First synthesis of 3-methoxy-4-aminopropiophenone

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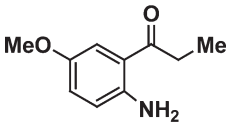
The transformation of 3-methoxyphenylacetone to 4-amino-3-methoxypropiophenone is described.

Keywords: camptothecins, reduction, irradiation, oxidation, amino ketone

Several routes[1] have been developed for the synthesis of 2-amino-5-methoxypropiophenone **1** which is a convenient starting material for the construction of the A/B ring of the alkaloid CPT (camptothecin), of CPT-11 (a semi-synthetic water-soluble derivative of CPT) and of SN-38 (a metabolite of CPT-11), all three of which have exhibited antitumour effects. However, to the best of our knowledge, there are no reports on the synthesis of 3-methoxy-4-aminopropiophenone **2** which on condensation[2] with dimethyl acetylenedicarboxylate and cyclisation is expected to lead to the formation of kynurenic acid derivatives.[3]



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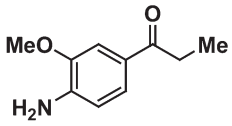


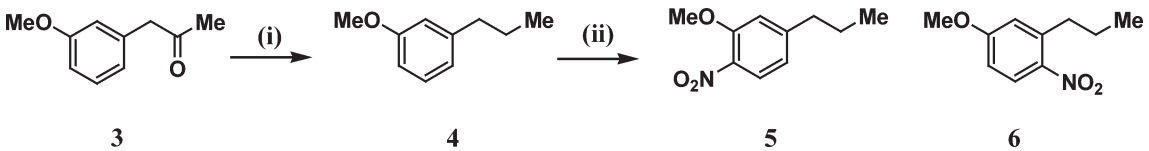
2

Kynurenic acid derivatives have been evaluated[3] for their *in vitro* antagonist activity at the excitatory amino acid receptors that are sensitive to N-methyl-D-aspartic acid, quisqualic acid and kainic acid. ε-Aminoquinolinecarboxylic acid has recently been utilised for the synthesis of novel macrocyclic peptides.[4] Keeping in mind the biological properties of quinolone derivatives we have developed the first synthesis of the substituted propiophenone **2**. The synthetic details are described in Scheme 1.

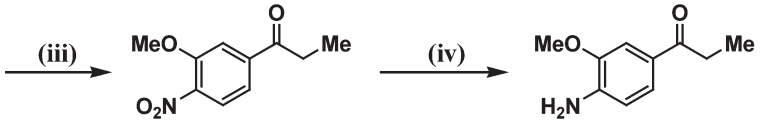
Results and discussion

Wolff–Kishner reduction of the commercially available of 3-methoxyphenylacetone **3** under microwave irradiation[5] led to the known compound **4** in 82% yield. Although **4** has been synthesised by different methods[6,7] our method is different and easy to manipulate compared to those reported. Nitration[8] of **4** with copper(II) nitrate hydrate and acetic anhydride in ether afforded the nitro compound **5** in 53% yield.

Nitration under solvent-free conditions using a mixture of nitric acid (65%) and sulfuric acid and nitric acid (65%) in the presence of P_2O_5 supported on silica gel[9] yielded the nitro compound **5** in low yield. The position of the NO_2 at C-4 was confirmed not only by ^1H and ^{13}C NMR spectroscopy but also by two dimensional (2D HMQC and HMBC) spectroscopy. In the HMQC spectra, the signals at δ 6.78 and δ 120.2 were correlated with the proton and carbon at C-6. Similarly the signals at δ 7.75 and δ 125.7 and the signals at δ 6.84 and δ 113.3 exhibit a correlation between the proton and the carbon at C-5 and C-2 respectively. In the HMBC spectra, the signals at δ 2.59 and δ 137.2 showed a correlation between the proton at C-7 and C-4. Similarly the signals at δ 7.75 and δ 137.2 and the signals δ 6.84 and δ 137.2 showed a correlation between the protons and carbons at H-5 and C-4 and H-2 and C-4 respectively. These spectroscopic data lend strong support in favour of the structure of **5**. No trace of 5-methoxy-2-nitropropylbenzene **6** was detected. Oxidation[10] of **5** with pyridinium chlorochromate (PCC) afforded the nitroketone **7** in 43% yield. Oxidation was also attempted with $KMnO_4$/bentonite in hexane,[11] nitric acid in hexane[12] and 2,6-dichloro-5,6-dicyano-1,4- benzoquinone (DDQ) in THF[13] but the yield of the nitroketone could not be improved. The difficulty in obtaining high yield of the nitroketone can only be explained by assuming that the nitro group deactivated not only the aromatic ring but also the benzylic group. The synthesis of the nitroketone **7** had been reported[14] by Katritzky and collaborators by a different route but without experimental details and spectroscopic data. Finally the conversion of **7** to the desired aminoketone **2** in 60% yield was accomplished by reduction[15] with Pd/C (10%) and ammonium formate (HCO_2NH_4). The spectroscopic data of **2** were consistent with the structure assigned to the aminoketone.



