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Microwave Assisted Synthesis of Melatonin

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ABSTRACT

Melatonin was prepared from phthalimide by *N*- and *C*-alkylation, cyclization, hydrolytic, decarboxylation, and acetylation. The four-pot reactions were carried out on microwave irradiation in good yield with short time.

Key Words: Melatonin; Microwave assisted organic synthesis; Phase-transfer catalytic condensation.

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1. INTRODUCTION

Melatonin (*N*-acetyl-5-methoxytryptamine) was primarily isolated from pineal body of cattle in 1958.[1] It possesses of abroad bioactivities of increasing evidence suggests that melatonin may somehow delay the aging process and/or the progression of age-related disease processes, perhaps owing to its ability to eliminate free radicals.[2] The total synthesis of melatonin has been reported by Szmuszkovicz et al. using 5-methoxyindole as starting material.[3] Flaugh et al. took nine steps for synthesis.[4,5] The method of Franschini et al. showed not facility in reaction condition control.[7] This article reported a convenient green chemical synthesis method of melatonin by means of a four-pot reaction route using phthalimide as starting material. *N*-Alkylation of phthalimide with 1,3-dibromo-propane in the presence of potassium carbonate and phase-transfer catalysts under the condition of microwave irradiation for just only 6 min, then *C*-alkylation of ethyl acetacetate with the resulting bromide at another 6 min gave compound (2) in 81% yield. It condensed and cyclized with 4-methoxyphenyl hydrazine at same microwave irradiation condition for 15 min to get the desired 2-ethoxycarbonyl-3-(2-phthalimidoethyl)-5-methoxylindole (3) in 80% yield through the Fischer indole synthesis. Then through saponification and treatment with the solution of sulfuric acid under microwave irradiation afforded 5-methoxytryptamine (4) in 70% yield. The resulting product was acetylated under microwave irradiation for 2 min to give melatonin in 85% yield. The synthetic route is shown in Sch. 1.

This synthesis proceeds much faster with higher yield under microwave irradiation in comparison with conventional heating conditions, under which normally reactions would require many hours at reflux for completion, but only several minutes or less than 20 min required under microwave irradiation. It yielded purer reaction product, as well as it needed less solvent. Therefore, the reactions promoted by microwave irradiation produced less pollutant with low cost.

2. RESULTS AND DISCUSSION

Herein we also report a catalytic condensation method promoted by microwave irradiation using a phase-transfer catalyst. While exploring interest on triethylbenzenylamine chloride (TEBA) as an effective catalyst for condensation from 1 to 2, not only TEBA as a solid–liquid phase-transfer catalyst for the condensation was very effective, but also microwave-absorbing rate was high for the reaction system. Alkylation of

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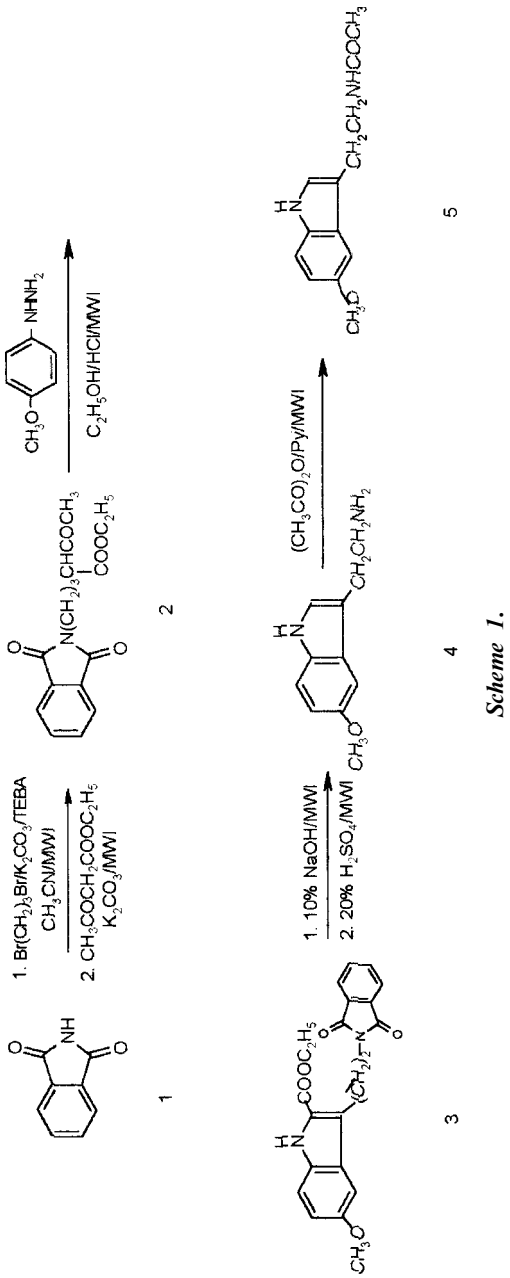
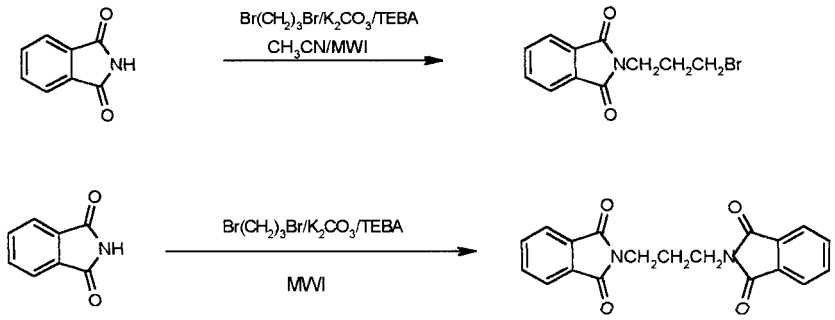


Scheme 1.



