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## One-pot Preparation of 2,4,5-Trisubstituted and 1,2,4,5-Tetrasubstituted Imidazoles Using Poly(4-vinylpyridinium Butane Sulfonic Acid) Hydrogen Sulfate, as an Efficient Heterogeneous Poly(ionic Liquid) Solid Acid Catalyst under Solvent-free Conditions

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One-pot preparation of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles has been conducted in the presence of poly(4-vinylpyridinium butane sulfonic acid) hydrogen sulfate, P(4VPBSA)HSO<sub>4</sub>, as an efficient dual acidic catalyst under solvent-free conditions. Reusability of the catalyst, easy work-up procedure, eco-friendly reaction conditions, short reaction times and high yields of the products illustrate the utility of this approach.

**Keywords:** Solvent-free, Substituted imidazoles, Poly(ionic liquid), Benzil, Multicomponent reaction

### INTRODUCTION

Poly(ionic liquid)s (PILs) have emerged as new materials with numerous potential applications in many fields such as energy and environment, analytical chemistry, materials science, biotechnology, catalysts or surface science to name a few. The superiority of PILs over ionic liquids (ILs) are the enhanced mechanical stability, improved processability, durability and spatial controllability. PILs have been synthesized *via* two basic strategies, 1) direct polymerization of IL monomers and 2) chemical modification of existing polymers [1,2].

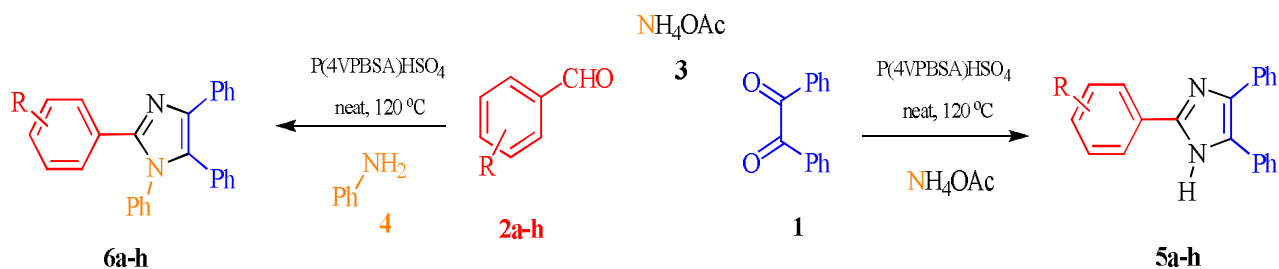
Multi-component reactions (MCRs) are defined as one-pot processes that three or more substrates combine either simultaneously (so called tandem or domino reactions), or through a sequential addition procedure that does not require any change of solvent. MCRs which are conducted

under solvent-free conditions have provided a synergic approach in the total synthesis of natural products, and medicinal heterocyclic compounds [3-4].

Due to the biological importance of substituted imidazoles [5,6], multi-component condensation of 1,2-diketones, aldehydes, ammonium acetate and primary amines has gained great interest. While different catalysts such as Lewis acids [7-9], Brønsted acids [10-12], heteropolyacids [13,14] and ionic liquid [15], have been proposed for 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles synthesis, exploration for greener methodologies still remains as an active research area.

In continuation of our effort in the synthesis of new solid acid catalysts, and their applications in organic synthesis [16,17], poly(4-vinylpyridinium butane sulfonic acid) hydrogen sulfate, P(4VPBSA)HSO<sub>4</sub>, has been recently introduced as a novel dual acidic poly(ionic liquid) heterogeneous catalyst for the one-pot preparation of 1,8-dioxo-octahydro-xanthenes under solvent-free conditions

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Scheme 1. One-pot preparation of 2,4,5-trisubstituted (5a-h) and 1,2,4,5-tetrasubstituted imidazoles (6a-h)

[18]. We decided to explore the catalytic activity of this catalyst in the one-pot preparation of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles (Scheme 1) under solvent-free conditions.

