An Efficient Noncatalytic Protocol for the Synthesis of Trisubstituted Imidazole in Polyethylene Glycol Using Microwaves

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Abstract: An efficient and green procedure for the synthesis of 2, 4, 6-triaryl-1H-imidazole in polyethylene glycol under microwave irradiation in excellent yield has been developed. Polyethylene glycol is non toxic, reusable, inexpensive and easily available.

Keywords: PEG, microwave irradiation, trisubstituted imidazole.

Multi substituted imidazole and derivatives are an important class of compounds in the field of pharmaceuticals. They exhibit a wide range of biological activities such as, inhibitors of p38 MAP Kinase [1], B-Raf kinase [2], anti-HIV [3], anticonvulsant [3], HIV-1 protease [4], calcium antagonist and inhibitors of thromboxane A2 synthesase [5] therapeutic agent [6], antihistaminic [7], tranquilizer [8], antimuscarinic [9], antiarthritic [10], cardiotonic [11], HMG CoA reductase(HMGR) [12], and antitumor agents [13]. In recent years substituted imidazoles are substantially used as Ionic liquids [14], a new approach to "green chemistry".

Literature survey reveals that several methods have been developed for the synthesis of 2,4,5-triaryl-1H-imidazoles by three component cyclocondensation of 1,2-diketone, α-hydroxy ketone with aldehydes and ammonium acetate, which comprises the use of ionic liquids [15], silica sulphuric acid [16], refluxing in acetic acid [17a-b], alum [18a], sulphanilic acid [18b], $NiCl_2.6H_2O$ [19], H_3PO_4 [20], CAN [21], grinding with I_2 [22], from N-acylated α-amino in presence of triphenyl phosphine followed by coupling with Pd catalyst [23]. Recently, Konwar, *et al.* reported the synthesis of imidazole using $InCl_3.H_2O$ [24]. Moreover, imidazoles have also been prepared by the reaction of aryl nitriles and α,α-dithioaryl nitromethanes [25a],. Microwave assisted synthesis of tri- and tetrasubstituted derivatives was reported by Kidwai *et al.* But during the reaction they got sticky solid which indicates that, it is not a cleaner approach [25b]. Many of these synthetic methods suffer from one or more drawbacks such as harsh reaction conditions, poor yield, laborious work-up and purifications, prolonged reaction time, etc.

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Moreover, the synthesis of heterocycles in polar solvents led to hazardous complex isolation and recovery procedures. Therefore, the development of new non catalytic method is necessary to overcome their shortcoming, and fulfil mild conditions, efficient and environmentally benign protocol for the synthesis of multisubstituted imidazoles.

Nowadays, interest of chemists increases toward the use of polyethylene glycol as reaction medium as well as catalyst due to its non-toxicity, high efficiency, easy separation and purification, cost effectiveness and reusability. From environmental point of view, it is desirable to use polyethylene glycol as reaction medium and catalyst instead of organic solvents and catalyst, since polyethylene glycol is environmentally benign, cheap, and easily available.

Herein, we report one-step synthesis of imidazoles by the combination of Benzil or Benzoin with aldehyde and ammonium acetate in polyethylene glycol under scientific microwave irradiation. It represents a significant improvement over existing methods of imidazoles synthesis. An advantage of this protocol is the solvent PEG-200 which was recovered by evaporation of water and reused for several times.

In recent years, the use of microwave irradiation in organic synthesis has become an attractive tools [26]. We develop a simple synthetic protocol for imidazoles synthesis from readily available starting materials. The reaction [27] of benzil or benzoin, aldehyde and ammonium acetate in polyethylene glycol under microwave irradiation for 5 to 10 minutes at 900W yields imidazoles (Schemes **1** and **2**). This result prompted us to investigate the imidazole synthesis using different aldehydes (Table **1**).

The synthesis of trisubstituted imidazole in different PEG (Scheme **3**) was also attempted and no change in the yield was found. Thus the reaction was optimized in PEG-200, 400, 600 (Table **2**). In conclusion, a simple one step multicomponent methodology has been developed for the synthesis of 2, 4,5-triaryl-1H-imidazole.

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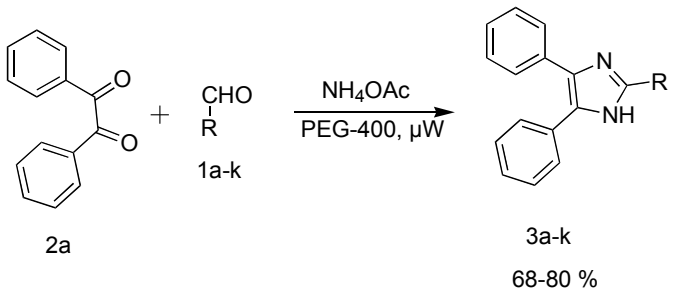
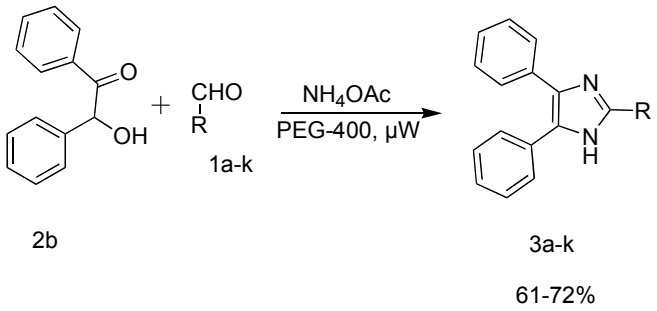
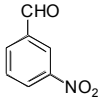
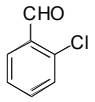
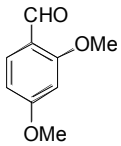
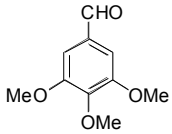
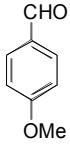


Scheme 1.

