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AN ENVIRONMENTALLY BENIGN SYNTHESIS OF N-ALKYL-2-((BENZIMIDAZOL-2-YL) THIO) ACETONITRILE

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ABSTRACT
An environmentally benign synthesis of N-substituted-2-((benzimidazol-2-yl) thio) acetonitrile (2) under different conditions has been developed under green conditions. In this method, 2-((1H-benzimidazol-2-yl)thio)acetonitrile (1) was treated with an alkylating agent such as DMS/DES/$PhCH_2Cl$ under green conditions i.e., by physical grinding in the presence of K_2CO_3 at RT or by heating in PEG-600 as a green solvent at 100 ^{0}C or by irradiation with micro-waves at RT to obtain N-alkyl-2-((benzimidazol-2-yl)thio)acetonitrile (2).

KEYWORDS 2-mercaptobenzimidazole, thiourea, green synthesis, physical grinding.

INTRODUCTION
Benzimidazoles are very important class of compounds due to their wide spectrum of biological activity[I]. Benzimidazole derivatives play an important role with diverse types of pharmacological actions [II-X]. In continuation of our earlier studies [9] on alkylation of 2-mercapto benzimidazole, we now wish to report our studies on alkylation of 2-((benzimidazol-2-yl) thio) acetonitrile using Green methods.

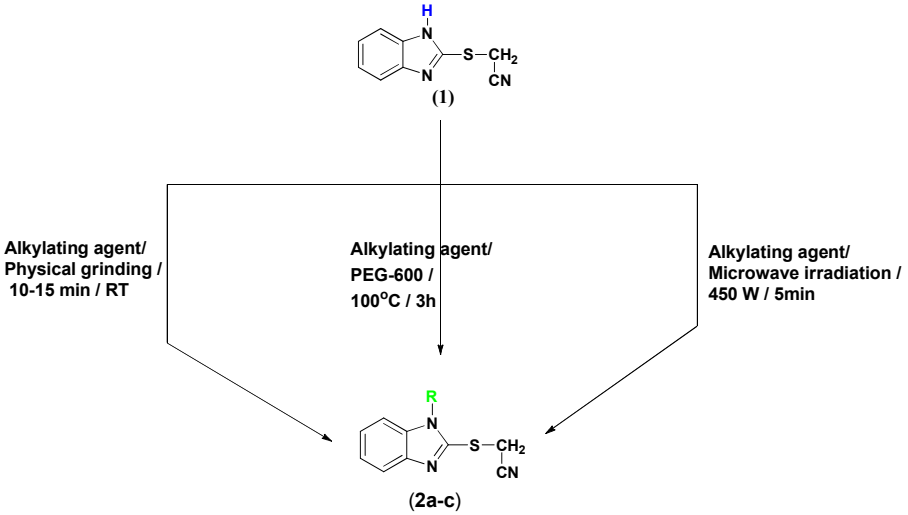
RESULTS AND DISCUSSION
Treatment of 2-mercaptobenzimidazole with chloroacetonitrile in dimethylformamide containing K_2CO_3 as base and tetra-n-butyl ammonium bromide (TBAB) as phase transfer catalyst for 3 h gave previously reported[X] 1H-benzimidazol-2-ylsulfanyl)acetonitrile (**1**). Reaction of **1,** independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) in the presence of K_2CO_3 as a mild base, 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-chlorobenzimidazole (**2a**, i.e., R=CH_3) , 1-ethyl-2-chlorobenzimidazole (**2b**, i.e., R=C_2H_5), 1-benzyl-2-chlorobenzimidazole (**2c**, i.e., R=$PhCH_2$), as the products identical with the ones reported in the earlier methods[10] in all respects (m.p. m.m.p. and co-tlc analysis).
The reaction was also carried out in PEG-600 as a solvent. Thus, heating a mixture of **1,** independently, with each of dimethylsulphate (DMS), diethylsulphate (DES) and benzyl

chloride ($PhCH_2Cl$) in PEG-600 at 100°C for 3hrs without the use of any added base, followed by simple processing, gave respectively **2a** (i.e.**, 2,** R=CH_3)**, 2b** (i.e., **2**, R=CH_2CH_3) and **2c** (i.e., **2**, R=$PhCH_2$) identical with the same products obtained above.

2 could also be prepared by an alternative method. Thus, **1** on treating, independently, with each of dimethyl sulphate (DMS), diethyl sulphate (DES) and benzyl chloride ($PhCH_2Cl$) under microwave irradiation conditions for 5 min and subsequent processing, gave respectively **2a** (i.e., **2,** R=CH_3) **2b** (i.e., **2,** R=CH_2CH_3) **, 2c** (i.e., **2,** R=$PhCH_2$) identical with the products obtained earlier above.

