



**IONIC LIQUID MEDIATED ONE POT SYNTHESIS OF 2,4,5-
TRIARYLIMIDAZOLES FROM 1,3-DIARYL PYRAZOLE CARBALDEHYDES
UNDER SOLVENT-FREE CONDITION**

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Abstract:

A facile protocol has been established for the one-pot synthesis of 2,4,5-trisubstituted imidazoles derivatives via three-component condensation of 1,3-diaryl pyrazole aldehydes, benzil and ammonium acetate in the presence of catalytic amount of an ionic liquid [HNMP][HSO₄] as a catalyst under solvent-free condition. The significant features of this protocol include high-atom economy, smooth work-up procedure, inexpensive catalyst, easy for handling, shorter reaction time, high yield, multi-component approach and solvent-free reaction.

Keywords:

1,3-diaryl pyrazole aldehyde, imidazole, benzil, multi-component strategy, ionic liquid, solvent free etc.

Introduction:

In the last decades, Ionic liquids (ILs) has attracted the interest of the scientific community, due to their versatile properties and their applications in organic synthesis, catalysis, biocatalysis. The ILs are an excellent alternative to substitute volatile organic solvents in more eco-friendly technologies, due to their various outstanding properties such as low vapor pressure, thermal and chemical stability, catalytic activity, non-flammability and non-corrosive nature^{i, ii}.

The multicomponent reaction has a great importance due to various properties such as high atom economy, one step operation, short reaction time, used for synthesis of various heterocycles. The synthesis of 2,4,5-triaryl imidazole derivatives is an important illustration of multicomponent reactionⁱⁱⁱ. They are synthesized via three component condensation of aldehyde, benzil and ammonium acetate in the presence of various catalysts such as nanomaterials, metal catalyst, zeolites, metal supported catalyst, and acidic as well as basic catalyst. Also, various ionic liquids (ILs) are used as an efficient catalyst for the synthesis of 2,4,5-triaryl imidazole derivatives^{iv-viii}.

Imidazoles and their derivatives are an important class of five-membered aromatic heterocyclic compounds that show various biological activities such as anti-allergic, anti-bacterial, anti-clotting, anti-fever, anti-HIV, anti-inflammatory, anti-Parkinson, anti-tumor, analgesic and fungicide^{ix, x}. Also imidazoles are used to prepare ionic liquids which are applied in various organic transformations as a green media^{xi}.

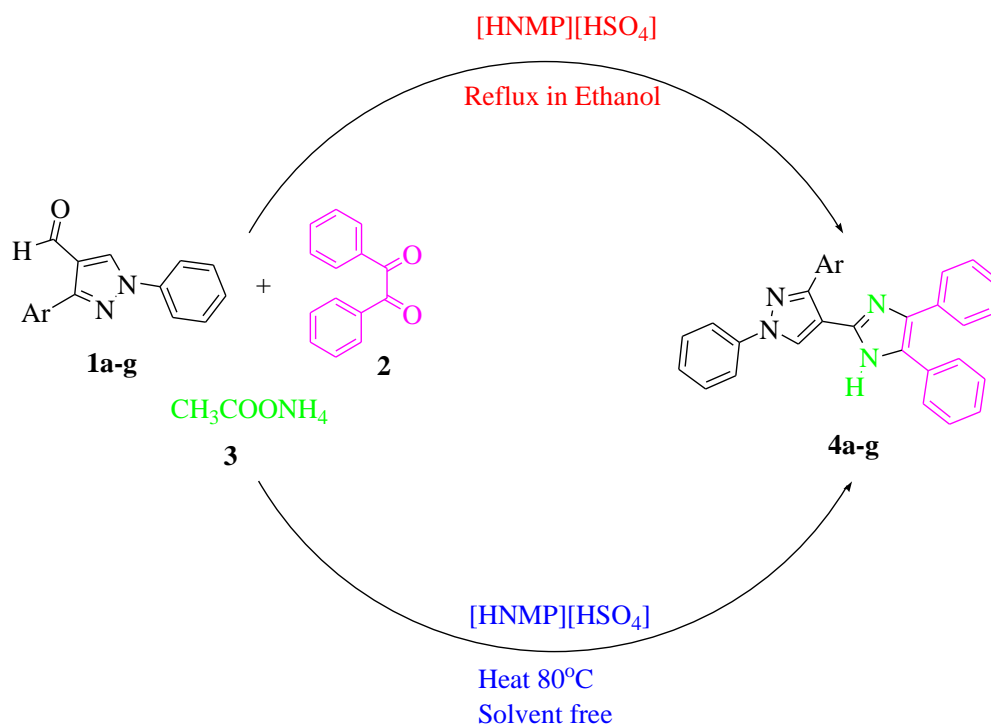
As part of our study of ILs as a catalyst under solvent free reactions, herein we have used reported^{xii} ionic liquid [HNMP][HSO₄] for the synthesis of 2,4,5-trisubstituted imidazoles from the more biologically potent and bulkier 1,3-diaryl pyrazole aldehydes.

