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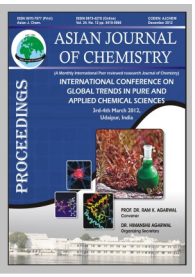

Ultrasound Promoted Simple and Efficient N-Alkylation of 2-Substituted Benzimidazoles†

P.N. KISHORE BABU*, B. RAMA DEVI and P.K. DUBEY

Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500 085, India

*Corresponding author: E-mail: kishore1136@gmail.com

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N-Alkylation of 2-chlorobenzimidazole was carried out using different alkylating agents under ultrasound irradiation technique. These reactions were completed in shorter times and with higher percentage of yields. Among all the green solvents, triethanolamine was found to be very effective and also acts as a base. The above reaction conditions were extended to other 2-substituted benzimidazoles. Thus, a simple and efficient route for *N*-alkylation has been developed using ultrasound irradiation technique.

Key Words: Ultrasonic waves, PEG-600, Triethanolamine, *N*-alkylations.

INTRODUCTION

Ultrasound irradiation technique was viewed as a convenient technique and has been considerably used in organic synthesis[1]. Several applications in organic synthesis have made, sonochemistry as an important tool in many synthetic reactions[2,3]. Compared to conventional method, many organic reactions could be carried out smoothly with higher percentage of yields and also in lowering reaction times[4].

Benzimidazoles are an important class of heterocyclic compounds, which found several applications as important bio-active molecules[5]. Substitutedbenzimidazole derivatives have got diverse applications in the field of medicinal chemisry such as antimicrobial[6], antiulcerous[7], antiviral[8], antihypertensive[9], antihistaminics[10], anticancer[11] *etc*. to name only a few.

In continuation of our earlier work[12-15] on the synthesis of *N*-alkylbenzimidazole derivatives, we report a novel and safer procedure for the preparation of the title compounds in the abscence of phase transfer catalyst (PTC) by using triethanolamine as a green solvent under ultrasound irradiation technique. The effect of ultrasound on % yield and reaction time has been studied and the same is reported in this communication.

EXPERIMENTAL

Melting points were uncorrected and are determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G, spotting was done using UV light. **1a** and **1e** was prepared based on the synthetic procedure available from the literature[16,17]. Triethanolamine, acetonitrile and PEG-600 were purchased from Finar reagents, India. Tetrabutylammonium-bromide and K_2CO_3 was purchased from SD Fine Chemicals Ltd., India.

Ultrasound for sonication is generated with the help of ultrasonic instrument. The specifications, operating parameters and the details of the set-up are as follows: Make: China; operating frequency: 36+_3 kHz; rated output power: 700 W; Tank size: 240 mm × 135 mm × 100 mm.

Preparation of 3a using sonochemical method: To a mixture of tetrabutylammonium bromide (PTC, 0.2 g), K_2CO_3 (1.4 g, 10 mM) and **1a** (1.52 g, 10 mM) in CH_3CN (10 mL), dimethyl sulphate (1.2 mL, 10 mM) was added under sonication, by keeping all sonication parameters constant till the completion of the reaction. The reaction progress was monitored by TLC; after 6-8 min, the reaction was found to be completed. The mixture was filtered and the insoluble material washed with CH_3CN (2 × 5 mL). The acetonitrile filtrate was evaporated to dryness and the residue treated with chloroform (25 mL), the chloroform layer was washed with water (3 × 30 mL) and evaporated to dryness to give **3a**. The obtained crude product was recrystallized using ethyl acetate as solvent to obtain pure light yellow coloured 2-chloro-1-methyl-1*H*-benzimidazole **3a**. The reaction time was confirmed by repeating the procedure for three more times.

