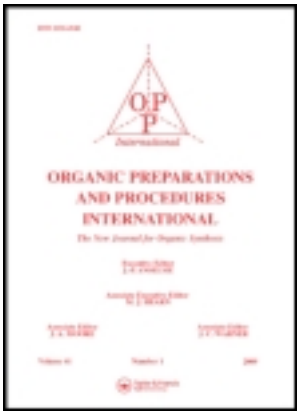

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OPPI BRIEF

An Efficient Synthesis of 7-Methoxy-1-naphthylacetic Acid

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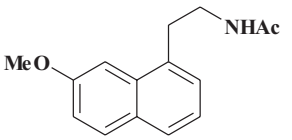
Naphthalenic ligands have a high affinity for the melatonin receptors.[1] *Agomelatin* (*N*-[2-(7-methoxynaphth-1-yl)ethy]acetamide **(1)**, a naphthalene analog of melatonin, is both an agonist of human cloned melatonergic MT1 and MT2 receptors and a serotonin 5-HT2C receptor antagonist.[2] 7-methoxy-1-naphthylacetic acid **(2)**, which is a key intermediate[1] for the synthesis of compound **1**, has recently been reported[3] in three steps from 7-methoxy-1-tetralone with a 76% overall yield. The acetic acid side chain was introduced using a Wittig-Horner reagent (diethyl ethoxycarbonylmethanephospho-nate) which is commercially available and can also be readily prepared.[4] The reagent causes eye and skin irritation. It may also cause irritation of the digestive and respiratory tract.[5] Thus it was considered worthwhile to develop an alternative method for the synthesis of the acid **2** as depicted in *Scheme 1*.



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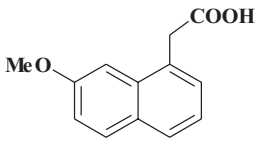

2

The reported[6] naphthalene **3**, was brominated by heating at 76°C in a microwave oven for 1.5 h with *N*-bromosuccinimide (NBS) and benzoyl peroxide in carbon tetrachloride (CCl_4) to afford bromide **4** in 97% yield. Heating the bromide **4** with sodium cyanide (NaCN) in dimethyl sulfoxide (DMSO) afforded the nitrile **5** in 99% yield whose conversion to the acid **2** was achieved in 93% yield (overall yield 89% from naphthalene **3**) by heating under reflux in a microwave oven for 40 min with an aqueous solution of sodium hydroxide

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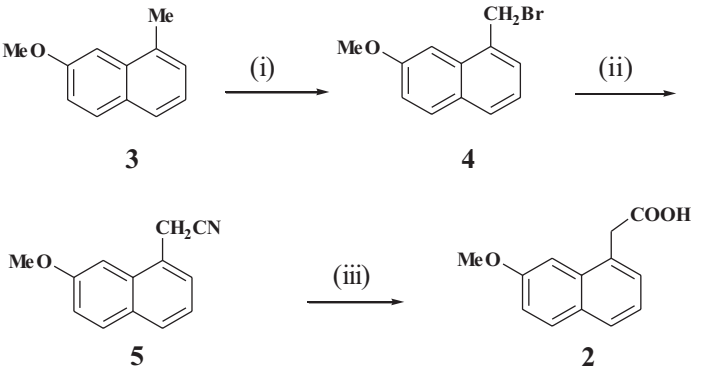

Reagents: (i) NBS, $(C_6H_5CO)_2O_2$, CCl_4; (ii) NaCN, DMSO; (iii) NaOH (50%).

Scheme 1

(50% NaOH in water). The spectral data (^{1}H NMR and ^{13}C NMR) strongly supported the structure of the acid **2**. The mp. of the acid was identical with that of the reported compound.[3]

In conclusion, an efficient and convenient route has been developed for acid **2** from naphthalene **3**. The overall yield of our route is 89% which is higher compared with the published[3] yield (76%). This route may be suitable and adapted for large scale synthesis of **2** as it avoids tedious purifications; all three steps proceed in high yields.

Experimental Section

Unless otherwise stated all melting point are uncorrected and were determined on an Electrothermal melting point apparatus. Infrared (IR) were recorded on a Nicolet-Fourier Transform (FT) instrument and NMR (^{1}H and ^{13}C) spectra were determined on a Bruker AM-300 spectrometer in CD_2Cl_2. Chemical shifts (δ) are expressed in ppm. Mass spectra (MS) were determined on a Dupont 21–492B instrument. Microwave irradiations were carried out using a CEM Discovery Labmate microwave oven (2.45 GHz, 300W), using flask (100 mL) of made of pyrex glass (No 4320), size 24/40 mm. Oberon chemically- resistant safety goggles (Aldrich Chemical Company) were utilized for carrying out experiments with Microwave irradiations. North vitron fluoroelastomer gloves and masks (3M) were utilized for carrying out reactions with sodium cyanide. Microwave irradiations and reactions with sodium cyanide were carried out in well-ventilated hood using appropriate aprons and hand gloves. Column chromatography was carried out on silica gel 60 (Merck). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Thin layer chromatography (TLC) plates were coated with silica gel and the spots were visualized using ultraviolet light. Elemental analyses were performed on a Carlo-Erba 1108 elemental analyser.

