An Efficient Synthesis of 3H-1,5-benzodiazepine Derivatives Catalyzed by Heteropolyacids as a Heterogeneous Recyclable Catalyst

Majid M. Heravi,* Samaheh Sadjadi, Hossein A. Oskooie,
Rahim Hekmatshoar and Fatemeh F. Bamoharram
Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

3H-1,5-benzodiazepines were synthesized by the condensation of *o*-phenylendiamine and various 1,3-diketones in the presence of various heteropolyacid (HPA) catalysts under mild conditions in very good yields and with high selectivity.

Keywords: 3H-1,5-benzodiazepine; Recyclable catalyst; Heteropolyacid; Heterocyclization.

Heteropolyacids, HPAs, and their salts are useful acid and oxidation catalysts for various reactions. There are several advantages of using HPA catalysts. One of the most interesting aspects may be the fact that they can be used in various kinds of reaction media or fields[1-7] and are promising candidates as green, eco-friendly and effective catalysts.[8-11] Pseudoliquid behavior is observed for some HPAs in the solid state. Because of the flexible lattice (variable secondary structure), reactant molecules are absorbed into the three-dimensional solid bulk and react there. In other words, the reaction field of the solid catalyst becomes three-dimensional like reactions in solution (catalytically active solid solvent). Owing to this behavior, HPA catalysts often exhibit very high catalytic activities and unique selectivities.[12]

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 anti-convulsant, anti-inflammatory, analgesic, hypnotic, sedative and anti-depressive agents. Benzodiazepines are also valuable intermediates for synthesis of fused ring compounds such as triazolo, oxadiazolo-, oxazino-, and furanobenzodiazepines.[13] Due to their wide range of pharmacological activity in synthetic and industrial applications, the synthesis of these compounds have recently received a great deal of attention for the discovery of improved protocols towards milder and high yielding approaches.

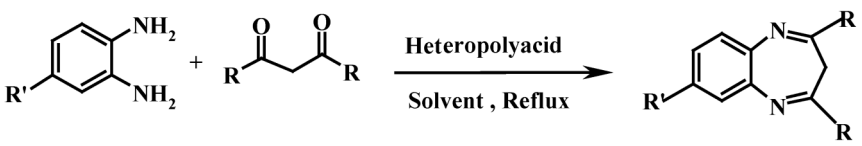
Herein we report a simple method for the condensation of *o*-phenylenediamines (*o*-PDA) with 1,3-diketones using catalytic amounts of different types of HPAs including $H_{14}[NaP_5W_{30}O_{110}]$, $H_5[PMo_{10}V_2O_{40}]$, and $H_6[P_2W_{18}O_{62}]$ as the catalyst to synthesize 3H-1,5-benzodiazepines (Scheme I).

During the course of our studies on the development of HPAs as efficient heterogeneous catalysts,[14-18] in this work, we investigated the efficiency of various types of HPAs and the effects of reaction conditions such as reaction time, temperature and solvent on condensation of *o*-PDA and 1,3-diketones. For this reason we have employed HPAs of three types including Preyssler, $H_{14}[NaP_5W_{30}O_{110}]$, Keggin, $H_5[PMo_{10}V_2O_{40}]$, and Wells-Dawson, $H_6[P_2W_{18}O_{62}]$ as the catalyst for the mentioned reaction. The results are summarized in Table 1.

We found that the presence of an electron-donating or an electron-withdrawing group on the aromatic ring of *o*-PDA affects the reaction yields.

As shown in Table 1, an electron-withdrawing group decreases the yield of the reaction but an electron-donating

Scheme I



* Corresponding author. E-mail: mmh1331@yahoo.com

Table 1. Synthesis of 3H-1,5-benzodiazepine derivatives using various heteropolyacids under refluxing conditions

Entry	Solvent	R′	R	Yield (%)[a]		
				$H_{14}[NaP_5W_{30}O_{110}]$	$H_6[P_2W_{18}O_{62}]$	$H_5[PMo_{10}V_2O_{40}]$
1	THF	H	CH_3	98	90.4	85
2	acetonitrile	H	CH_3	96.4	85.7	82
3	THF	CH_3	CH_3	98	91	87
4	acetonitrile	CH_3	CH_3	93	85	72
5	THF	NO_2	CH_3	80	78.2	74.8
6	acetonitrile	NO_2	CH_3	75.7	73	68
7	THF	H	C_6H_5	63	48	35
8	acetonitrile	H	C_6H_5	55	37	25
9	THF	CH_3	C_6H_5	65	51	40
10	acetonitrile	CH_3	C_6H_5	58	42	28

[a] Yields are analyzed by GC

group increases it. It is noteworthy to mention that the steric effect of phenyl groups of 1,3-diphenyl-propane-1,3-dione contribute to lower yields of reaction (entry 7-10).

The results indicate that the nature of the catalyst plays an important role in their catalytic activities. The highest yield of products has been achieved in the presence of $H_{14}[NaP_5W_{30}O_{110}]$ as catalyst, and $H_5[PMo_{10}V_2O_{40}]$ gave lowest yields.

