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Convenient Formal Synthesis of (±)-Paroxetine

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Abstract: A formal total synthesis of antidepressant (±)-paroxetine employing a solvent-free Heck reaction is disclosed.

Keywords: antidepressants, carbamate, electrophile, Heck reaction, piperidines

INTRODUCTION

In connection with an ongoing program on the synthesis of biologically active compounds, we have recently developed a technically and economically viable protocol[1] for synthesis of the antidepressant drug venlafaxine **1**. Our interest in development of practical routes for such molecules prompted us to undertake synthesis of another highly active antidepressant drug, paroxetine **2**.

The piperidine nucleus is ubiquitous in a wide variety of naturally occuring and synthetic compounds. Of these, 3,4-disubstitued piperidine derivatives[2] exhibit a profile of biological and pharmacological properties, for example, paroxetine **2**, femoxetine **3** and Roche-1 **4** (Fig. 1). (-)-Paroxetine in the form of its hydrochloride salt is used in the treatment of depression, obsessive–compulsive disorder, and panic and is popularly known as an SSRI (selective serotonin reuptake inhibitor) marketed under various trade names such as Paxil and Seroxat.

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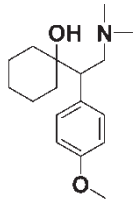


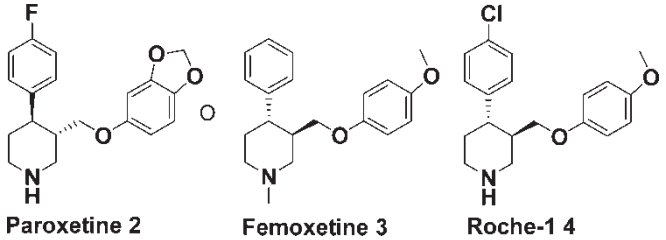
Venlafaxine 1

Figure 1. Antidepressant venlafaxine **1**.

RESULTS AND DISCUSSION

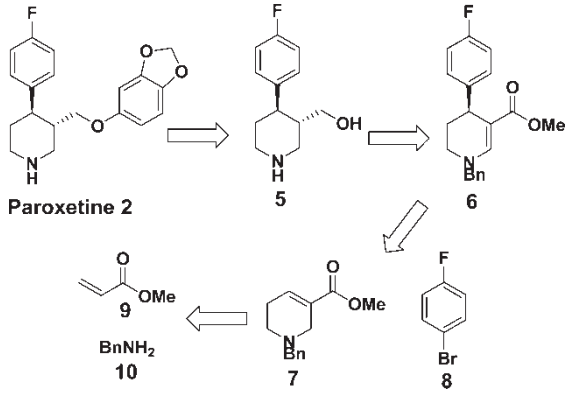
A literature survey revealed that several methods[3–12] have been devised to prepare a 4-arylpiperidine motif (Figure 2). Although organic synthesis has enormously benefited from Heck chemistry,[13–17] to our surprise, until recently not a single approach was reported[3a] where the Heck protocol is employed to a construct 4-arylpiperidine system, forging a bond between C-4 of piperidine nucleus and an aryl moiety. This may be attributable to the resistance of such complex acrylates to undergo arylation, resulting in low conversions or yields of the desired Heck adducts, serious drawbacks. Accompanying decomposition, polymerization, or side reactions under the harsh reaction conditions generally employed for such substrates could be other possible factors. A recent report on the synthesis of paroxetine[3a] prompted us to disclose our findings in this area. We investigated our synthetic plan employing traditional, commercially available halide (viz., *p*-fluorobromobenzene) as the coupling partner as compared to more a conventional iodo compound or the *p*-fluorobenzenediazonium tetrafluoroborate salt recently reported in literature (Scheme 1).

