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$H_{14}[NaP_5W_{30}O_{110}]$ as a heterogeneous recyclable catalyst for the synthesis of 1,5-benzodiazepines in refluxing ethanol

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Abstract

2,3-Dihydro-1H-1,5-benzodiazepines are synthesized by the condensation of *o*-phenylenediamine and various ketones in the presence of Preyssler heteropolyacid as a recyclable catalyst in refluxing ethanol.

Keywords: 1,5-Benzodiazepines; Recyclable catalyst; Heteropolyacid; Preyssler; Heterogeneous catalyst

1. Introduction

The application of heteropolyacids as catalytic materials is growing continuously in the catalytic field. These compounds possess unique properties such as: well-defined structure, Brönsted acidity, possibility to modify their acid-base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, etc. [1]. In view of green chemistry, the substitution of harmful liquid acids by solid reusable HPAs as catalyst in organic synthesis is the most promising application of this acids.

Benzodiazepines and their polycyclic derivatives are a very important class of bio-active compounds. They are finding numerous new applications and are widely used as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative and anti-depressive agents [2,3]. Benzodiazepines are also valuable intermediates for synthesis of fused ring compounds such as triazolo, oxadiazolo-, oxazino-, and furano-benzodiazepines [4–6].

In spite of their importance from a pharmaceutical, industrial and synthetic point of view, comparatively few methods for their preparation are reported in the literature, a great number of which have appeared only very recently. These include condensation reactions of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds [7], β-haloketones [8], or ketones in the presence of BF_3-etherate [9], $NaBH_4$ [10], polyphosphoric acid [11], SiO_2 [11], MgO and $POCl_3$ [12], $Yb(OTf)_3$ [13], Al_2O_3/P_2O_5 [14], AcOH under microwave irradiation [15] and ionic liquid [16]. Many of these processes suffer from some limitations such as drastic reaction conditions, expensive reagents, low to moderate yields, relatively long reaction times and the occurrence of several side reactions. So, the development of clean, high-yielding and environmentally friendly approaches is desirable.

To the best of our knowledge, there are no examples of the use of preyssler type heteropolyacids as catalyst for the synthesis of benzodiazepines. 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 [17–26], herein we report the use of $H_{14}[NaP_5W_{30}O_{110}]$ as a recyclable green catalyst for the synthesis of 1,5-benzodiazepines (Scheme 1).

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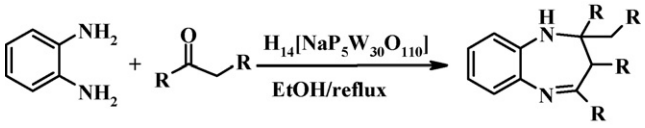


Scheme 1.

2. Experimental

2.1. Synthesis of 2,3-dihydro-1H-1,5-benzodiazepines: general procedure

A mixture of ketone (2.2 mmol), *o*-phenylenediamine derivative (1 mmol) and $H_{14}[NaP_5W_{30}O_{110}]$ (0.1 mol%) was refluxed in ethanol (3 cm^3) at 78 °C. After completion of reaction (monitored by TLC) the solvent was evaporated and dichloromethane (5 cm^3) was added to the residue. All products are soluble in dichloromethane but the catalyst is not. So the catalyst could be separated by a simple filtration.

After evaporation of solvent, products were obtained in good yields. More purification was obtained by column chromatography. The products are identified via comparison with authentic samples.

The filtered catalyst could be washed with a portion of dichloromethane and re-used in another reaction.

All products gave satisfactory spectral data in accord with the assigned structures [e.g. for entry 1: light yellow solid: mp 138 °C (literature [27] 136–138 °C). IR (KBR): 3340, 1650 and 1600 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7–7.25 (m, 4H, Ar–H), 3.5 (br, s, 1H, N–H), 3 (s, 2H, N=C–CH_2), 2.5 (m, 3H, N=C–CH_3), 1.50–1.75 (s, 6H, $2CH_3$)].

3. Results and discussion

We have recently used zeolites as catalysts for synthesis of benzodiazepines [28]. In this work, we investigated the synthesis of benzodiazepines using Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$.

At the first stage, because of complexity of behavior for this catalyst in a solvent, we studied the reaction of acetophenone and *o*-phenylenediamine in the presence of catalytic amount of $H_{14}[NaP_5W_{30}O_{110}]$ (as a model reaction) in a solvent-free system (entry 6, Table 1). However, initial attempts to carry out the reaction in a solvent-free system showed long reaction time. Thus, among the tested solvents, i.e. water, chloroform, dichloromethane, 1,2-dichloroethane and ethanol, the last one was applied as solvent of choice at 78 °C (Table 1).

Table 1
The reaction of *o*-phenylenediamine and acetophenone in the presence of catalytic amount of $H_{14}[NaP_5W_{30}O_{110}]$ in different solvents

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]
1	Ethanol	78.3	75	92
2	Water	100	75	10
3	Dichloromethane	40	75	60
4	1,2-Dichloroethane	83	75	70
5	Chloroform	61	75	55
6	Solvent free	70	75	70

[a] Yields are analyzed by GC.