Yield = 1.49 g, 90 %; m.p. = 94-96 ºC

Preparation of 3a using triethanolamine as solvent as well as base in sonochemical method: To a solution of 1a (1.52 g, 10 mM) in triethanolamine (10 mL), dimethyl sulphate (1.2 mL, 11 mmol) was added under sonication and

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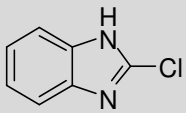
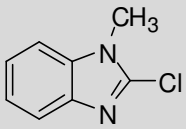
TABLE-1
METHYLATION OF **1a** UNDER CONVENTIONAL AND ULTRASONIC METHOD USING DIFFERENT SOLVENTS

Entry	Solvent	PTC	Conventional method		Ultrasound irradiation		Product
			Time (h)	Yield (%)	Time (min)	Yield (%)	
 **1a**	CH_3CN	TBAB	3	76	6-8	90	
		PEG-600	4	72	9	89	
		$N(C_2H_4OH)_3$	2-3	70	5	92	
	PEG-600	None	2-3	84	10-12	94	
	$N(C_2H_4OH)_3$	None	3	83	4-6	95	

the same was continued for about 4 min keeping all sonication parameters constant till the completion of the reaction. The reaction progress was monitored by TLC; after 4-6 min, the reaction was found to be completed. The reaction time was confirmed by repeating the procedure for three more times, rest of the reaction workup is same as followed as above.

Yield = 1.57 g, 95 %; m.p. = 94-96 ºC

Preparation of 3a using conventional method: To a mixture of tetrabutylammoniumbromide (PTC, 0.2 g), K_2CO_3 (1.4 g, 10 mM) and **1a** (1.52 g, 10 mM) in CH_3CN (20 mL), alkylating agent dimethylsulphate (1.2 mL, 11 mM) was added and continued stirring for 3 h at room temperature. After completion of the reaction (monitored by TLC), the mixture was filtered and the rest of the reaction workup is same as followed as above. Yield = 1.26 g, 76 %; m.p. = 94-95 ºC (lit. m.p. = 96 ºC).

RESULTS AND DISCUSSION

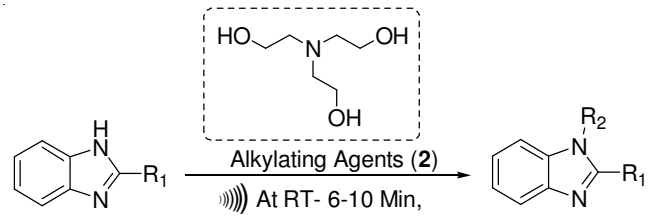
In our earlier communication[18], we reported the *N*-methylation of 2-chloro-1*H*-benzimidazole **1a** using tetra-*n*-butylammonium bromide (TBAB) as phase transfer catalyst, K_2CO_3 as base and dimethyl sulfate as alkylating agent in acetonitrile solution which resulted in 2-chloro-1-methyl-1*H*-benzimidazole **3a** in 76 % yields, reaction time being 3 h. When the same reaction was carried out under ultrasound technique, the reaction time was just 6-8 min and the yield obtained was 90 %.

By the above obtained results we tried to investigate the role of phase transfer catalyst in alkylation reactions. Intially we carried out the *N*-methylation studies of **1a** by using alkylating agent in acetonitrile containing K_2CO_3 and of PEG-600 as phase transfer catalyst, followed by simple processing for 3-4 h, gave the corresponding product **3a** in 72 % yield. We also carried out the above mentioned alkylation studies by employing triethanolamine as phase transfer catalyst in acetonitrile containing K_2CO_3 for 2-3 h, which resulted in the corresponding methylated product in 70 % yield. The obtained results were almost similar to the earlier reported method. We introduced green solvents like PEG-600 and triethanolamine as phase transfer catalysts as well as reaction media in *N*-alkylation studies. We achieved very good yields by using PEG-600 (84 % yield, 2-3 h) and triethanolamine (83 % yield, 3 h), However, reaction time is higher compared to the reaction carried out by using acetonitrile as solvent (Table-1).

When the same alkylation studies were carried out under ultrasound irradiation, yields obtained with PEG-600 was 89 % and reaction time was just 9 min. When triethanolamine was used yields obtained were 92 % in 5 min, with acetonitrile as solvent, K_2CO_3 as base and dimethyl sulphate as methylating agent.

