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Facile One Pot Multi-Component Solvent-Free Synthesis of 2,4,5-Trisubstituted Imidazoles Using "Green" and Expeditious Ionic Liquid Catalyst under Microwave Irradiation[1]

B. Sonyanaik, K. Ashok, S. Rambabu, D. Ravi, A. Kurumanna, P. Madhu, and B. Sakram*

Department of Chemistry, Osmania University, Telangana, Hyderabad, 500007 India
**e-mail: bschemou@gmail.com*

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Abstract—Acetic acid functionalized poly(4-vinylpyridinium) bromide is a highly efficient and recyclable catalyst for the construction of 2,4,5-trisubstituted imidazole derivatives by a three-component condensation of benzyl with various aldehydes and ammonium acetate under solvent free conditions. The microwave initiated process leads to analytically pure compounds within 2–5 min. The advantages of this "green" methodology are cost-effectiveness, simple procedure, low energy consumption, no involvement of organic solvents, safe operation, clean reaction profile, high yields, and recyclability of the catalyst.

Keywords: one pot synthesis, solvent-free conditions, microwave irradiation, 2,4,5-trisubstituted imidazoles

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Imidazole based compounds play a vital role in biochemical processes [1, 2] and demonstrate a broad range of beneficial biological activities such as antibacterial [3], antiviral [4], antitumor [5], B-Raf kinase [6], analgesic [7], anti-HIV [8], and Alzheimer's disease [9]. The imidazole ring system is an active component of several drug molecules includes Eprosartan, Losartan, Trifenagrel, and Olmesartan.

Due to important biological applications of imidazoles, various methods of their synthesis have been developed for structurally related imidazole derivatives [10–12, and many more]. However, most of the methods were characterized by certain disadvantages, including harsh reaction conditions, low yields, long reaction time, and high expense. Thus, for dismissing such restrictions and in continuation of our earlier studies on the development of eco-friendly synthetic methods [13], here in, we report the construction of 2,4,5-trisubstituted imidazoles using acetic acid functionalized poly(4-vinylpyridinium) bromide catalyst under solvent-free microwave-assisted conditions that led to the products **4a–4m** accumulated with high yields. To the best of our knowledge, there are no reports on application of this catalyst in the synthesis of 2,4,5-trisubstituted imidazoles.

RESULTS AND DISCUSSION

2,4,5-Trisubstituted imidazole derivatives **4a–4m** were synthesized by the reaction of benzyl with arylaldehydes and ammonium acetate under solvent-free conditions supported by microwave irradiation and the eco-friendly ionic liquid, acetic acid functionalized poly (4-vinylpyridinium) bromide (Scheme 1). The catalyst was prepared according to the developed earlier procedure [14] (Scheme 2).

Optimization of the process conditions was carried out for the synthesis of 2,4,5-triphenyl-1H-imidazole **4a** by condensation of benzil **1** (1 mmol) with benzaldehyde **2** (1 mmol) and ammonium acetate **3** (3 mmol) in presence of the ionic liquid catalyst (Table 1). It was determined that application of 10 mol % of the catalyst efficiently led to the highest yield (92%) of the product.

Amount of the catalyst 15 mol % did not improve the yield of the process but somewhat slowed down the reaction accompanied by formation of side products. Comparative study was carried out for microwave irradiation and heating conditions. The best results were achieved under solvent-free microwave irradiation conditions (Table 2). Structures of all synthesized products were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectra. Elemental analyses results and

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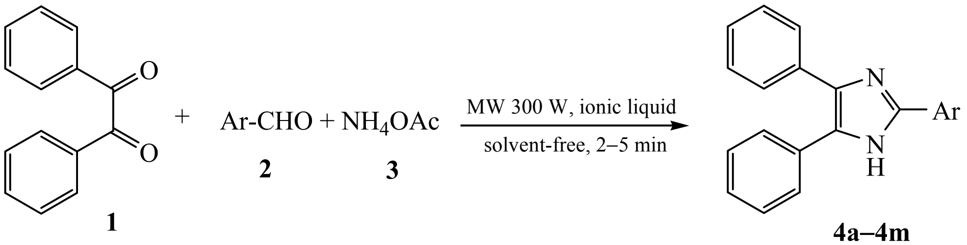
[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 2,4,5-trisubstituted imidazoles catalyzed by acetic acid functionalized poly(4-vinylpyridinium) bromide.



