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One Pot Three Component Synthesis of 2,4,5-triaryl-1H-imidazole Using PEG-400 and their Antibacterial Screening

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ABSTRACT

2,4,5-triarylimidazoles could be obtained in excellent yields by one-pot three component condensation of benzil, aromatic aldehydes and ammonium acetate in presence of polyethylene glycol PEG-400 as medium and catalyst. The synthesis highlights a comparative study of conventional and ultrasound methods. The compound 4c was investigated in vitro against Gram +ve and Gram –ve bacteria at different concentrations and compared with standard drug ciprofloxacin.

Keywords: 2,4,5-triarylimidazoles, PEG-400, Conventional, Ultrasound

INTRODUCTION

Imidazole derivatives are a very interesting class of heterocyclic compounds because they are found in many natural products and pharmacologically active compounds, such as antiulcerative agent cimetidine [1], the proton pump inhibitor omeprazole [2], and the benzodiazepine antagonist flumazenil [3], are imidazole derivatives. Many of the substituted imidazoles are known as inhibitors of p38 MAP kinase, fungicides, herbicides, plant growth regulators, and therapeutic agents [4-7]. As a new approach to 'Green Chemistry' the substituted imidazole ring systems are substantially used in ionic liquids [8].

Triarylimidazole compounds have gained remarkable importance due to their widespread biological activities and their use in synthetic chemistry. Due to their great importance, many synthetic strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazole from 1,2-dicarbonyl compound, various aldehydes and ammonia, to obtain the 2,4,5-triphenyl imidazoles [9-11]. However, these methods require prolonged reaction time and exotic reaction condition. Thus, the development of a new method for the synthesis of 2,4,5-triarylimidazoles derivatives would be highly desirable.

The use of volatile, toxic, and hazardous organic solvents has been replaced by different alternatives. Where Polyethylene Glycols (PEGs) play an important role in organic synthesis it has become a popular reaction media since last decade. PEGs are known as nontoxic, inexpensive, nonflammable, and nonionic liquid reaction media of low volatility [12]. This kind of solvent system fully meets the demands of green chemistry [13] and is found to be useful for various organic transformations [14]. PEG-400 has been found as an accelerator in various synthetic reactions [15,16].

MATERIALS AND METHODS

Experimental section

General consideration

All reagents and solvents were of LR grade purchased from commercial sources were used as received without further purification. All reactions were carried out in oven-dried glassware and were magnetically stirred. Melting points are determined following open capillary method and are uncorrected. FTIR spectra were taken on F.T. Infra-Red Spectrophotometer Model RZX (Perkin Elmer) and ^{1}H and ^{13}C spectra were taken on bruker AVANCE II 400 MHz spectrometer with TMS as internal standard $CDCl_3$/DMSO as solvent. ESI-Mass spectral data were recorded on Q-TOF Micro Waters (ESI-MS) Spectrometer.

General procedure for the screening of solvents

To achieve suitable conditions for the synthesis of 2,4,5-trisubstituted imidazoles, various reaction conditions have been investigated in the reaction of benzil 1, benzaldehyde 2c and ammonium acetate 3 as a model reaction (Scheme 1). We examined the effect of different solvents such as EtOH, MeOH, THF, CH_3CN, H_2O, H_2O-EtOH, PEG-400 on a model reaction and the reaction carried out using conventional and under ultrasound irradiation (power intensity: 40%) at 50°C. and it was observed that under ultrasound irradiation all the solvents used gives good yield but the use PEG-400 afforded 95% yield (Table 1, entry 7) of the desired product. The results were summarized in Table 2. Therefore PEG-400 was chosen as solvent for the reaction.

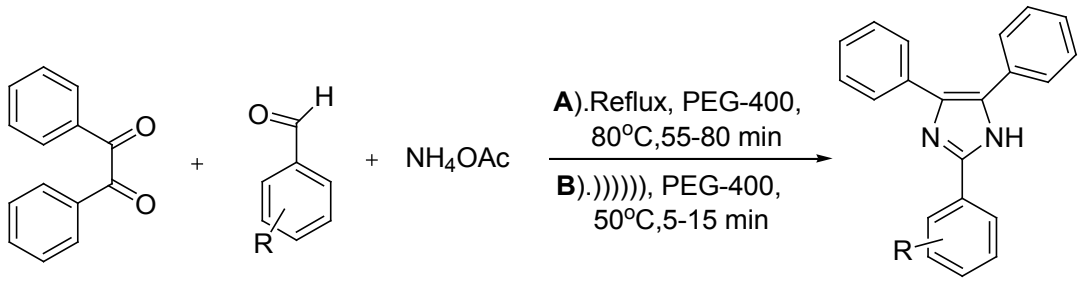
General procedure for the synthesis of 2,4,5-triarylimidazole

