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NEW AND GENERAL NITROGEN HETEROCYCLE SYNTHESIS: USE OF HETEROPOLY ACIDS AS A HETEROGENEOUS RECYCLABLE CATALYST

Rahim Hekmatshoar,[1] Sodeh Sadjadi,[1] Samaheh Sadjadi,[1] Majid M. Heravi,[1] Yahya S. Beheshtiha,[1] and Fatemeh F. Bamoharram[2]

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An efficient synthetic method of six- and five-member nitrogen heterocyclic compounds was developed. Nitrogen heterocyclic compounds were prepared by condensation of the β-dicarbonyl compounds with the corresponding β- or γ-amino alcohols, subsequent cyclization, and spontaneous aromatization in the presence of a catalytic amount of Keggin-type heteropoly acids under very mild conditions.

Keywords: Amino alcohols; bifunctional (acid and redox) catalyst; β-dicarbonyl compounds; Keggin-type heteropoly acid

INTRODUCTION

The biological activity of some pyrrole derivatives has prompted the development of new synthetic pathways for 4,5,6,7-tetrahydroindoles with various substitution patterns.[1] Different tetrahydroindoles are found in the structures of many biologically active compounds, such as antibiotics, antipsychotic agents,[2] and blood platelet aggregation inhibitors.[3] They can also be used as ligands for transition metals.[4] Various multistep synthetic procedures have been described in the literature, including reduction of indoles[5] or annulation reactions.[1]

Synthesis of the pyridine ring system and its derivatives[6] occupies an important place in the realm of natural and synthetic organic chemistry because of the therapeutic and pharmacological properties of these compounds. They have emerged as integral backbones of more than 7,000 existing drugs.[6,7] The pyridine ring is also an integral part of agrochemicals, preparative organic chemistry, and coordination chemistry. In addition to these important biological applications, pyridine derivatives are ideal scaffolds for making libraries of drug-like compounds and generating

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libraries of inhibitors of HIV-1 protease and factor Xa. Thus, the synthesis of these heterocycles is of current importance.[7]

The catalytic function of heteropoly compounds[8] (heteropoly acids and salts) has attracted much attention, and they are used in solution as well as in the solid state. Because of their weak superacidic and redox properties, low toxicity, ease of handling, low cost, stability, water tolerance, recoverability, and reusability, heteropoly compounds are useful as versatile catalysts in reactions requiring electrophilic catalysis.[9]

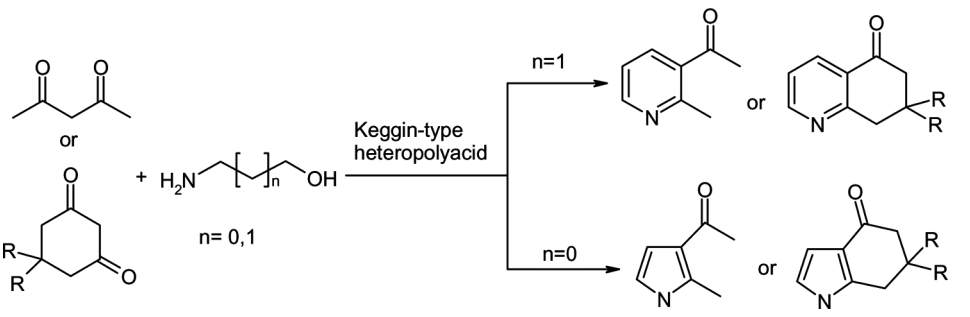
The successful applications of Keggin-type heteropoly acid as acid, redox, and bifunctional (acid and redox) catalyst for a wide variety of organic transformations prompted us to explore the potential of Keggin-type heteropoly acids as catalysts for a one-pot heterocyclocondensation process.

The present work was initiated to test the scope and practicality of a general approach to the syntheses of unsaturated nitrogen heterocyclic compounds envisioned as a cyclocondensation of amino alcohols and β-dicarbonyl compounds, using Keggin-type heteropoly acids as the catalyst, as shown in Scheme 1. From a synthetic point of view, the heteropoly acid is required for the aromatization of the heterocycle products.