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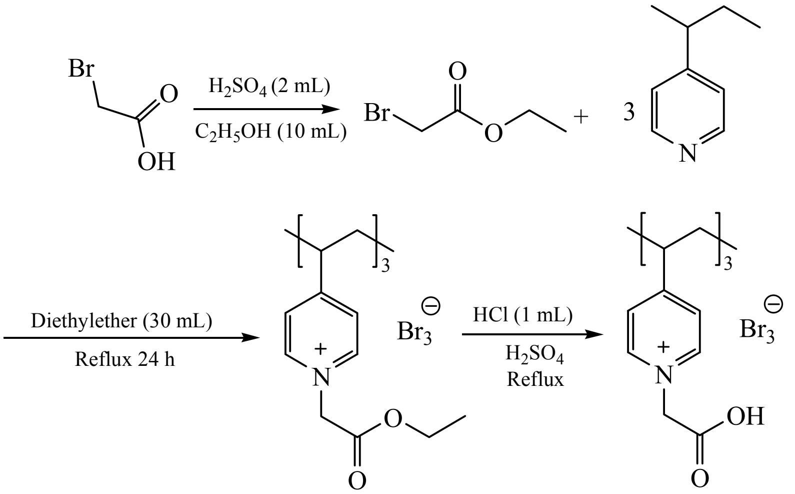
4a–4m

Ar = C_6H_5 (**4a**), C_9H_6NO (**4b**), 4-(OMe)C_6H_4 (**4c**), 4-ClC_6H_4 (**4d**), $C_6H_5CH{=}CH$ (**4e**), C_9H_5ClN (**4f**), 4-FC_6H_4 (**4g**), 4-OHC_6H_4 (**4h**), 2-ClC_6H_4 (**4i**), 3-NO$_2$$C_6H_4$ (**4j**), 4-Cl-2-OHC_6H_3 (**4k**), 5-Me-C_5H_5N (**4l**), 5-Cl-C_5H_4N (**4m**).

Scheme 2. Synthesis of acetic acid functionalized poly(4-vinylpyridinium) bromide catalyst.



melting points of the synthesised compounds were in good agreement with the literature data (Table 2).

Recyclability of acetic acid functionalized poly(4-vinylpyridinum) bromide was studied after completion of the process. The reaction mixture was filtered and the solvent of the filtrate (H_2O) was removed under reduced pressure. The residue was washed with ethanol and diethyl ether (2× 30 mL) and dried. Upon addition of acetone the mixture was stirred and refluxed for 4 min. Then, the mixture of a product with the catalyst was centrifuged for separation of the catalyst which was washed with warm acetone (3 mL) and dried. The recycled this way catalyst could be reused in five consequent cycles of the process (see the figure).

Table 1. Optimization of the reaction conditions[a]

Solvent	Conventional method		Microwave method	
	time, h	yield, %[b]	time, min	yield, %[b]
C_2H_5OH	3.0	79	8	87
CH_3OH	2.5	81	10	89
CH_2Cl_2	3.0	77	8	84
THF	2.0	82	6	86
Solvent-free	2.0	90	2	92

[a] Reaction conditions: Ionic liquid catalyst (27.41 mg, 10 mol % 0.1 mmoL), benzil **1** (1 mmoL), benzaldehyde **2** (1 mmoL) and ammonium acetate **3** (3 mmoL) in solvent-free conditions.

[b] Isolated yields.

EXPERIMENTAL

All solvents and chemicals were purchased from Aldrich/Fisher and used without further purification. Melting points were determined on a Buchi melting point apparatus. The progress of the reaction, as well as purity of the compounds, were monitored and tested by TLC using F254 silica-gel pre-coated plates using the mixture of hexane with ethyl acetate (8 : 3) as an eluent. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer using KBr pellets. ^{1}H NMR

Table 2. Synthesis of imidazole derivatives **4a–4m** in the presence of acetic acid functionalized poly (4-vinylpyridinum) bromide catalyst