Retrosynthetic analysis revealed that the target molecule **2** could be obtained from aminoalcohol **5**, which in turn could be derived from aminoester **6**, which presumably could be built from the olefin **7** and *p*-fluorobromobenzene **8** employing the Heck reaction. Olefin **7** could be conveniently prepared from the simplest and commercially available materials (viz, methyl acrylate **9** and benzylamine **10**) (Scheme 1).



Paroxetine 2 Femoxetine 3 Roche-1 4

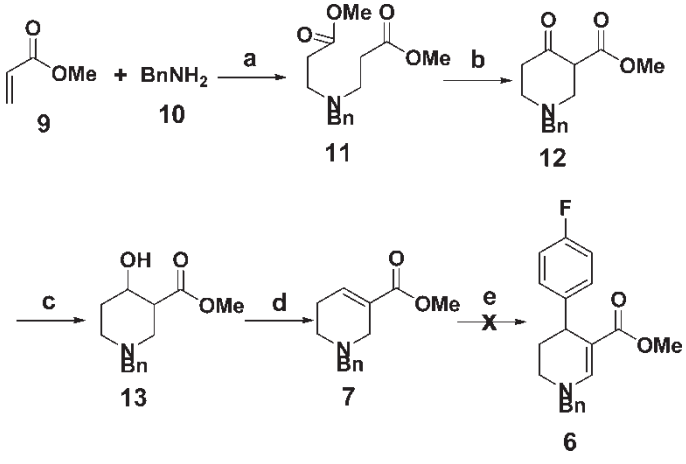
Figure 2. Antidepressant paroxetine **2**, femoxetine **3**, and renin inhibitor Roche-1 **4**.



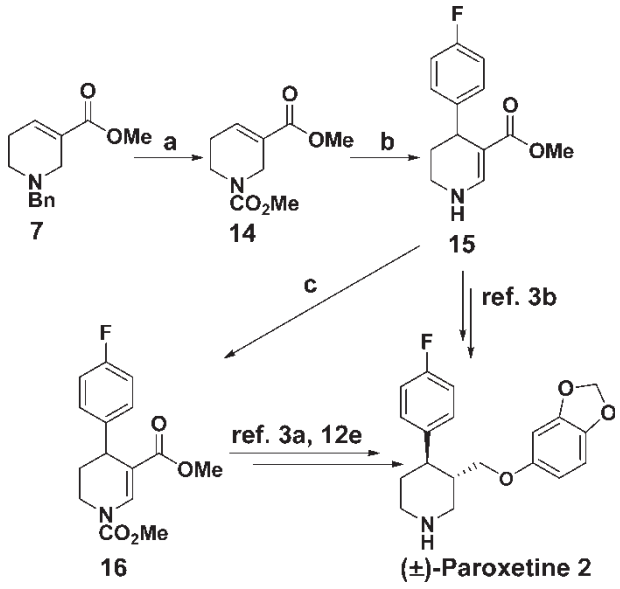
Scheme 1. Retrosynthetic analysis.

Accordingly, methyl acrylate **9** and benzylamine **10** were refluxed in the presence of triethylamine to furnish the double Michael adduct **11**, which was further subjected to Dieckmann condensation using sodium hydride in refluxing benzene to give ketoester **12**. Ketoester **12** was reduced with sodium borohydride in methanol at 0°C. The resulting alcohol was mesylated in dichloromethane, which underwent concomitant elimination to afford the desired olefin **7** (Scheme 2).

The feasibility of the Heck protocol was tested under various conditions. Arylation of the olefin **7** with $Pd(OAc)_2$ was not successful in different



Scheme 2. Reagents and conditions: (a) Et_3N, reflux (neat), overnight, 90%; (b) NaH, PhH, reflux, 3 h, 82%; (c) $NaBH_4$, MeOH, 0°C-rt, 2 h; (d) MsCl, Et_3N, DCM, 0°C–rt, overnight, 75% (for two steps); (e) $Pd(Ph_3P)_4$, K_2CO_3, Bu_4NBr, 120°C, 2 d.