A comparison between $H_{14}[NaP_5W_{30}O_{110}]$ and $H_5[PMo_{10}V_2O_{40}]$ shows that the number of protons as well as the number of metal ions are important factors.

The number of protons is apparently responsible for the catalytic activities of these salts. The larger number of protons may lower the activation barrier to the reaction.[19]

Preyssler's anion, $[NaP_5W_{30}O_{110}]^{14-}$, has an approximate D_5h symmetry and consists of a cyclic assembly of five PW_6O_{22} units. A sodium ion is located within the polyanion on the fivefold axis and 1.25 above the pseudo mirror plane that contains the five phosphorus atoms.[20] Preyssler's polyanion as a large anion can provide many ''sites'' on the oval-shaped molecule that are likely to render the catalyst effective. The Keggin anions have an assembly of 12 corner-shared octahedral MoO_6 from trimetallic groups $[Mo_3O_{13}]$ around a heteroatom tetrahedron PO_4. The introduction of vanadium(V) into the Keggin framework of $[PMo_{12}O_{40}]^{3-}$ is beneficial for catalysis reactions. Usually positional isomers are possible and coexist when two or more vanadium atoms are incorporated into the Keggin structure. Studies on these isomers in catalytic reactions indicate that different isomers cause different reactivities.

With respect to the catalytic performance of these catalysts and the overall effects of all isomers, we cannot control the reaction conditions for the synthesis of positional vanadium substituted isomers separately, indicating that the relationship between the H_3+xPMo_{12}-$xVxO_{40}$ ($x = 2$) structures and hence study of their catalytic activity is difficult. However, because the metal substitution may modify the energy and composition of the LUMO and redox properties, for the mentioned heteropolyacids with different charges, the energy and composition of the LUMOs have significant effects on the catalytic activity. Substitution of vanadium ions into the molybdenum framework stabilizes the LUMOs because these orbitals derive, in part, from vanadium d-orbitals which have been assumed to be more stable than those of molybdenum and tungsten.[21] The abundance of different isomers may also play an important role in catalytic performance. In addition, different positional Mo atom(s) substituted by the V atom(s) in $[PMo_{12}O_{40}]^{3-}$ may create different vanadium chemical environments, thus causing these catalysts to exhibit varying catalytic performances. Considering the above explanations we suggest that the rigidity, steric hindrance and lower number of protons in $H_5[PMo_{10}V_2O_{40}]$ are tentatively assumed to be responsible for its observed lower activity.

To investigate the effect of the solvent, THF and acetonitrile were selected and all reactions carried out under refluxing conditions. As shown in Table 1, THF is a better solvent for this reaction in terms of yield.

The effect of temperature was studied by carrying out the reactions in all solvents at different temperatures (room

Table 2. Effect of different reaction times and temperatures on synthesis of 3H-1,5-benzodiazepine derivatives using $H_{14}[NaP_5W_{30}O_{110}]$

Entry	R′	R	Time (h)	Yield (%)[a]		
				25 °C	50 °C	Reflux
1	H	CH_3	0.5	62	67	70
2	H	CH_3	1	74	78	82
3	H	CH_3	1.5	83	88	91
4	H	CH_3	2	88	90	98
5	CH_3	CH_3	0.5	61	68	72
6	CH_3	CH_3	1	74	87	83
7	CH_3	CH_3	1.5	75	87	92
8	CH_3	CH_3	2	85	90	98
9	NO_2	CH_3	0.5	45	50	58
10	NO_2	CH_3	1	55	60	68
11	NO_2	CH_3	1.5	59	65	72
12	NO_2	CH_3	2	70	75	80
13	H	C_6H_5	0.5	30	37	41
14	H	C_6H_5	1	41	46	50
15	H	C_6H_5	1.5	49	53	57
16	H	C_6H_5	2	51	59	63
17	CH_3	C_6H_5	0.5	38	42	48
18	CH_3	C_6H_5	1	44	50	55
19	CH_3	C_6H_5	1.5	50	55	60
20	CH_3	C_6H_5	2	56	60	65

[a] Yields are analyzed by GC

temperature, 50 °C, and under reflux). As shown in Table 2, the yields of reactions increased as the reaction temperature was raised. From these results, it was decided that refluxing conditions would be the best temperature for all reactions.

In each reaction, the yield is a function of the reaction time and the best time for all reactions was optimized to be 2 h.

When 3,5-dinitrophenylenediamine was used as substrate in this reaction, the correspondent 3H-1,5-benzodiazepines were not obtained. It is presumed that the amine group *meta* to the NO_2 group participated in the reaction, while the amine groups *para* or *ortho* to the nitro could not participate because the latter are considered to be powerful electron withdrawing groups and may reduce the nucleophilicity of the amine. The 1,3-diphenyl-propane-1,3-dione steric effect of phenyl groups also reduced the yield of reactions.

In order to demonstrate the efficiency of these catalysts using lesser amounts of catalysts, all of the reactions were performed with various, lesser amounts of heteropolyacid. The results using different amounts of $H_{14}[NaP_5W_{30}O_{110}]$ heteropolyacid in synthesis of 3H-1,5-benzodiazepine derivatives are summarized in Table 3. As shown in this table, although the amount of entry 1 is the amount of choice, the yields of other reactions are still high and acceptable.

