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SHORT COMMUNICATION

HETEROPOLYACIDS IN SYNTHESIS OF BENZOYL HYDRAZONE DERIVATIVES

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ABSTRACT. Keggin type of heteropolyacids as green reusable and efficient catalyst was used in the synthesis of benzoyl hydrazones from reaction of benzoic acid hydrazide and aldehyde and ketone derivatives. The synthesis of N-acetyl and N-benzoyl derivatives has also been performed by the reaction of obtained benzoyl hydrazones with acylcholorides in presence of this kind of heteropolyacids.

KEY WORDS: Benzoyl hydrazone, Recyclable catalyst, Keggin, Heteropoly acid

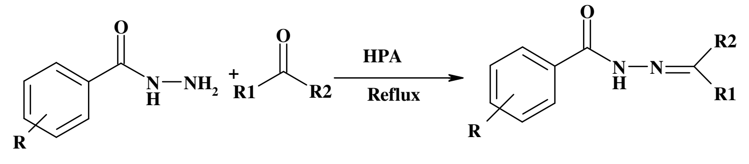
INTRODUCTION

It is well known that the hydrazone group plays an important role for the antimicrobial activity. Furthermore, a number of hydrazide-hydrazone derivatives have been claimed to possess interesting antibacterial, antifungal [1], anticonvulsant [2], antiinflammatory [3], antimalarial [4] and antituberculosis activities [5].

The application of heteropolyacids, HPAs, as catalytic materials is growing continuously in the catalytic field. These compounds possess unique properties such as: 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, easy work-up procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of these catalysts [6-10]. Because of their stronger acidity, they generally exhibit higher catalytic activity than conventional catalysts such as mineral acids, ion exchange resins, mixed oxides, zeolites, etc [11-13].

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 these acids [14, 15].

Herein we report synthesis of benzoyl hydrazone and N-acyl-benzoyl hydrazone derivatives in the presence of catalytic amounts of four Keggin type of heteropolyacids including, $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, and $H_3[PMo_{12}O_{40}]$ as the catalyst (Scheme 1, 2).



Scheme 1. Synthesis of benzoyl hydrazones.

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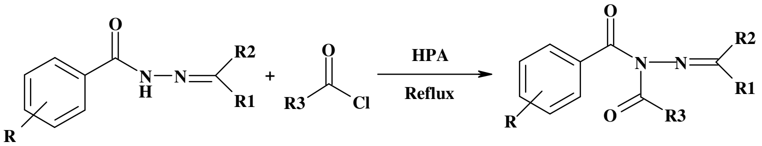


Scheme 2. Synthesis of N-acyl-benzoyl hydrazones.

EXPERIMENTAL

Chemicals and apparatus. All the chemicals were obtained from Merck Company (Germany) and used as received. Melting points were measured using Barnstead Electrothermal (Germany). Yields are based on GC/mass analysis using Agilent 6890 GC system Hp-5 (Germany) capillary 30 m × 530 µm × 1.5 µm nominal. Heteropolyacids were synthesized and characterized according to pervious works [16].

Typical procedure for synthesis of Keggins. For synthesis of $H_4[PMo_{11}VO_{40}]$ the following procedure was used: 18.0 g of $Na_2HPO_4.12H_2O$ was dissolved in 250 mL distilled water and 4.6 g of V_2O_5 was dissolved in 100 mL of 2 M Na_2CO_3 solution. Then, they were mixed and heated until boiling. Thirty minutes later, 400 mL solution containing 133.0 g of $Na_2MoO_4.2H_2O$ was added into the above solution, keeping the temperature at 90.8 ^{o}C for 30 min. Then, 1:1 H_2SO_4 was added (drop wise and with stirring) to the solution until pH 2. The mixture was cooled to room temperature under stirring, and 50 mL ether was added. After thorough shaking, 1:1 H_2SO_4 was added until three layers appeared in the solution. The middle oil-like red material was heteropolyacid-ether compound. This solution was separated and the ether was removed. Then, a suitable amount of distilled water was added and the product was kept in a vacuum desiccator for about 2 days. The resulting fine orange powders were characterized and used in the hydroxylation of benzene.

