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A FACILE AND ECO-FRIENDLY SYNTHESIS OF 1-METHYL-2-((ALKYLTHIO)METHYL)-1H-BENZIMIDAZOLE

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ABSTRACT
A green approach for the synthesis of 1-methyl-2-(alkylthio)-1*H*-benzimidazoles **5** (R^1= CH_3, C_2H_5, CH_2Ph) under, different conditions has been developed from N-methyl-2-thiomethylbenzimidazole (*i.e.* CH_3) **4** 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, benzimidazole, grinding, microwave, MWI, N-methyl-2-chloromethylbenzimidazole,

INTRODUCTION
Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest[I]. Benzimidazoles are an important class of bioactive molecules in the field of drugs and pharmaceuticals[II]. 2-Mercaptobenzimidazole derivatives having substitution at either the nitrogen or sulfur are reported to exhibit a broad spectrum of biological activity. [III-VII]
Aoyama *et al* reported[VIII] that 2-((methylthio)methyl)-1H-benzimidazole was prepared on treatment of S-methylthio acetic acid with o-phenylenediamine in aq. HCl under reflux for 16 h. 2-thiomethyl benzimidazole on treatment with methyl bromide in sodium methoxide gave 2-((methylthio)methyl)-1H-benzimidazole was reported [IX] by Sekikawa. Using this strategy and in continuation of our earlier studies [X,XI], on the preparation of new derivatives of benzimidazole thiol, herein is now report green syntheses of 1-methyl-2-(alkylthio)-1*H*-benzimidazoles. In S-alkylated benzimidazole, S-alkyl is a easily replaced by various nitrogen nucleophiles and the derivatives which are obtained from this are very useful to prepare Schiff's bases, which leads to biological products[XII].

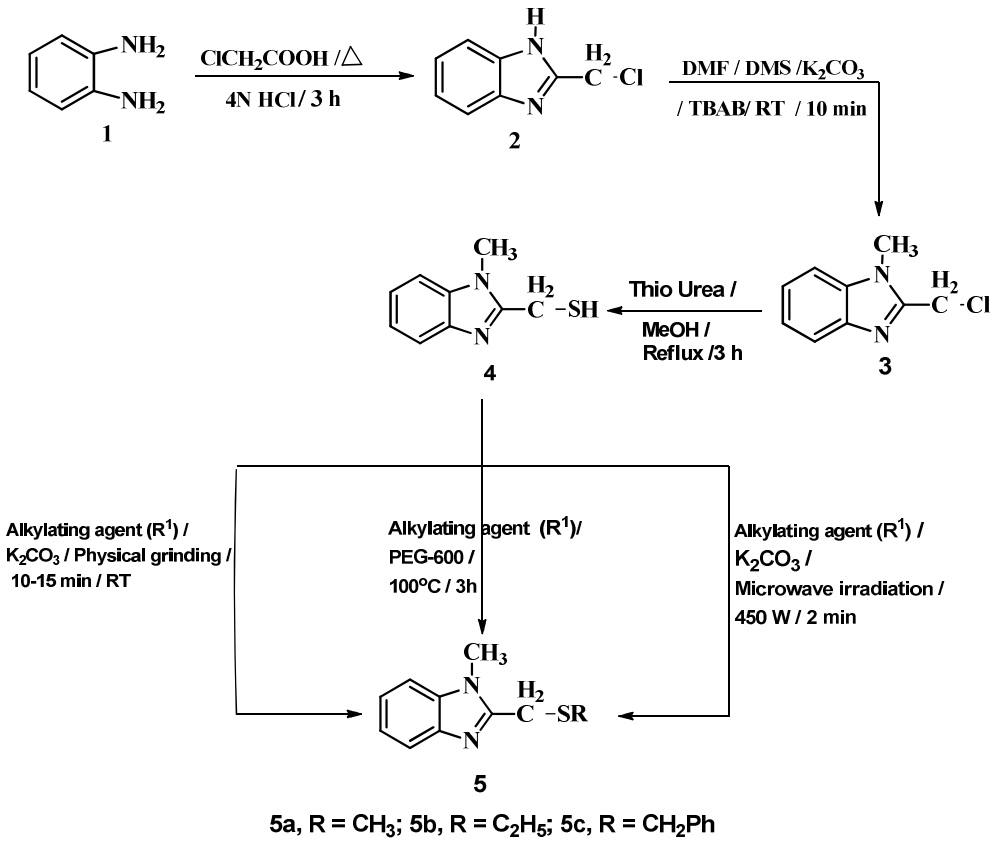
RESULTS AND DISCUSSION
Condensation of *o*-phenylenediamine **1** with chloroacetic acid in 4N HCl under reflux for 3 h gave the known 2-(chloromethyl)-1H-benzimidazole **2.** The latter on alkylation with an

alkylating agent such as dimethyl sulfate in the presence of K_2CO_3 in CH_3CN medium using tetra-*n*-butylammonium bromide (TBAB) as phase transfer catalyst at RT for 3 hr gave previously reported [13,14] N-methyl-2-chloromethylbenzimidazole **3**. Reaction of **3** on treatment with thiourea in methanol under reflux for 3 h gave (1-methyl-1H-benzimidazol-2-yl)methanethiol **4**.