Result and Discussion:

In continuing our studies towards the development of eco-friendly routes for the synthesis of more biological potent and bulkier molecules, we report a facile protocol for the synthesis of 2,4,5-trisubstituted imidazoles eco-friendly catalyst. Initially, we have studied the efficiency of ionic liquid [HNMP][HSO₄] for the model reaction using 1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde (1 mmol), benzil (1 mmol) and ammonium acetate (2 mmol).

Firstly, the reaction was carried out in the presence of ethanol as a solvent (Table 1, Entry 2) and solvent-free conditions (Table 1, Entry 1) under stirring at room temperature. Secondly, it was carried out under reflux condition (Table 1, Entry 3), but it was taken very long time for completion of the reaction and gives lower yield. In order to further increase the yield and minimize the reaction time, the model reaction was carried out under solvent-free condition at 90°C to afford the product in a good yield (Table 1, Entry 4).

Scheme:



Scheme I: Synthesis of 2,4,5-trisubstituted imidazoles (4a-g)

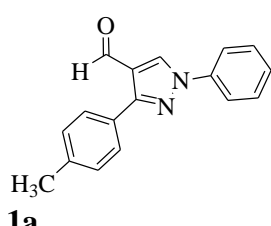
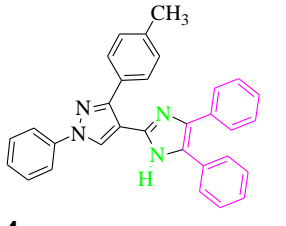
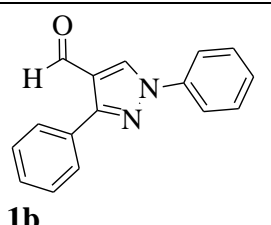
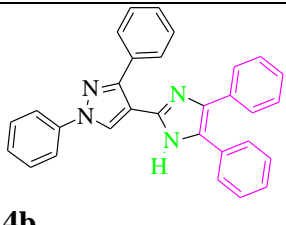
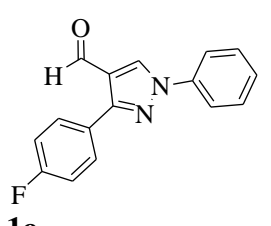
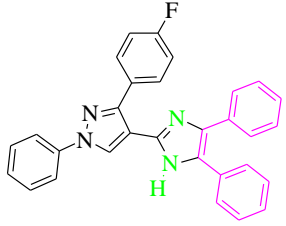
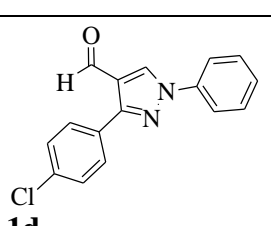
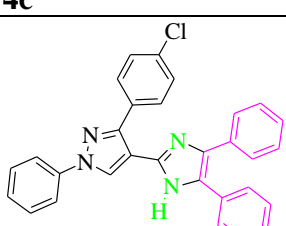
To simplify this methodology, A series of other 1,3-diaryl pyrazole aldehydes have been investigated under optimal condition (Table 2). It was observed that, aromatic aldehydes having electron-donating as well as electron-withdrawing groups provided excellent yields within a short time under solvent-free condition as compared to reflux in ethanol.

