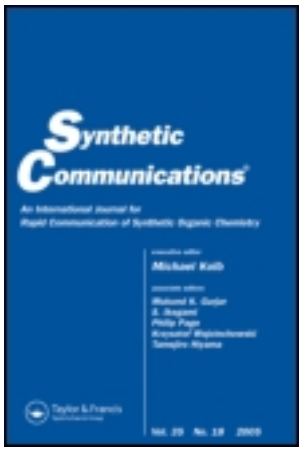

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A SIMPLE METHOD FOR THE SYNTHESIS OF 2-AMINO-1-(4′-METHOXYPHENYL)-PROPANE

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A SIMPLE METHOD FOR THE SYNTHESIS OF 2-AMINO-1-(4′-METHOXYPHENYL)-PROPANE

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ABSTRACT

Synthesis of 2-amino-1-(4′-methoxyphenyl)-propane (**II**) starting from *p*-anisaldehyde (**1**) in 67% overall yield is described. Key reactions involved Horner–Wadswoth–Emmons olefination of **1** to form the ester **2** and Hoffmann degradation of amide **5** to obtain the amine **II**.

β-Arylethylamine functionality is essential to many amphetamine drugs that offer high selectivity for β_2-adrenoceptors.[1] A variety of β_2-adrenoceptor agonists have been prepared for treatment of asthma and chronic bronchitis.[2] Among them formoterol (**I**) offers high selectivity for β_2-adrenoceptors and has excellent safety, tolerance profile and has been commercialized in racemic form.[3] Synthesis of **I** requires preparation of 2-amino-1-(4′-methoxyphenyl)-propane (**II**) by a process which is amenable to scale up, avoids use of hazardous reagents, elevated temperature and pressure. Synthetic procedures to prepare β-phenyl ethylamine **II** describes Henry reaction of *p*-anisaldehyde

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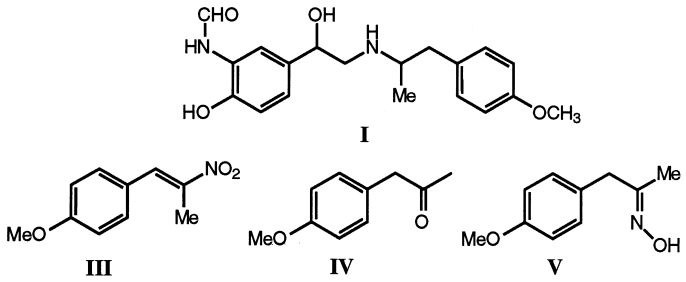
(**1**) to obtain the key intermediate β-nitrostyrene[4] **III** followed by hydrogenation at high pressure in presence of Pd/C[5] or RED-AL[4b] or by refluxing with $LiAlH_4$ in Et_2O[4f] to obtain the amine **II** in 70–85% yield in one approach and in the second **III** was converted to the keto compound **IV** by reaction with Fe/aq. HCl[4a], or $NaH_2PO_2.H_2O$/Raney–Ni at pH 5[6] or $HClO_4$[7] or Zn–TFA.[8] The keto compound **IV** was converted to the corresponding oxime **V**[9b] by reaction with $NH_2OH.HCl$ followed by reduction with Raney–Ni at high pressure[4a] to obtain the amine **II** in 40–43% overall yield.



We report herein a simple laboratory method for the preparation of amine **II**. Horner–Wadsworth–Emmons reaction of **1** with ethyl-(2-dimethoxyphosphinyl)-2-propanoate[10] (1.1 mol equiv.) and NaO^tBu (1.5 mol equiv.) in toluene at room temperature for 15 min gave the α/β-unsaturated ester **2** which on catalytic hydrogenation (1 atm.) with 10% Pd/C in MeOH for 4 h gave the saturated ester **3**, while progress of the reaction was monitored by HPLC (experimental). Hydrolysis of **3** with aq. NaOH (20%) and a catalytic amount of cetrimide at reflux temperature for 5 h gave the acid derivative **4**. Compound **4** was transformed to the amide **5** (mp: 119–121°C) by reaction with $SOCl_2$ followed by quenching with methanolic ammonia solution at −5°C. Hoffman degradation of amide **5** by reaction with NaOBr at 70°C for 2 h gave the amine **II** in 67% overall yield from *p*-anisaldehyde (**1**).

In conclusion a simple, high yielding laboratory method for the preparation of racemic amphetamine derivative **II** has been achieved starting from *p*-anisaldehyde.