Scheme 3. Reagents and conditions: (a) $ClCO_2Me$, $NaHCO_3$, DCM, rt, 24 h, 80%; (b) **8**, $Pd(Ph_3P)_4$, K_2CO_3, Bu_4NBr, 120°C, 2 d, 45%; (c) $ClCO_2Me$, K_2CO_3, DCM, rt, overnight, 85%.

solvents such as DMF, MeOH, or CH_3CN in the presence or absence of tetrabutylammonium bromide (TBAB) using different bases such as Et_3N, K_2CO_3, Na_2CO_3, and $NaHCO_3$. Even $Pd(Ph_3P)_4$ was not able to bring about arylation under the aforementioned reaction conditions. Also, subjection of the olefin **7** as per the procedure reported by Correia et al.[3a] employing traditional commercially available electrophile *p*-fluorobromobenzene did not furnish the expected Heck adduct.

Benzyl protection of the acrylate was then exchanged with methyl carbamate, and the carbamate was resubjected to Heck arylation. To our delight, carbamate **14** underwent arylation smoothly under solvent-free conditions 18 in a TBAB melt accompanied by concomitant unmasking of the carbamate protection to furnish free amine **15**, albiet in moderare yields (Scheme 3). Conversion of amine **15** into paroxetine is known in the literature.[3b] Also, the carbamate derivative of **15**, **16**, was prepared whose conversion to paroxetine is known.[3a,12e] Thus, formal total synthesis of (±)-paroxetine is achieved.

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) instrument. ^{13}C spectra were recorded on Bruker AC-200 (50 MHz) or Bruker AC-400 (100 MHz) instruments. The carbon spectra were assigned using a dimentionless enhancement by polarization transfer (DEPT) experiment. 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 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 was monitered by thin-layer chromatography (TLC) using Merck silica-gel 60 F_{254} precoated plate, and compounds were visualized by fluorescence quenching, using iodine, or 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 size).

Methyl 4-(4-Fluorophenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (15)

A mixture of olefin **14** (1 g, 5.024 mmol), *p*-fluorobromobezene **8** (1.76 g, 10.05 mmol), $Pd(Ph_3P)_4$ (0.58 g, 10 mol%), K_2CO_3 (1.386 g, 10.05 mmol), and TBAB (2.33 g, 10.05 mmol) was heated at 120°C under an argon atmosphere for 2 days. The reaction mixture was allowed to cool; water was added to it and extracted with ethyl acetate. It was washed with brine and dried (anhydrous Na_2SO_4); solvent was evaporated in vacuo. Column chromatographic purification using a ethyl acetate–pet. ether system (3:7–1:1) furnished amine **15** as a colorless solid (0.531 g, 45% yield). Mp 156–158°C. IR ($CHCl_3$): 3467, 3019, 1682, 1626, 1506, 1438, 1353, 1314, 1284, 1216, 1108, 1070, 930, 757, 669 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ_H 7.73 (1H, d, $J = 6.31$ Hz), 7.09–7.16 (2H, m), 6.90–6.99 (2H, m), 4.66 (1H, bs), 3.96 (1H, d, $J = 4.80$ Hz), 3.59 (3H, s), 3.15 (1H, m), 2.93 (1H, dt, $J = 3.6$, 12.8 Hz) 2.07–1.89 (1H, m) 1.79 (1H, m); δ_c 168.6 (C), 161.3 (C proximal to F), 143.9 (CH), 142.0 (C), 129.0 (C-*meta* to F), 114.7 (C-*ortho* to F), 95.9 (C), 50.5 (CH_3), 36.0 (CH_2), 35.5 (CH), 28.9 (CH_2); MS (ESI) m/z, 235 (M^+), 221, 201, 199, 195, 187, 157, 130, 102. Analysis calculated for $C_{13}H_{14}FNO_2$: C,66.37; H,6.00; F,8.08; N,5.95. Found: C,66.25; H,5.82; F,7.88; N,9.45.

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