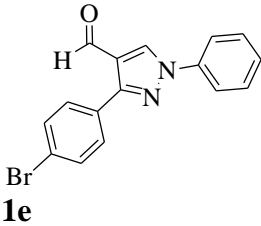
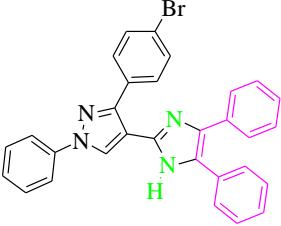
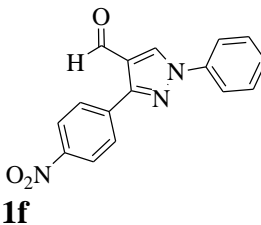
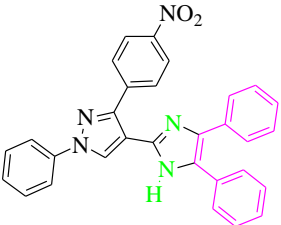
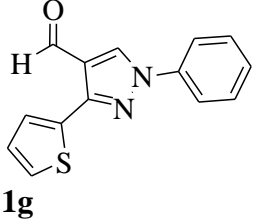
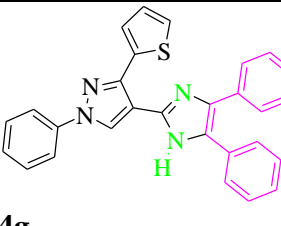
Table 1: Optimization of the reaction condition for the synthesis of 4,5-diphenyl-2-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-imidazole

Entry	Catalyst/ Solvent	Reaction Condition	Time	Yield (%)
1	100 mg [HNMP][HSO ₄]/SF	Stirring at RT	10 h	Trace
2	100 mg [HNMP][HSO ₄]/Ethanol	Stirring at RT	10 h	Trace
3	100 mg [HNMP][HSO ₄]/Ethanol	Reflux condition	20.5 h	70 %
4	100 mg [HNMP][HSO ₄]/SF	Heating at 90°C	1 h 15 min	84 %

Reaction condition: 1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbaldehyde **1** (1 mmol), benzil **1** (2 mmol), NH₄OAc **3** (2 mmol) and 100 mg [HNMP][HSO₄]

Table 2: Synthesis of 2,4,5-trisubstituted imidazoles (4a-g)

Sr. No.	Aldehyde	Imidazole Derivative	Reflux ^a in Ethanol		Solvent free ^b condition		M.P. (°C)
			Time	Yield %	Time	Yield %	
1	 1a	 4a	20.5 hrs	70	1hr 15min	84	262
2	 1b	 4b	19 hrs	72	1hr	85	258
3	 1c	 4c	20.5 hrs	64	1hr 20min	82	264
4	 1d	 4d	19.5 hrs	68	1hr 15min	85	252

		4d					
5	 1e	 4e	20.5 hrs	65	1hr 20min	78	286
6	 1f	 4f	21.5 hrs	56	1hr 40 min	75	246
7	 1g	 4g	18 hrs	70	1hr	86	240

Reaction condition: 1,3-diaryl pyrazole-4-carbaldehyde **1** (1 mmol), benzil **1** (2 mmol), NH₄OAc **3** (2 mmol) and 100 mg [HNMP][HSO₄], a-reflux in 10 ml ethanol, b- heating at 90°C under solvent free condition.