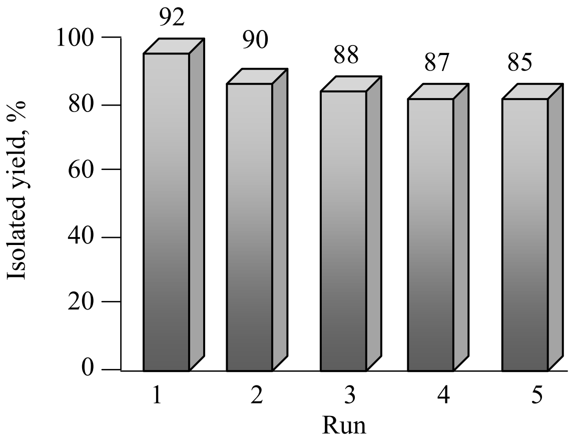
Analog	Aldehyde	Time, min	Yield, %[a]	mp, °C		References
				found	calculated	
4a	Benzaldehyde	4.0	91	278–280	280–282	[12]
4b	3-Indolebenzaldehyde	2.5	92	254–255	252–254	[11]
4c	4-Methoxybenzaldehyde	5.0	89	227–229	228–230	[12]
4d	4-Chlorobenzaldehyde	4.0	92	262–264	260–262	[12]
4e	Cinnamaldehyde	2.5	90	74–76	70–72	[11]
4f	2-Chloroquinolinecarbaldehyde	3.0	91	218–220	219–221	[11]
4g	4-Fluorobenzaldehyde	2.0	92	190–192	187–189	[12]
4h	4-Hydroxybenzaldehyde	3.5	91	270–272	268–270	[13]
4i	2-Chlorobenzaldehyde	4.0	90	191–193	190–192	[12]
4j	3-Nitrobenzaldehyde	3.0	87	317–319	315–317	[13]
4k	4-Chloro-2-hydroxybenzaldehyde	2.5	90	176–178	177–178	[11]
4l	5-Methylpicolinaldehyde	4.0	91	219–221	–	–
4m	5-Chloropicolinaldehyde	5.0	90	169–171	–	–

[a] Isolated yields of the pure compound based on aldehyde using microwave irradiation.

spectra were measured on a Bruker 400 MHz spectrometer. Mass spectra were measured on a Jeol JMSD-400 spectrometer. Elemental analyses were performed on a Carlo-Erb model EA1108 analytical unit.

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles 4a–4m by the conventional method. The mixture of benzil (210.23 mg, 1 mmol) with an aldehyde (1 mmol), ammonium acetate (231.24 mg, 3 mmol), and acetic acid functionalized poly (4-vinylpyridinum) bromide (27.41 mg, 10 mol %, 0.1 mmol) was stirred for an appropriate time (Table 2). Upon completion of the reaction (as monitored by TLC), 5 mL of water were added. Following stirring at room temperature lasted for 5 min. The reaction mixture was filtered and the solvent of the filtrate (H_2O) was removed under reduced pressure. The mixture was washed with ethanol and diethyl ether (2×30 mL) and dried. Upon following addition of acetone, stirring and refluxing lasted for 5 min. Then, the mixture of the product with the catalyst was centrifuged for separation of the catalyst from the product.

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles 4a–4m under microwave irradiation. A mixture of benzil (210.23 mg, 1 mmol) with ammonium acetate (231.24 mg, 3 mmol), aldehyde (1 mmol), and acetic acid functionalized poly-(4-vinylpyridinum) bromide (27.41 mg, 10 mol %, 0.1 mmol) was loaded in a cell of the microwave reactor and irradiated at 300 W for 2–5 min (TLC). The reaction mixture was washed with cool water and



Activity of the recycled acetic acid functionalized poly (4-vinylpyridinum) bromide catalyst in the synthesis of 2,4,5-triphenyl-1*H*-imidazole (**4a**).

filtered. The solvent of the filtrate (H_2O) was removed under reduced pressure. The reaction mixture was washed with ethanol and diethyl ether (2×30 mL) and dried. Upon addition of acetone, the mixture was stirred and refluxed for 4 min. Then, the mixture of a product and the catalyst was centrifuged for separation of the catalyst from the product.

The sample of the spectra and elemental analysis of the products is presented for the compound **4b**. For the other products data see the corresponding references presented in Table 2.

3-(4,5-Diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (4b). IR spectrum, ν, cm^{-1}: 3412, 1623, 1597. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.14–8.01 m (14H), 8.48 d (J = 7.6 Hz, 1H), 11.36 s (1H), 12.31 s (1H). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 106.5, 110.2, 118.7, 121.9, 123.6, 125.1, 125.6, 126.1, 126.7, 127.2, 129.0, 132.7, 135.6, 136.0, 136.1, 143.9. MS (ESI): *m/z:* 336 $[M + H]^+$. Found, %: C, 82.27; H, 5.41; N, 12.36. $C_{23}H_{17}N_3$. Calculated, %: C, 82.36; H, 5.11; N, 12.53.

CONCLUSIONS

In summary, we have developed a mild and efficient approach to the synthesis of 2,4,5-trisubstituted imidazoles via one pot multi component condensation of a representative 1,2-diketone (benzil) with various aromatic aldehydes and ammonium acetate using the ionic liquid APVPB as a catalyst, and supported by MWI under solvent-free conditions. This method has distinctive advantages such as clean reaction profile, short reaction time, high yields, simple workup procedures, and reusability of the catalyst.

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