

Heteropolyacid –Catalyzed Efficient and Convenient Synthesis of 2-Substituted Benzimidazoles

Fatemeh F. Bamoharram,^{a*} Majid M. Heravi,^{a,b*} Maryam Hosseini,^a Khadijeh Bakhtiari^b

^aDepartment of Chemistry, Islamic Azad University of Mashhad, Mashhad-Branch, Iran

^bDepartment of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

Abstract: *o*-Phenylenediamine readily reacts with benzoyl chloride derivatives in the presence of Keggin type heteropolyacids as catalyst to yield 2-substituted benzimidazoles in very good yields.

Keywords: 2-Substituted benzimidazoles, Keggin type heteropolyacid, Heterocyclization, Reusable Catalyst.

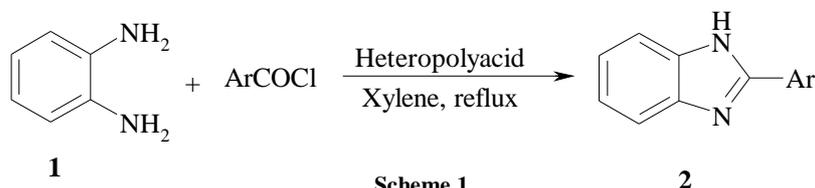
Introduction

2-Substituted benzimidazoles are widely used in medicinal chemistry because of their diverse biological activity and clinical applications [1]. Recent publications have reported benzimidazole-containing compounds showing biological properties such as fungicide, antitumour, immunosuppressant and anticonvulsant [2,3] and have also been prepared as ligands for asymmetric catalysis [4]. The traditional synthesis of benzimidazoles involves the reaction between a phenylenediamine and a carboxylic acid under harsh dehydrating reaction conditions [5]. A number of synthetic methods have been developed in recent years to uncover a variety of new reagents for the synthesis of 2-substituted benzimidazoles under milder conditions by the addition of Lewis acids [6], inorganic clays [7], and mineral acids [8]. Long reaction times for this reaction have been mitigated by the use of microwave heating [9,10], both with and without polyphosphoric acid [11].

Heteropolyacids (HPAs), due to their unique physicochemical properties, are widely used as homogeneous and heterogeneous acid and oxidation catalysts. They have found industrial applications in

several processes [12-16]. Many heteropoly compounds have very high solubility in polar solvents and fairly high thermal stability in the solid state. HPAs with the Keggin structure constitute the most extensively studied and important class of polyoxometalates. Keggin-type HPAs, typically represented by the formula $[XM_{12}O_{40}]^{p-}$, where X is the heteroatom (e.g. P^V or Si^{IV}), and M is the addenda atom (usually Mo⁶⁺ or W⁶⁺). The most important examples are H₃PW₁₂O₄₀, H₃PMo₁₂O₄₀, and H₄SiW₁₂O₄₀. Their significant higher Bronsted acidity, compared with the acidity of traditional mineral acid catalysts, is of great importance for catalysis. Heteropolyacids are promising solid acids and can replace environmentally harmful liquid acid catalysts such as H₂SO₄ [14-16].

As a part of our ongoing interest in synthesis of heterocyclic compounds containing nitrogen [17-20], and in continuation of our investigation on the use of heteropolyacids as catalyst for chemical preparation [21-25] herein, we wish to report the synthesis of 2-substituted benzimidazoles in good to excellent yields in the condensation reaction between 1,2-phenylenediamine and benzoyl chloride derivatives in refluxing xylene in the presence of a catalytic amount of Keggin type heteropolyacids (Scheme 1).



Results and Discussion

2-Substituted benzimidazoles were obtained by the condensation of *o*-phenylenediamine with various

benzoyl chlorides in the presence of HPAs in xylene. The reaction proceeds very cleanly under reflux condition and free of side products. In the absence of the catalyst, the reaction did not complete even after 24h. The results are shown in Table 1. The optimum

*Corresponding authors. Fax: +(98) 21 88047861. Email: abamoharram@yahoo.com, mmh1331@yahoo.com

yields of the products are obtained when 20 mol% of HPA is used.

