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Synthesis of 1-Alkyl-2-chloromethylbenzimidazole Under Green Conditions

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A green approach for the synthesis of 1-alkyl-2-chloromethylbenzimidazoles (**3**) ($R^1 = CH_3$, C_2H_5, CH_2Ph) under, different conditions has been developed from 2-chloromethylbenzimidazole (**2**) by reaction with an alkylating agent (*i.e.* DMS, DES, $PhCH_2Cl$) by physical grinding or by using green solvent like PEG-600 or by using micro-wave irradiation technique.

Keywords: Green synthesis, Grinding, Microwave, N-alkyl-2-chloromethylbenzimidazole, Benzimidazole.

INTRODUCTION

Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest[1]. Benzimidazoles are an important class of bioactive molecules in the field of drugs and pharmaceuticals[2]. 2-Mercaptobenzimidazole derivatives having substitution either at the nitrogen or sulfur are reported to exhibit a broad spectrum of biological activity[3-8].

Verma *et al.*[9] reported that N-methyl-*o*-phenylenediamine on treatment with chloro acetic acid in aq. HCl under reflux for 1 h gave 1-methyl-2-chloromethylbenzimidazole in 80-82 % yield. Flosi *et al.*[10] described that 1-methyl-1*H*-benzimidazole-2-carbaldehyde on treatment with diisobutylaluminium hydride in THF for 1 h followed by chlorination with $SOCl_2$ in dichloromethane gave 1-methyl-2-chloromethylbenzimdazole. In continuation of our earlier studies on alkylation of 2-acetyl-benzimidazole[11] and thiolation of N-methyl-2-chlorobenzi-midazole[12], we now wish to report on alkylation of 2-chloro-methylbenzimidazole using green methods.

EXPERIMENTAL

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. IR spectra were recorded with Jasca FT-IR 5300. ^{1}H NMR and spectra were recorded in $CDCl_3$/DMSO using Varian 400-MHz instrument. Mass spectra were recorded on an Agilent LC-MS instrument giving only M^+ values in Q + 1 mode. Thin-layer chromato-graphy (TLC) analyses were carried out on glass plates coated with silica gel GF-254 and visualization was achieved using iodine vapours or UV lamp. Experiments under microwave irradiation were carried out by using the commercially available CEM Discover Microwave Reactor.

Synthesis of 1-alkyl-2-chloromethylbenzimidazoles (3) ($R_1 = CH_3$, C_2H_5, CH_2Ph) from 2-chloromethylbenzimidazole (2)

Physical grinding method: A mixture of **2** (10 mM), alky-lating agent (10 mM) and K_2CO_3 (1.38 g, 10 mM) was ground together for about 10-15 min in a mortar with a pestle at room temperature to obtain a homogeneous mixture. The completion of the reaction was monitored by TLC on silica gel-G plates using samples of the starting material and authentic target compounds as references. The mixture was then treated with ice-cold water (about 30-40 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude **3a-c**. Recrystallization of the crude product from ethyl acetate gave pure **3a-c**. IR, ^{1}H NMR and LC-MS spectra for the compounds **3a-c** were found to be in agreement with the structures assigned to them. Yields are shown in Table-1.

In PEG-600: A mixture of **2** (10 mM), alkylating agent (10 mM) and PEG-600 (20 mL) was heated on a steam-bath at 100 °C for 3 h. At the end of this period, the mixture was cooled to room temperature and poured into ice-cold water (about 50 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude products were purified by recrystallization from ethyl acetate to obtain pure **3a-c**, identical with the same products obtained above. Yields are shown in Table-1.

Under microwave condition: A mixture of **2** (10 mM) and alkylating agent (10 mM) was taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 2 min in a commercial microwave

TABLE-1
PREPARATION OF COMPOUND **3** FROM COMPOUND **2** UNDER DIFFERENT GREEN CONDITIONS

S. No.	SM	Reagent	Product	Methods: Physical grinding Time (min)	Physical grinding Temp. (°C)	Physical grinding Yield* (%)	PEG-600 Time (min)	PEG-600 Temp. (°C)	PEG-600 Yield* (%)	Microwave irradiation Time (min)	Microwave irradiation Temp. (°C)	Microwave irradiation Yield* (%)
		DMS		10-15	RT	78	180	100	68	2	RT / 450 W	80
		DES	**3b**	10-15	RT	74	180	100	72	2	RT / 450 W	83
		$PhCH_2Cl$	**3c**	10-15	RT	81	180	100	66	2	RT / 450 W	78

m.p. of **3a:** 118-22 °C (Lit.[9,10] m.p. 116-20 °C) *Yield refers to isolated crude product only
m.p. of **3b:** 102-104 °C (Lit.[9,10] m.p. 98-102 °C)
m.p. of **3c:** 84-89 °C (Lit.[9,10] m.p. 86-89 °C)

reactor. After that, the tube was cooled and the completion of reaction was checked by TLC. Then the reaction mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried. The crude products were purified by recrystallization from ethyl acetate to obtain pure **3a-c**, identical with the same products obtained above. Yields are shown in Table-1.