Table 2
The reaction of *o*-phenylenediamine and acetophenone in the presence of catalytic amount of $H_{14}[NaP_5W_{30}O_{110}]$ in ethanol and at different temperatures

Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	25	75	50
2	45	75	77
3	78	75	92

[a] Yields are analyzed by GC.

The effect of temperature was studied by carrying out the model reactions at different temperatures in the presence of this catalyst in ethanol (room temperature, 45 and 80 °C). It was observed (Table 2) that yield is a function of temperature, so the yield increased as the reaction temperature was raised.

We also investigate the reusability of the catalyst. For this purpose after completion of the model reaction in refluxing ethanol the solvent was evaporated and dichloromethane (5 cm^3) was added to the residue. All products are soluble in dichloromethane but the catalyst is not. So it could be separated by a simple filtration and washed with dichloromethane. The recycled catalyst was used for three reactions with the same substrate without observation of appreciable lost in its catalytic activity. The results of the first experiment and subsequent experiments were almost consistent in yields (86, 84 and 81%).

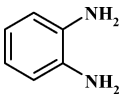
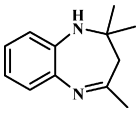
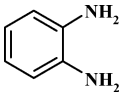
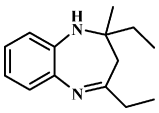
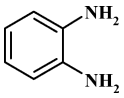
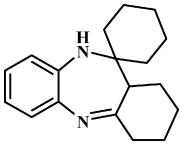
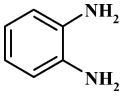
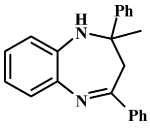
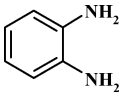
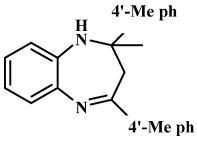
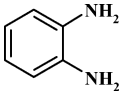
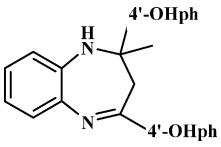
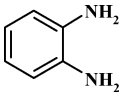
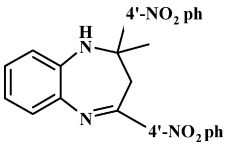
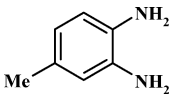
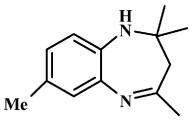
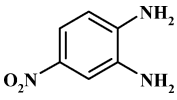
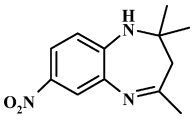
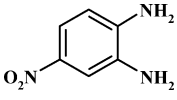
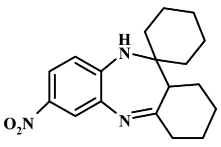
To show the generality of this method the optimized system used for the synthesis of a variety of 1,5-bebnzodiazepines (Table 3). Various cyclic and acyclic ketones and three derivatives of *o*-phenylenediamine subjected to this reaction and all products were obtained in good yields (Table 1). It should be noted that, this method is effective for the preparation of benzodiazepines from both electron-rich as well as electron-deficient ketones and *o*-phenylenediamine derivatives. But in the case of cyclohexanone as a cyclic ketone the reaction times are longer than others (entries 3 and 10), it may be because of the steric effect of cyclic ketones.

Comparison of the obtained results by this preyssler type heteropolyacid with those reported for $Ag_3PW_{12}O_{40}$ as a Keggin type, show some advantages in the reaction times [18]. The obtained yields for both of them are comparable but reaction times for $H_{14}[NaP_5W_{30}O_{110}]$ are shorter than $Ag_3PW_{12}O_{40}$. So $H_{14}[NaP_5W_{30}O_{110}]$ is a more effective catalyst for the synthesis of benzodiazepine derivatives than $Ag_3PW_{12}O_{40}$.

The efficiency of $H_7K_7[NaP_5W_{30}O_{110}]$ as a salt of our used catalyst was also studied for this reaction, but the model reaction did not go to complete in the presence of this polyacid even after long reaction times.

In summary, we describe a convenient and efficient protocol for the synthesis of 2,3-dihydro-1,5-benzodiazepines via condensation of *o*-phenylenediamine derivatives with a variety of ketones using $H_{14}[NaP_5W_{30}O_{110}]$ as a green recyclable and heterogeneous catalyst. The simple experiment procedure combined with ease of recovery and reuses of this catalyst make this procedure quite simple, more convenient and environmentally benign.

Table 3
$H_{14}[NaP_5W_{30}O_{110}]$ catalyzed synthesis of 1,5-benzodiazepines in ethanol at 78 °C

Entry	Diamine	Ketone	Product	Reaction time (min)	Yield (%)[a]
1		Acetone[b]		75	92
2		2-Butanone		60	94
3		Cyclohexanone		120	95
4		Acetophenone		75	92
5		4′-Methyl acetophenone		60	89
6		4′-Hydroxy acetophenone		105	85
7		4′-Nitro acetophenone		100	84
8		Acetone[b]		60	95
9		Acetone[b]		90	94
10		Cyclohexanone		3	80

[a] Yields are analyzed by GC.
[b] The reactions are carried out in refluxing acetone as solvent.

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