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Convenient Synthesis of Tolcapone, a Selective Catechol-*O*-methyltransferase Inhibitor

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Abstract: A convenient and efficient synthesis of tolcapone from commercial 4-benzyloxy-3-methoxybenzaldehyde is presented. Grignard reaction of 4-benzyloxy-3-methoxybenzaldehyde (**1**) with *p*-tolylmagnesium bromide followed by Oppenauer oxidation of the hydroxyl functionality and subsequent *O*-debenzylation gave phenol **5**. Compound **5** was regioselectively nitrated and then subjected to *O*-demethylation to produce tolcapone in 60% overall yield.

Keywords: catechol-*O*-methyltransferase, nitration, tolcapone

INTRODUCTION

Tolcapone is a highly potent and selective peripheral and central catechol-*O*-methyltransferase (COMT) inhibitor used as an adjunct to the levodopa/carbidopa medication of Parkinson's disease, a dopamine-deficiency disorder.[1] Tolcapone potentiates and prolongs the effect of levodopa in the central nervous system (CNS) by enhancing levodopa's transport into the CNS and slowing the metabolism of brain dopamine. Unfortunately, because of concerns about its liver toxicity, tolcapone was recently withdrawn from the market in some countries.[2] The cause of

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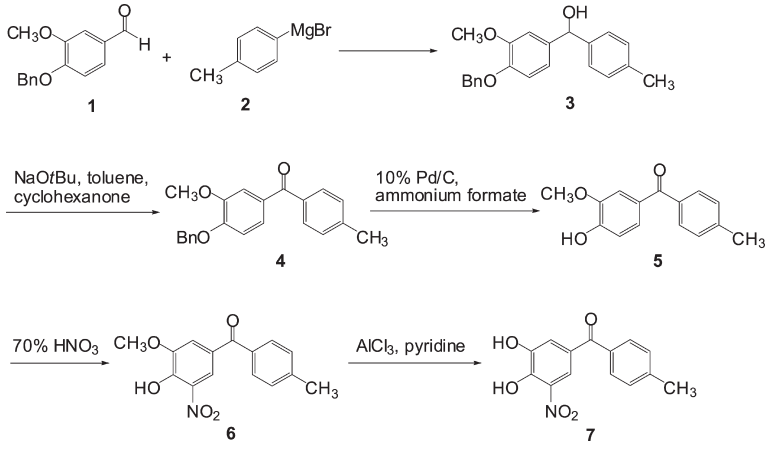
tolcapone's liver toxicity is currently not fully understood. To further investigate the mechanism of tolcapone's toxicity and obtain a more potent, selective, and safe COMT inhibitor, tolcapone and its 3-nitrocatechol-based derivatives continue to be investigated.[3]

The synthesis of tolcapone was first reported in a patent by Bernauer et al.[4] However, their synthesis involved a low-temperature reaction (−70°C for addition of *p*-tolyl-lithium to 4-benzyloxy-3-methoxybenzaldehyde) and toxic (e.g., pyridinium chlorochcamate (PCC) for oxidation) and corrosive (e.g., HBr for *O*-dealkylation) reagents, which are neither environmentally friendly nor suitable for large-scale preparation. In addition, the experimental details and characterization data of key intermediates, as well as tolcapone, were not well reported.[4] In this article, an efficient, economical, and environmentally acceptable synthesis of tolcapone from commercially available 4-benzyloxy-3-methoxybenzaldehyde is described. The full characterization data of all intermediates and tolcapone are also presented for future comparison.

RESULTS AND DISCUSSION

Synthesis of tolcapone was accomplished following the route outlined in Scheme 1. Treatment of commercial 4-benzyloxy-3-methoxybenzaldehyde (**1**)[5] with *p*-tolylmagnesium bromide (**2**) in tetrahydrofuran (THF) at 0°C gave the Grignard adduct **3** in 91% yield. Oppenauer oxidation[6] of **3** using sodium *tert*-butoxide as the base and cylcohexanone as a hydrogen acceptor afforded an 89% yield of ketone **4**. This Oppenauer oxidation is more convenient than PCC oxidation[4] both in terms of operational simplicity and use of inexpensive and nontoxic reagents. Palladium-catalyzed deprotection



Scheme 1.

of the benzyl protecting group using ammonium formate as a hydrogen donor provided phenol **5** in 92% yield. Regioselective nitration of **5** was first tried following the literature procedure.[4] However, addition of 70% nitric acid to the solution of **5** in acetic acid at room temperature gave only a small amount of desired product **6**, along with other unidentified by-products. ^{1}H NMR analysis of the major by-product suggested that it was a dinitrated compound, but a full characterization of this by-product was not conducted to confirm its structural assignment. The nitric acid addition was observed to generate a significant amount of heat, possibly contributing to the low yield and by-product profile. Therefore, the procedure was modified by using a lower reaction temperature (0°C) and a more dilute nitric acid solution. As a result of these modifications, the nitro compound **6** was obtained in 88% yield after recrystallization from ethanol.

