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Ultrasound assisted convenient, rapid and environmentally benign synthesis of N-alkylbenzimidazoles

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ABSTRACT

*A convenient, rapid, efficient and environmentally benign route has been developed for the synthesis of N-alkylbenzimidazoles **3(a-k)** by the reaction of 2-substituted 1H-benzimidazoles **1(a-k)** with different alkylating agents **2** using triethanolamine as solvent under ultrasonic irradiation. This method provides several advantages of being completely green, giving high yields, environmentally benign and minimizing the use of hazardous solvents.*

Keywords: Ultrasonic waves, PEG-600, triethanolamine and N-alkylations, Green synthesis.

INTRODUCTION

The use of ultrasonic waves is a convenient technique in organic synthesis[1], its development in the past few years has been considerebly increaed to know its mechanism of action inside the reaction flask[2, 3]. Several applications in organic synthesis have made sonochemistry attractive to many researchers[4] and it is increasingly used in organic synthesis[5,6]. It has proved to be a great tool for improving yields and decreasing the reaction time[7].

Benzimidazoles are an important class of heterocyclic compounds, several derivatives of which were found to be useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest[8]. Substitutedbenzimidazole derivatives have got diverse applications in therapeutic areas such as anti-ulcerous, anti-hypertensive, anti-viral, antimicrobial, anti-histaminics, anti-cancer *etc.* to name only a few[9-14].

Phase Transfer Catalysts (PTC) are applied successfully to a great variety of N-alkylation reactions of N-containing heterocyclic compounds. In continuation of our earlier work[15-18] on the synthesis of N-alkylbenzimidazole derivatives, we now would like to report the preparation of the title compounds under **phase transfer catalyst (PTC)**-free conditions *i.e.* without using any PTC, in triethanolamine (TEOA) as green solvent at room temperature under the irradiation of ultrasound and also under conventional methods. The effect of ultrasound on % yield and reaction time has been studied and the same is presented in this communication.

MATERIALS AND METHODS

Melting points are uncorrected and are determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr phase, ^{1}H NMR on VARIAN 400 MHz instrument, ^{13}C NMR on Bruker Avance 75

MHz and Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}$+1 or $M^{+\cdot}$-1 values. (1H-benzimidazole-2-yl)-acetonitrile was prepared based on the synthetic procedure available from the literature[22]. Triethanolamine, acetonitrile, DMF, PEG-600, K_2CO_3 and tetrabutylammoniumbromide was purchased from commercial suppliers.

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: 240mm x 135mm x 100mm.

Synthesis 1-(1-Methyl-1H-benzoimidazol-2-yl)-ethanone using sonochemical method (1a): To a mixture of tetrabutylammonium bromide (PTC, 0.2 gm), K_2CO_3 (1.4 gm, 10 mM) and **1** (1.6 gm, 10mM) in CH_3CN (10 mL), dimethylsulphate (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 10-12 min, the reaction was found to be completed. The mixture was filtered and the insoluble material washed with CH_3CN (2x5 mL). The acetonitrile filtrate was evaporated to dryness and the residue treated with chloroform (25 mL), the chloroform layer was washed with water (3x30 mL) and evaporated to dryness to give **2.** The obtained crude product was recrystallised using ethyl acetate as solvent to obtain pure light yellow coloured (N-methylbenzimidazole-2-yl)-acetonitrile The reaction time was confirmed by repeating the procedure for three more times.

Yield = 1.52 gm, 89%; M.P = 71˚-73˚C.

Synthesis of (1-(1-Methyl-1H-benzoimidazol-2-yl)-ethanone by using triethanolamine as solvent as well as base in sonochemical method: To a solution of **1** (1.6 gm, 10mM) in triethanolamine (10 mL), dimethylsulphate (1.2 mL, 11mmol) was added under sonication and 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 6-8 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 = 1.64 gm, 96%; M.P = 71˚-73˚C.

Synthesis of 1-(1-Methyl-1H-benzoimidazol-2-yl)-ethanone using conventional method: To a mixture of tetrabutylammoniumbromide (PTC, 0.2 gm), K_2CO_3 (1.4 gm, 10 mM) and **1** (1.6 gm, 10mM) in CH_3CN (20 mL), alkylating agent dimethylsulphate (1.2 mL, 11 mM) was added and continued stirring for 3 hr at RT. 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 = 1.31 gm, 77%; M.P = 71˚-73˚C (Lit. M.P = 134˚C).

