

## Silica Gel-Supported Polyphosphoric Acid: A Mild, Efficient and Reusable Catalyst for the One-Pot Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles

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An efficient and convenient method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles has been developed by a one-pot multi-component reaction of benzil, aromatic aldehydes, primary amines and ammonium acetate in the presence of silica gel-supported polyphosphoric acid (PPA-SiO<sub>2</sub>), as a green and reusable catalyst under solvent-free conditions. The present methodology offers several advantages such as simple procedure with an easy work-up, relatively short reaction times and high yields.

**Key Words:** PPA-SiO<sub>2</sub>, Multi-component reactions, Tetrasubstituted imidazoles, Solvent-free conditions.

### INTRODUCTION

As an important member of the five-membered ring heterocycles, imidazole moiety is present in a wide range of naturally occurring molecule<sup>1</sup>. Compounds with imidazole moiety have many pharmaceutical activities<sup>2</sup>. The biological importance of the imidazole ring system has made it a common structure in numerous synthetic compounds, such as fungicides<sup>3</sup>, herbicides<sup>3</sup>, plant growth regulators<sup>4</sup> and therapeutic agents<sup>5</sup>. There are several methods reported in literature for the synthesis of tetrasubstituted imidazoles, such as hetero-Cope rearrangement<sup>6</sup>, four component condensation of 1,2-diketones, aromatic aldehydes, primary amines and ammonium acetate in the presence of several catalysts<sup>7,8</sup> and by N-alkylation of trisubstituted imidazoles<sup>9</sup>. However, many of the synthetic protocols for imidazoles reported above, suffer from one or more disadvantages, such as harsh reaction conditions, poor yields, prolonged reaction time period, use of hazardous and often expensive acid catalysts. Therefore, the development of simple, efficient, high-yielding and environmentally friendly methods using new catalysts for the synthesis of these compounds is still necessary.

Solid supported reagents are unique catalysts that have become popular over the last two decades. Since the activity and selectivity of a reagent dispersed on the surface of the support, is improved, as the effective surface area of reagent can be increased manifold, they expected to be performed better than the individual

reagents<sup>10</sup>. Low toxicity, moisture, air tolerance and low price are other common features make the use of solid supported reagents as attractive alternate to the conventional Lewis acid and triflates. Although, the catalytic applications of silica supported reagents for organic synthesis have been established, but to the best of our knowledge only few examples are reported on the use of polyphosphoric acid supported on silica gel-supported polyphosphoric acid (PPA-SiO<sub>2</sub>)<sup>11</sup>.

In continuation of our previous works on the applications of reusable acid catalysts in the synthesis of organic compounds<sup>12-14</sup> herein we wish to report the new efficiently synthesis of tetrasubstituted imidazoles catalyzed by silica gel-supported polyphosphoric acid.

## EXPERIMENTAL

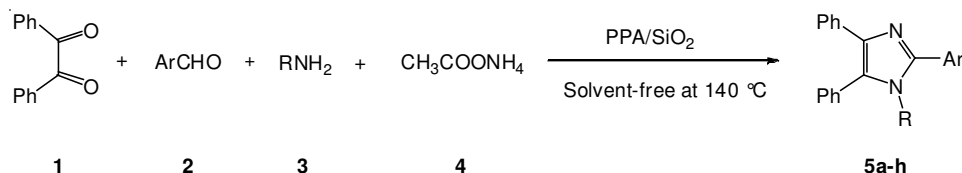
All chemicals were commercially available and used without further purification. Silica gel-supported polyphosphoric acid (PPA-SiO<sub>2</sub>) was synthesized according to the literature<sup>11c</sup>. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The <sup>1</sup>H NMR (500 MHz) spectra were recorded on Bruker DRX500 spectrometer.

