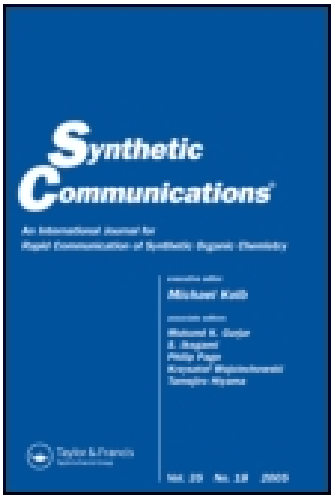

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Novel Carbon-Carbon Bond Formation between N-Methyl-3-phenyl-3-hydroxypropylamine and Cresols Catalyzed by p-Toluenesulphonic Acid

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Novel Carbon–Carbon Bond Formation between N-Methyl-3-phenyl-3-hydroxypropylamine and Cresols Catalyzed by *p*-Toluenesulphonic Acid

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Abstract: The *p*-toluenesulphonic acid–catalyzed reaction between appropriate cresols and N-methyl-3-phenyl-3-hydroxypropylamine in refluxing toluene resulted in the formation of *o*-substituted phenol derivatives by an aromatic nucleophilic substitution reaction.

Keywords: Anti-depressant drug, aromatic nucleophilic substitution, Atomoxetine, carbon–carbon bond formation, cresol, N-methyl-3-phenyl-3-hydroxypropylamine, *p*-toluenesulphonic acid

INTRODUCTION

Atomoxetine is one of the potent inhibitors of the presynaptic norepinephrine transporter with minimal affinity for other monoamine transporters or receptors.[1,2] Atomoxetine is used as a therapeutic agent for the treatment

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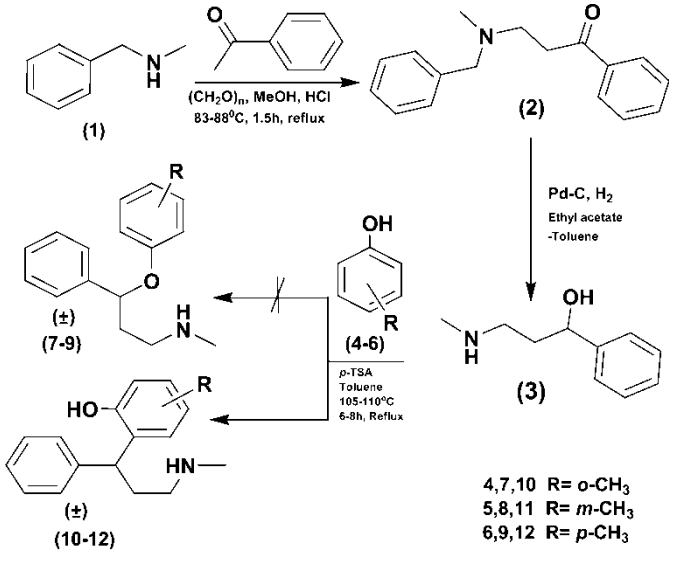
of attention deficit hyperactivity disorder (ADHD) in children, adolescents, and adults. Recently, Atomoxetine hydrochloride, a noradrenalin-reuptake inhibitor,[3] was approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD, a neuropsychiatric disorder of childhood. In the literature, several synthetic methods were reported for Atomoxetine.[4–6]

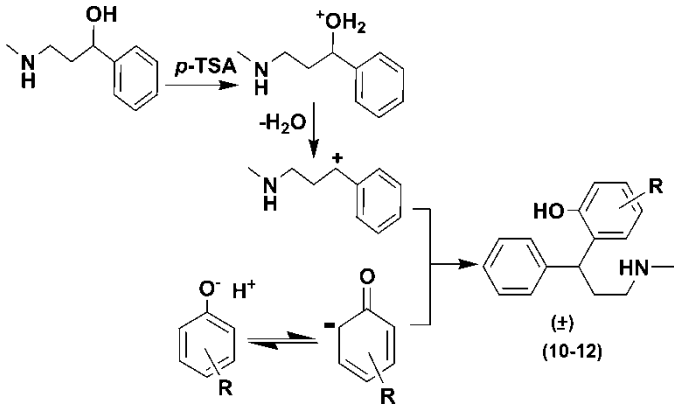
RESULTS AND DISCUSSION

During the course of our study aimed at synthesizing Atomoxetine, we discovered a new synthetic rearrangement obtained during the condensation of N-methyl-3-phenyl-3-hydroxypropylamine **3** with appropriate cresols **4**–**6** catalyzed by *p*-toluenesulphonic acid (*p*-TSA) (Scheme 1). The synthesis of N-methyl-3-phenyl-3-hydroxypropyl amine[7] **3** was carried out by a conventional four-step procedure. Treatment of N-benzylmethylamine **1** with acetophenone, formaldehyde (excess) in the presence of methanol, and hydrogen chloride under reflux yielded **2**, whose reduction in the presence of Pd-C afforded N-methyl-3-phenyl-3-hydroxypropylamine **3**. Treatment of **3** with appropriate cresols **4**–**6** in the presence of *p*-TSA in toluene furnished C-arylated products **10**–**12** and not the expected derivatives **7**–**9**.