Reaction of **4,** 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 RT, followed by processing, gave respectively 1-methyl-2-(methylthio)-1*H*-benzimidazole **5a** (*i.e.***, 5,** R=CH_3**),** 1-methyl-2-(ethylthio)-1*H*-benzimidazole **5b** (*i.e.***, 5,** R=CH_2CH_3**)** and 1-methyl-2-(benzylthio)-1*H*-benzimidazole **5c** (*i.e.***, 5**, R=$PhCH_2$), as the products identical with the ones reported in the earlier methods [VIII] 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 **4** with an alkylating agent in PEG-600 for 3h without the use of any added base, followed by simple processing, gave respectively **5a** (*i.e.***, 5,** R=CH_3**), 5b** (*i.e.***, 5,** R=CH_2CH_3**)** and **5c** (*i.e.***, 5,** R= CH_2Ph**)** identical with the same products obtained above (**Scheme I**).

Compound **5** could also be prepared by an alternative, green method. Thus, **4** 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 **5a** (*i.e.*, **5,** R= CH_3**), 5b** (*i.e.*, **5,** R= CH_2CH_3**) , 5c** (*i.e.***, 5,** R= CH_2Ph**)** identical with the products obtained above (**Scheme I**).



Scheme-1 Synthesis of N-alkyl-2-thiomethylbenzimidazole

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 5 from 4:

(i) Physical grinding method

A mixture of **4** (10 mM), alkylating agent (10 mM) and K_2CO_3 (1.38g, 10mM) was ground together for about 10-15 min in a mortar with a pestle at RT 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 **5a-c**. Recrystallization of the crude product from ethyl acetate gave pure **5a-c**. IR, ^{1}H NMR and LC-MS spectra for the compounds **5a-c** were found to be in agreement with the structures assigned to them. Yields are shown in **Table I.**

(ii) In PEG-600

A mixture of **4** (10 mM), alkylating agent (10 mM) and PEG-600 (20 mL) was heated on a steam-bath at 100^{o}C for 3hr. At the end of this period, the mixture was cooled to RT 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 **5a-c**, identical with the same products obtained above. Yields are shown in **Table I.**

(iii) Under Microwave condition

A mixture of **4** (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 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 **5a-c,** identical with the same products obtained above. Yields are shown in **Table I.**

Spectral Data:

1-Methyl-2-(methylthio)-1H-benzimidazole 5a. IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm^{-1}, indicating absence of -NH group; ^{1}H- NMR (400 MHz, DMSO-d_6/ TMS): δ 3.69 (s, 3H, -NC**H**$_3$), 2.90 (s, 2H, -CH_2), 2.63 (s, 3H, -SC**H**$_3$), 8.13 (d, J = 7.68 Hz, 2**H,** Ar-H), 7.89 - 7.85 (m, 2**H,** Ar-H); ^{13}C NMR: δ 149.3, 143.6, 138.8, 124.5, 119.0, 117.7, 110.7, 32.2, 18.7 ppm; MS (CI): m/z 179 [$M^{\cdot+}$+1].

1-methyl-2-(ethylthio)-1H-benzimidazole 5b. IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm^{-1}, indicating absence of -NH group; ^{1}H- NMR (400 MHz, DMSO-d_6/ TMS): δ 3.46 (s, 3H, -NC**H**$_3$), 2.87 (s, 2H, -CH_2), 2.75 (s, 3H, -SC**H**$_3$), 8.08 (d, J = 7.56 Hz, 2**H,** Ar-H), 7.79 -

7.65 (m, 2**H,** Ar-H); ^{13}C NMR: δ 148.3, 144.5, 136.8, 124.5, 115.0, 116.7, 108.7, 30.2, 22.5, 18.7 ppm; MS (CI): m/z 193 [M^{+}+1].

1-methyl-2-(benzylthio)-1H-benzimidazole 5c. IR (KBr): No diagnostic peak in IR region 3500 – 3000 cm^{-1}, indicating absence of -NH group; ^{1}H- NMR (400 MHz, DMSO-d_6/ TMS): δ 3.52 (s, 3H, -NC**H**$_3$), 2.98 (s, 2H, -CH_2), 2.82 (s, 3H, -SC**H**$_3$), 8.34 (d, J = 7.66 Hz, 2**H,** Ar-H), 7.24 (d, J= 7.13 Hz, 2**H,** Ar-H), 7.16-6.73 (m, J = 6.95 Hz, 5**H,** Ar-H); ^{13}C NMR: δ 149.9, 142.8, 137.8, 137.2, 128.5, 127.9, 125.8, 124.6, 123.6,120.6, 118.2, 111.7, 110.7, 107.9, 49.6, 35.6, 19.3 ppm;; MS (CI): m/z 255 [M^{+}+1].

Table -I

Preparation of **5** from **4** under different green conditions

S.No.	SM	Reagent	Product	Physical grinding			Green solvent irradiation PEG-600			Microwave		
				Time (Min)	Temp (^{0}C)	Yield* (%)	Time (Min)	Temp (^{0}C)	Yield* (%)	Time (Min)	Temp (^{0}C)	Yield* (%)
1.	**4**	DMS	**5a**	10-15	RT	85	180	100	68	2	RT / 450 W	88
		DES	**5b**	10-15	RT	87	180	100	73	2	RT / 450 W	86
		$PhCH_2Cl$	**5c**	10-15	RT	80	180	100	65	2	RT / 450 W	74

*Yield refers to isolated crude product only.
M.P. of **5a:** 122- 25^{0}C (Lit.[XI] m.p. 120-24^{0}C)
M.P. of **5b:** 98- 102^{0}C (Lit.[XI] m.p. 96-99^{0}C)
M.P. of **5c:** 142- 47^{0}C (Lit.[XI] m.p. 138-42^{0}C)

CONCLUSION

In conclusion, the use of solvents like DMF / CH_3CN for S-alkylation are not green and hence we have developed a green approach for the synthesis of 1-methyl-2-(alkylthio)-1*H*-benzimidazoles under different conditions.

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