

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

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Received: 20 November 2013;

Accepted: 27 January 2014;

Published online: 26 December 2014;

AJC-16514

A green approach for the synthesis of 1-alkyl-2-chloromethylbenzimidazoles (**3**) ($R^1 = \text{CH}_3, \text{C}_2\text{H}_5, \text{CH}_2\text{Ph}$) 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 interest¹. Benzimidazoles are an important class of bioactive molecules in the field of drugs and pharmaceuticals². 2-Mercaptobenzimidazole derivatives having substitution either at the nitrogen or sulfur are reported to exhibit a broad spectrum of biological activity³⁻⁸.

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-chloromethylbenzimidazole. In continuation of our earlier studies on alkylation of 2-acetylbenzimidazole¹¹ and thiolation of N-methyl-2-chlorobenzimidazole¹², we now wish to report on alkylation of 2-chloromethylbenzimidazole 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. ¹H NMR and spectra were recorded in $\text{CDCl}_3/\text{DMSO}$ 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 chromatography (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**) ($R_1 = \text{CH}_3, \text{C}_2\text{H}_5, \text{CH}_2\text{Ph}$) from 2-chloromethylbenzimidazole (**2**)

Physical grinding method: A mixture of **2** (10 mM), alkylating 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, ¹H 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			PEG-600			Microwave irradiation		
				Time (min)	Temp. (°C)	Yield* (%)	Time (min)	Temp. (°C)	Yield* (%)	Time (min)	Temp. (°C)	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 ₂ Cl	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 (PhCH₂Cl) in the presence of K₂CO₃, 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 = CH₃), 1-ethyl-2-chloromethylbenzimidazole **3b** (*i.e.*, **3**, R = CH₂CH₃) and 1-benzyl-2-chloromethylbenzimidazole **3c** (*i.e.*, **3**, R = CH₂Ph) 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 = CH₃), **3b** (*i.e.*, **3**, R = CH₂CH₃) and **3c** (*i.e.*, **3**, R = CH₂Ph) identical with the same products obtained above (**Scheme-I**).

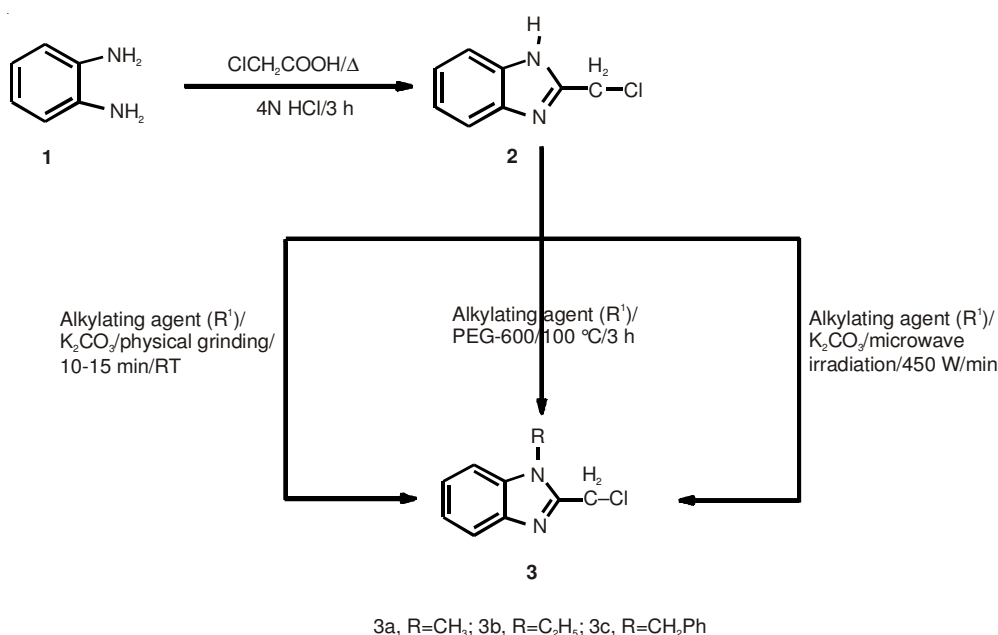
Compound **3** could also be prepared by an alternative, green method. Thus, **2** with an alkylating agent and K₂CO₃ as a base under microwave irradiation at RT conditions for 2 min and subsequent processing gave, respectively **3a** (*i.e.*, **3**, R = CH₃), **3b** (*i.e.*, **3**, R = CH₂CH₃), **3c** (*i.e.*, **3**, R = CH₂Ph) 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.

ACKNOWLEDGEMENTS

The authors are indebted to the authorities of Jawaharlal Nehru Technological University Hyderabad, India for providing the research facilities.



Scheme-I

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