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Wells-Dawson Type Heteropolyacid Catalyzed Synthesis of Quinoxaline Derivatives at Room Temperature

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Summary. *Wells-Dawson* heteropolyacid ($H_6P_2W_{18}O_{62} \cdot 24H_2O$) was used as an effective catalyst for the synthesis of biologically active quinoxaline derivatives from the condensation of *o*-phenylenediamines with 1,2-dicarbonyl compounds at room temperature in excellent yields.

Keywords. Quinoxalines; 1,2-Diketones; *o*-Phenylenediamines; Heteropolyacid $H_6P_2W_{18}O_{62} \cdot 24H_2O$; *Wells-Dawson*.

Introduction

In the past ten years, the average number of publications including the keywords 'synthesis' and 'quinoxaline' has doubled. A large part of these papers concerns highly functionalized molecules with a quinoxaline skeleton designed for biological activities. Quinoxaline derivatives are an important class of nitrogen-containing heterocycles and have shown a broad spectrum of biological activities, such as antibacterial and anti-inflammatory activities [1, 2]. They have been reported for their applications in dyes [3], pharmaceuticals [4, 5], and have also been used as building blocks for the synthesis of organic semiconductors [6, 7]. Quinoxaline ring is part of various antibiotics such as Echinomycin, Levomycin, and Actinoleutin [8, 9] that are known to inhibit growth of *Gram* positive bacteria, and are active against various transplantable tumors [10].

A number of synthesis strategies has been developed for the preparation of substituted quinoxalines [11–14]. Their synthesis on solid phase has also been reported [15]. By far the most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h giving 34–85% yields [16].

The problems associated with the handling and disposal of inorganic acids, and their environmental and potential hazards have raised our interest in the development of alternative procedures using solid acid catalysts [17, 18]. Due to their super-acidic properties, heteropolyacids, *HPA*s, can be used in reactions requiring electrophilic catalysis. *HPA*s are applied both in bulk or supported form, with homogeneous and heterogeneous catalysis being possible. The structure of the *Wells-Dawson* heteropolyacid ($H_6P_2W_{18}O_{62} \cdot 24H_2O$) consists of a close-packed framework of WO_6 octahedra surrounding a central P atom, two identical 'half units' PW_9 are linked through the oxygen atoms [19].

As a part of a research project to develop environmentally friendly organic reactions [20, 21], we have recently applied a variety of heteropolyacid catalysts to different reactions, such as *Biginelli* reaction [22], synthesis of 1,1-diacetates [23], and others [24, 25].

Very recently, we have reported the synthesis of quinoxaline derivatives catalyzed by $CuSO_4 \cdot 5H_2O$ [26], IBX [27] and Zn[(*L*)-proline] [28]. In this article, we wish to report the catalytic activity of the *Wells-Dawson* heteropolyacid $H_6P_2W_{18}O_{62} \cdot 24H_2O$

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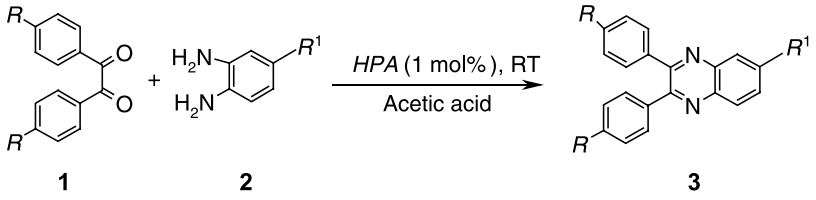

Scheme 1

in a sustainable, simple preparation of functionalized quinoxalines at room temperature in excellent yields (Scheme 1).

Results and Discussion

The synthesis strategy involves the preparation of quinoxalines **3** from diamines **1** and 1,2-dicarbonyl compounds **2** using $H_6P_2W_{18}O_{62} \cdot 24H_2O$ as the catalyst. The reaction proceeds very cleanly at room temperature and no undesirable side reactions were observed. In the absence of the catalyst, the reaction did not complete, even after 24 h. The results are shown in Table 1.