3 **4** **5** **6**



7 **2**

Reagents: (i) $N_2H_4 \cdot H_2O$, KOH , DEG ; (ii) $Cu(NO_3)_2 \cdot H_2O$, Ac_2O , Et_2O ;

(iii) PCC , C_6H_6 ; (iv) HCO_2NH_4 , Pd/C (10%)

Scheme 1

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In conclusion the synthesis of the 3-methoxy-4-aminopropiophenone is described for the first time from commercially available methoxyphenylacetone **3**. Its transformation into the kynurenic acid derivative following the literature procedure[2,3] will be attempted shortly.

Experimental

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet-Fourier Transform (FT) instrument and NMR (^{1}H and ^{13}C) spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$. Chemical shifts (δ) are expressed in ppm. Mass spectra (MS) were determined on a Dupont 21-492B. Column chromatography was carried out on silica gel 60 (Merck). The organic extracts (ether or chloroform) were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. TLC plates were coated with silica gel 60F254 and the spots were visualised using UV light. Elemental analyses were performed on a Carlo-Erba 1108 elemental analyser. Microwave irradiations were carried out with a microwave oven (2.45 GHz, 300W) (Trade Mark Discover, CEM).

3-Methoxypropylbenzene (**4**): A solution of 3-methoxyphenylacetone **3** (1.01 g, 6.1 mmol) in diethylene glycol (DEG) (12 mL) was treated with KOH (2.22 g, 39.6 mmol) and 80% hydrazine monohydrate ($N_2H_4.H_2O$) (1.10 mL, 22.8 mmol) and was irradiated in a microwave oven at 100W for 20 min at 112 °C and then for 30 min at 180 °C. The reaction mixture was cooled to room temperature, diluted with water (30 mL) and extracted with ether (150 mL). The ethereal extract was washed, dried and evaporated to afford an oil which was chromatographed (hexane) to yield **4** (750 mg, 82%) as a colourless oil. MS (*m/z*): 150 (M^+) (100%); ^{1}H NMR: δ 7.27 (t, 1H, 5-H, *J* = 7.6 Hz), 6.88–6.80 (m, 3H, H-2, H-6, H-4), 3.86 (s, 3H, OMe), 2.66 (t, 2H, *J* = 7.8 Hz), 1.78–1.68 (m, 2H), 1.04 (t, 3H, *J* = 7 Hz) (H-7, H-8, H-9); ^{13}C NMR: δ 159.6 (C-3), 144.2 (C-1), 129.1 (C-5). 120.9 (C-6), 114.2 (C-2), 110.8 (C-4), 54.9 (C-10), 38.1 (C-7), 24.4 (C-8), 13.7 (C-9). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.16; H, 9.24%.