According to the procedure of Bernauer et al.,[4] the methyl ether cleavage was achieved with moderate yield under standard forcing conditions (48% HBr, acetic acid, and reflux). Recently, Learmonth and coworkers[7] have reported an improved *O*-demethylation of nitro catechol methyl ethers using aluminum chloride and pyridine in warm ethyl acetate, which is suitably mild and appropriate for large-scale demethylation of **6**. Accordingly, treatment of **6** with aluminum chloride and pyridine in ethyl acetate at reflux for 2 h furnished tolcapone (**7**) in 91% yield.

In summary, we have developed an efficient and economical synthesis of tolcapone in 60% overall yield from commercial 4-benzyloxy-3-methoxybenzaldehyde (**1**). No column purifications were needed for this synthesis. Our synthesis of tolcapone is potentially applicable to other biologically active 3-nitrocatechol analogues.

EXPERIMENTAL

Reagents were obtained from Aldrich Chemical Company and used as received. Melting points were determined on a Mel-Temp II capillary melting-point apparatus and are uncorrected. NMR (^{1}H and ^{13}C) spectra were obtained using a Bruker Avance DPX 300-MHz or a Varian Unity Inova 500-MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Mass spectra (MS) were recorded on a Perkin-Elmer Sciex APR 150 EX mass spectrometer. Elemental analysis was done by Atlantic Microlab, Inc., Norcross, GA. Analytical thin-layer chromatography (TLC) was carried out using EMD silica-gel 60 F_{254} TLC plates.

1-(4-Benzyloxy-3-methoxyphenyl)-1-(4-methylphenyl)methanol (3)

A solution of 4-benzyloxy-3-methoxybenzaldehyde (**1**) (30.0 g, 0.12 mol) in THF (120 mL) was slowly added to a stirred 1 M solution of

p-tolylmagnesium bromide (**2**) (150 mL, 0.15 mol) in THF at 0°C under nitrogen. After being stirred at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in Et_2O (450 mL) and cooled to 0°C, and a 2 N HCl solution (50 mL) was carefully added. The phases were separated, and the aqueous phase was extracted with Et_2O (100 mL). The combined organic extract was washed with brine (100 mL), dried, (Na_2SO_4), and concentrated in vacuo. The resultant crude product was recrystallized from CH_2Cl_2–petroleum ether to give **3** (37.6 g, 91% yield) as a white solid: mp 101–103°C (lit.[4] oil); ^{1}H NMR (300 MHz; $CDCl_3$) δ 2.19 (1H, d, $J = 3.5$ Hz), 2.32 (3H, s), 3.84 (3H, s), 5.11 (2H, s), 5.72 (1H, d, $J = 3.5$ Hz), 6.79–7.42 (12H, m); ^{13}C NMR (75 MHz; DMSO-d_6) δ 20.9, 55.8, 70.4, 74.2, 110.8, 113.8, 118.6, 126.4, 128.0, 128.1, 128.4, 128.7, 128.8, 129.2, 135.9, 137.6, 139.3, 143.2, 146.9, 149.2.

1-(4-Benzyloxy-3-methoxyphenyl)-1-(4-methylphenyl)methanone (4)

Sodium *tert*-butoxide (11.7 g, 0.12 mol) was added to a stirred suspension of **3** (26.0 g, 0.08 mol) in toluene (350 mL) at room temperature under nitrogen, followed by cyclohexanone (47.7 g, 0.49 mol). After being refluxed for 1 h, the reaction mixture was cooled to 50°C, and H_2O (60 mL) was slowly added with stirring. The phases were separated, and the aqueous phase was extracted with EtOAc (60 mL). The combined organic extract was washed with brine (100 mL), dried, (Na_2SO_4), and concentrated in vacuo. The resultant crude product was recrystallized from 95% EtOH (75 mL) to give **4** (23.1 g, 89% yield) as a white solid: mp 70–72°C (lit.[4] 79–81°C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 2.43 (3H, s), 3.94 (3H, s), 5.23 (2H, s), 6.88–7.68 (12H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 23.3, 56.1, 70.8, 112.0, 112.7, 125.0, 127.2, 128.0, 128.6, 128.8, 130.0, 130.8, 131.5, 135.4, 136.4, 142.6, 149.4, 152.0, 195.4; MS (ESI) m/z 333.5 $[M + H]^+$.