The compounds **10**–**12** were characterized by elemental analysis, IR, mass, and NMR (^{1}H and ^{13}C) spectral data. The probable mechanism of the reaction is depicted in Scheme 2. The mechanism of the reaction would have been the result of the ability of the cresols **4**–**6** to exhibit *keto-enol* tautomerism.



Scheme 1. Possible synthetic pathway.



Scheme 2. Probable mechanistic route.

The present article describes a mild and efficient synthesis of *o*-substituted phenol derivatives **10**–**12** by the formation of novel carbon–carbon bond formation between N-methyl-3-phenyl-3-hydroxypropylamine and cresols catalyzed by *p*-TSA.

EXPERIMENTAL

General Remarks

TLC was performed to ascertain proof of the reactions and purity of products. Melting points were recorded in open capillaries (uncorrected). IR spectra were recorded with a Perkin-Elmer FT-IR spectrophotometer in KBr pellets, and only noteworthy absorption levels are listed. ^{1}H NMR spectra were recorded on a Gemini-2000 spectrometer (200 MHz) in $CDCl_3$ using TMS as the internal standard. ^{13}C NMR spectra were recorded on a Gemini-2000 spectrometer (50 MHz) in $CDCl_3 + CD_3CN$. The Atmospheric Pressure Chemical Ionization (APCI) +ve mass spectra were recorded on a Shimadzu LC MS-QP8000α spectrometer. Satisfactory microanalysis was obtained with a Carlo Erba 1106 and a Perkin-Elmer 240 CHN analyzer.

Typical Procedure for the Synthesis of N-Methyl-3[3-(2-hydroxy-3-methylphenyl)]phenylpropylamine 10

A suspension of N-methyl-3-phenyl-3-hydroxypropyl amine **3** (20.0 g, 0.12 mol), *o*-cresol **4** (16.0 g, 0.14 mol), and *p*-TSA (27.6 g, 0.15 mol), in toluene (150 mL) was heated with continuous removal of water for 8 h. The pH of the reaction mixture was adjusted between 7.5 and 8.5 by adding

water (150 mL) and 10% NaOH solution, and layers were separated. The organic layer was washed with water (2 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated to furnish the compound **10**, crystallized from petroleum ether (40 : 60), mp 99°C. IR: cm^{-1} (KBr) 3435, 3300, 2945, 2911, 2853, 1592, 744, 708. Mass: m/z 256 (M^+). ^1H NMR: $CDCl_3$ δ ppm 2.72–2.75 (m, 2H), 2.25 (s, 3H), 2.04–2.33 (m, 2H), 4.60 (d, 1H), 2.40 (s, 3H), 6.47–7.28 (m, Ar-H). ^{13}C NMR: $CDCl_3 + CD_3CN$ δ ppm 16.16, 47.12, 32.77, 38.23, 34.38, 126.3–129.3.

N-Methyl-3[3-(2-hydroxy-4-methylphenyl)]phenylpropylamine 11

Mp 96–97°C. IR: cm^{-1} (KBr) 3433, 3302, 2925, 2860, 2799, 1600, 744, 698. Mass: m/z 256 (M^+). ^1H NMR: $CDCl_3$ δ ppm 2.58–2.65 (m, 2H), 2.38 (s, 3H), 2.02–2.35 (m, 2H), 4.49 (d, 1H), 2.47 (s, 3H), 6.25–7.15 (m, Ar-H). ^{13}C NMR: $CDCl_3 + CD_3CN$ δ ppm 17.16, 57.12, 30.29, 37.23, 36.38, 126.7–129.6.

N-Methyl-3[3-(2-hydroxy-5-methylphenyl)]phenylpropylamine 12

Mp 94°C. IR: cm^{-1} (KBr) 3436, 3310, 2924, 2854, 2799, 1603, 731, 700. Mass: m/z 256 (M^+). ^1H NMR: $CDCl_3$ δ ppm 2.58–2.66 (m, 2H), 2.15 (s, 3H), 2.04–2.40 (m, 2H), 4.49 (d, 1H), 2.47 (s, 3H), 6.43–7.28 (m, Ar-H). ^{13}C NMR: $CDCl_3 + CD_3CN$ δ ppm 18.16, 51.12, 30.29, 39.23, 36.08, 126.4–129.3.

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