Scheme 2.

phthalimide with 1,3-dibromo-propane in the presence of phase-transfer catalysts TEBA under microwave irradiation just took 6 min, but the alkylation reaction could not be completed in 50 min without TEBA.

It is also important to choose the solvent for the alkylation. We experimented acetonitrile, phenyl methyl ether, chloroform, and 1,3-dibromo-propane. But acetonitrile was found to be the optimal solvent for the purpose. Bisubstituent product would be produced if 1,3-dibromo-propane is used as solvent in excess for the alkylation (Sch. 2).

Comparison with the traditional heating method (Table 1).

3. EXPERIMENTAL

Melting points (uncorrected) were determined by electro thermal melting point apparatus. ^{1}H NMR spectra in $CDCl_3$ on Bruker AC-E200 (200 MHz) using TMS as an internal standard. Microwave irradiation was carried out using a MCL-T domestic oven with maximum power output of 850 W.

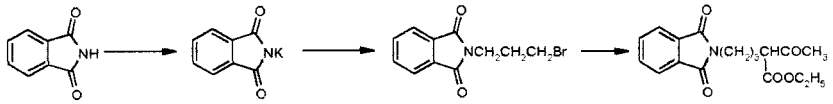
3.1. The Synthesis of 3-(3-Phthalimidopropyl) Ethyl Acetacetate (2)

The mixture of phthalimide (5 g, 0.034 mol); 1,3-dibromo-propane (6.8 mL, 0.068 mol); potassium carbonate (6.9 g, 0.05 mol); TEBA (0.77 g, 0.0034 mol), and acetonitrile (8 mL) was refluxed under microwave irradiation for 6 min. Then the reaction mixture was charged with potassium carbonate (0.05 mol) and ethyl acetacetate (5.3 g, 0.041 mol), to the resulting mixture refluxed at same condition for another 6 min.

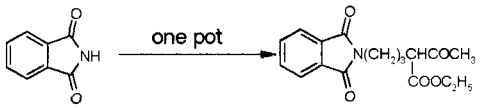
Table 1. Reaction time and yields in different preparing methods.

	From 1 to 2	Yield[a]	From 2 to 3	Yield	From 3 to 4	Yield	From 4 to 5	Yield
Traditional heating method	6 h	85%; 77%; 72%	10–20 h	74%	8 h	66%	1–2 h	85%
Microwave irradiation	6 + 6 min	81%	15 min	80%	5 + 10 min	70%	2 min	85%

[a]Note: Traditional heating method.



Microwave irradiation method.



After cooling, acetone was added and then the mixture was filtered, the filtrate was concentrated in vacuo, the residue was recrystallized from ethyl acetate-ligroin to give 2 in 81% yield.

3.2. The Synthesis of 2-Ethoxycarbonyl-3-phthalimido-ethyl-5-methoxylindole (3)

To a solution of 4-methoxyphenyl hydrazine (4 g, 0.03 mol) and 3-(3-phthalimidopropyl) ethyl acetacetate (2) (9.5 g, 0.03 mol) in 10 mL of *n*-butanol was added dropwise with a solution of hydrochloride acid (0.2 mol) in 70 mL of butanol (0.2 mol acetochloride + *n*-butanol). The mixture was refluxed under microwave irradiation for 15 min, then cooled and put in refrigerator overnight. The resulting yellow solid was collected by filtration. The solid was recrystallized from ethanol to give 3 in 80% yield, m.p. 239–241°C.

3.3. The Synthesis of 5-Methoxytryptamine (4)

A mixture of 2-ethoxycarbonyl-3-phthalimido-ethyl-5-methoxy-lindole (3) (11 g, 0.03 mol) and sodium hydroxide (10%, 30 mL) was

refluxed under microwave irradiation for 5 min, and then sulfuric acid (20%, 130 mL) was added dropwise slowly over 10 min. After that, the mixture was refluxed in microwave oven for 10 min. It was then extracted with ethyl acetate (3×50 mL). The pH of aqueous layer was adjusted to 8–9 with 40% sodium hydroxide and extracted with ethyl acetate. The combined extract was washed with saturated brine and dried with sodium sulfate anhydrous. The solvent was removed in vacuo and the residue was recrystallized from benzene to give light yellow crystals substance, in 70% yield, m.p. 119–121°C. ^{1}H NMR ($CDCl_3$): 7.90 (s, bs, 1H), 6.83–7.27 (m, 4H), 3.86 (s, 3H), 2.87 (t, 2H, $J = 3.1$ Hz, CH_2; $J = 9.0$ Hz, CH_2CH_2), 3.02 (t, 2H, $J = 3.1$ Hz, CH_2), 1.41 (s, bs, 2H).

3.4. The Synthesis of Melatonin (5)

A mixture of 5-methoxytryptamine (4) (5.7 g, 0.03 mol), pyridine (0.2 g, 0.003 mol), and acetic anhydride (20 mL) was warmed in the presence of N_2 under microwave irradiation for 2 min, and then the resulting reaction mixture was poured into ice-water (300 mL), the solid was collected, to give melatonin (5) in 85% yield, m.p. 117–118°C. The spectral data of the synthesized melatonin were identical with those in literature[4] or of an authentic sample.

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