## EXPERIMENTAL

### General

All commercially available chemicals were purchased from Fluka and Merck companies and used without further purification. Poly(4-vinyl pyridine) cross-linked with 2% DVB ~100-200 mesh, MW: 60,000 was purchased from Fluka. Products were characterized by their physical constant and comparison with authentic samples. Reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. The IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrophotometer using KBr pellets for the samples and the catalyst in the range of 4000-400 cm<sup>-1</sup>. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub> on a Bruker Advanced DPX 400 MHz spectrometer using TMS as internal standard. Thermal stability of the supported catalyst was examined by BÄHR, SPA 503 Thermo-gravimetric Analyzer (TGA) at heating rate of 10 °C min<sup>-1</sup> over the temperature range of 40-950 °C. The SEM analyses were carried out using a LEO 1455VP Scanning Electron Microscope, operating at 1-30 KV. CHNS-O analysis was conducted by Costech elemental combustion system, ECS 4010. P(4VPBSA)HSO<sub>4</sub> was prepared according to our recently reported procedure [18].

### Typical Procedure for the Preparation of 2,4,5-Trisubstituted Imidazoles

A mixture of benzil (1.0 mmol), aromatic aldehyde (1.0 mmol), ammonium acetate (3 mmol) and P(4VPBSA)HSO<sub>4</sub> (0.05 g, 10 mol%) were thoroughly mixed and heated for 15-30 min under solvent-free conditions at 120 °C. Completion of the reaction was indicated by TLC [ethyl acetate/n-hexane (2:5)]. After completion of the reaction (as indicated in Table 2) the insoluble crude product was dissolved in acetone or hot ethanol and P(4VPBSA)HSO<sub>4</sub> was filtered. The filtrate was concentrated and the products were recrystallized from aqueous acetone.

### Typical Procedure for the Preparation of 1,2,4,5-Tetrasubstituted Imidazoles

A mixture of benzil (1.0 mmol), aromatic aldehyde (1.0 mmol), ammonium acetate (2 mmol), aniline (1.0 mmol) and P(4VPBSA)HSO<sub>4</sub> (0.05 g, 10 mol%) were thoroughly mixed and heated for 30-60 min under solvent-free conditions at 120 °C. Completion of the reaction was indicated by TLC [ethyl acetate/n-hexane (2:5)]. After completion of the reaction (as indicated in Table 3) the insoluble crude product was dissolved in acetone or hot ethanol and P(4VPBSA)HSO<sub>4</sub> was filtered. The filtrate was concentrated and the products were recrystallized from aqueous acetone.

## RESULTS AND DISCUSSION

P(4-VPBSA)HSO<sub>4</sub> was easily prepared and

**Table 1.** Optimum Conditions for the Reaction of Benzil (1 mmol), Benzaldehyde (1 mmol), Ammonium Acetate (2-4 mmol) with Different P(4VPBSA)HSO<sub>4</sub> Loadings

Entry	Solvent	Ammonium acetate (mmol)	Catalyst mol (%)	T (°C)	Time (min)	Yield (%)
1	Water	2.0	5	Rflux	60	58
2	Ethanol	2.0	5	Rflux	60	37
3	Solvent-free	2.0	-	80	60	12
4	Solvent-free	2.0	-	120	60	23
5	Solvent-free	2.0	5	100	60	60
6	Solvent-free	2.2	5	110	60	65
7	Solvent-free	2.5	5	120	60	70
8	Solvent-free	2.0	10	110	60	80
9	Solvent-free	3.0	10	120	15	95
10	Solvent-free	3.5	15	120	15	96

**Table 2.** One-pot Preparation of 2,4,5-Trisubstituted Imidazoles Promoted by 10 mol% of P(4VPBSA)HSO<sub>4</sub> under Solvent-free Conditions at 120 °C