1-Bromomethyl-7-methoxynaphthalene (4)

To a solution of the naphthalene **3** (1.08 g, 6.19 mmol) in carbon tetrachloride (60 mL) was added *N*-bromosuccinimide (1.86 g, 10.45 mmol) and benzoyl peroxide (477 mg, 1.97 mmol). The mixture was stirred and heated under reflux in a microwave oven at 280W for 1.5 h. The reaction mixture was cooled to room temperature, filtered to remove succinimide and washed with carbon tetrachloride. The combined filtrate was evaporated *in vacuo* to afford an oil which was chromatographed (hexane:ether 9:1) to afford the naphthalene **4** (1.51 g, 97%) as a pale yellow solid, R_f 0.62 (hexane), mp. 85–87°C (from hexane). MS (m/z): 251 (M^+), 171 ($M^+ - 80$); ^{1}H NMR: δ 7.82 (d, 1H, ArH-4, $J = 8$ Hz); 7.80 (d, 1 H, ArH-5, $J = 8$ Hz), 7.55–7.52 (dd. 1H, ArH-6, $J = 7.1$ Hz, 1.2 Hz), 7.41 (d, 1H, ArH-8, $J = 2.5$ Hz), 7.22–7.18 (dd, 1H, ArH-2, $J = 8$ Hz, 2.5 Hz), 7.31–7.26 (t, 1H, ArH-3, $J = 7.1$ Hz), 4.98 (s, 2H, H at C-11), 3.98 (s, 3H, OMe); ^{13}C NMR: δ 158.4 (ArC-7), 132.7 (ArC-9), 132.3 (ArC-10), 131.9 (ArH-1), 130.6 (ArC-4), 129.7 (ArC-2), 128.6 (ArC-5), 123.3 (ArC-3), 119.1 (ArC-6), 102.9 (ArC-8), 55.7 (ArC-12), 33.1 (ArC-11).

Anal. Calcd. for $C_{12}H_{11}BrO$: C, 57.37; H, 4.38. Found: C, 57.62; H, 4.54.

7-Methoxy-1-naphthylacetonitrile (5)

To a solution of the compound **4** (501 mg, 1.99 mmol) in dimethyl sulfoxide (15 mL) was added sodium cyanide (129 mg, 1.84 mmol) and the solution was heated (140–145°C) for 3 h. The reaction mixture was cooled, diluted with water and extracted with ether. The organic extract was washed with brine, dried and evaporated *in vacuo*. The resulting oil was chromatographed (hexane:ether 1:1) to afford the nitrile **6** (388 mg, 99%) as pale orange colored solid, R_f 0.64 (ether), mp. 56–58°C (from ether). IR (cm^{-1}): 2500 (CN); MS (m/z): 197 (M^+); ^{1}H NMR: δ 7.84 (d, 1H, ArH-4, $J = 9$ Hz), 7.81 (d, 1H, ArH-5, $J = 8$ Hz), 7.55–7.52 (dd, 1H, ArH-6, $J = 7$ Hz, 1 Hz), 7.35 (t, 1H, ArH-3, $J = 7$ Hz), 7.25–7.21 (dd, 1H, ArH-2, $J = 9$ Hz, $J = 2$ Hz), 7.11 (d, 1H, ArH-8, $J = 2$ Hz), 4.10 (s, 2H, ArH-11), 3.96 (s, 3H, OMe); ^{13} C NMR: δ 158.8 (ArC-7), 131.1 (ArC-4), 129.4 (ArC-9), 129.1 (ArC-3), 128.1 (ArC-1), 127.4 (ArC-5), 125.2 (ArC-10), 123.5 (ArC-2), 119.0 (Ar C-6), 118.1 (ArC-13), 101.7 (ArC-8), 55.7 (ArC-12), 22.2 (ArC-11).

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.18; H, 5.58. Found: C, 79.41; H, 5.74.

7-Methoxy-1-naphthylacetic acid (2)

A mixture of the nitrile **5** (100 mg, 0.50 mmol) and an aqueous solution of sodium hydroxide (15 mL, 50%) was heated under reflux in a microwave oven at 60W for 40 min at 120°C. The reaction mixture was cooled, diluted with water, neutralized with aqueous HCl (10%) and extracted with chloroform. The organic extract was washed with brine, dried and evaporated *in vacuo* to afford the acid **2** (100 mg, 93%) as white solid (from ether), R_f 0.4 (ether), mp. 148–150°C (from ether), (lit.[3] 150–152°C). IR (cm^{-1}): 3548 (OH), 1700 (CO); MS (m/z) 216 (M^+) and 171 ($M^+ -$COOH); ^{1}H NMR: δ 7.78 (d, 1H, ArH-4, $J = 8$ Hz), 7.6 (d, 1H, ArH-5, $J = 8$ Hz), 7.39 (d, 1H, ArH-6, $J = 8$ Hz), 7.31 (t, 1H, ArH-3, $J =$ 8 Hz), 7.23 (d, 1H, ArH-8, $J = 2$ Hz), 7.18–7.16 (dd, 1H, ArH-2, $J = 8$ Hz, $J = 2$ Hz), 4.06 (s, 1H, ArH-11), 3.88 (s, 3H, OMe); ^{13}C NMR: δ 177.8 (ArC-13), 158.5 (ArC-7), 133.6

(ArC-10), 130.6 (ArC-1), 129.5 (ArC-4), 129.1 (ArC-5), 128.2 (ArC-3), 123.5 (ArC-2), 118.6 (ArC-6), 102.7 (ArC-8), 55.6 (ArC-12), 39.3 (ArC-11).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.22; H, 5.56. Found: C, 72.35; H, 5.64.

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