Supplimentary data:

1-(1-Methyl-1H-benzoimidazol-2-yl)-ethanone(1a): **Dimethylsulphate** is used as alkylating agent. Yellow colored crystalline solid; mp 71-73˚C; **IR** (KBr, cm^{-1}): 1693 (strong, sharp, **C=O**). ^{1}H NMR (300 MHz/DMSO-d_6/TMS): δ, ppm: 2.83(s, 3**H**, -COC**H**$_3$), 4.07(s, 3**H**, N-C**H**$_3$), 7.3-7.85(complex m, 4**H**, aryl protons). ^{13}C NMR spectrum(75 MHz, $CDCl_3$), δ, ppm: 27.1(-**C**O**C**H$_3$), 32.2(N-**C**H$_3$), 110.32, 121.66, 123.55, 125.70(four aryl carbons), 136.70, 141.40, 145.94(three quaternary carbons), 193.12(-**C**O); ms: m/z: 174(19.3), 146(48.6), 132(30.6), 131(100), 105(15.77), 104(27.2); Elemental analysis(%) calculated for $C_{10}H_{10}N_2O$: **C**, 68.95; **H**, 5.79; **N**, 16.08. Found: **C**, 70.02; **H**, 5.85, **N**, 16.20.

1-(1-Ethyl-1H-benzoimidazol-2-yl)-ethanone (1b): **Diethylsulphate** is used as alkylating agent. Light yellow colored crystalline solid; mp 81-83˚C; **IR** (KBr, cm^{-1}): 1688 (strong, sharp, **C=O**). ^{1}H NMR (300 MHz/DMSO-d_6/TMS): δ, ppm: 1.42(t, 3**H**, -CH$_2$C**H$_3$**, J=8 Hz) , 2.85(s, 3**H**, -COC**H$_3$**), 4.57(q, 2**H**, N-C**H$_2$**CH$_3$, J=8 Hz), 7.25-8.05(complex m, 4**H**, aryl protons). ^{13}C NMR spectrum(75 MHz, $CDCl_3$), δ, ppm: 15.62(-CH$_2$**C**H$_3$), 28.21(-CO**C**H$_3$), 40.65(N-**C**H$_2$CH$_3$), 110.72, 122.16, 123.85, 126.50(four aryl carbons), 136.21, 141.80, 145.84(three quaternary carbons), 193.22(-**C**O); ms: m/z: 189(9.5), 187(13.5), 174(11.7), 17(84.4), 160(33.3), 159(5.6), 146(18.8), 145(87), 143(6.8), 132(53.3), 131(99.4); Elemental analysis(%) calculated for $C_{11}H_{12}N_2O$: **C**, 70.19; **H**, 6.43; **N**, 14.88. Found: **C,** 70.33; **H**, 6.52; **N**, 14.96.

1-(1-Benzyl-1H-benzoimidazol-2-yl)-ethanone (1c): **Chloromethyl-benzene** is used as alkylating agent. Light brown colored powder; mp 102-104; **IR** (KBr, cm^{-1}): 1698 (strong, sharp, **C=O**). ^{1}H NMR (300 MHz/DMSO-d_6/TMS):δ, ppm:2.85(s,3H, -COC**H**$_3$), 5.87(S, 2**H**, benzylic protons), 7.28-8.1(complex m, 9**H**, four aryl and five

phenyl protons). ^{13}C NMR spectrum(75 MHz, $CDCl_3$), δ, ppm: 28.25(**C**H_3), 48.63(-N-**C**H_2), 111.18, 112.18, 113.78, 121.99, 123.96, 126.44, 126.75, 127.71, 128.71, 136.66, 141.6, 145.65(six benzene ring carbons, six phenyl ring carbons and one quaternary imidazole carbon), 193.1(**C**=O). ms: m/z: 249(100), 248(20), 207(29), 118(44), 91(59). Elemental analysis (%) calculated for $C_{16}H_{14}N_2O$: **C**, 76.78; **H**, 5.64; **N**, 11.19. Found: **C**, 76.88; H, 5.67; N, 11.26.

