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Heteropoly acid in ionic liquid — An efficient and recyclable system for one-pot three-component Mannich reaction

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Abstract: This paper describes a one-pot three-component Mannich reaction, catalyzed by phosphotungstic acid ($H_3PW_{12}O_{40}$), a heteropoly acid in ionic liquid. The catalyst was found to be mild and efficient, and the protocol affords β-amino ketones in good yields under ambient conditions. Several ionic liquids and conventional organic solvents were employed for the reaction. The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) offered the best results in terms of yield of the products. It was observed that a homogeneous reaction medium proved beneficial for the yield of the reaction.

Key words: Mannich reaction, β-amino ketones, phosphotungstic acid, ionic liquid, recyclability.

Résumé : Dans ce travail on a réalisé une réaction de Mannich monotope à trois composants, catalysée par l'acide phosphotungstique ($H_3PW_{12}O_{40}$), un hétéropolyacide, dans un milieu ionique. On a trouvé que ce catalyseur est doux et efficace et que la méthode conduit à la formation de β-aminocétones avec de bons rendements, en opérant dans des conditions ambiantes. Pour réaliser cette réaction, on a utilisé plusieurs liquides ioniques ainsi que plusieurs solvants organiques conventionnels. Le liquide ionique du nom de tétrafluoroborate de 1-butyl-3-méthylimidazolium ([bmim]BF_4) est celui qui donne les meilleurs résultats en terme de rendement des produis. On a observé que le milieu réactionnel homogène s'avère utile pour le rendement de la réaction.

Mots-clés : réaction de Mannich, β-aminocétones, acide phosphotungstique, liquide ionique, possibilité de recycler.

[Traduit par la Rédaction]

Introduction

The Mannich reaction is very useful in the preparation of nitrogen-containing compounds (1–4). The reaction essentially proceeds via the condensation of an amine, an aldehyde, and a ketone to form β-amino carbonyl compounds. These compounds are very important biologically active molecules. Novel modifications of the Mannich reaction have been attempted by other researchers (5–10).[2] Some groups have reported the reaction of silyl enol ethers with imines in the presence of Lewis acids (11–13). Lanthanide triflates are quite attractive catalysts for Mannich reaction because of their high catalytic activity and low toxicity (14, 15). However, their high cost restricts their use. Other reports involve the use of HCl in H_2O–SDS and HBF_4 in organic solvent – H_2O systems (16, 17).

Recently, the research in the field of heterogeneous catalysis has experienced considerable growth. Heteropoly acids (HPAs) are polyoxometalate inorganic cage structures belonging to a promising class of solid acid catalysts. They may adopt the Keggin form (18) with the general formula $H_3MX_{12}O_{40}$, where M is the central atom and X is the heteroatom. Typically, M can be either phosphorous (P) or silicon (Si) and X can be tungsten (W) or molybdenum (Mo). HPAs have an enormous potential in catalyzing various types of synthetic organic transformations, which has not yet been fully realized. The low cost, availability, and environment-friendly nature make them suitable candidates for replacing

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[2] During the preparation of this manuscript, a one-pot three-component Mannich reaction, employing heteropoly acids in water, was reported; see ref. 10.

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hazardous and expensive catalysts. HPAs are Brönsted acids, composed of heteropoly anions, with protons as the counter cations. They are more efficient than many conventional solid acid catalysts, such as mixed oxides, zeolites, and so forth. Some reactions, e.g., Friedel–Crafts acylation (19) and Fries rearrangement (20), are catalyzed by HPAs. The HPA catalysts are easily separated from the reaction mixture and recycled. The chemistry and general physical properties of these catalysts have been extensively discussed in a number of review articles (21, 22).

In the past decade, a new approach has been adopted for catalyst separation and recycling in catalytic reactions involving the use of room-temperature ionic liquids, especially those based upon 1-*n*-alkyl imidazolium cation. Ionic liquids, also called “the designer solvents”, have been largely successful in replacing obnoxious organic solvents. Their high thermal stability and ability to solvate various substrates have made them highly useful in a variety of organic reactions (23, 24). Amongst other reports, an asymmetric version of the Mannich reaction, employing L-proline in ionic liquids, demonstrated by Barbas et al. (25) is worth mentioning (26–28). For the past few years, our group has been actively involved in exploring the field of ionic liquids (29–31) and has investigated various aspects of the different reactions using ionic liquid as solvents.