RESULTS AND DISCUSSION

Condensation of *o*-phenylenediamine (**1**) with chloroacetic acid in 4N HCl under reflux for 3 h gave the known 2-(chloromethyl)-1*H*-benzimidazole (**2**). Reaction of **2** with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in the presence of K_2CO_3, by a simple physical grinding of the reaction mixture in a mortar with a pestle under solvent-free conditions for 10-15 min at room temperature, followed by processing, gave, respectively 1-methyl-2-chloromethylbenzimidazole **3a** (*i.e.*, **3**, R = CH_3), 1-ethyl-2-chloromethylbenzimidazole **3b** (*i.e.*, **3**, R = CH_2CH_3) and 1-benzyl-2-chloromethylbenzimidazole **3c** (*i.e.*, **3**, R = CH_2Ph) as the products identical with the ones reported in the earlier methods[9,10] in all respects (m.p. m.m.p. and co-tlc analysis).

The reaction was also carried out in PEG-600 as the green solvent. Thus, heating a mixture of **2** with an alkylating agent in PEG-600 for 3 h without the use of any added base, followed by simple processing, gave, respectively **3a** (*i.e.*, 3, R = CH_3), **3b** (*i.e.*, **3**, R = CH_2CH_3) and **3c** (*i.e.*, **3**, R = CH_2Ph) identical with the same products obtained above (**Scheme-I**).

Compound **3** could also be prepared by an alternative, green method. Thus, **2** with an alkylating agent and K_2CO_3 as a base under microwave irradiation at RT conditions for 2 min and subsequent processing gave, respectively **3a** (*i.e.*, **3**, R = CH_3), **3b** (*i.e.*, **3**, R = CH_2CH_3), **3c** (*i.e.*, **3**, R = CH_2Ph) identical with the products obtained above (**Scheme-I**).

Conclusion

In conclusion, we have developed a green approach for the synthesis of 1-alkyl-2-chloromethylbenzimidazoles under different conditions.

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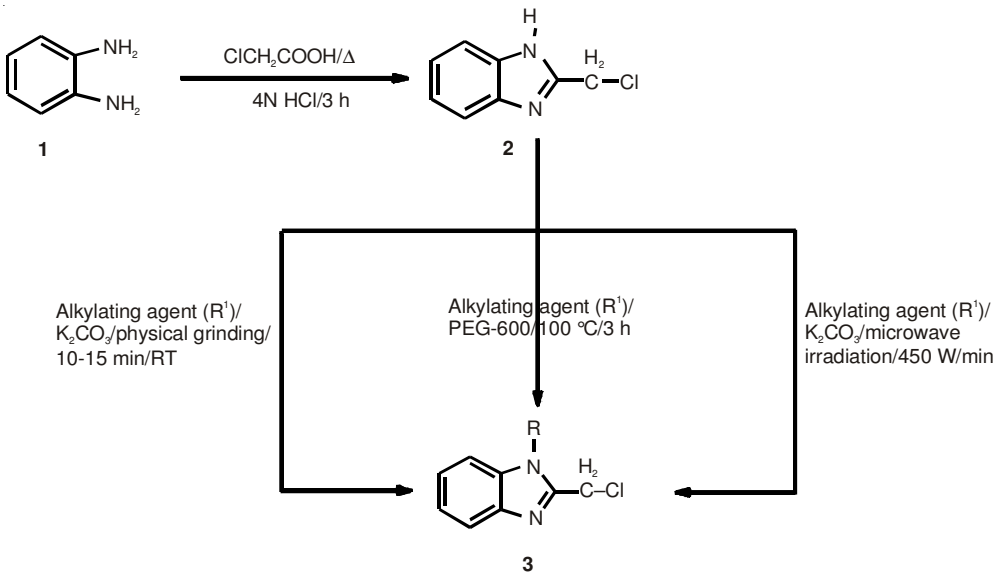

3a, R=CH_3; 3b, R=C_2H_5; 3c, R=CH_2Ph

Scheme-I

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