1-(1-Benzenesulfonyl-1H-benzoimidazol-2-yl)-ethanone (1d): Benzenesulfonyl chloride is used as alkylating agent**.** Brown colored crystalline solid, mp 92-94; **IR** (KBr, cm^{-1}): 1705 (strong, sharp, **C=O**), 1498(sharp, **S=O**). ^{1}H NMR (300 MHz/DMSO-d_6/TMS):δ, ppm:2.81(s, 3**H**, -OC**H**$_3$), 7.3-8.4(complex m, 9**H**, four aryl and five phenyl protons); ^{13}C NMR spectrum(75 MHz, $CDCl_3$), δ, ppm: 28.88(**C**H3), 114.33, 121.9, 123.77, 125.44, 126.47, 127.77, 128.05, 129.14, 133.89, 134.66, 138.24, 141.01, 148.55(six benzene ring carbons, six phenyl ring carbons and quaternary imidazole carbon), 191.11(**C**=O). ms: m/z: 300(30), 145(18), 132(14), 118(100), 91(9.8), 77(18). Elemental analysis (%) calculated for $C_{15}H_{12}N_2O_3S$: **C**, 59.99; **H**, 4.03; **N**, 9.33. Found: **C,** 60.22; **H**, 4.06; **N**, 9.44.

1-[1-(Toluene-4-sulfonyl)-1H-benzoimidazol-2-yl]ethanone(1e):4-Methylbenzenesulfonyl chloride used as as alkylating agent Light brown colored powder, mp 98-100, **IR** (KBr, cm^{-1}): 1695 (strong, sharp, **C=O**), 1480(sharp, **S=O**). ^{1}H NMR (300 MHz/DMSO-d_6/TMS): δ, ppm: 2.40(s, 3**H**, phenyl C**H**$_3$), 2.8(s, 3**H**, -COC**H**$_3$), 7.2-8.3(four aryl and four phenyl protons). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 21.75(phenyl, -CH_3), 28.90(-COCH3), 114.32, 121.96, 125.33, 127.66, 128.22, 129.81, 133.30, 135.10, 141.05, 146.11, 148.55(six benzene ring carbons, six phenyl ring carbons and one quaternary imidazole carbon), 192.05(**C=O**). ms: m/z: 314(70.6), 250(13), 249(18), 160(19.6), 155(92.6), 145(8.7), 139(7.7), 132(14.3), 131(7), 118(44.1), 92(11). Elemental analysis (%) calculated for $C_{16}H_{14}N_2O_3S$: **C**, 61.13; **H**, 4.49; **N**, 8.91; Found: **C**, 61.26; **H**, 4.52; **N**, 8.99.

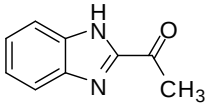
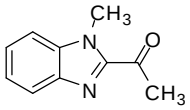
RESULTS AND DISCUSSION

In our earlier communication[19], we reported the N-methylation of 1-(1H-benzoimidazol-2-yl)ethanone **1a** using tetra-n-butylammonium bromide(TBAB) as PTC, K_2CO_3 as base and dimethylsulfate as alkylating agent in acetonitrile solution which resulted in 1-(1-methyl-1H-benzimidazol-2-yl)-ethanone **3a** in 76% yields. The reaction time of conventionally synthesised product **3** was 3-4 hrs. When the same reaction was carried out sonochemically, the reaction time was just 3-6 min and the yield obtained was 91%.

By the results obtaind in both conventional and sonochemical method , to study the role of PTC in the above reaction **3a**, conventionally we replaced TBAB by using PEG-600 and triethanolamine as PTC. When PEG-600 used as PTC and acetonitrile as solvent yield obtained was 72% and triethanolamine as PTC yielded 75%. Results obtained was almost similar as reported earlier. Later PEG-600 and triethanolamine was also tried directly as solvent and also as PTC, yield obtained with PEG-600 was 85% and triethanolamine was 87%, which were in higher compared to the reaction done using acetonitrile as solvent**(Table-I**).

But, when the same reaction(**1a** to **3a)** carried out under ultrasound irradiation, yields obtained by replacing the TBAB with PEG-600 was 93% and in triethanolamine was 94% respectively where acetonitrile used as solvent, which were comparatively higher than the results obtained by using TBAB as PTC. When PEG-600 used as PTC and also as solvent yield obtaind was 94% and in triethanolamine it yielded 96%.

