

Short communication

# Highly efficient, four-component one-pot synthesis of tetrasubstituted imidazoles using Keggin-type heteropolyacids as green and reusable catalysts

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## Abstract

An efficient and improved procedure for the synthesis of tetrasubstituted imidazoles is developed by Keggin-type heteropolyacid (HPA) catalyzed four-component one-pot coupling protocol in refluxing ethanol.

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## 1. Introduction

The multi-component coupling reactions [1] are emerging as a useful source for accessing small drug-like molecules with several levels of structural diversity. They are welcome too in terms of economic and practical considerations. Multi-component reaction (MCR) condensations involve three or more compounds reacting in a single event, but consecutively to form new products, which contains the essential parts of all the starting materials.

The search and discovery for new MCRs on one hand [2], and the full exploitation of already known multi-component reactions on the other hand, is therefore of considerable current interest.

The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles. There are several methods for the synthesis of highly substituted imidazoles. The mostly used methods in the last decade are as follows: condensation of diones, aldehydes, primary amines and ammonia [3]; *N*-alkylation of trisubstituted imidazoles [4]; condensation of benzoin or benzoin acetate with aldehydes, primary

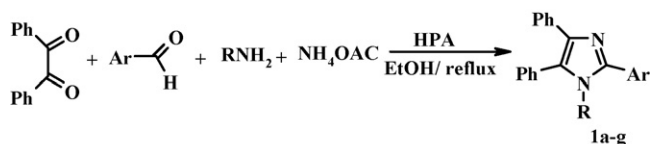
amines and ammonia in the presence of copper acetate [5]; cyclization of sulfonamides with mesoionic 1,3-oxazolium-5-olates [6]; four-component condensations of diones, aldehydes, primary amines, and ammonium acetate in HOAc under reflux conditions [7]; condensation of  $\beta$ -carbonyl-*N*-acyl-*N*-alkylamines with ammonium acetate in refluxing HOAc [8]; conversion of *N*-(2-oxo)amides with ammonium trifluoroacetate under neutral conditions [9]. We have also reported the microwave assisted synthesis of trisubstituted imidazoles from 1,2-diphenylethanedione or 2-hydroxy-1,2-diphenylethanone in the presence of  $\text{NH}_4\text{OAc}/\text{NaHSO}_4$  [10]. In recent years, Mjalli and co-workers reported the synthesis of tetrasubstituted imidazoles using Wang's resin in refluxing HOAc [11].

In the classic approach for the synthesis of tetrasubstituted imidazoles, cyclocondensations proceed with low yields after many hours in refluxing HOAc [7]. Other methods also need special and complex reagents. So the development of clean, high-yielding and environmentally friendly approaches is still desirable and much in demand.

Heteropolyacids HPAs have many advantages finding economically and environmentally attractive in both academic and industrial significance; they are strong Brønsted acids composed of heteropolyanions and protons as the counter cations.

The Keggin-type HPAs typically represented by the formula  $\text{H}_{x-8}[\text{XM}_{12}\text{O}_{40}]$ , where X is the heteroatom, *x* is its oxidation state, and M is the addenda atom (usually  $\text{Mo}^{6+}$  or  $\text{W}^{6+}$ ), are

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Scheme 1.

the most important for catalysis [12–14]. They are stronger than many conventional solid acids such as mixed oxides, zeolites, and so forth. In the last three decades, HPAs have been widely used as acid and oxidation catalysts for organic synthesis and they are found in several industrial applications [12–14]. To the best of our knowledge, there are no examples of the use of heteropolyacids as catalyst for the synthesis of tetrasubstituted imidazoles.

Following our previous work on the synthesis of triarylimidazoles [10], and in view of the importance of heterogeneous solid acids as reusable catalyst in organic synthesis and in continuation of our work on catalytic properties of heteropolyacids [15–26] here we report the four-component condensation of benzil, benzaldehyde derivatives, primary amines and ammonium acetate catalyzed by Keggin heteropolyacids such as  $H_3[PW_{12}O_{40}]$ ,  $H_4[SiW_{12}O_{40}]$ ,  $H_3[PMo_{12}O_{40}]$ ,  $H_4[PMo_{11}VO_{40}]$ ,  $HNa_2[PMo_{12}O_{40}]$  as an efficient and facile one-pot synthesis of tetrasubstituted imidazoles (Scheme 1).

## 2. Experimental

All products were known and characterized by comparison of their physical and spectra data with those of already reported [27].

### 2.1. Synthesis of tetrasubstituted imidazoles: general procedure

A mixture of benzil (10 mmol), amine (10 mmol), aldehyde (10 mmol), ammonium acetate (10 mmol) and heteropolyacid (1 mol%) was refluxed in ethanol (10 cm<sup>3</sup>). After completion of reaction (monitored by TLC) the mixture was cooled to room temperature and the precipitated products were separated by filtration. The catalyst could be recycled after evaporation of solvent from the residue solution and washing with dichloromethane, and reused in another reaction.

All products gave satisfactory spectral data in accord with the assigned structures [e.g. for 5c, 1-benzyl-2,4,5-tetraphenylimidazole (5c): mp 158–160 °C, lit. [27] 165 °C; IR (KBr): 1600 (CNC), 1580 (CNN), 1480 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.15 (s, 2H, CH<sub>2</sub>), 6.70–6.80 (m, 20H, Ph)].