Table 3. Synthesis of 3H-1,5-benzodiazepine derivatives using different amounts of $H_{14}[NaP_5W_{30}O_{110}]$ under refluxing conditions in THF

Entry	R′	R	Catalyst amount (mmol)	Yield (%)[a]
1	H	CH_3	1	98
2	H	CH_3	0.5	97.3
3	H	CH_3	0.1	97
4	CH_3	CH_3	1	98
5	CH_3	CH_3	0.5	97.5
6	CH_3	CH_3	0.1	97.1
7	NO_2	CH_3	1	80
8	NO_2	CH_3	0.5	79
9	NO_2	CH_3	0.1	78.2
10	H	C_6H_5	1	63
11	H	C_6H_5	0.5	62.3
12	H	C_6H_5	0.1	61.8
13	CH_3	C_6H_5	1	65
14	CH_3	C_6H_5	0.5	64.3
15	CH_3	C_6H_5	0.1	64.1

[a] Yields are analyzed by GC

EXPERIMENTAL

Chemicals and apparatus

All chemicals were obtained from Merck and used as received. $H_{14}[NaP_5W_{30}O_{110}]$ was prepared according to earlier reports.[22] $H_5[PMo_{10}V_2O_{40}]$ was prepared according to reports in the literature.[26] The Wells-Dawson species $H_6[P_2W_{18}O_{62}]$ was prepared as described elsewhere,[23] from an aqueous solution of α/β $K_6P_2W_{18}O_{62}\cdot 10H_2O$ salt, which was treated with ether and concentrated (37%) HCl solution.

Instruments

GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective detector, GC 6890 Agilent. IR spectra were obtained with a Buck 500 scientific spectrometer. ^{1}H NMR spectra were recorded on a FT NMR Bruker 90 MHz.

General procedure

To a mixture of *o*-PDA (10 mmol) and appropriate 1,3-diketone (10 mmol) a hetropolyacid (1 mmol) was added and the mixture was refluxed in an appropriate solvent (10 mL). The reaction was monitored by TLC and it was found to be completed by 2 h. After completion of the reaction, the catalyst was recovered by filteration and the

solvent was evaporated to dryness. The residue was subjected to column chromatography over silica gel to afford pure 3H-1,5-benzodiazepine. The products are identified by comparison of their physical and spectral data with those of authentic samples. The recoverd catalyst was washed with diethyl ether and can be reused. All products gave satisfactory spectral data in accordance with the assigned structures.

Spectral data for selected products

2,4-Dimethyl-3H-benzo[b][1,4]diazepine (Table 1, Entry 1)

IR (KBr) cm^{-1}: 1700 (C=N), 1630 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): 7.30-7.35 (m, 4H, Ar-H), 0.9 (s, 6H, N=C-CH_3), 2.4 (s, 2H, N=C-CH_2), GC/MS: *m/z* 172 [M^+].

2,4,7-Trimethyl-3H-benzo[b][1,4]diazepine (Table 1, Entry 3)

IR (KBr) cm^{-1}: 1706 (C=N), 1636 (C=C) cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): 7.0-7.15 (m, 3H, Ar-H), 2.4 (s, 2H, N=C-CH_2), 0.9 (s, 6H, N=C-CH_3), 2.35 (s, 3H, Ar-CH_3), GC/MS: *m/z* 186 [M^+].

Reusability of catalyst

At the end of the reaction, the catalyst could be recovered by a simple filtration. The recycled catalyst could be washed with dichloromethane and subjected to a second run of the reaction process. To assure that the catalyst did not solve in solvent the filtered catalysts were weighed before reusing. The results show that these catalysts are not soluble. The results of the first and subsequent experiments were almost consistent in yields.

In Table 4 the efficiency of recycled $H_{14}[NaP_5W_{30}O_{110}]$ in the synthesis of 3H-1,5-benzodiazepine derivatives after five times is reported. As is shown in Table 4, the yields of reactions after using $H_{14}[NaP_5W_{30}O_{110}]$ for five times show a slight reduction. Therefore we concluded that the catalyst sites were not poisoned by un-reacted reagents.

Table 4. The results of recycled $H_{14}[NaP_5W_{30}O_{110}]$ in synthesis of 3H-1,5-benzodiazepine derivatives after five times of recovery in THF

Entry	R′	R	Yield%[a] (after five times of recycling)				
			First	second	third	fourth	fifth
1	H	CH_3	98	97	96	95.5	93.2
2	CH_3	CH_3	98	96.3	94.9	93.5	90.8
3	NO_2	CH_3	80	78.6	75.2	72.7	71.2
4	CH_3	CH_3	63	61.2	60.5	58.2	57.3
5	H	C_6H_5	59	58.2	57.5	55.8	53.4
6	CH_3	C_6H_5	65	63.6	62.2	60.6	59.3

[a] Yields were analyzed by GC.

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