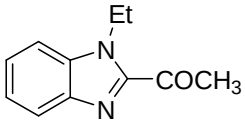
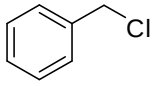
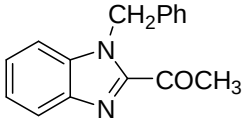
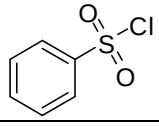
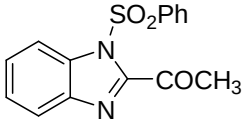
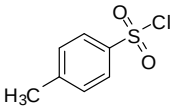
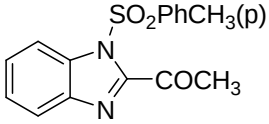
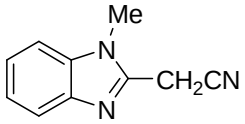
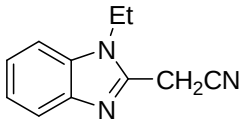
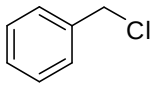
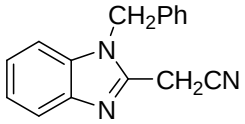
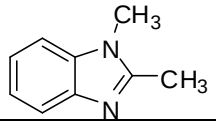
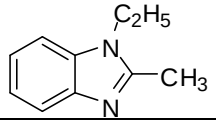
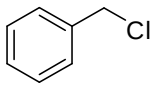
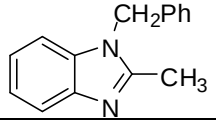
Table-I: Methylation of 1a under conventional and ultrasonic method using different solvents.

Entry	Solvent	PTC	Conventional method		Ultrasound irradiation		Product
			Time (Min)	Yield (%)	Time (Min)	Yield (%)	
 1a	CH_3CN	TBAB	3	76	9	91	
		PEG-600	6	72	6	92	
		$N(C_2H_4OH)_3$	2-3	75	5	94	
	PEG-600	None	2-3	85	15	94	
	$N(C_2H_4OH)_3$	None	3	87	4	96	

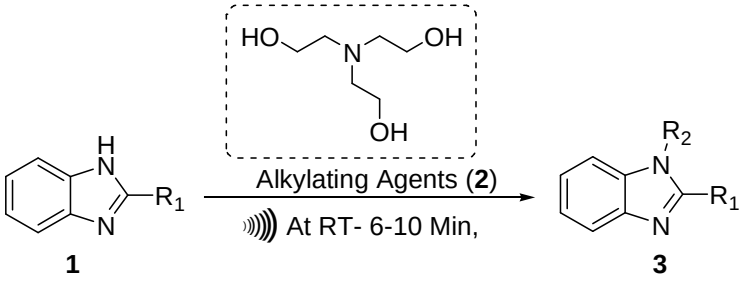
Triethanolamine and PEG-600 used as solvent as well as PTC resulted in good yields. Among both, ($N(C_2H_4OH)_3$) worked more efficiently in terms of external base-free, external phase transfer catalyst-free and external solvent-

free, but when PEG-600 is used as solvent cum PTC the use of base was mandatory for completion of the reaction(**Table-I**). 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.

Table-II: Reactions done under ultrasound irradiation using triethanolamine as solvent

S.No.	Entry	Reagent	Conventional method		Ultrasound irradiation		Product
			Time (Hrs)	Yield (%)	Time (Min)	Yield (%)	
1.	1b	Diethyl sulphate	3	81	4	96	
2.	1c		3	87	6	95	
3.	1d		2-3	65	6	93	
4.	1e		3-4	69	5	95	
5.	1f[22]	Dimethyl sulphate	3	81	4	96	
6.	1g[22]	Diethyl Sulphate	2-3	85	5	94	
7.	1h[22]		1-2	65	5	94	
8.	1i[23]	Dimethyl sulphate	3	81	4	96	
9.	1j[23]	Diethyl Sulphate	2-3	85	5	94	
10.	1k[23]		1-2	65	5	94	

In optimized conditions, we screened the reaction of alkylating agents with 1H-2-substitutedbenzimidazoles in a variety of solvent-PTC 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 mins.



1 **3**

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

Scheme 1.

This reaction was found to be general and extended to other alkylating agents and also with 2-cyanomethylbenzimidazole(**Table-II**). The products obtained were compared with literature values[20].

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^{o}C[21],where the product obtained were insoluble in diethyl ether. Extracted triethanolamine was separated and washed successively with Et_2O (2x5 mL) and hexane (5 mL) in order to remove adsorbed organic substrates. Triethanolamine *i.e.* leftover solvent was reused directly without further purification for more runs.

CONCLUSION

Based on the above work, it is obvious 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 alkylation reaction was carried out in triethanolamine which is 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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