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Practical and Phase Transfer–Catalyzed Synthesis of 6-Methoxytryptamine

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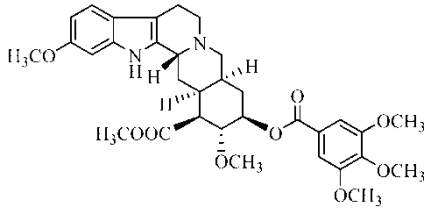
Abstract: A convenient and cost-effective synthesis of 6-methoxytryptamine (**1**), starting from commercially available phthalimide and 1-bromo-3-chloropropane via PTC *N*-alkylation, PTC *C*-alkylation, Japp–Klingemann reaction, hydrolysis, and decarboxylation, has been accomplished with a 44% overall yield.

Keywords: Japp–Klingemann reaction, 6-methoxytryptamine, PTC alkylation, reserpine

INTRODUCTION

6-Methoxytryptamine (**1**) is an important intermediate for the total synthesis



(-)-Reserpine

of pentacyclic indole alkaloid reserpine.[1] Although several reported approaches to **1** have been developed with varying degrees of success,[1,2]

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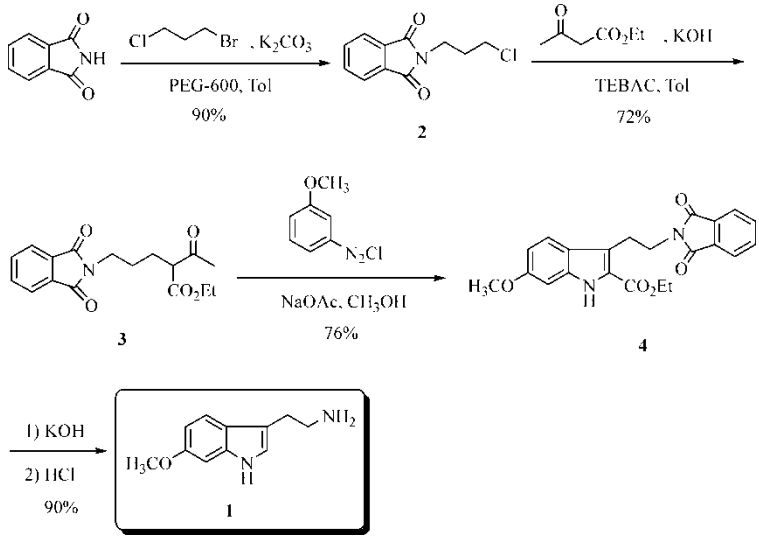
none of them is attractive enough for the scale-up synthesis of **1** because of drawbacks such as the use of expensive materials (6-methoxyindole or 3-methoxycarbonyl-6-methoxyindole), tedious workup, low reaction temperature (−78°C), poor overall yield, and so forth. Therefore, a simple and economical preparation of **1** that is amenable to large-scale synthesis and that delivers consistently high levels of purity is required.

As part of a development project on the total synthesis of reserpine in our laboratory,[3] herein we describe the practical and efficient preparation of **1** starting from commercially available phthalimide and 1-bromo-3 chloropropane.

The synthetic route to **1** is depicted in Scheme 1. Treatment of phthalimide and 1-bromo-3-chloropropane using a catalytic amount of PEG-600 and K_2CO_3 under reflux for 7 h afforded the chloropropylphthalimide **2** in 90% yield,which was recrystallized from CH_3OH to remove formed impurities such as 1,3-diphthalimidopropane and bromopropylphthalimide. The phase transfer–catalyzed (PTC) alkylation of ethyl acetoacetate with **2** in the presence of a catalytic amount of triethylbenzylammoniun chloride (TEBAC) and KOH was carried out in refluxing toluene to provide the phthalimidopentanoate **3** in 72% yield. Treatment of **3** with the diazonium salt of *m*-anisidine in CH_3OH via a Japp–Klingemann reaction[4] led to the 5-methoxyindole **4** in 76% yield. Hydrolysis of ester group in **4** with 15% aqueous KOH, without isolation, followed by acid treatment with 15% HCl at reflux temperature gave 6-methoxytryptamine (**1**) in 90% yield.



Scheme 1.

In summary, we have developed a simple and practical protocol for the synthesis of **1** in an overall yield of 44%, starting from commercially available phthalimide and 1-bromo-3-chloropropane. The notable advantages of the present method are its mild experimental conditions, short reaction time, simple operation, and high overall yield compared to those literature procedures.

EXPERIMENTAL

Melting points were measured on a WRS-1B digital melting-point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Erba 1006 elemental analyzer. IR spectra were recorded on a Nicolet FI-IR 360 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker DMX500 using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. Mass spectra were determined on a HP5988A instrument by direct inlet at 70 ev. All reagents and solvents were purchased from commercial sources and used as received without further purification.