EXPERIMENTAL

Flame dried glassware, commercially available solvents and reagents were used without further purification unless otherwise stated. Melting

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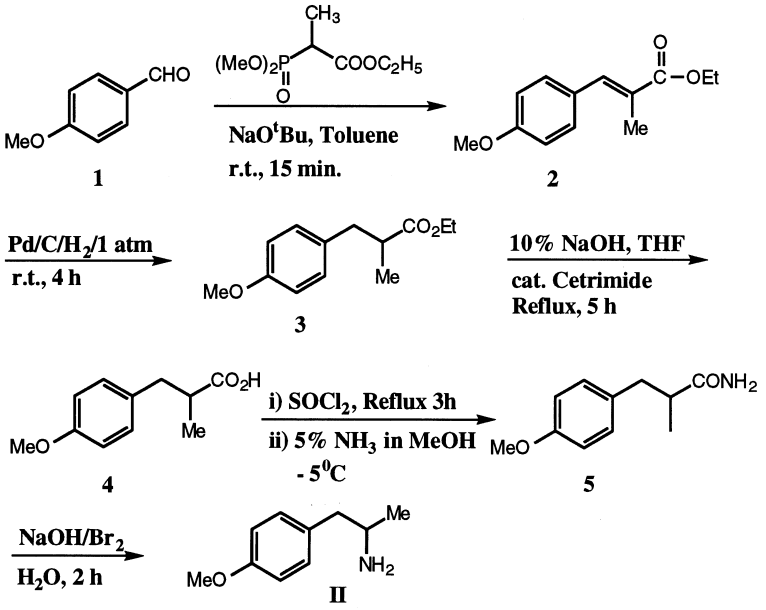

Scheme.

points were measured using capillary tubes and are uncorrected. ^{1}H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer with a tetramethyl silane as an internal standard for solutions in deuterochloroform. IR spectra were taken with a Perkin Elmer 1310 spectrometer. Mass spectra were obtained on a VG 70-70H instrument.

Ethyl-3-(4′-methoxyphenyl)-2-methyl-2-propenoate (2)

To a solution of *p*-anisaldehyde **1** (32 g, 0.24 mol), toluene (160 mL) and ethyl-(2-dimethoxyphosphinyl)-2-propanoate (58.8 g, 0.28 mol) was added NaO^{t}Bu (33.6 g, 0.35 mol) at 0°C under N_2 atmosphere during half an hour. The reaction mixture was brought to room temperature and stirred for 15 min. Progress of the reaction was monitored by t.l.c. [AcOEt : Hexane; 1:4] from the appearance of a faster moving spot. After completion of the reaction, the reaction mixture was neutralised with 10% aq. HCl. The toluene layer was separated, washed with water (2×100 mL), dried (Na_2SO_4) and concentrated to obtain the title compound **2** in quantitative yield as a syrup (51.6 g). IR (neat): 1694, 1600, 1514, 1200, 1050, 965, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, J = 6.5 Hz, -CH_2-C$\underline{H}_3$), 2.15 (s, 3H, -C$\underline{H}_3$),

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3.85 (s, 3H, -OC$\underline{H}_3$), 4.25 (q, 2H, OC$\underline{H}_2$-CH_3), 6.91 (d, 2H, J = 10 Hz, Ar-$\underline{H}$), 7.35 (d, 2H, Ar-$\underline{H}$), 7.62 (s, 1H, H-3); EI MS (*m*/*z*, %): 220 (M^+, 100%); Anal. Calcd. (Found) for $C_{13}H_{16}O_3$: C, 70.89 (70.72); H, 7.32 (7.37).

Ethyl-3-(4′-methoxyphenyl)-2-methyl-propanoate (3)

To a solution of **2** (32 g, 0.145 mol) in MeOH (160 mL) was added Pd/C 10% (1.0 g) and subjected to hydrogenation (1 atm.) for 4 h. Progress of the reaction was monitored by HPLC (Eluant: 70% CH_3CN in H_2O, **2** had a retention time of 8.3 min and compound **3** of 7.3 min). After completion of the reaction, the catalyst was filtered off and the filtrate was concentrated to obtain the title compound **3** in quantitative yield (31.8 g) as a syrup. IR (neat): 1725, 1513, 1450, 1247, 1176, 1003, 800 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 6.0 Hz, -CH_2-C$\underline{H}_3$), 1.21 (d, 3H, J = 6.5 Hz, -CHC$\underline{H}_3$), 2.50–2.75 (m, 2H, Ph-C$\underline{H}_2$), 2.80–3.10 (m, 1H, -CH-C$\underline{H}_3$), 3.72 (s, 3H, -OC$\underline{H}_3$), 4.08 (q, 2H, O-C$\underline{H}_2$-CH_3), 6.81 (d, J = 8.0 Hz, 2H, Ar-$\underline{H}$), 7.08 (d, 2H, Ar-$\underline{H}$); EI MS (*m*/*z*, %): 222 (M^+, 26%); Anal. Calcd. (Found) for $C_{13}H_{18}O_3$: C, 70.24 (70.01); H, 8.16 (8.11).

