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Abstract: Benzimidazoles have been synthesized in very good yield from *o*-phenylenediamine and aromatic aldehydes in the presence of monoammonium salt of 12-tungstophosphoric acid [$(NH_4)H_2PW_{12}O_{40}$], an efficient heterogeneous catalyst. This catalyst has the advantages of simple workup procedure, water insolubility, and good activity with high yield for the synthesis of benzimidazole derivatives.

Keywords: aldehydes, benzimidazole, monoammonium salt of 12-tungstophosphoric acid, *o*-phenylenediamines

INTRODUCTION

The development of a simple, efficient, environmentally benign, and economically viable chemical process or methodologies for widely used organic

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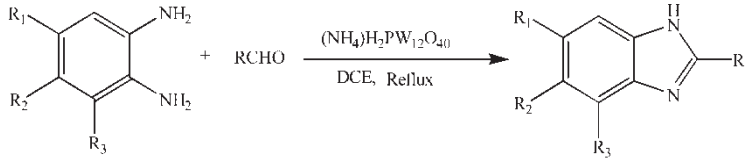
compounds are in great demand. Benzimidazole structures are classified under several classes of drugs,[1] based on the possible substitutions at different positions of the benzimidazole nucleus. The benzimidazole nucleus is found in variety of pharmaceuticals as an cardiotonic,[2a] potential antitumor, antiulcer, and antiviral agent.[3] In particular the triflouromethyl benzimidazoles[4] have important pesticidal and antibacterial activities. The importance of benzimidazole units, especially in biochemistry, is increasing recently, because they are found in many biological activity compounds.[5]

Hence, several methodologies for synthesizing benzimidazole derivatives have already been optimized where azalactones, 2-aryl-1, 1-dibromoethanes, nitriles, and amino amides[6] are used as starting materials for this synthesis. All these compounds contain the benzimidazole skeleton, and hence it has been assumed that this is neccesarry for the therapeutic effect. The condensations of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid or mineral acids[7] and other reagents such as $I_2/KI/K_2CO_3$[8] N-halosuccinimide (X = Cl, Br, I),[9] $Yb(OTf)_3$,[10] and palladium, as well as using microwave irradiation[11] and solid-phase reactions,[12] are reported in literature. However, many of the synthetic protocols reported so far suffer from disadvantages, such as a requirement for anhydrous conditions, use of organic solvents, harsh reaction conditions, prolonged reaction times, expensive reagents, and low to moderate yields. Almost all the reported methods make use of an acid catalyst, giving rise to tedious workup procedures. Therefore, the development of a cost-effective, safe, and environmentally friendly reagent is still needed.

RESULTS AND DISCUSSION

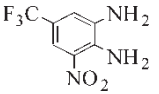
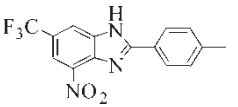
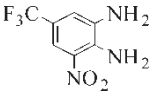
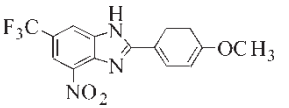
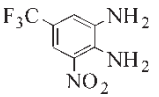
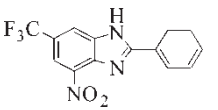
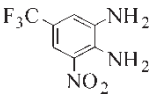
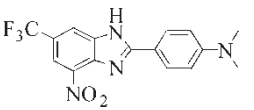
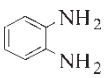
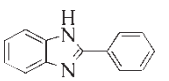
Recently, we have employed monoammonium salt of 12-tungstophosphoric acid catalyst,[13] in organic reactions for the selective esterification of aliphatic carboxylic acids[14] and synthesis of 1, 5-benzodiazepines.[15] In the present study, the versatility of this catalyst for the synthesis of benzimidazole derivatives was attempted and found to be more efficient for the condensation of *o*-phenylenediamine with aromatic aldehydes (Scheme 1).