## 3. Results and discussion

To optimize the catalytic system, the synthesis of 1,2,4,5-tetraphenylimidazoles (1a) in the presence of  $H_4[PMo_{11}VO_{40}]$  was used as a model reaction. At the first stage, because of complexity of behavior for this catalyst in a solvent, we studied the model reaction in a solvent-free system. However, initial

Table 1

Synthesis of 1,2,4,5-tetraphenylimidazole (1a) in the presence of  $H_3[PW_{12}O_{40}]$  in different solvents

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%) <sup>a</sup>
1	EtOH	78.3	5	84
2	CHCl <sub>3</sub>	61	20	80
3	Solvent free	70	100	82

<sup>a</sup> Yields refer to isolated pure products.

Table 2

Synthesis of 1,2,4,5-tetraphenylimidazole (1a) in the presence of  $H_3[PW_{12}O_{40}]$  in ethanol and at different temperatures

Entry	Temperature (°C)	Time (min)	Yield (%) <sup>a</sup>
1	25	60	75
2	45	30	77
3	78	5	84

<sup>a</sup> Yields refer to isolated pure products.

attempts to carry out the reaction in a solvent-free system needed long reaction times. Thus, among the tested solvents, such as ethanol and chloroform, ethanol was applied as solvent of choice (Table 1).

The effect of temperature was studied by carrying out the model reaction in ethanol and at different temperatures in the presence of this catalyst (room temperature, 45 and 78 °C). It was observed (Table 2) that yield is a function of temperature, so the yield increased as the reaction temperature was raised. So in other studies all reactions carried out in refluxing ethanol.

Comparison of  $H_3[PW_{12}O_{40}]$ ,  $H_4[SiW_{12}O_{40}]$ ,  $H_3[PMo_{12}O_{40}]$ ,  $H_4[PMo_{11}VO_{40}]$ ,  $HNa_2[PMo_{12}O_{40}]$  showed that the higher activity could be achieved with  $H_4[PMo_{11}VO_{40}]$ . The results are represented in Table 3. Although it is difficult to offer an explanation for the different activity between these heteropolyacids, certainly there is a complex relationship between the activity and structure of polyanion. By changing the constituent elements of polyanion (both hetero and addenda atoms), the acid strength of HPA as well as its catalytic activity is able to vary in a wide range [28]. Transition metal cations have an important effect on the catalytic properties of these compounds when they substitute molybdenum cations in the Keggin units or when they are present as counter cations. The case of vanadium, which can occupy both anionic and cationic positions, is more complex. In fact, under catalytic conditions a rebuilding of the heteropolyanion generally occurs and vanadyl salts are formed.

Table 3

Synthesis of 1,2,4,5-tetraphenylimidazole (1a) using different heteropolyacids (1 mol%) in refluxing ethanol

Entry	Heteropolyacid	Time (min)	Yield (%) <sup>a</sup>
1	$H_3[PW_{12}O_{40}]$	10	84
2	$H_4[SiW_{12}O_{40}]$	15	84
3	$H_3[PMo_{12}O_{40}]$	18	83
4	$HNa_2[PMo_{12}O_{40}]$	120	88
5	$H_4[PMo_{11}VO_{40}]$	5	85

<sup>a</sup> Yields refer to isolated products.

Table 4  
Synthesis of tetrasubstituted imidazoles using catalytic amount of  $H_4[PMo_{11}VO_{40}]$  in refluxing ethanol

Entry 1	Ar-	R-	Time (min)	Yield (%) <sup>a</sup>	mp (°C)	
					Found	Reported [26]
a	ph	Me	25	68	144–145	143–144
b	ph	ph	5	85	218	216–218
c	ph	phCH <sub>2</sub>	8	88	165	158–160
d	4-Meph	Me	30	70	221–223	218–220
e	4-Meph	ph	10	89	189	185–188
f	4-Meph	phCH <sub>2</sub>	14	90	165–166	165–166
g	4-Brph	Me	33	77	201–202	199–200

<sup>a</sup> Yields refer to isolated products.

To show the generality of this method the optimized system used for the synthesis of other imidazoles derivatives (Table 4). It should be noted that, this method is effective for the preparation of tetrasubstituted imidazoles from both aliphatic as well as aromatic amines. However, the catalytic system works best for aromatic amines.

It should be mentioned that the desired products could be easily separated in this condition. Heteropolyacid is soluble in ethanol at room temperature but the products are not. While the mixture cooled to room temperature the products were appeared from solution and could be separated by a simple filtration.

$H_4[PMo_{11}VO_{40}]$  catalyst was also found to be reusable, although gradual decline of activity was observed. Better results were obtained when, after the first run, the product filtered off, the solvent was evaporated and the remained catalyst was washed with  $CH_2Cl_2$ , and reused. Apparently, the treatment with  $CH_2Cl_2$  removed tars more efficiently from the catalyst surface. Such procedure applied for 1a and in second run the product was obtained in 80% yield.

#### 4. Conclusion

Keggin-type heteropolyacid  $H_4[PMo_{11}VO_{40}]$  is a highly efficient solid acid catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles. The catalyst can be reused after a simple work-up, with a gradual decline of its activity being observed. The reaction appears to be heterogeneously catalyzed. High yields, relatively short reaction times, simplicity of operation and easy work-up are some advantages of this protocol.

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