Synthesis of benzoyl hydrazone. To a mixture of benzoic acid hydrazide (10 mmol), and aldehyde or ketone derivatives (10 mmol), catalytic amount of Keggin type of heteropolyacids (0.03 mmol) was added and the mixture was refluxed in acetonitrile (10 mL). The progress of the reaction was monitored by TLC. After the end of reaction, the catalyst was filtered off and the products were recrystallized from ethanol-water 4:1 mixture.

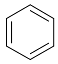
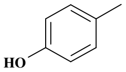
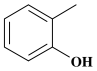
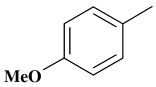
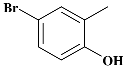
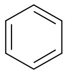
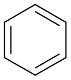
All products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples [17].

Synthesis of N-acyl-benzoyl hydrazone. Benzoyl hydrazone (10 mmol), acylcholoride (10 mmol) and catalytic amount of Keggin type of heteropolyacids (0.03 mmol) were mixed together and refluxed in appropriate acetonitrile (10 mL). The progress of the reaction was monitored by TLC. After the end of reaction, the catalyst was filtered off and the products were recrystallized from ethanol-water mixture.

All products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples [18].

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. Based on the previous reports heteropolyacids are not solvable in acetonitrile [16]. To assure that the catalyst did not solved in solvent the filtered catalysts were weighted before reusing. In Table 1 the comparison of efficiency of $H_6[PMo_9V_3O_{40}]$ in synthesis of benzoyl hydrazone after three times is reported. As it is shown in Table 1 the yields of reactions after using $H_6[PMo_9V_3O_{40}]$ for five times show slight reduction.

Table 1. The comparison of efficiency of $H_6[PMo_9V_3O_{40}]$ in synthesis of benzoyl hydrazone after three times.

Entry	R1	R2	R	Yield %^{a} (after different times of recycling)		
				First	second	third
1		H	H	93	90	88
2		H	H	91	88	85
3		H	H	90	88	85.6
4		H	H	88	86	84.7
5		H	H	90	88	84.5
6		H	Cl	90	87	85
7		Me	Cl	85	83	81
8	Me	Me	Cl	87	85	83

a) Yields refer to isolated products.

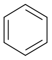
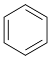
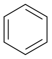
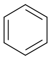
As heteropolyacids are acidic catalysts the proposed mechanism for this reaction can be activation of carbonyl group through coordination to catalyst. In the other word the heteropolyacid can catalyze the reaction by facilitation of nucleiofilic attack of amine group to carbonyl.

For studying the effect of catalyst type on this reaction, synthesis of two benzoyl hydrazone and N-acyl-benzoyl hydrazone derivatives were selected as model reactions and the yields of these reactions, using four Keggin, type of heteropolyacids including, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, $H_6[PMo_9V_3O_{40}]$ and $H_3[PMo_{12}O_{40}]$ were obtained. The results are reported in Table 2. The order of efficiency of these catalysts is as follow: $H_6[PMo_9V_3O_{40}] > H_5[PMo_{10}V_2O_{40}] > H_4[PMo_{11}VO_{40}] > H_3[PMo_{12}O_{40}]$.

This observation is in accord with our proposed mechanism, based on the previous works [16] the higher the number of hydrogen atoms, more acidic activity is expected.

$H_6[PMo_9V_3O_{40}]$ with the most hydrogen atoms is the most effective catalyst and $H_3[PMo_{12}O_{40}]$ with the least hydrogen atoms is the less effective catalyst for this reaction.

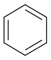
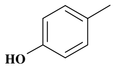
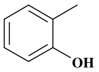
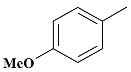
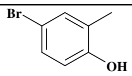
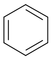
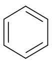
Table 2. Effect of various Keggin type of heteropolyacid (0.03 mmol) on yields of two benzoyl hydrazone and N- acyl-benzoyl hydrazone derivatives under refluxing in acetonitrile at 100 ^{0}C.