Method A: By conventional method

A mixture of benzil (1) (1.0 mmol), aromatic aldehyde (2) (1 mmol) ammonium acetate (3 mmol) (3) to that PEG-400 (5 ml) was added as medium and as catalyst to it and the reaction mixture was reflux at 80°C for the respective time given in Table 3. Progress of the reaction was monitored with the help of TLC. After completion of the reaction, the reaction mixture was cooled and then extracted by diethyl ether. With the help of vacuum distillation the ether was removed and the obtained compound was crystallized using (1:1) DMF-Ethanol. And the ether layer containing PEG-400 was washed two to three times with diethyl ether (20 mL) and was separated by separating funnel and the obtained PEG-400 was reused for reaction. The products obtained are reported compounds and they were characterized by comparing with their spectral data (IR, mass, ^{1}H-NMR and ^{13}C-NMR) and physical properties with those reported in literature.

Method B: By ultrasound method

A mixture of benzil (1) (1.0 mmol), aromatic aldehyde (2) (1 mmol) ammonium acetate (3) (3 mmol) to that PEG-400 (5 ml) was added as medium and as catalyst to it and the reaction mixture containing RBF was placed into the ultrasonic water bath, in such a way that the surface of the reactants is slightly lower as compared to the level of the water, and irradiated at 40% of the power of the ultrasonic bath at 50°C for 10-15 min. Progress of the reaction was monitored with the help of TLC. After completion of the reaction the process of recyclation of PEG-400, crystallization and characterization was done as given in (Method A).



1 **(2a-h)** **3** **(4a-h)**

Where,

R = OMe, Me, H, F, NO_2, OH, Cl

Scheme 1: One pot synthesis of 2,4,5-triaryl-1H-imidazoles using PEG-400 under ultrasound irradiation at ambient temperature

Table 1: Screening of solvents for the synthesis of 2,4,5-triphenyl-1H-imidazole (4c)

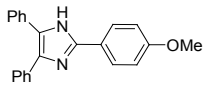
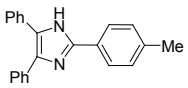
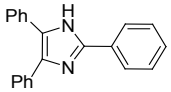
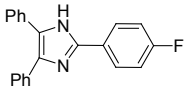
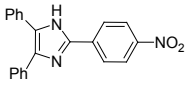
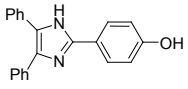
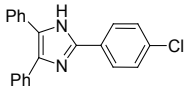
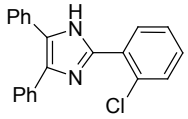
Entry	Solvent	Conventional Method[a]		Ultrasound Method[b]	
		Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	Methanol	73	50	53	63
2	Ethanol	70	43	50	55
3	Water	70	40	52	50
4	CH_3CN	70	30	50	38
5	THF	75	Trace	50	30
6	H_2O-EtOH	72	42	57	54
7	PEG-400	60	85	15	95

[a]Reaction condition: benzil (**1**) (1.0 mmol) ,benzaldehyde (**2**) (1.0 mmol), ammonium acetate (3.0 mmol) and PEG-400 (5 mL) under conventional heating.
[b]Reaction condition: benzil (**1**) (1.0 mmol) ,benzaldehyde (**2**) (1.0 mmol), ammonium acetate (3.0 mmol) and PEG-400 (5 mL) under ultrasound irradiation.
[c]Isolated yields.

Table 2: Recyclability and reusability of PEG-400

Cycle	Yield[a]
Fresh	95
Ist	90
IInd	84
IIIrd	78

Table 3: One pot synthesis of 2,4,5-triarylimidazoles (4a-h) using PEG-400

Comp.	Aldehyde R	Product	m.p °C	Conventional Method		Ultrasound Method	
				Time (min)	Yield (%)	Time (min)	Yield (%)
4a	4-OMe		228-230	55	74	15	95
4b	4-Me		230-232	57	72	13	93
4c	H		276-278	60	70	15	95
4d	4-F		188-190	60	74	10	92
4e	4-NO_2		232-233	80	67	8	87
4f	4-OH		269-270	53	75	15	94
4g	4-Cl		260-262	58	73	12	92
4h	2-Cl		195-197	64	70	10	88

Spectral data for representative 2,4,5-triarylimidazoles

Compound 4c: Yield 95%; white solid; mp 276 – 278°C. FTIR Model RZX (Perkin Elmer) cm^{-1}: 3040, 1487, 1462, 1127, 697. 1H-NMR (400 MHz, DMSO-d_6, d ppm): 12.60 (brs, 1H, NH), 8.11 (d, 2H, J=7.6 Hz, ArH), 7.28 –7.56

(m,15H, ArH); ^{13}C-NMR (400 MHz, DMSO-d_6, d ppm): 125.1,126.3,127.08,128.42,129.5,130.39,131.16,135.1,137.1,154.5 MS (EI): m/z (%) =297 [M^+].