Realizing the growing significance of the use of heterogeneous solid acids as recyclable catalysts in organic synthesis, we describe here, for the first time, the use of a heteropoly acid in conjunction with an ionic liquid for a one-pot three-component Mannich reaction (Scheme 1). Our technique combines and maximizes the individual advantages of using heteropoly acids and ionic liquids in organic syntheses while satisfying the basic principles of green chemistry.

Results and discussion

Because it is more efficient to perform a direct Mannich reaction, which eliminates a separate step for imine preparation prior to the reaction, a one-pot reaction between benzaldehyde, *p*-anisidine, and acetone with heteropoly acid as the catalyst was carried out as a prototype. Initially, we chose a hydrophilic ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) for the reaction. A simple procedure was used to carry out the Mannich reaction, wherein all the substrates, namely, an amine (1 mmol), HPA, an aldehyde (1 mmol), and a ketone (in excess) were mixed with the ionic liquid, respectively. To begin with, we decided to screen various heteropoly acids for the model reaction. We employed three different heteropoly acids, namely, phosphotungstic acid ($H_3PW_{12}O_{40}$) (PW_{12}), tungstosilicic acid ($H_4SiW_{12}O_{40}$) (SiW_{12}), and phosphomolybdic acid ($H_3PMo_{12}O_{40}$) (PMo_{12}) for the reaction. All the HPAs completely dissolved in the ionic liquid. 5 mol% of each of these HPAs were used. The reaction mixture was stirred at room temperature.

The reaction furnished the product 4-(4-methoxyphenylamino)-4-phenylbutan-2-one. However, it was observed that the substrates completely disappeared after 18 h only with PW_{12}. In case of other heteropoly acids, TLC showed the presence of *p*-anisidine even after prolonged reaction times.

Scheme 1. One-pot three-component Mannich reaction catalyzed by a heteropoly acid.

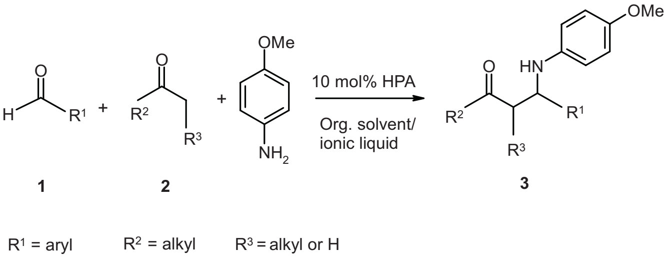


Table 1. Comparison of different heteropoly acids (HPAs) employed for Mannich reaction between *p*-anisidine, benzaldehyde, and acetone in [bmim]BF_4 at room temperature.

Heteropoly acid[a]	Time (h)	Yield[b] (%)
$H_3PW_{12}O_{40}$	18	70
$H_4SiW_{12}O_{40}$	18	61
$H_3PMo_{12}O_{40}$	18	45

[a] 5 mol% of the HPA was used.
[b] Isolated yields.

These HPAs vary in their acidity, and hence, it was expected that this would affect the outcome of the reaction in terms of the yield. Studies have proven that PW_{12} is the strongest and most active heteropoly acid (32). It was observed that the yield of the reaction was directly related to the acid strength of the catalyst, as the yield for the various catalysts decreased in the order of PW_{12} > SiW_{12} > PMo_{12}. Hence, the best yield of the product of the reaction, i.e., 4-(4-methoxyphenylamino)-4-phenylbutan-2-one (70%), was obtained in 18 h with the strongest of the three heteropoly acids, i.e., phosphotungstic acid (PW_{12}). Considering PW_{12} as the superior heteropoly acid for the present study, we employed it in further investigations. The results are presented in Table 1.

The amount of catalyst was optimized to improve the yields. The yield was quite low (~40%) when phosphotungstic acid was used in low concentrations (1 mol%). Marked improvement in yields (88%) and reduced reaction times (12 h) were observed when the catalyst loading was increased to 10 mol%.