1-(4-Hydroxy-3-methoxyphenyl)-1-(4-methylphenyl)methanone (5)

A mixture of **4** (19.5 g, 0.06 mol), 10% Pd-C (1.00 g), and ammonium formate (17.6 g, 0.28 mol) in MeOH (200 mL) was refluxed under nitrogen for 30 min. After being cooled to 0°C, H_2O (70 mL) and concentrated HCl (20 mL) were slowly added, followed by additional H_2O (80 mL) and CH_2Cl_2 (300 mL). The mixture was filtered through a short pad of Celite®, and the filter cake was washed with CH_2Cl_2 (60 mL). The organic phase of the filtrate was separated, washed with brine (100 mL), dried, (Na_2SO_4), and concentrated in vacuo. The resultant crude product was recrystallized from CH_2Cl_2–petroleum ether to give **5** (13.0 g, 92% yield) as a white solid: mp 98–100°C (lit.[4] 103–105°C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 2.43 (3H, s),

3.94 (3H, s), 6.24 (1H, br s), 6.93 (1H, d, $J = 8.2$ Hz), 7.28–7.35 (3H, m), 7.49 (1H, s), 7.67 (2H, d, $J = 8.2$ Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ 21.6, 56.1, 111.9, 113.5, 126.3, 128.8, 129.0, 129.1, 135.5, 142.5, 146.6, 149.9, 195.3; MS (ESI) m/z 243.4 $[M + H]^+$.

1-(4-Hydroxy-3-methoxy-5-nitrophenyl)-1-(4-methylphenyl) methanone (6)

A mixture of 70% HNO_3 (1.5 mL) and acetic acid (2 mL) was slowly added to a stirred solution of **5** (2.40 g, 0.01 mol) in acetic acid (20 mL) at 0°C under nitrogen. After being stirred at 0°C for 30 min, the reaction mixture was poured into ice water. The resultant precipitate was collected by filtration and washed with cold H_2O. The crude product was recrystallized from EtOH to give **6** (2.50 g, 88% yield) as a white solid: mp 135–137°C (lit.[4] 137–139°C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 2.47 (3H, s), 4.03 (3H, s), 7.33 (2H, d, $J = 8.0$ Hz), 7.69 (2H, d, $J = 8.0$ Hz), 7.71 (1H, d, $J = 1.5$ Hz), 8.10 (1H, d, $J = 1.5$ Hz); ^{13}C NMR (75 MHz; DMSO-d_6) δ 21.4, 57.0, 115.6, 119.6, 127.3, 129.1, 129.5, 129.7, 129.9, 134.3, 136.5, 143.4; MS (ESI) m/z 288.4 $[M + H]^+$.

1-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-methylphenyl)methanone (Tolcapone) (7)

$AlCl_3$ (3.50 g, 0.026 mol) was added to a stirred suspension of **6** (6.00 g, 0.021 mol) in EtOAc (60 mL) at room temperature under nitrogen, followed by pyridine (6.60 g, 0.084 mol). The red solution was refluxed for 2 h and then cooled to 60°C, whereupon the reaction mixture was carefully added to a mixture of ice and concentrated HCl (24 mL). After being stirred at 50°C for 1 h, the mixture was kept in the refrigerator overnight. The resultant precipitate was collected by filtration, washed with cold H_2O, and dried in vacuo for 10 h at 60°C to give **7** (5.20 g, 91% yield) as a yellow solid: mp 141–143°C (lit.[4] 146–148°C); ^{1}H NMR (500 MHz; DMSO-d_6) δ 2.42 (3H, s), 7.37 (2H, d, $J = 8.0$ Hz), 7.47 (1H, d, $J = 1.5$ Hz), 7.64 (2H, d, $J = 8.0$ Hz), 7.66 (1H, d, $J = 1.5$ Hz); ^{13}C NMR (75 MHz; DMSO-d_6) δ 21.1, 117.7, 119.1, 127.0, 129.1, 129.5, 134.2, 136.6, 142.9, 145.7, 147.7, 192.7; MS (ESI) m/z 274.5 $[M + H]^+$; Anal. calcd. for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.83; H, 4.05; N, 5.19.

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