R = Ph; R_1 = H, CH_3, CF_3; R_2 = H, CH_3; R_3 = H, NO_2

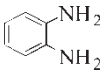
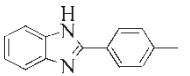
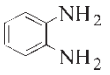
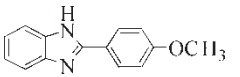
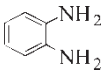
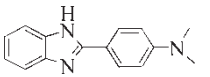
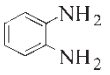
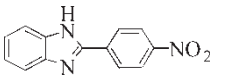
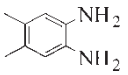
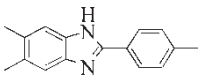
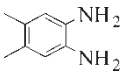
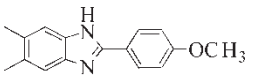
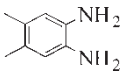
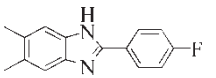
Scheme 1. Synthesis of benzimidazole derivatives.

Table 1. Condensation of *o*-phenylenediamine with various aldehydes catalyzed by monoammonium salt of 12-tungstophosphoric acid

Entry	Diamine	Aldehyde	Product	Yield (%)[a]
1		4-Methyl benzaldehyde		84
2		4-Methoxy benzaldehyde		86
3		Benzaldehyde		85
4		4-N,N-Dimethyl benzaldehyde		84
5		Benzaldehyde		92

(*continued*)

Table 1. Continued

Entry	Diamine	Aldehyde	Product	Yield (%)[a]
6		4-Methyl benzaldehyde		94
7		4-Methoxy benzaldehyde		94
8		4-N,N-Dimethyl benzaldehyde		91
9		4-Nitro benzaldehyde		90
10		4-Methyl benzaldehyde		91
11		4-Methoxy benzaldehyde		94
12		4-Flouro benzaldehyde		89

[a]Isolated yield.

Note. All the reactions were completed in 45–60 min.

The reactions were carried out by taking a 1:1 molar ratio mixture of *o*-phenylenediamine and aldehyde in 1,2-dichloroethane (5 ml) as solvent in the presence of 5 wt% of the catalyst of diamine with stirring at reflux conditions for the appropriate time. In a specific experiment, the reaction is mainly the condensation of 3-nitro-5-trifluoromethyl-o-phenylene diamine and benzaldehyde in 1,2-dichloroethane as a solvent in the presence of a catalyst. The reaction proceedes efficiently, giving 84 to 94% yields of benzimidazoles. The scope and efficiency of our method are summarized in Table 1. Completion of the reaction was monitored by thin-layer chromatography (TLC) using 30% EtOAc in hexane as the solvent system. The products were characterized by spectroscopic methods such as NMR, IR, and gas chromatography-mass spectroscopy (GC-MS). After completion of the reaction, the organic layer was filtered from the catalyst and concentrated, and the product was purified by silica-gel chromatography by gradient elution of hexane and ethyl acetate. The monoammonium salt of 12-tungstophosphoric acid catalyzed the condensation reactions and gave excellent yields under reflux conditions in relatively short reaction times (45–60 min).

In conclusion, the use of monoammonium salt of 12-tungstophosphoric acid catalyst for the synthesis of benzimidazoles from *o*-phenylenediamine and aldehyde is an environmentally benign and economic process. The advantages of the present protocol are mild, heterogeneous conditions, shorter reaction times, easy workup, low toxicity, and inexpensive catalyst, which make the procedure an attractive alternative to the existing methods for the synthesis of benzimidazoles.

EXPERIMENTAL

^{1}H NMR spectra were recorded a Varian 200- or Bruker 300-MHz spectrometer. IR spectra were recorded on a Perkin Fourier transform-infrared spectrometer (FT-IR) spectrometer. The reaction monitoring was accomplished by TLC on silica-gel plates.

Typical Procedure for the Preparation of Benzimidazole Derivatives

O-phenylenediamine (1 mmol), *p*-methoxybenzaldehyde (1 mmol), and monoammonium salt of 12-tungstophosphoric acid catalyst (5 wt% of diamine) were stirred rapidly at reflux temperature for an appropriate time. The reaction was monitered by TLC (hexane–EtOAc v/v). The reaction mixture was taken in chloroform and filtered to separate the catalyst. The filtrate was concentrated under vacuum, and the product was purified on a silica-gel column eluting with EtOAc–hexane to afford a pure product in 84–94% yield.

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