Entry	R1	R2	R3	R	Catalyst	Time (min)	Yield %^{a}
1		H	-	H	$H_6[PMo_9V_3O_{40}]$	15	93
2		H	-	H	$H_5[PMo_{10}V_2O_{40}]$	25	90
3		H	-	H	$H_4[PMo_{11}VO_{40}]$	25	88
4		H	-	H	$H_3[PMo_{12}O_{40}]$	30	87
5	Me	H	Me	Cl	$H_6[PMo_9V_3O_{40}]$	20	90
6	Me	H	Me	Cl	$H_5[PMo_{10}V_2O_{40}]$	30	88
7	Me	H	Me	Cl	$H_4[PMo_{11}VO_{40}]$	35	86
8	Me	H	Me	Cl	$H_3[PMo_{12}O_{40}]$	35	84

a) Yields refer to isolated products.

As it is shown in Table 2, $H_6[PMo_9V_3O_{40}]$ gave the best yields for this reactions and was selected as the catalyst of choice for synthesis benzoyl hydrazone derivatives. The results for synthesis of benzoyl hydrazone and N-acyl-benzoyl hydrazone, using $H_6[PMo_9V_3O_{40}]$ are summarized in Table 3 and 4, respectively.

Table 3. Synthesis of benzoyl hydrazone using 0.03 mmol $H_6[PMo_9V_3O_{40}]$ under refluxing in acetonitrile at 100 ^{0}C.

Entry	R1	R2	R	Time (min)	Yield %^{a}
1		H	H	15	93
2		H	H	15	91
3		H	H	20	90
4		H	H	20	88
5		H	H	25	90
6		H	Cl	30	90
7		Me	Cl	30	85
8	Me	Me	Cl	25	87

a)Yields refer to isolated products.

Table 4. Synthesis of N-acyl-benzoyl hydrazone using 0.03 mmol $H_6[PMo_9V_3O_{40}]$ under refluxing in acetonitrile at 100 ^{0}C.

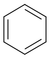
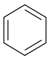
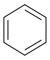
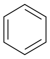
Entry	R1	R2	R3	R	Time (min)	Yield %^{a}
1	Me	H	Me	Cl	15	90
2	Ph	H	Me	Cl	20	85
3	Ph	Me	Me	Cl	20	83
4	Me	Me	Ph	Cl	20	85
5	Me	Me	Me	Cl	15	87

a) Yields refer to isolated products.

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 to show different reactivity.

With respect to the catalytic performances of these catalysts and the overall effects of all isomers, for synthesizing of them, we cannot control the reaction conditions to the synthesis of positional vanadium-substituted isomers separately, revealing the relationship between the structures of $H_{3+x}PMo_{12-x}VxO_{40}$ (x = 1, 2) 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 mentioned heteropoly acids 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 stabilize 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 [16]. The presence of vanadium atoms increase the acidic activity of heteropoly acids so $H_6[PMo_9V_3O_{40}]$ with three vanadium atoms is the most effective catalyst for this reaction. 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.

Table 5. The results of using different amount of $H_6[PMo_9V_3O_{40}]$ in synthesis of benzoyl hydrazone and N-acyl-benzoyl hydrazone derivatives under refluxing in acetonitrile at 100 ^{0}C.

Entry	R1	R2	R3	R	Catalyst amount (mol %)	Time (min)	Yield %^{a}
1		H	-	H	0.1	30	90
2		H	-	H	0.3	15	93
3		H	-	H	0.5	15	93
4		H	-	H	0.7	15	93.2
5	Me	H	Me	Cl	0.1	40	86
6	Me	H	Me	Cl	0.3	20	90
7	Me	H	Me	Cl	0.5	20	90
8	Me	H	Me	Cl	0.7	20	91

a) Yields refer to isolated products.

To optimize the amount of catalyst, the yields of reaction using various amounts of catalysts (0.1, 0.3, 0.5 mol %) were obtained. The results for synthesis of benzoyl hydrazone and N-acyl-benzoyl hydrazone derivatives using different amount of $H_6[PMo_9V_3O_{40}]$ are shown in Table 5. It is clear in this table that the yields of reactions in very small amount of catalysts are very high. Although there is no remarkable differences among various amounts of catalysts but it is obvious that in the presence of 0.1 mol % of catalyst the reaction time is longer than other amounts of catalysts so the optimum amount of catalyst was selected as 0.3 mol % for all derivatives.

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