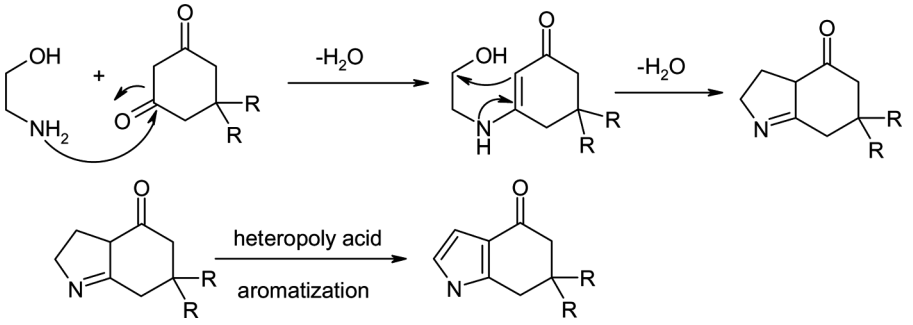
In previous papers,[9,10] the preparation of 4,5,6,7-tetrahydroindol-4-one derivatives by applying the Knorr pyrrole synthetic methodology to several 5-substituted-1,3-cyclohexanediones has been reported. For the synthesis of 2,3-unsubstituted tetrahydroindoles, a modification of the Knorr method reported by Bobbit et al.[11] was used, giving the desired compounds in poor yields.[9] The synthesis of pyrroles and indoles via palladium-catalyzed oxidation of hydroxyenaminones was reported by Ohta,[12] and this procedure was extended to the synthesis of potential central nervous system agents by Ravina.[7]

In this communication, we describe the alternative efficient synthesis of six-membered (tetrahydroquinolin-5-ones, pyridine) and five-membered (pyrrole and tetrahydroindol-4-ones) nitrogen heterocyclic compounds, which were prepared by condensation of the β-dicarbonyl compounds with the corresponding β- or γ-amino alcohols, and subsequent cyclization followed by spontaneous aromatization (Scheme 2).

Our first efforts were directed to the simple, fully aromatic, five-membered heterocycles.



Scheme 1. Nitrogen heterocycles synthesis.



Scheme 2. Plausible reaction mechanism.

To determine the optimum conditions for the reaction, similar reactions were conducted under different conditions, and the experimental results are shown in Table 1.

To determine the appropriate ratio of the reagents, the model reaction (reaction between cyclohexane-1,3-dione and 2-amino-ethanol) was carried out with different molar ratios of two reactants. First, 2 mmol of cyclohexane-1,3-dione, 1 mmol of 2-amino-ethanol, and 0.01 mmol of Keggin-type heteropoly acid ($H_3PW_{12}O_{40}$) were added to 15 mL of water, and the solution was then refluxed for 1 h; 24% of 1,5,6,7-tetrahydro-indol-4-one was observed (Table 1, entry 1). Although it is possible to increase the yield of 1,5,6,7-tetrahydro-indol-4-one by increasing the reaction time under similar conditions, mild reaction conditions would be highly desirable. Only traces of product were formed when the reaction was conducted at room temperature for 6 h in a water solution using cyclohexane-1,3-dione reagent (Table 1, entry 2). To increase the yield of 1,5,6,7-tetrahydro-indol-4-one, the reaction was carried out using a different solvent (tetrahydrofuran, THF) because of the low solubility of the starting material in water. When the THF solution was stirred at room temperature for 6 h, traces of 1,5,6,7-tetrahydro-indol-4-one were generated (Table 1, entry 3). However, when the volume of THF was decreased to 1 mL, the yield of 1,5,6,7-tetrahydro-indol-4-one was increased to 39% (Table 1,

Table 1. Reaction of cyclohexane-1,3-dione with 2-amino-ethanol in the presence of $H_3PW_{12}O_{40}$ under different conditions to generate 1,5,6,7-tetrahydro-indol-4-one

Entry	1,3-Dicarbonyl compound	Amino alcohol	Solvent (ml)	Reaction condition[a]	Product (%)
1	2	1	Water (15 ml)	Reflux, 1 h	24
2	2	1	Water (1 ml)	rt, 6 h	Trace
3	2	1	THF (10 ml)	rt, 6 h	Trace
4	2	1	THF (1 ml)	rt, 6 h	39
5	2	1	Solventless	rt, 6 h	47
6	1.5	1	Solventless	rt, 6 h	65
7	1	1	Solventless	rt, 6 h	84
8	1	1.5	Solventless	rt, 6 h	90
9	1	2	Solventless	rt, 6 h	79

[a]In all entries, 0.01 mmol $H_3PW_{12}O_{40}$ was added to the reaction solution.

entry 4). Comparing entry 4 to entry 3 (Table 1), an increase in the concentration of the reactants led to an efficient increase in the yield of 1,5,6,7-tetrahydro-indol-4-one. The same reaction was carried out under solventless conditions (Table 1, entry 5). The results indicate that solvent-free system was found to be the best choice for the reaction. Based on conditions used in entry 5 (Table 1), we were also surprised to find that changing the limiting reagent from 2-amino-ethanol to cyclohexane-1,3-dione also dramatically increases the yield of 1,5,6,7-tetrahydro-indol-4-one to 90% (Table 1, entry 8). Since heteropoly acids were also used as a catalyst in the reaction with carbonyl compounds, with excess amounts of 1,3-dicarbonyl compound as expected, 1,5,6,7-tetrahydro-indol-4-one and the aldol condensation product were observed in the solution.

