A Green Approach for the Synthesis of 1-Methyl-2-(alkylthio)-1H-benzimidazoles

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A green approach for the synthesis of 1-methyl-2-(alkylthio)-1H-benzimidazoles **6** ($R^1 = \text{CH}_3, \text{C}_2\text{H}_5, \text{CH}_2\text{Ph}$) under, different conditions has been developed from N-methyl-2-mercaptobenzimidazole (*i.e.* CH_3) **5** by reaction with an alkylating agent by physical grinding or by using green solvent like PEG-600 or by using micro-wave irradiation technique.

Keywords: Green synthesis, Grinding, Microwave, N-methyl-2-chlorobenzimidazole, Benzimidazole, N-alkyl-2-mercaptobenzimidazole.

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 at either the nitrogen or sulfur are reported to exhibit a broad spectrum of biological activity³⁻⁸.

Lee and Kim⁹ reported that benzimidazol-2-thione on treatment with alkyl halides in the presence of sodium naphthalenide in tetrahydrofuran at room temperature under an atmosphere of nitrogen afforded 1-alkyl-2-mercaptobenzimidazoles in 88-93 % yield. Stanovnik *et al.*¹⁰ reported that selective alkylation of some compounds containing both SH and NH groups took place to give first the S-alkyl and subsequently the S,N-dialkyl derivatives. Using this strategy and in continuation of our earlier studies¹¹⁻¹³, on the preparation of new derivatives of benzimidazole thiol, herein we report green syntheses of N-methyl-2-alkylthiobenzimidazoles.

EXPERIMENTAL

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. IR Spectra were recorded with Jasco FT-IR 5300. ¹H NMR and spectra were recorded in CDCl₃/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.

Preparation of compound **6** from **5**

(i) Physical grinding method: A mixture of **5** (10 mM), alkylating agent (10 mM) and K₂CO₃ (2.6 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 authentic samples of the starting material and the target compounds as references. The mixture was then treated with ice-cold water (30-40 mL). The separated solid was filtered, washed with water (2 × 10 mL) and dried to obtain crude **6a-c**. Recrystallization of the crude product from ethyl acetate gave pure **6a-c**. IR, ¹H NMR and LC-MS spectra for the compounds **6a-c** were found to be in agreement with the structures assigned to them. Yields are shown in Table-1.

(ii) In PEG-600: A mixture of **5** (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 (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 **6a-c**, identical with the same products obtained above. Yields are shown in Table-1.

(iii) Under Microwave condition: A mixture of **5** (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 micro-wave reactor. After that, the tube was cooled and the completion of reaction was checked by TLC. Then the reaction mixture was

TABLE -1
PREPARATION OF 6 FROM 5 UNDER DIFFERENT GREEN CONDITIONS

S.No.	SM	Reagent	Product	Physical grinding			Green solvent			Microwave irradiation		
				PEG-600			PEG-600			PEG-600		
				Time (Min)	Temp (°C)	Yield* (%)	Time (Min)	Temp (°C)	Yield* (%)	Time (Min)	Temp (°C)	Yield* (%)
1.	1	DMS	6a	10-15	RT	88	180	100	69	2	RT / 450 W	89
	2	DES	6b	10-15	RT	86	180	100	73	2	RT / 450 W	87
	3	PhCH ₂ Cl	6c	10-15	RT	82	180	100	64	2	RT / 450 W	85
m.p. of 6a: 218- 23°C (Lit. ^(9,10) m.p. 222-27°C) *Yield refers to isolated crude product only; RT: Room temperature												
m.p. of 6b: 194- 98°C (Lit. ^(9,10) m.p. 197-99°C), m.p. of 6c: 169- 73°C (Lit. ^(9,10) m.p. 166-69°C)												

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 **6a-c**, identical with the same products obtained above. Yields are shown in Table-1.

RESULTS AND DISCUSSION

Condensation of *o*-phenylenediamine (**1**) with urea by dry fusion of reactants at 130 °C gives the known benzimidazole-2-one (**2**) which on treatment with SOCl₂, in the presence of catalytic amount of phenol, yields the previously reported¹¹ 2-chlorobenzimidazole **3**. The latter on alkylation with dimethyl sulfate in the presence of K₂CO₃ in CH₃CN medium using tetra-*n*-butylammonium bromide (TBAB) as phase transfer catalyst at room temperature for 3 h gave the previously reported¹² N-methyl-2-chlorobenzimidazole (**4**). Reaction of N-methyl-2-chlorobenzimidazole with thiourea in methanol under reflux for 3 h gave N-methyl-2-mercaptobenzimidazole (i.e., **5**, R = CH₃) (**Scheme-I**).

Reaction of compound **5**, independently, 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-methylthiobenzimidazole (**6a**, i.e., R = CH₃), 1-ethyl-2-methylthiobenzimidazole (**6b**, i.e., R = C₂H₅), 1-benzyl-2-methylthiobenzimidazole (**6c**, i.e., R = PhCH₂), 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 **5** with an alkylating agent in PEG-600 for 3 h without the use of any added base, followed by simple processing, gave respectively **6a** (i.e., **6**, R = CH₃), **6b** (i.e., **6**, R = CH₂CH₃) and **6c** (i.e., **6**, R = CH₂Ph) identical with the same products obtained above (**Scheme-I**).

Compound **6** could also be prepared by an alternative, green method. Thus, **5** with an alkylating agent and K₂CO₃ as a base under microwave irradiation at RT conditions for 2 min and subsequent processing, gave respectively **6a** (i.e., **6**, R = CH₃), **6b** (i.e., **6**, R = CH₂CH₃), **6c** (i.e., **6**, R = CH₂Ph) identical with the products obtained above (**Scheme-I**).

Conclusion

In conclusion, we have developed a green approach for the synthesis of 1-methyl-2-(alkylthio)-1*H*-benzimidazoles under different conditions.

Scheme-I

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