Antibacterial activity

The synthesized compound 4c was screened for *in vitro* antimicrobial activity against two gram positive bacterial strains, *S. aureus* and *B. subtilis* and two gram negative strains, *E. coli* and *P. aeruginosa* [17,18]. Ciprofloxacin was used as standard drug. Here agar disc-diffusion method was used.

General procedure: Determination of zone of inhibition by agar disc-diffusion method

Test solutions of concentration of 125-1000 µg/mL were prepared with known weight of compound in DMSO and half diluted suitably to give the resultant. Solution and Whatmann no. 1 sterile filter paper discs (6 mm) were impregnated and allowed to dry at room temperature. By using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai the *in vitro* antibacterial activity was determined. And then the petri plates were prepared by pouring 20 mL of Mueller Hinton Agar for bacteria containing microbial culture then it was allowed to solidify. 24 h old cultures were used to get 10^8 suspensions. This suspension of 4 pathogenic cultures was spread on Muller Hinton Agar plates by sterile cotton swabs. The impregnated discs were then kept on these plates and were incubated at 37^{o}C for 24 h (bacteria) and after incubation zone of inhibition was measured in mm as diameter in four directions and expressed as mean. The results were compared against Ciprofloxacin as a standard drug and are reported in Table 4.

After the antibacterial assessment the obtained data was shown in Table 4, which indicates that the compound 4c activity against Gram positive bacteria is moderate activity against *S. aureus* no activity against *B. subtilis*. In case of gram negative bacteria, 4c showed moderate activity against *E. coli* and it is inactive against *P. aeruginosa* at all 4 concentrations. Thus on the basis of data it is clear that imidazole based derivatives possesses moderate antibacterial activity.

RESULTS AND DISCUSSION

One pot cyclocondensation of Bezil (1), with aromatic aldehydes (2a -h) and ammonium acetate (3) in presence of PEG-400 as a medium and as a catalyst it was carried out under conventional and also ultrasound irradiation which result into the subsequent 2,4,5-triaryl-1H-imidazoles (4a-h) (Table 3).

We have screened different solvents and studied their effect for the synthesis of 4c as a model reaction by reacting benzyl 1c, benzaldehyde 2c, and ammonium acetate 3 using different solvents. We observed that PEG-400 (Table 1, entry 7) have affords the product in good yields as compared to other solvents. The reason is that the intermolecular hydrogen bonding between aldehyde carbonyl with terminal hydroxyl group of PEG-400 which enhancing the electrophilic behavior of carbonyl carbon and give good yield in shorter time. And the PEG-400 is also recycled and reused in the synthesis, the PEG-400 was recycled three times each time there is a loss of 5 and 6% as shown in Table 2. Each time we got good yield and the reaction proceeded cleanly.

Table 4: Antibacterial activity of 4c

S. No.	Conc. µg/mL	Zone of inhibition in (mm)							
		Gram +ve				Gram-ve			
		4c							
		Pathogen–*Staphylococcus aureus*		Pathogen–*Bacillus subtilis*		Pathogen–*Escherichia coli*		Pathogen–*Pseudomonas aeruginosa*	
		Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
1	125	12	11	-	-	8	7	-	-
2	250	15	16	-	-	10	8	-	-
3	500	17	19	-	-	14	11	-	-
4	1000	22	20	-	-	13	17	-	-
Standard Ciprofloxacin									
1	125	31	31	27	27	26	26	27	27
2	250	35	36	29	29	28	28	32	32
3	500	40	41	30	31	29	31	36	34
4	1000	44	45	32	33	30	33	38	39

Further synthesis of different derivatives of 2,4,5-triaryl-1H-imidazoles was performed by using PEG-400 under conventional and also repeated in ultrasound irradiation here it was noticed that using ultrasound irradiation give good yield in shorter time as compared to conventional method and the obtained result are shown in Table 3.

The synthesized compound 4c was screened for *in vitro* antimicrobial activity against two gram positive bacterial strains, *S. aureus* and *B. subtilis* and two gram negative strains, *E. coli* and *P. aeruginosa*. Ciprofloxacin was used as standard drug. Here agar disc-diffusion method was used and the result was shown in Table 4.

CONCLUSION

In conclusion, we report PEG-400 as medium and catalyst for the synthesis 2,4,5-triarylimidazoles which is eco-friendly and a comparative study of conventional and ultrasound method where we found that using ultrasound method product obtained in good yield in shorter reaction time and it is also a very clean method. Antibacterial screening of 4c compound was found to possess moderate activity against selected strains of bacteria also found inactive for *B. subtilis* and *P. aeruginosa* and rest of synthesized will be assessed in future study.

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