Based on the results of Table 1, it appears that the experimental procedures and conditions shown for entry 8 are the best choices for other similar reactions, and all the experimental results shown in Table 2 were conducted under these conditions.

Turning our attention to six-membered heterocycles, we allowed β-dicarbonyl compounds to react with 3-amino-propan-1-ol under the optimized conditions to form the simple adduct (Table 2).

In our studies, we investigated the activity of various Keggin-type heteropoly acids. Representative results are shown in Table 3. The results indicate that the nature of the catalyst plays an important role on their catalytic activities. The greatest yield of products has been achieved in the presence of $H_5[PMo_{11}VO_{40}]$ as catalyst, and $H_3[PW_{12}O_{40}]$ gave the lowest yields.

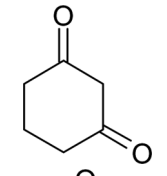
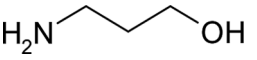
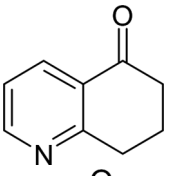
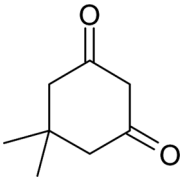
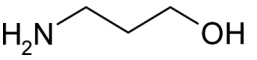
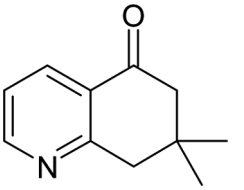
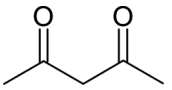
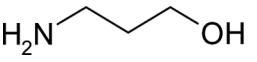
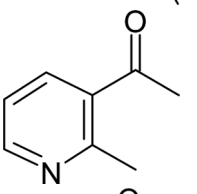
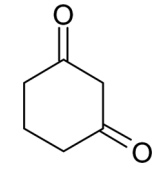
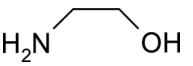
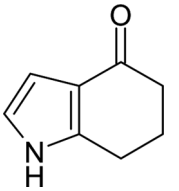
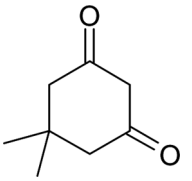
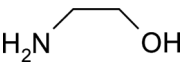
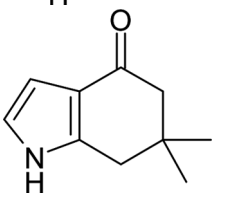
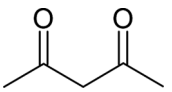
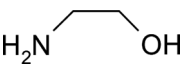
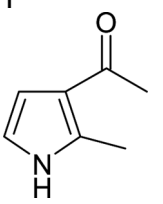
Because of the complicated nature of the reaction, it seemed rather difficult to make an exact assessment of the catalyst role. However, we may make some assumptions that agree with the experimental data and literature.

The Keggin anion has 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 the catalytic reaction.[13] Because the metal substitution may modify the energy and composition of the lowest unoccupied molecular orbital (LUMO) and redox properties, the energy and composition of the LUMOs have significant effects on the catalytic activity heteropoly acids with different charges.[14] 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.[15] 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.

By variation of the addenda atoms, the electrochemical character of them can be widely changed. The addenda atoms can be ordered by decreasing oxidizing ability in the following way: V(V) > Mo(VI) > W(VI).[16]

The liquid-phase oxidation of organic substances catalyzed by heteropoly acids is usually carried out in homogenous or biphasic systems. Heterogeneous liquid–solid systems are also used but less frequently. Among various oxidants that can be used in these reactions, oxygen (air) and hydrogen peroxide are the most important.[17]

Table 2. Reaction of 1,3-dicarbonyl compound with amino alcohol in the presence of Keggin-type heteropoly acid

Entry	1,3-Dicarbonyl compound	Amino alcohol	Product	Yield (%)
1				94
2				91
3				89
4				98
5				93
6				87

[a]Reaction conditions: Keggin-type heteropoly acids (0.01 mmol), 1,3-dicarbonyl compound (1 mmol), amino alcohol (1.5 mmol), solvent-free system, rt, 6 h.