3-Methoxy-4-nitro-propylbenzene (**5**): Compound **4** (0.425 g, 2.83 mmol) was added to a stirred suspension of copper (II) nitrate hydrate (0.531 g, 2.83 mmol), acetic anhydride (3 mL) and diethyl ether (6 mL) and stirred at room temperature until the consumption of the starting material was complete (*ca* 4 h, TLC). The mixture was filtered through Celite, washed with ether (150 mL) and the filtrate was concentrated *in vacuo*. Preparative chromatography (hexane: ether 9:1) afforded **5** (295 mg, 53%) as a yellow oil. MS (*m/z*): 196 (M^+ + 1), 195 (M^+); ^{1}H NMR: δ 7.75 (d, 1H, *J* = 8.3 Hz), 6.84 (d, 1H, *J* = 1.1 Hz) (H at C-5 and C-2), 6.78 (dd, 1H, *J* = 8.3 Hz, *J* = 1.1 Hz), (H at C-6), 3.90 (s, 3H, OMe), 2.59 (t, 2H, *J* = 7.8 Hz), 1.63–1.58 (m, 2H, *J* = 7.6 Hz) (H at C-7 and C-8), 0.90 (t, 3H, *J* = 7.6 Hz) (H at C-9); ^{13}C NMR: δ 153.1 (C-3), 150.6 (C-1), 137.2 (C-4), 125.7 (C-5), 120.2 (C-6), 113.3 (C-2), 56.2 (C-10), 38.1 (C-7), 23.9 (C-8), 13.5 (C-9). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.66. Found C, 61.31; H, 6.81%.

3-Methoxy-4-nitropropiophenone (**7**): Pyridinium chlorochromate (3.84 g, 17.8 mmol) was added to a solution of the nitro compound **5** (661 mg, 3.4 mmol) in benzene (40 mL). The mixture was stirred, heated under reflux for 24 h, cooled and filtered through a short pad of Celite. The filtrate was evaporated and purified using a preparative chromatography plate. Elution with hexane: ether (9:1) afforded the nitroketone **7** (307 mg, 43%) as a pale yellow crystalline solid, m.p. 65–67 °C (from hexane); MS (*m/z*): 210 (M^++1), 209 (M^+); ^{1}H NMR: δ 7.84 (d, 1H, *J* = 8.3 Hz), 7.66 (d, 1H, *J* = 1.5 Hz), 7.56–7.53 (dd, 1H, *J* = 8.3 Hz, *J* = 15 Hz) (H at C-5, C-2 and C-6), 3.99 (s, 3H, MeO), 3.01 (q, 2H, *J* = 7 Hz) (H at C-8), 1.22 (t, 3H. *J* = 7 Hz) (H at C-9); ^{13}C NMR: δ 199 (C-7), 152.8 (C-3), 142.2 (C-4), 140.9 (C-1), 125 (C-5), 119.8 (C-6), 112.6 (C-2), 56.7 (C-10), 32.3 (C-8), 7.9 (C-9). Anal. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.26. Found: C, 57.23; H, 5.38%.

3-Methoxy-4-aminopropiophenone (**2**): Ammonium formate (177 mg, 2.8 mmol) was added to a solution of the nitroketone **7** (125 mg, 0.59 mmol) in methanol (2 mL). After stirring for 10 min under nitrogen, Pd–C (10%, 67 mg) was added. The reaction mixture was heated using a microwave oven at 45W for 20 min. The catalyst was removed by filtration and washed with methanol. The filtrate was concentrated under reduced pressure and the resulting residue on purification using a preparative chromatography plate (hexane: ether 9:1), afforded the aminoketone **2** (63 mg, 60%) as pale yellow crystalline solid, m.p. 89–92 °C (from hexane); IR (cm^{-1}): 3437–3338 (NH_2), 1660 (CO); MS (*m/z*): 179 (M^+); ^{1}H NMR: δ 7.46–7.43 (m, 2H), 6.63 (d, 1H, *J* = 8.5 Hz) (H at C-6, C-2, C-5), 4.26 (bs, 2H, NH_2), 3.88 (s, 3H, OMe), 2.89 (q, 2H, *J* = 7.3 Hz), 1.18 (t, 3H, *J* = 7.3 Hz) (H at C-8 and C-9); ^{13}C NMR: δ 199.4 (C-7), 146.5 (C-3), 141.4 (C-4), 127.5 (C-1), 123.4 (C-6), 112.6 (C-2), 109.3 (C-5), 55.6 (C-10), 31.0 (C-8), 8.9 (C-9). Anal. Calcd for $C_{10}H_{13}O_2N$: C, 67.03; H, 7.26. Found: C, 66.84; H, 7.38%.

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