2. Retrosynthetic analysis.

aminoester **6** gives the target molecule **2**. Aminoester **6** in turn could be derived from ester **8**.

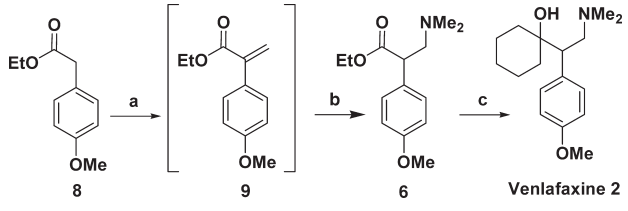
The literature procedure[15] for the preparation of aminoester **6** from ester **8** involves use of a strong base such as LDA or BuLi under cryogenic conditions and anhydrous organic solvents followed by reduction of the resultant *N,N*-dimethylamino acrylate derivative with various reagents such as Pd/C, $LiAlH_4$, and $NaBH_4$. These conditions are not suitable for a large-scale synthesis.

Accordingly, a solution of ester **8** in toluene was heated with commercially available anhydrous paraformaldehyde, in the presence of K_2CO_3 and tetrabutylammonium iodide (TBAI) to furnish α,β-unsaturated ester **9**, which upon treatment with a THF solution of Me_2NH at 0°C in the presence of a catalytic amount of $FeCl_3$ rendered aminoester **6** in 79% yield (in two steps).[16] Grignard reaction of aminoester **6** with 1,5-dibromopentane in THF afforded venlafaxine **2** as a colorless solid in 50% yield (Scheme 3).

Thus, a very short and practical synthesis of the commercially important antidepressant (±)-venlafaxine has been accomplished employing Michael addition followed by the Grignard reaction.

EXPERIMENTAL

All solvents were freshly distilled before use. IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer model 68B or on a Perkin-Elmer 1615 FT infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC-200 (200 MHz). ^{13}C spectra were recorded on a Bruker AC-200 (50 MHz). The carbon spectra were assigned using dimensionless enhancement by polarization transfer (DEPT) experiments. Coupling constants (J) were recorded in hertz. Mass spectra were recorded at an ionization energy of 70 eV on a Finnigan MAT-1020 and on an API Q Starpulsar using electron spray ionization (ESI). Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 elemental analyzer. Progress of the reactions were monitered by thin-layer chromatography (TLC) using Merck silica-gel



Scheme 3. Reagents and conditions: (a) $(HCHO)_n$, K_2CO_3, TBAI, PhMe, 80°C, 3.5 h; (b) Me_2NH, $FeCl_3$ (cat.), rt, 45 min, 79% (two steps); (c) $BrMg(CH_2)_5MgBr$, THF, 0°C then reflux, 3.5 h, 50%.

60 F_{254} precoated plates, and compounds were visualized by fluorescence quenching or using iodine or by charring after treatment with the mixture of *p*-anisaldehyde + AcOH + H_2SO_4 in ethanol. Column chromatography was performed using flash silica gel (230–400 mesh).

Ethyl 3-(Dimethylamino)-2-(4-Methoxyphenyl) Propanoate (6)

A mixture of ethyl *p*-methoxyphenylacetate **8** (4 g, 20.62 mmol), paraformaldehyde (1.05 g, 35.0 mmol), and TBAI (0.381 g, 1.03 mmol) was heated in PhMe (16 mL) at 80–85°C for 3.5 h. The reaction mixture was allowed to cool. Then, a solution of Me_2NH in THF was added to the reaction mixture at 0°C in the presence of catalytic $FeCl_3$ (0.160 g, 0.001 mol) and stirred for 45 min. After completion of the reaction, 100 mL of water was added to the reaction mixture, and the aqueous layer was acidified with conc. HCl (pH = 2). The aqueous layer was washed with DCM (3 × 50 mL), made alkaline (pH = 8) using 5% NaOH solution, extracted with DCM (3 × 50 mL), washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatographic purification over silca gel (0.5% MeOH in $CHCl_3$) furnished aminoester **6** as a thick colorless oil (3.08 g, 79%). IR ($CHCl_3$): 3498, 3356, 3018, 2978, 1727, 1611, 1513, 1249, 1216, 1178, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.23 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 4.14 (m, 2H), 3.78 (s, 3H), 3.73 (dd, $J = 9.8$ Hz and 12.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.4, 158.6, 129.4, 128.5, 113.7, 62.7, 59.8, 54.5, 49.3, 45.2, 13.8; MS (ESI) m/z: 251 (M^+), 206, 162, 148, 133, 119, 101, 91, 77, 65, 58. Analysis calculated for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.75, H, 7.38; N, 5.17.

Venlafaxine (2)

To a suspension of Mg (0.114 g, 4.75 mmol) in THF (2 mL), a solution of dibromopentane **7** (0.536 g, 2.33 mmol) in THF (2 mL) was added dropwise at 0–5°C. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. Again, the reaction mixture was cooled to 0–5°C, and a solution of amino ester **6** (0.45 g, 1.79 mmol) in THF (5 mL) was added to it dropwise. After the addition, the reaction mixture was first allowed to come to room temperature within 0.5 h and then refluxed for 3.5 h. The reaction mixture was allowed to cool, and 50% aq. NaOH solution was added to the reaction mixture (pH = 12). It was extracted with ethyl acetate (2 × 50 mL), washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (20 g of silica gel, 5% MeOH in $CHCl_3$ as eluent) to furnish venlafaxine **2** as a colorless solid

(0.25 g, 50%). Mp 74–76°C. IR ($CHCl_3$): 3164, 2982, 2938, 2860, 2832, 2782, 1610, 1512, 1465, 1445, 1277, 1246, 1217, 1180, 1039, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.03 (d, $J = 8.79$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 2H), 3.79 (s, 3H), 3.28 (t, $J = 12.2$ Hz, 1H), 2.93 (dd, $J = 2.9$ Hz and 12.2 Hz, 1H), 2.33 (s, 6H), 2.28 (dd, $J = 3.4$ Hz and 12.7 Hz, 1H), 1.23–1.27 (m, 8H), 0.83–1.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7 (C), 132.0 (C), 129.4 (CH), 112.7 (CH), 73.4 (C), 60.7 (CH_2), 54.3 (CH_3), 51.2 (CH), 44.8 (CH_3), 37.5 (CH_2), 30.7 (CH_2), 25.5 (CH_2), 21.0 (CH_2), 20.7 (CH_2); MS (ESI) m/z: 277 (M^+), 258, 219, 179, 162, 134, 119, 99, 91, 81. Analysis calculated for C, 73.61; H, 9.81; N, 5.05. Found: C, 73.49; H, 9.55; N, 4.82.

ACKNOWLEDGMENT

D. A. K. and M. T. thank Council for Scientific and Industrial Research (CSIR), New Delhi, India, for providing fellowships.

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