The optimum yield of the product **3** was obtained when 1 mol% of *HPA* was used. Among the solvents tested for this reaction $CHCl_3$, CH_3CN, H_2O, and *Ac*OH, the latter was found to be the most efficient with respect to short reaction times and maximum yield of the products.

Although water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns, use of water in this reaction gave only moderate yields of products (30% after 24 h).

Table 1. Synthesis of quinoxaline derivatives using the *Wells-Dawson* heteropolyacid $H_6P_2W_{18}O_{62} \cdot 24H_2O$ as the catalyst

Product	R	R^1	*Time*/min	Yield/%[a,b]	mp/°C
3a	H	H	5	98	128–129
3b	H	CH_3	5	98	117–118
3c	H	NO_2	5	98	193–194
3d	H	COOH	10	97	272
3e	OCH_3	H	20	98	151–152.5
3f	OCH_3	CH_3	20	97	125–127
3g	OCH_3	NO_2	20	98	192–194
3h	F	H	5	99	135–137
3i	F	CH_3	5	98	165–167
3j	F	NO_2	2	99	174–176
3k	F	COOH	5	97	230

[a] All products were well characterized using ^{1}H NMR and IR spectra; [b] Yields refer to isolated pure products

Table 2. Reuse of the catalyst for synthesis of 2,3-diphenylquinoxaline **3a**

Run	1	2	3	4	5
Yield/%[a]	99	97	94	92	89

[a] Yields were analyzed by GC

o-Phenylenediamines and 1,2-dicarbonyl compounds which have electron-donating or electron-withdrawing groups were used and, as expected, in all cases quinoxalines were obtained in good yields.

It is noteworthy to mention that the catalyst is recyclable and could be reused without significant loss of activity. Even after five runs the catalytic activity of $H_6P_2W_{18}O_{62} \cdot 24H_2O$ was almost the same as that of the freshly used catalyst (see Table 2).

In conclusion, we developed the use of the *Wells-Dawson* heteropolyacid $H_6P_2W_{18}O_{62} \cdot 24H_2O$ as an inexpensive, reusable, easy to handle, non-corrosive, and environmentally benign catalyst for the synthesis of biologically active quinoxalines from aromatic *o*-diamines and 1,2-dicarbonyl compounds. The advantages of the present procedure are simplicity of operation, the high yields of products, and the recyclability of the catalyst. In this reaction the catalyst can be recovered by filtration and washing with *n*-hexane, and subjected to further reaction. Thus, the recycled catalyst could be used for five successive reactions without appreciable loss of activity.

Experimental

All chemicals were purchased from commercial suppliers and were used as received. All products were identified by their spectra and physical data. Melting points were measured by using the capillary tube method with an electrothermal 9100 apparatus. IR spectra were recorded from KBr disks on the FT-IR Brucker Tensor 27. Mass spectra were recorded on MS 5973 Network Mass Selective detector. All yields were calculated from isolated products, and GC was used to establish their purities. All products were well characterized by comparison of TLC, spectral and physical data with data of authentic samples [26–30].

Preparation of Quinoxalines Catalyzed by Wells-Dawson Heteropolyacid (General Procedure)

In this condensation reaction, 1 mmol *o*-phenylenediamine and 1 mmol 1,2-dicarbonyl compound were dissolved in 3 cm^3 acetic acid. The mixture was stirred at room temperature in the presence of a catalytic amount of *Wells-Dawson* $H_6P_2W_{18}O_{62} \cdot 24H_2O$ (1 mol%, 0.03 g). The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered off and washed with 5 cm^3 Et_2O. The filtrate then was washed with 5% $NaHCO_3$ (5 cm^3) and brine (2×5 cm^3) successively, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the pure product was obtained. A variety of substituted *o*-phenylenediamines were condensed with different 1,2-dicarbonyl compounds. The results are shown in Table 1.

Reusability of the Catalyst

At the end of the reaction, the catalyst was filtered off, washed with diethyl ether, dried at 130°C for 1 h, and re-used in another reaction (Table 2).

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