In Table 1, the catalytic activities of $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, $H_4SiW_{12}O_{40}$ and $H_{14}NaP_5W_{30}O_{110}$ are compared. The highest yield was obtained when $H_3PW_{12}O_{40}$ was employed as the catalyst. The highest isolated yield in this case was 91% whereas in the case of $H_4SiW_{12}O_{40}$ the yield obtained was 78.2%. The results of this study show that $H_3PW_{12}O_{40}$ is an effective catalyst for this purpose having the highest acidity compared to the other catalysts studied.

Many properties of the heteropolyacids in solution depend on the concentration, the pH value of the solution, the reaction temperature, and other factors such as solvent type and catalyst structure. The relative activity of Keggin heteropolyacids primarily depends on their acid strength. Other properties, such as the oxidation potential as well as the thermal and hydrolytic stability are also important. Generally, if the reaction rate is controlled by the catalyst acid strength, $H_3PW_{12}O_{40}$ shows the highest catalytic activity in the Keggin series. In most cases, reactions catalyzed by

heteropolyacids may be represented by the conventional mechanisms of Bronsted acid catalysis. Heteropolyacids are capable of protonating the substrate and activating it for subsequent chemical reactions more effectively than usual inorganic acids. According to physiochemical data, heteropolyacids with different structures and compositions will differ in the catalytic activity in water and organic solvents. The activity series may differ in different solvents or for different substrates. With respect to the $H_3PW_{12}O_{40}$ in our studies shows the higher activity, it is suggested that, product yield has been affected by acidic properties of the heteropolyacids by the protonation of the substrate followed by the conversion of the ionic intermediate to yield the reaction product.

To explore the scope and limitations of this reaction, we extended the procedure to various substituted benzoyl chlorides in the presence of a catalytic amount of catalyst (Scheme 1). We found that the reaction proceeds very efficiently with benzoyl chloride, electron-withdrawing and electron-releasing substituted benzoyl chlorides.

Table 1. Synthesis of benzimidazole derivatives catalyzed by HPAs

Ar-	Heteropolyacid/Yield (%) ^a					m.p. (°C)	Lit. m.p.(°C)
	$H_3PW_{12}O_{40}$	$H_3PMo_{12}O_{40}$	$H_4SiW_{12}O_{40}$	$H_4SiW_{12}O_{40}$ ^b	$H_{14}NaP_5W_{30}O_{110}$		
C_6H_5	72	71.4	70	71.3	71	287-290	294-295[26]
4- NO_2 - C_6H_4	91	81.3	78.2	80	79	322-325	322-323[26]
3- NO_2 - C_6H_4	83.4	72.5	71	73.8	72.5	203-205	-
2- Cl - C_6H_4	78	70	68.5	70.7	70.3	233-235	234[27]
4- Me - C_6H_4	70	68	67.5	69	69	265-267	270[26]

^aYields refer to isolated pure products.

^bSupported onto silicagel.

Experimental

All products are known compounds and were characterized by melting point, IR, and ¹HNMR spectra. Melting points were measured by using the capillary tube method with an electrothermal Bamstead 9200 apparatus. ¹HNMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. All products were characterized by spectra and physical data. Keggin type heteropolyacids were purchased from Merck Company and $H_{14}NaP_5W_{30}O_{110}$ was synthesized according to our earlier research [23].

Preparation of benzimidazoles: General Procedure

To a stirred solution of *o*-phenyldiamine (1.85 mmol) in xylene (5 mL), an appropriate benzoyl chloride (1.85 mmol) in xylene (5 mL) was added dropwise at 0°C for 20 min. Then, heteropolyacid (0.1g) was added. The mixture was refluxed for 1h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and catalyst was filtered off. The filtrate was then washed with 5% $NaHCO_3$ (5mL) and brine (2×5mL) successively, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was obtained. The resulting solid product was recrystallized from ethanol to give the pure product.

1.2 Reusability of the catalyst

At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 130 °C for 1 h, and re-used in another reaction. The recycled catalyst was

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