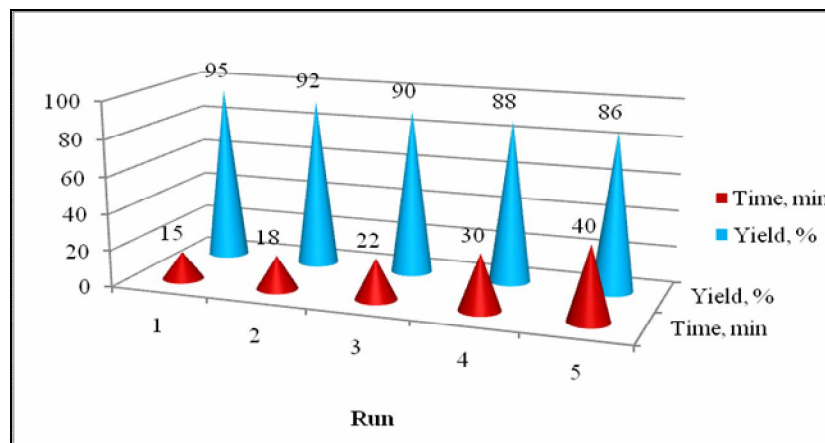
Entry	R	Product	Time (min)	Yield (%)	Melting point (°C)	
					Found	Lit. [Ref.]
1	H	5a	15	95	272-274	270-272 [19]
2	4-Me	5b	20	98	232-234	230-233 [19]
3	3-NO <sub>2</sub>	5c	25	98	262-264	265-267 [19]
4	2-OH	5d	30	89	196-198	198-201 [19]
5	3-Cl	5e	25	92	284-286	282-283 [19]
6	4-OMe	5f	30	90	230-231	228-231 [19]
7	4-Cl	5g	25	94	261-263	260-261 [19]
8	4-OH	5h	30	93	259-261	259-260 [19]

characterized by FTIR, TGA and SEM in order to be qualified as a solid acid catalyst [18]. After qualification of the catalyst, it was decided to evaluate the catalytic activity of the catalyst in the preparation of 2,4,5-trisubstituted imidazoles. A model reaction of benzil (1.0 mmol), benzaldehyde (1.0 mmol) and ammonium acetate (2-4 mmol), with different P(4VPBSA)HSO<sub>4</sub> loadings were

conducted (Table 1). The model reaction with 5, 10 and 15% of the catalyst at 120 °C was conducted. It was found that 10 mol% of the catalyst, and 3 mmol ammonium acetate at 120 °C shows maximum yield in minimum time. Higher percentage of loading of the catalyst (15 mol%) neither increases the yield nor lowers the conversion time substantially (Table 1).

**Table 3.** One-pot Preparation of 1,2,4,5-Tetrasubstituted Imidazoles Promoted by 10 mol% of P(4VPBSA)HSO<sub>4</sub> under Solvent-free Conditions at 120 °C

Entry	R	Product	Time (min)	Yield (%)	Melting point (°C)	
					Found	Lit. [Ref.]
1	H	6a	40	91	219-220	218-221 [12]
2	3-Me	6b	45	87	185-187	184-186 [20]
3	4-Me	6c	45	92	192-194	190-192 [12]
4	3-NO <sub>2</sub>	6d	30	98	240-242	243-246 [20]
5	4-OH	6e	55	97	282-284	282-285 [20]
6	2-OH	6f	60	85	254-256	252-254 [20]
7	4-OMe	6g	45	86	178-180	177-180 [20]
8	4-Cl	6h	40	92	162-164	160-163 [20]

**Fig. 1.** Reusability of the catalyst in the reaction of benzil (1.0 mmol), benzaldehyde (1.0 mmol) and ammonium acetate (3 mmol) at 120 °C under solvent-free conditions.

Subsequently, with optimal conditions in hand, 1:1:3 molar ratios of benzil, benzaldehyde, ammonium acetate and 10 mol% of P(4VPBSA)HSO<sub>4</sub> at 120 °C under solvent-free conditions; the generality and synthetic scope of this coupling protocol were demonstrated by synthesizing a series of 2,4,5-trisubstituted imidazoles (Table 2). Gratifyingly, a wide range of aromatic aldehydes were well tolerated under the optimized reaction conditions. The time taken for the complete conversion (monitored by TLC) and

the isolated yields are recorded in Table 2. All compounds were characterized by their satisfactory spectral (IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR) studies, and compared with authentic samples.