Thus, the above four methods have different yields with one suffering from relatively poor yields. Among these, in solvent system ethanol giving high yields where as PEG-600 giving lower yields. Due to high molecular weight and viscous nature of PEG-600 (135 cp at 25°C) may lower reaction rates, reduce product yields and cause the reaction to be mass-transfer limited. Because of this, three of the four methodologies result in the preparation of the compounds giving high yields whereas PEG-600 gives lower yields. Among these four methodologies, the microwave irradiation is superior than that of three methods because of microwave dielectric heating is more energy efficient than classical conductive heat transfer methods (**Scheme -1**)

Scheme: 1



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 $CDCl_3$ / 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 4 from 3:

1) <u>Physical grinding method</u>:

A mixture of **1** (10mM), K_2CO_3 (20mM) and alkylating agent(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 prepared 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 (≈30-40ml). The separated solid was filtered, washed with water (2x10ml) and dried to obtain crude **2a-c**. For yields please

see **Table-1.** Recrystallization of the crude product from a suitable solvent gave pure **2a-c**. IR, ^{1}H-NMR and LC-MS spectra for the compounds **2a-c** were found to be in agreement with the structures assigned to them.

2) In PEG-600:

A mixture of **1** (10 mM), alkylating agent (10mM) and PEG-600 (20 ml) was heated on a steam-bath at 100^{o}C for 3hrs. At the end of this period, the mixture was cooled to RT and poured into ice-cold water (≈50ml).The separated solid was filtered, washed with water (2x10ml) and dried. The crude products were recrystallized from a suitable solvent to obtain pure **2a-c,** identical with the same products obtained above**.** For yields please see **Table-1.**

3) Under microwave condition:

A mixture of **1** (10 mM) and alkylating agent (10mM) was taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 2 min in the 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 (2x10ml) and dried. The crude products were recrystallized from a suitable solvent to obtain pure **3a-c,** identical with the same products obtained above. For yields, please see **Table-1.**

Table -1

Preparation of **2a-c** from **1** 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.	**1**	DMS	**2a**	10-15	RT	89	180	100	69	2	RT / 450 W	87
		DES	**2b**	10-15	RT	87	180	100	72	2	RT / 450 W	89
		$PhCH_2Cl$	**2c**	10-15	RT	85	180	100	63	2	RT / 450 W	83

M.P. of **2a:** 108-111 ^{0}C (Lit.[10] m.p. 110-112 ^{0}C)
M.P. of **2b:** 99-101 ^{0}C (Lit.[10] m.p. 98-100 ^{0}C)
M.P. of **2c:** 85-88 ^{0}C (Lit.[10] m.p. 86-88 ^{0}C)

*Yield refers to isolated crude product only.

CONCLUSION

In conclusion, we have developed a green methodology for the synthesis of N-substituted-2-thiobenzimidazole under different conditions.

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References

I. (a) G L Gravatt, B C Baugley , W R Wilson W.A.Denny, *J Med Chem,* 37, 4338 (1994),
(b) J. S. Kim, B. Gatto and L. F .Liu, *Eur J Med Chem*, 39, 992 (1996); (c) T Roth, M L Morningstr, P L Boyer, S H Hughes, R W Buckheit and C J Michejda, *J Med Chem*, 40, 4199 (1997); (d) D A Horton, G T Bourne and M L Smythe, *Chem Rev,* 893 (2003),.

II. (a) G L Gravatt, B C Baugley , W R Wilson and Denny W A, *J Med Chem,* 37, 4338(1994); b) B Jayasankara and K M L Rai, *Arkivoc* 75 (2008); (c) T Roth, M L Morningstar, P L Boyer, S H Hughes, R W Buckheit and C J Michejda, *J Med Chem*, 40, 4199 (1997).

III. H Hasegawa, N Tsuda and M Hasoya, *Japanese Pat,* 198 (1974); *Chem Abstr*, (1975), 156308.

IV. G Rovnyak, V L Narayana, R D Haugwitz and C M Cimarusti, *US Pat*, 014, (1973); *Chem Abstr*, 1974, 105596.

V. S C Bell and P H Wei, *J Med Chem,* 19, 524 (1976).

VI. D R Graber, R A Morge and Raenko, *J Org Chem,* 52, 4620 (1987).

VII. N I Korotkikh, G F Raenko and O P Shavaika, *Chem Heterocycl compd,* 31, 359 (1995).

VIII. V Andre, A Hardeman, I Halasz, RS Stein, GJ Jackson and DG Reid, *Angew. Chem. Int. Ed*, 50, 7858 (2011).

IX. S S Rao , P K Dubey and Y B Kumari, *Indian J Chem*, 52B, 1210 (2013); S S Rao, Ch V R Reddy and P K Dubey, *J Heterocyclic Chem*. 53,74 (2016).

X. S S Rao, Ch V R Reddy and P K Dubey, *Indian J Chem,*54, 829 (2013); S S Rao, *HeteroLetters* 6, 181 (2016).

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