Experimental:

1) Preparation of ionic liquid *N*-methyl-2-pyrrolidonium hydrogen sulphate [HNMP][HSO₄]

N-methyl-2-pyrrolidone (20 mmol) was taken in a 250 mL multi necked round bottom flask. Then the equimolar quantity of sulfuric acid was added dropwise into the flask at 75-80 °C for 6 h with constant stirring by magnetic stirrer. The resultant content was washed with ether more than 3 times to remove unreacted material and dried at a rotary evaporator to obtain the ionic liquid [HNMP][HSO₄] i.e. *N*-methyl-2-pyrrolidonium hydrogen sulfate [12].

2) Synthesis of 2, 4, 5-tri substituted imidazole derivatives under reflux condition:

A mixture of substituted 1, 3-diaryl pyrazole aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (2 mmol) and ionic liquid [HNMP][HSO₄] (100 mg) was refluxed in 10 ml ethanol. After the completion of the reaction evident from TLC, the resultant reaction mixture was poured over crushed ice. The obtained crude product was filtered and recrystallized using ethanol.

3) Synthesis of 2, 4, 5-tri substituted imidazole derivatives under solvent free heating:

A mixture of substituted 1, 3-diaryl pyrazole aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (2 mmol) and ionic liquid [HNMP][HSO₄] (100 mg) was heated in a round bottom flask

at 90°C under solvent free condition. After the completion of the reaction evident from TLC, the resultant reaction mixture was poured over crushed ice. The obtained crude product was filtered and recrystallized using ethanol.

Spectral Data:

4a: 4,5-diphenyl-2-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-1*H*-imidazole

White Solid; M.P. 262°C; FT-IR (KBr) ν : 3358 (N-H), 3055, 1655, 1594, 1502, 1450, 1379, 1072, 960, 784; ¹H NMR (DMSO-*d*₆, 400 MHz) δ : 2.45 (s, 3H, CH₃), 7.26-7.36 (m, 9H, Ar-H), 7.49 (t, 3H, Ar-H), 7.66 (d, 4H, Ar-H), 7.81 (d, 3H, Ar-H), 8.65 (s, 1H, Ar-H), 12.46 (s, 1H, N-H); ESI MS: *m/z* 453 (M+1).

4b: 4,5-diphenyl-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1*H*-imidazole

White Solid; M.P. 258°C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.17-7.45 (m, 10H, Ar-H), 7.49-7.59 (m, 6H, Ar-H), 7.91 (d, 2H, Ar-H), 8.13 (t, 2H, Ar-H), 8.87 (s, 1H, Ar-H), 12.43 (s, 1H, N-H); ESI MS: *m/z* 439 (M+1).

4g: 4,5-diphenyl-2-(1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)-1*H*-imidazole

Faint Yellow Solid; M.P. 240°C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.23-7.40 (m, 10H, Ar-H), 7.51-7.68 (d, 4H, Ar-H), 7.85-7.97 (t, 3H, Ar-H), 8.25 (d, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 12.49 (s, 1H, N-H); ESI MS: *m/z* 445 (M+1).

Abbreviations:

MCRs= Multi-component reactions, [HNMP][HSO₄]= *N*-Methyl-2-Pyrrolidonium Hydrogen Sulphate, ILs= Ionic liquids, TLC= Thin Layer Chromatography

Conclusion:

We have demonstrated a green path for the synthesis of 2,4,5-trisubstituted imidazoles in the presence of an ionic liquid [HNMP][HSO₄] as an inexpensive and efficient catalyst under solvent-free condition. The significant features of this protocol include high-atom economy, smooth work-up procedure, inexpensive catalyst, easy for handling, shorter reaction time, high yield, multi-component approach and solvent-free reaction.

Acknowledgements:

We are grateful to the Principal, ASC College, Rahata for providing infrastructural facility and constant encouragement in research work. We are also very much thankful to SAIF, Panjab University, Chandigarh for providing the characterization.

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Received on June 12, 2021.