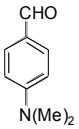
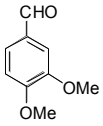
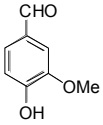
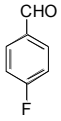
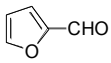


Scheme 2.

Table 1. Synthesis of Trisubstituted Imidazole in Polyethylene Glycol

Entry	Aldehyde 1a-k	Product	Reaction Time/min		Yield[a] %		mp/°C
			Benzil (2a)	Benzoin (2b)	Benzil (2a)	Benzoin (2b)	
1		3a	5	5	80	72	274[27]
2		3b	4	6	72	67	>300[27]
3		3c	5	5	70	69	188[27]
4		3d	10	10	68	61	165
5		3e	10	10	70	65	258
6		3f	5	6	72	71	230[27]

(Table 1) Contd…..

Entry	Aldehyde 1a-k	Product	Reaction Time/min		Yield[a] %		mp/°C
			Benzil (2a)	Benzoin (2b)	Benzil (2a)	Benzoin (2b)	
7		3g	6	7	70	69	257[27]
8		3h	6	7	77	68	218
9		3i	6	7	68	71	166[22]
10		3j	5	6	70	67	238[27]
11		3k	7	7	68	70	235

[a]Isolated yield.
[b]All compounds are known in the literature and were characterized by using LC-MS and (400 $CDCl_3$) Varian Spectrophotometer.

CONCLUSIONS

A series of 2,4,5-triaryl-1H-imidazole was synthesized in one step. We demonstrated an efficient protocol for the synthesis of substituted imidazole from benzil/benzoin, aldehydes and ammonium acetate without catalyst in polyethylene glycol. Product isolation *via* filtration without any hazardous organic solvent claims an environmentally benign protocol for the synthesis of substituted imidazoles.

Table 2. Synthesis of Trisubstituted Imidazole in different PEG

Entry	PEG	Reaction Time/min	Yield %
1	PEG-200	5	70
2	PEG-400	5	70
3	PEG-600	5	71

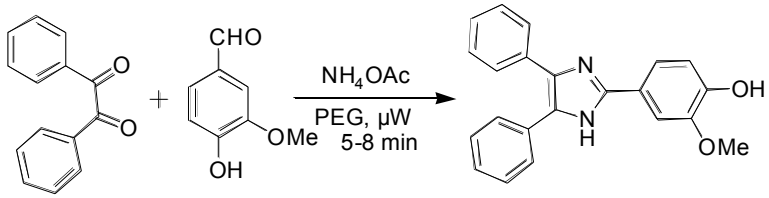
GENERAL PROCEDURE FOR THE PREPARATION OF TRISUBSTITUTED IMIDAZOLE

All organic solvents used for the synthesis were of analytical grade. Melting points were determined and are uncorrected. IR spectra were recorded on a Shimadzu IR 200 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Varian 400 MHz spectrometer using tetramethylsilane as internal reference. Column chromatography was performed on Merck silica gel 60 (70-230 mesh). Thin layer chromatographic separations were performed on Merck Kiesselgel 60 (70-230 mesh).

The microwave reactions were carried out in a Catalyst Systems Model CATA-R 2450 MHz Sciencetific Microwave Oven at 120-140°C and 300 W for the period shown in the Table **1**.

A mixture of benzil (1mmol), aromatic aldehyde (1mmol), ammonium acetate (4mmol) and polyethylene glycol (2 ml) was irradiated under microwave oven for appropriate time. The progress of reaction was monitored by TLC (ethyl acetate:methnol 4:1). After completion of reaction, the reaction mixture was cooled to room temperature and poured on 100 ml ice water. The separated solid was filtered and washed with water. The residue was dried, and recrystallized from methanol: water (9:1) mixture.

2,4,5-Triphenyl-1*H*-imidazole (3a): Light- yellow solid mp. 271-272°C (Lit. [13] 272-273°C). (Found C, 85.02, H, 5.1, N, 9.12%. $C_{21}H_{16}N_2$ requires C, 85.11, H, 5.44, N, 9.45%) IR (KBr) cm^{-1} 3434, 2993, 2470, 1638 1216. ^{1}H NMR (400 MHz, $CDCl_3$/ DMSO-d6): δ_H 8.91 (s, brs, 1H),



Scheme 3.

7.42-8.12 (m 6H), 7.68-7.71(m, 3H),7.87(m, 6H); ^{13}C NMR (CDCl3/ DMSO-d6): δC 136.5, 129.1, 128.5. 127.2, 122.1.

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