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

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A green approach for the synthesis of 1-methyl-2-(alkylthio)-1*H*-benzimidazoles **6** (R^1= CH_3, C_2H_5, CH_2Ph) 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 interest[1]. Benzimidazoles are an important class of bioactive molecules in the field of drugs and pharmaceuticals[2]. 2-Mercaptobenzimidazole derivatives having substitution at either the nitrogen or sulfur are reported to exhibit a broad spectrum of biological activity[3-8].

Lee and Kim[9] 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 studies[11-13], 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 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 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 K_2CO_3 (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, ^{1}H 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 PEG-600 Time (Min)	Physical grinding PEG-600 Temp (^{0}C)	Physical grinding PEG-600 Yield* (%)	Green solvent PEG-600 Time (Min)	Green solvent PEG-600 Temp (^{0}C)	Green solvent PEG-600 Yield* (%)	Microwave irradiation PEG-600 Time (Min)	Microwave irradiation PEG-600 Temp (^{0}C)	Microwave irradiation PEG-600 Yield* (%)
	1	DMS	**6a**	10-15	RT	88	180	100	69	2	RT / 450 W	89
1.	**2**	DES	**6b**	10-15	RT	86	180	100	73	2	RT / 450 W	87
	3	$PhCH_2Cl$	**6c**	10-15	RT	82	180	100	64	2	RT / 450 W	85

m.p. of **6a:** 218- 23^{0}C (Lit.[9,10] m.p. 222-27^{0}C) *Yield refers to isolated crude product only; RT: Room temperature
m.p. of **6b:** 194- 98^{0}C (Lit.[9,10] m.p. 197-99^{0}C), m.p. of **6c:** 169- 73^{0}C (Lit.[9,10] m.p. 166-69^{0}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 $SOCl_2$, in the presence of catalytic amount of phenol, yields the previously reported[11] 2-chlorobenzimidazole **3**. The latter on alkylation with dimethyl sulfate in the presence of K_2CO_3 in CH_3CN medium using tetra-*n*-butylammonium bromide (TBAB) as phase transfer catalyst at room temperature for 3 h gave the previously reported[12] 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 = CH_3) (**Scheme-I**).

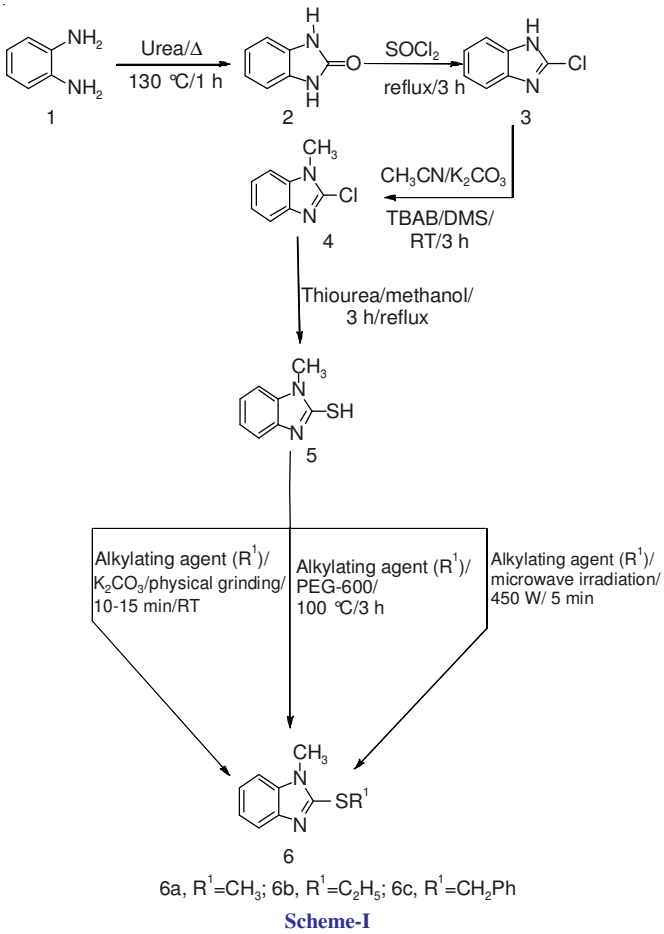
Reaction of compound **5**, independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in the presence of K_2CO_3, by a simple physical grinding of the reaction mixture in a mortar with a pestle under solvent-free conditions for 10-15 min at room temperature, followed by processing, gave respectively 1-methyl-2-methylthiobenzimi-dazole (**6a**, *i.e.*, R = CH_3), 1-ethyl-2-methylthiobenzimidazole (**6b**, *i.e.*, R = C_2H_5), 1-benzyl-2-methylthiobenzimidazole (**6c**, *i.e.*, R = $PhCH_2$), 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 = CH_3), **6b** (*i.e.*, **6**, R = CH_2CH_3) and **6c** (*i.e.*, **6**, R = CH_2Ph) 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 K_2CO_3 as a base under microwave irradiation at RT conditions for 2 min and subsequent processing, gave respectively **6a** (*i.e.*, **6**, R = CH_3), **6b** (*i.e.*, **6**, R = CH_2CH_3), **6c** (*i.e.*, **6**, 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-methyl-2-(alkylthio)-1*H*-benzimidazoles under different conditions.



Scheme-I

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