N-(3-Chloropropyl)phthalimide (2)

1-Bromo-3-chloropropane (51 g, 0.32 mol) was added dropwise to a well-stirred mixture of phthalimide (40 g, 0.27 mol), K_2CO_3 (75.8 g, 0.55 mol), and PEG-600 (1.0 g) in toluene (500 mL) under stirring at room temperature. The reaction mixture was stirred under reflux for 7 h, and then cooled to room temperature and filtered. The filtrate was evaporated in vacuo to give the crude product, which was recrystallized from CH_3OH to afford pure **2** (54.2 g, 90%) as a white crystal, mp 70–72°C. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 2H), 7.7 (m, 2H), 3.86 (t, 2H), 3.58 (t, 2H), 2.2 (m, 2H); EI-MS (m/z): 223 (M^+); IR (KBr) υ (cm^{-1}): 1773, 1710, 1395, 1111, 1033, 871, 724.

Ethyl 2-Acetyl-5-phthalimidopentanoate (3)

The mixture of ethyl acetoacetate (22 g, 0.17 mol), KOH (12 g, 0.21 mol), and TEBAC (1.1 g, 48 mmol) in toluene (200 mL) was stirred under reflux for 30 min. Then **2** (35.7 g, 0.16 mol) was added, and the reaction mixture was refluxed with stirring for an additional 5 h, cooled to room temperature, and filtered. The filtrate was evaporated under reduced pressure. Water (75 mL) was added to the residue and acidified to pH 4 with 10% HCl. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed several times with water and dried over Na_2SO_4. The solvent was evaporated in vacuo to give the crude product, which was recrystallized from CH_3OH to afford pure **3** (36.5 g, 72%) as a white powder, mp

59–60°C. ^{1}H NMR ($CDCl_3$): δ 7.70–7.86 (m, 4H), 4.15–4.23 (q, 2H), 3.70 (t, 2H), 3.50 (t, 1H), 2.23 (s, 3H), 1.68–1.92 (m, 4H), 1.27 (t, 3H); EI-MS (m/z): 317 (M^+); IR (KBr) υ (cm^{-1}): 1737, 1711, 1402, 1244, 1190, 1141.

2-Carboxyethyl-3-(2-phthalimidoethyl)-6-methoxy Indole (4)

Conc. HCl (200 mL) was added dropwise to a well-stirred mixture of *m*-anisidine (60 g, 0.56 mol), methanol (200 mL), and H_2O (30 mL) at 0°C over a period of 45 min. Stirring was continued at the same temperature for 20 min. A solution of $NaNO_2$ (38.4 g, 0.56 mol) in H_2O (140 mL) was added dropwise to the reaction mixture at 0°C over a period of 45 min. Stirring was continued at the same temperature for 45 min to give a solution of the diazonium salt of *m*-anisidine.

Sodium acetate (330 g, 4.2 mol) was added to a stirred mixture of **3** (160 g, 0.5 mol) in methanol (3.0 L) and the reaction mixture was stirred at room temperature for 1 h and cooled to 0°C. The solution of the diazonium salt of *m*-anisidine as prepared previously was added dropwise at 0°C over a period of 1.5 h. The reaction mixture was stirred at room temperature for an additional 4 h. Then CH_2Cl_2 (1.2 L) was added to the reaction mixture. The organic layer was washed several times with water and dried over Na_2SO_4. The solvent was evaporated in vacuo, and 10% HCl in EtOH (750 mL) was added to the residue and stirred under reflux for 2.5 h. After cooling to 10°C, the precipitated product was collected by filtration and recrystallized from glacial HOAc to give pure **4** (154 g, 76%), mp 231.3–231.8°C. ^{1}H NMR ($CDCl_3$): δ 11.3 (br s, 1H), 7.8 (m, 4H), 7.5 (d, 1H), 6.8 (s, 1H), 6.7 (d, 1H), 4.2 (q, 2H), 4.0 (t, 2H), 3.8 (s, 3H), 3.4 (q, 2H), 1.4–1.5 (t, 3H). EI-MS (m/z): 392 (M^+); IR (KBr) υ (cm^{-1}): 3352, 1768, 1711, 1666, 1396, 1254, 1012, 719.

6-Methoxytryptamine (1)

Compound **4** (8.6 g, 21.9 mmol), was added to a stirred solution of 15% aq. KOH (37 mL) and the reaction mixture was stirred under reflux for 3 h. Then 15% HCl (250 mL) was added, and the reaction mixture was stirred under reflux for 10 h, then cooled to 0°C, and filtered. The filtrate was extracted with CH_2Cl_2 (3 × 30 mL). The aqueous phase was basified with 50% aq. NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed several times with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product, which was recrystallized from CH_3OH to afford the pure **1** (3.7 g, 90%) as white crystal, mp 140–142°C. ^{1}H NMR ($CDCl_3$): δ 8.26 (br s, 1H), 7.46 (d, 1H), 6.89 (s, 1H), 6.82 (s, 1H), 6.78 (d, 1H), 3.83

(s, 3H), 3.01 (t, 1H), 2.86 (t, 2H), 1.24 (d, 2H). EI-MS (m/z): 190 (M^+); IR (KBr) υ (cm^{-1}): 3408, 3344, 1626, 1460, 1204, 1105, 1026, 807, 773.

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