In our previous papers, we reported the oxidation of tertiary amines and primary aromatic amines with aqueous hydrogen peroxide under the influence of heteropoly acid catalyst,[18] N-oxidation of pyridine carboxylic acids using hydrogen peroxide catalyzed by heteropoly anion,[19] and oxidation of benzylic, allylic, and aliphatic alcohols to carbonyl compounds.[20]

Table 3. Reaction of cyclohexane-1,3-dione with 2-amino-ethanol in the presence of heteropoly acids catalysts; effect of the type of heteropoly acids catalysts

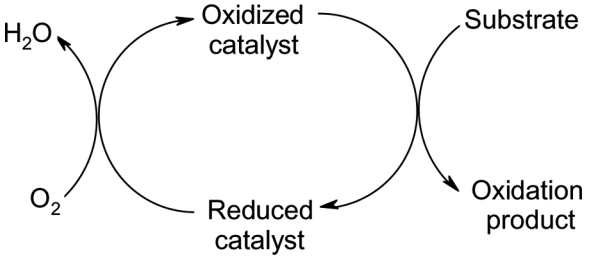
Entry	Heteropoly acids[a]	Product (%)[b]
1	$H_3[PW_{12}O_{40}]$	90
2	$H_3[PMo_{12}O_{40}]$	96
3	$H_5[PMo_{11}VO_{40}]$	98
4	$H_4[SiW_{12}O_{40}]$	93

[a]Reaction conditions: Keggin-type heteropoly acids (0.01 mmol), 1,3-dicarbonyl compound (1 mmol), amino alcohol (1.5 mmol), solvent-free system, rt, 6 h.
[b]Yields analyzed by gas chromatography.

Selective oxidation with mixed oxides and oxide-like catalysts such as heteropoly acids involves the activation of C−H or C−C bonds as well as that of the oxidant on the catalyst surface and frequently occurs by a Mars–van Krevelen redox mechanism,[17] which is shown in Scheme 3. The catalyst oxidizes the substrate and then, in another step, is reoxidized by O_2. The heteopoly acids maintained their Keggin structure in the course of the reactions, which were confirmed by examining their infrared (IR) spectra. Previous study indicated the reoxidation of the catalyst occurred without losing the Keggin structure.[19]

To know whether the catalyst would succumb to poisoning and loss of catalytic activity during the reaction, we investigate the reusability of the catalyst. For this purpose, we first carried out the reaction in the presence of the catalyst. After completion of the reaction, the catalyst was removed, washed with methanol, dried at 80 °C for 2 h, and subjected to a second run of the reaction process with the same substrate. The results of the first experiment and subsequent experiments were almost consistent in yields. We have found that Keggin catalyst can be reused several times without any appreciable loss of activity. The several recoveries only slightly decreased the catalytic activity, pointing to the stability and retention capability of this useful polyanion. In Table 4, the comparison of efficiency of the catalyst after five reuses is reported.

In summary, we describe a convenient and efficient protocol for the synthesis of six- and five-membered nitrogen heterocyclic compounds using heteropoly acid as a green, recyclable, and bifunctional (acid and redox) catalyst. The simple experimental procedure combined with ease of recovery and reuse of this catalyst make this procedure quite simple, more convenient, and environmentally benign.



Scheme 3. Mars–van Krevelen redox mechanism.

Table 4. Comparison of efficiency of catalysts after five reactions of cyclohexane-1,3-dione with 2-amino-ethanol in the presence of heteropoly acid catalysts

		Yield (%)[a]				
Entry	Heteropolyacid	First	Second	Third	Fourth	Fifth
1	$H_3[PW_{12}O_{40}]$	90	87	85	83	81
2	$H_3[PMo_{12}O_{40}]$	96	94	92	91	89
3	$H_5[PMo_{11}VO_{40}]$	98	95	94	92	91
4	$H_4[SiW_{12}O_{40}]$	93	91	91	88	85

Notes. Reaction conditions: Keggin-type heteropoly acids (0.01 mmol), 1,3-dicarbonyl compound (1 mmol), amino alcohol (1.5 mmol), solvent-free system, rt, 6 h.

[a]Yields were analyzed by gas chromatography.

EXPERIMENTAL

Chemicals and Apparatus

All the chemicals were obtained from Merck Company and used as received. Phosphotungstic acid and molybdophosphoric acid were purchased from Merck Company; $H_4[PMo_{11}VO_{40}]$ and $H_4[SiW_{12}O_{40}]$ were prepared according to the literature.[21,22]

Typical Procedure

A catalytic amount of Keggin-type heteropoly acid catalyst ($H_5[PMo_{11}VO_{40}]$) (1 mol%) was added to a mixture of β-dicarbonyl compounds (1 mmol) and amino alcohols (1.5 mmol), and the reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was diluted with chloroform and the catalyst was removed by simple filtration (the catalyst is not soluble in chloroform). The combined organic layer was dried over Na_2SO_4 and concentrated to dryness in vacuo, and the residue was purified by column chromatography (eluted with 2:8 EtOAc–petroleum ether) to afford the pure product.

The filtered catalyst was reactivated by heated at 80 °C for 2 h and reused at least five times. All products gave satisfactory spectral data in accord with the assigned structures.[7,23]

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