With the same manner, it was decided to evaluate the catalytic activity of the catalyst in the preparation of 1,2,4,5-tetrasubstituted imidazoles. After optimization of the reaction conditions, *i.e.* benzil (1.0 mmol), benzaldehyde (1.0 mmol), ammonium acetate (2.0 mmol), aniline (1

**Table 4.** Comparison of P(4VPBSA)HSO<sub>4</sub> with Reported Catalysts in the Reaction of Benzil, Benzaldehyde, and Ammonium Acetate

Entry	Catalyst/Condition	Catalyst loading (mol%)	Time (min)	Yield (%)	Ref.
1	MgO/neat 100 °C	5	30	94	[19]
2	I <sub>2</sub> /Grinding	10	10	90	[21]
3	InCl <sub>3</sub> / MeOH, r.t.	10	498	82	[9]
4	Acidic Alumina, MW	1.7 g	20	78	[23]
5	L-Proline, 60 °C	15	540	90	[27]
6	P(4VPBSA)HSO <sub>4</sub> /neat 120 °C	10	15	95	This work

**Table 5.** Comparison of P(4VPBSA)HSO<sub>4</sub> with Reported Catalysts in the Reaction of Benzil, Benzaldehyde, Aniline and Ammonium Acetate

Entry	Catalyst/Condition	Catalyst loading	Time (min)	Yield (%)	Ref.
1	Silica gel or Zeolite HY, MW	2 g	6	79 or 67	[22]
2	NaHSO <sub>4</sub> /SiO <sub>2</sub> , 140 °C heating	9.3 g	120	92	[24]
3	NaHSO <sub>4</sub> /SiO <sub>2</sub> , MW	9.3 g	12	96	[24]
4	HClO <sub>4</sub> -SiO <sub>2</sub> , 140 °C	1 mol%	6	96	[25]
5	Trifluoroacetic Acid, MW	20 mol%	4	92	[26]
6	Mercaptopropylsilica, H <sub>2</sub> O/MeOH, RT	5 mg	240	87	[28]
7	[(CH <sub>2</sub> ) <sub>4</sub> SO <sub>3</sub> HMIM][HSO <sub>4</sub> ]	15 mol%	150	88	[29]
8	MCM-41 or p-TsOH	0.04 g	30	85	[30]
9	SBPPSA, sf 140 °C	0.25 g	120	89	[31]
10	P(4VPBSA)HSO <sub>4</sub> /neat 120 °C	10 mol%	40	91	This work

mmol) and 10 mol% of P(4VPBSA)HSO<sub>4</sub>, 1,2,4,5-tetrasubstituted imidazoles were prepared at 120 °C under solvent-free conditions (Table 3)

With the increasing interest in green chemistry, we studied the recyclability and reusability of the catalyst in the preparation of 2,4,5-trisubstituted imidazoles. After

completion of the reaction the separated catalyst was washed with water, hot ethanol and dried. The catalyst was used for four subsequent cycles. Small decrease in the performance of the catalyst is observed in subsequent cycles (Fig. 1).

To demonstrate the superiority of P(4VPBSA)HSO<sub>4</sub>

over the reported catalysts, the reaction of benzil, benzaldehyde, and ammonium acetate and/or aniline was considered as a representative example (Table 4 and Table 5). According to Table 4, some procedures required long reaction times (Table 4, entry 3, 5), or lower yield of the products (Table 4, entry 3, 4). According to Table 5, some procedures required long reaction times (Table 5, entry 2, 6, 7 and 9), or lower yield of the products (Table 5, entry 1, 6 and 8), or high catalyst loading (Table 5, entry 1, 2, 3 and 5). These results clearly demonstrate that P(4VPBSA)HSO<sub>4</sub> is an equally or more efficient catalyst for this reaction.

## CONCLUSIONS

In conclusion, we have described a facile and green protocol for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles in the presence of P(4VPBSA)HSO<sub>4</sub> as a novel environmentally safe heterogeneous poly(ionic liquid) solid acid catalyst under solvent-free conditions. This method offers several advantages including high yields, recyclable catalyst, short reaction times, easy work-up and performing the reaction under green conditions.

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