3-(4′-Methoxyphenyl)-propanoic Acid (4)

To a solution of **3** (25 g, 0.11 mmol) in THF (93 mL) was added NaOH (8.96 g in 46 mL H_2O) (0.22 mol), citrimide (0.2 g) and refluxed for 5 h. The progress of the reaction was monitored by t.l.c. [AcOEt : Hexane; 2:3] from the appearance of a slower moving spot. After completion of the reaction, THF was removed on a rotary evaporator and the reaction mixture was acidified with 10% aq. HCl and extracted into CH_2Cl_2 (125 mL). The organic layer was separated, washed with water (2 × 100 mL), dried (Na_2SO_4) and concentrated to obtain the title compound **4** in quantitative yield (21.5 g) as a syrup. IR (neat): 1710, 1600, 1513, 1450, 1247, 1098, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (d, 3H, J = 5.9 Hz, -CH_2-C$\underline{H}_3$), 2.10–3.10 (m, 3H), 3.78 (s, 3H, -OC$\underline{H}_3$), 6.78 (d, 2H, J = 5.9 Hz, Ar-$\underline{H}$), 7.06 (d, 2H, Ar-$\underline{H}$); EI MS (*m*/*z*, %): 194 (M^+, 8%). Anal. Calcd. (Found) for $C_{11}H_{14}O_3$: C, 68.02 (68.19); H, 7.27 (7.21).

3-(4′-Methoxyphenyl)-2-methyl-propanamide (5)

A solution of **4** (20 g, 0.10 mol) in $SOCl_2$ (14.6 mL, 0.20 mol) was heated to reflux for 2 h. After completion of the reaction, thionyl chloride

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was distilled off to obtain a residue which was dissolved in MeOH (60 mL), cooled to −5°C under nitrogen atmosphere and a 5% solution of ammonia in MeOH (3.50 g in 70 mL MeOH, 0.20 mol) was added dropwise under efficient stirring at −5°C. After completion of the reaction, methanol was removed on a rotary evaporator to obtain a solid which was filtered, washed with water (100 mL) and dried to obtain the title compound **5** in quantitative yield (19.30 g). mp: 119–121°C; IR (KBr): 3388, 3200, 1662, 1600, 1498, 1459, 1247, 1035 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.18 (d, 3H, J = 5.0 Hz, -CH-C$\underline{H}_3$), 2.62 (dd, 1H, $J_{2,3a}$ = 5.0 Hz, J_{gem} = 12.5 Hz, Ph-C$\underline{H}_2$), 2.88 (dd, 1H, $J_{2,3b}$ = 7.5 Hz, Ph-C$\underline{H}_2$), 3.78 (s, 3H, -OC$\underline{H}_3$), 6.78 (d, 2H, J = 6.5 Hz, Ar-$\underline{H}$), 7.08 (d, 2H, Ar-$\underline{H}$); EI MS (*m*/*z*, %): 193 (M^+, 10%). Anal. Calcd. (Found) for $C_{11}H_{15}O_2N$: C, 68.37 (68.11); H, 7.82 (7.73); N, 7.25 (7.19).

2-Amino-1-(4′-methoxyphenyl)-propane (II)

To a stirred solution of sodium hypobromite [Br_2 (4.6 mL, 0.09 mol), NaOH (18.72 g, 0.48 mol) in 150 mL water] was added a finely divided amide **5** (15 g, 0.078 mol) at 0°C during 10 min. The reaction mixture was heated to 70°C for 2 h. The progress of the reaction was monitored by t.l.c. (BuOH : EtOH : NH_3, 7:2.6:0.3 mL). After completion of the reaction, the reaction mixture was extracted into CH_2Cl_2 (75 mL). Organic layer was separated, washed with water (2 × 75 mL), dried (Na_2SO_4) and concentrated to obtain the title compound **II** as a syrup (9.6 g, 75%) that exhibited comparable ^1H NMR spectrum with that reported in literature.[4f,11a] For the purpose of characterisation **II** was also converted to the corresponding hydrochloride[11b] [10.5 g, 65%, mp: 208–210°C (lit.[4a] 208°C)] by treating with 5% HCl in MeOH.

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