**General procedure for the synthesis of tetrasubstituted imidazoles:** A mixture of benzil (1 mmol), aromatic aldehyde (1 mmol), primary amine (1 mmol), ammonium acetate (1 mmol) and PPA-SiO<sub>2</sub> (0.1 g) was heated on the oil bath at 140 °C for 1.0-1.5 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, boiling ethanol was added and the mixture stirred for 5 min. The catalyst was filtrated and the filtrate ethanol solution was concentrated. The solid so obtained was recrystallized from ethanol to give compounds **5a-h** in high yields. All products were known and characterized by comparison of their physical and spectroscopic data with those of reported techniques<sup>7,8</sup>.

**Recycling and reusing of the catalyst:** The recyclability of the catalyst in the reaction of benzil, benzaldehyde, aniline, ammonium acetate in the presence of PPA-SiO<sub>2</sub> was checked. The separated catalyst can be reused after washing with ethanol and drying at 100 °C. It showed the same activity as fresh catalyst without any loss of its activity.

## RESULTS AND DISCUSSION

The one-pot synthesis of tetrasubstituted imidazoles was achieved by the four-component condensation of benzil, benzaldehyde derivatives, primary amines and ammonium acetate in the presence of PPA-SiO<sub>2</sub> as a heterogeneous catalyst (**Scheme-I**). To find optimum conditions, the reaction of benzil, benzaldehyde, aniline and ammonium acetate in the presence of PPA-SiO<sub>2</sub> (0.1 g) as a model was performed under thermal solvent-free conditions at different temperatures in an oil bath. As can be seen from Table-1, the shortest time and best yield were achieved at 140 °C.



Scheme-I

TABLE-1  
RESULTS OF THE SYNTHESIS OF 1,2,4,5-TETRAPHENYLIMIDAZOLE  
**5a** UNDER DIFFERENT CONDITIONS\*

Entry	Amount of PPA-SiO <sub>2</sub> (g)	T (°C)	Time (h)	Yield (%)**
1	0.02	120	2.0	43
2	0.02	140	2.0	46
3	0.05	120	1.5	54
4	0.05	140	1.5	62
5	0.10	120	1.0	75
6	0.10	140	1.0	86
7	0.10	160	1.5	87
8	0.20	140	1.5	87

\*1 mmol benzil, 1 mmol benzaldehyde, 1 mmol aniline, 1 mmol ammonium acetate under neat conditions. \*\*Isolated yields.

TABLE-2  
SYNTHESIS OF 1,2,4,5-TETRASUBSTITUTED IMIDAZOLES **5a-h**<sup>a</sup>

Entry	Ar	R	Products <sup>b</sup>	Time (h)	Yield <sup>c</sup> (%)	m.p. (°C)
1	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<b>5a</b>	1.0	86	215-217 (Lit. <sup>8</sup> 216-218)
2	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	<b>5b</b>	1.5	89	160-163 (Lit. <sup>8</sup> 163-165)
3	4-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>5c</b>	1.0	92	150-152 (Lit. <sup>8</sup> 149-151)
4	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>5d</b>	1.0	88	189-190 (Lit. <sup>7</sup> 187-189)
5	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	<b>5e</b>	1.0	90	182-184 (Lit. <sup>8</sup> 185-188)
6	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	<b>5f</b>	1.5	87	162-164 (Lit. <sup>8</sup> 165-166)
7	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>5g</b>	1.5	85	169-170 (Lit. <sup>7</sup> 167-169)
8	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>5h</b>	1.0	86	189-191 (Lit. <sup>7</sup> 188-191)

<sup>a</sup>1 mmol benzil, 1 mmol aromatic aldehyde, 1 mmol primary amine, 1 mmol ammonium acetate and 0.1 g PPA-SiO<sub>2</sub> at 140 °C. <sup>b</sup>All the products were characterized by <sup>1</sup>H NMR and IR spectral data and comparison of their melting points with those of authentic samples. <sup>c</sup>Isolated yields.