Triethanolamine and PEG-600 were used as solvents as well as phase transfer catalyst which resulted in good yields. When PEG-600 used as phase transfer catalyst and also as solvent, yields obtaind were 94 % and reaction time was 10-12 min, where as triethanolamine yielded 95 % in 4-6 min. Among both, $[N(C_2H_4OH)_3]$ worked more efficiently in terms of external base-free, external phase transfer catalyst-free and external solvent-free, but when PEG-600 is used as solvent cum phase transfer catalyst the use of base was mandatory for completion of the reaction(Table-1). Temperature variation studies were not carried out, since our aim was to find out the effect of ultrasound in *N*-alkylations. The temperature was maintained at room temperature throughout the reaction in conventional method as well as in sonochemical method.

In optimized conditions, we screened the reaction of alkylating agents with 1H-2-substitutedbenzimidazoles in a variety of solvent-phase transfer catalyst reaction system. From the results shown in Table-1, the optimized reaction conditions are 1 + 2 + $[N(C_2H_4OH)_3]$ under sonication, time of reaction being 6-12 min.



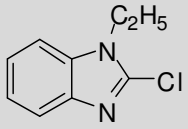
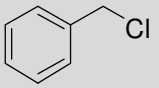
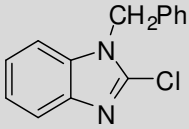
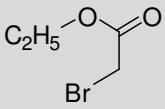
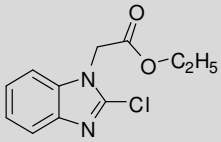
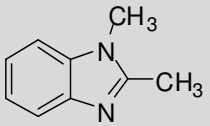
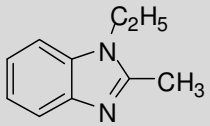
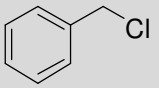
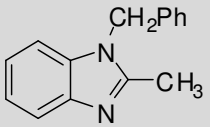
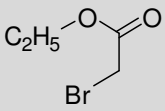
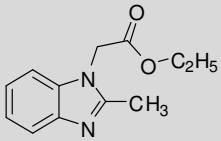
R_1= -$COCH_3$, -CH_2CN; **R_2**= -CH_3, -CH_2CH_3, -CH_2Ph, -SO_2Ph

Scheme-I

The above reaction was found to be general and extended to other alkylating agents and also with 2-methylbenzimidazole **1e** (Table-2). The products obtained were compared with literature values[17].

Recyclability of triethanolamine: After carrying out the reaction, the mixture was extracted with diethyl ether [note: the solubility of triethanolamine in diethyl ether is approx. 1.2-1.4 % at 25 ºC][19], where the product obtained was insoluble in diethyl ether. Extracted triethanolamine was separated and washed successively with Et_2O (2 × 5 mL) in order to remove adsorbed organic substrates. Triethanolamine *i.e.* left over solvent was reused directly without further purification for more runs.

TABLE-2
REACTIONS DONE UNDER ULTRASOUND IRRADIATION USING TRIETHANOLAMINE AS SOLVENT

S. No.	Entry	Reagent	Conventional method		Ultrasound irradiation		Product	m.p. (ºC)
			Time (h)	Yield (%)	Time (min)	Yield (%)		
1.	1b	Diethyl sulphate	3	75	4	94		103-104 ºC
2.	1c		3	79	7	95		150-151 ºC
3.	1d		2-3	68	6	93		137 ºC
4.	1e[18]	Dimethyl sulphate	3	80	4	95		135-136 ºC
5.	1f[18]	Diethyl Sulphate	2-3	78	5	90		95-96 ºC
6.	1g[18]		1-2	65	5	94		143-145 ºC
7.	1h[18]		2-3	72	6	92		128-129 ºC

Conclusion

By the results obtained, it shows that ultrasound irradiation can speed up the reaction time and increases the percentage (%) yields of the products *i.e. N*-alkyl 2-substitutedbenzimidazoles. Compared with traditional stirring methods, ultrasonic irradiation is more convenient and efficient. More importantly, the reactions carried out in triethanolamine was free from external base, external phase transfer catalyst and external solvent and also a reusable green solvent in short reaction times.

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