To determine the optimum quantity of PPA-SiO<sub>2</sub>, the same model reaction was carried out under the previously mentioned conditions using different quantities of catalyst at 140 °C. The use of 0.1 g of catalyst resulted in the highest yield in appreciate time (Table-1).

In order to evaluate the generality of this model reaction we then prepared a range of 1,2,4,5-tetrasubstituted imidazoles under the optimized reaction conditions. In all cases the yields obtained were excellent without formation of any side products such as 2,4,5-trisubstituted imidazoles (Table-2).

## Conclusion

In conclusion, a simple and efficient method for the synthesis of tetrasubstituted imidazoles through the four-components condensation of benzil, benzaldehyde derivatives, primary amines and ammonium acetate using PPA-SiO<sub>2</sub> as efficient, reusable and eco-friendly heterogeneous catalyst under solvent-free conditions has been developed. The catalyst can be reused after a simple work-up, with a gradual decline of its activity being observed. Other advantages of this protocol are high yields, relatively short reaction times, easy work-up and omitting any volatile and hazardous organic solvents.

## REFERENCES

1. (a) J.R. Lewis, *Nat. Prod. Rep.*, **19**, 223 (2002); (b) J.Z. Ho, R.M. Hohareb, J.H. Ahn, T.B. Sim and H. Rapoport, *J. Org. Chem.*, **68**, 109 (2003).
2. (a) J.G. Lombardino and E.H. Wiseman, *J. Med. Chem.*, **17**, 1182 (1974); (b) J.G. Lombardino, *Ger Offen*, 2155558 (1972), *Chem. Abstr.*, **77**, 1016074 (1972).
3. (a) T. Maier, R. Schmierer, K. Bauer, H. Bieringer, H. Buerstell and B. Sachser, German Patent 317094 (1983), *Chem. Abstr.*, **100**, 85699 (1984); (b) T. Maier, R. Schmierer, K. Bauer, H. Bieringer, H. Buerstell and B. Sachse, Canadian Patent 1201716 (1986), *Chem. Abstr.*, **105**, 148200 (1986).
4. R. Schmierer, H. Mildenerger and H. Buerstell, German Patent 3614364 (1987), *Chem. Abstr.*, **108**, 37838 (1988).
5. J. Heeres, L.J.J. Back, J.H. Mostmans and J. Vancutsem, *J. Med. Chem.*, **22**, 1003 (1979).
6. I. Lantos, W.Y. Zannig, Y. Shiu and D.S. Eggleston, *J. Org. Chem.*, **58**, 7092 (1993).
7. L. Nagarapu, S. Apuri and S. Kantevari, *J. Mol. Catal. A: Chem.*, **266**, 104 (2007).
8. B. Sadeghi, B.B.F. Mirjalili and M.M. Hashemi, *Tetrahedron Lett.*, **49**, 2575 (2008).
9. S. Balalaie, M.M. Hashemi and M. Akhbari, *Tetrahedron Lett.*, **44**, 1709 (2003).
10. A. Corma and H. Garcia, *Adv. Synth. Catal.*, **348**, 1391 (2006).
11. (a) T. Aoyama, T. Takido and M. Kodomari, *Synlett*, 2307 (2004); (b) H.R. Shaterian, A. Hosseinian and M. Ghashang, *Arkivoc*, Part 2, 59 (2009); (c) S. Kantevari, R. Bantu and L. Nagarapu, *J. Mol. Catal. A: Chem.*, **269**, 53 (2007).
12. A. Davoodnia, M. Bakavoli, Gh. Barakouhi and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, **18**, 1483 (2007).
13. A. Davoodnia, M.M. Heravi, L. Rezaei-Daghigh and N. Tavakoli-Hoseini, *Monatsh. Chem.*, **140**, 1499 (2009).
14. A. Davoodnia, M. Bakavoli, R. Moloudi, M. Khashi and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, **21**, 1 (2010).

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