We carried out the reaction in various other hydrophilic as well as hydrophobic ionic liquids and conventional organic solvents to compare the outcome of the reaction in terms of the yield and the rate of the reaction. HPA dissolved in organic solvents like DMSO, DMF, and acetonitrile and hydrophilic ionic liquids, such as 1-butyl-3-methylimidazolium chloride ([bmim]Cl) and 1-methoxyethyl-3-methylimidazolium methanesulphonate ([moemim]OMs), to produce a homogenous system. However, HPA was insoluble in hydrophobic ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) and 1-hexyl-3-methylimidazolium tetrafluoroborate ([hmim]BF_4), and solvents like toluene. Better yields were obtained when the catalyst was soluble in the reaction medium compared with those obtained when the catalyst was insoluble in the reaction solvent. From these observations, it can be deduced that the solubility of the catalyst in the medium plays an important

Table 2. Phosphotungstic acid (PW_{12}) catalyzed Mannich reaction involving *p*-anisidine, benzaldehyde, and acetone in various solvents.

Entry	Solvent	Time (h)	Yield[a] (%)
1	[bmim]BF_4	12	88
2	[bmim]PF_6	12	62
3	[hmim]BF_4	12	64
4	[bmim]Cl	13	80
5	[moemim]OMs	15	80
6	DMSO	14	83
7	DMF	15	65
8	Acetonitrile	15	60
9	Toluene	15	51
10	Dichloromethane	15	55

Note: 10 mol% of PW_{12} was used.
[a] Isolated yields.

role in enhancing the outcome of the reaction and that a homogeneous system produces better yields.

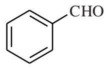
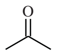
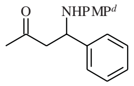
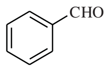
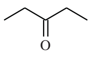
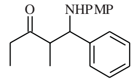
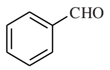
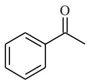
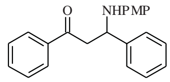
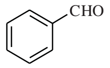
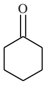
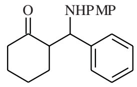
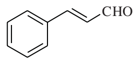
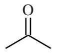
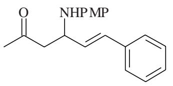
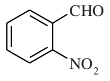
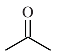
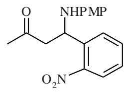
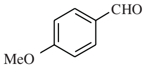
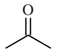
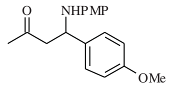
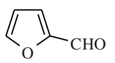
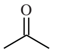
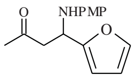
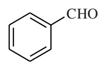
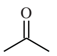
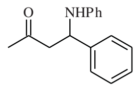
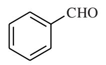
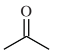
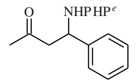
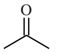
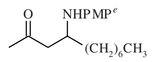
Amongst the various ionic liquids and organic solvents that were employed for the present study (see Table 2), the use of [bmim]BF_4 and DMSO resulted in good yields. The rate of the reaction was only slightly better in case of [bmim]BF_4 compared with DMSO. However, DMSO is highly obnoxious and has a detrimental effect on the environment. Hence, taking into account the various environmental constraints, [bmim]BF_4 was employed for further investigation.

Having ascertained the efficiency of the protocol for the model reaction between *p*-anisidine, acetone, and benzaldehyde, we next turned our attention to its synthetic utility in [bmim]BF_4 (Table 3). All the reactions were stirred for 24 h. At first, we decided to employ various aromatic aldehydes (**1**), keeping the ketone (**2**) and the amine moieties constant. Substituted benzaldehydes with electron-withdrawing or electron-donating groups (Table 3, entries 6 and 7) responded well to the reaction conditions, as the corresponding β-amino ketones (**3**) were obtained in 77% and 80% yield, respectively. A heteroaromatic aldehyde, namely, furfuraldehyde, was also chosen as a substrate, and it furnished the product in 72% yield (Table 3, entry 8). On the other hand, cinnamaldehyde, as an α,β-unsaturated aldehyde, gave comparatively lower yield (Table 3, entry 5).

Likewise, we altered the ketone moiety. Aliphatic ketones, such as 3-pentanone and cyclohexanone, and aromatic ketones, such as acetophenone, were selected. 3-Pentanone (Table 3, entry 2) gave better results than cyclohexanone (Table 3, entry 4). On the other hand, acetophenone (Table 3, entry 3) gave a moderate yield. Ketones were taken in excess to avert the formation of bis-Mannich product. Further, we chose two different amines, namely, aniline and *p*-amino phenol. The results were quite similar to those obtained with *p*-anisidine, albeit the yields were slightly lower. To examine the applicability of the protocol to aliphatic aldehydes, we decided to synthesize Mannich base taking *n*-octanal (Table 3, entry 11). However, the reaction yield was very low. The results are presented in Table 3.

The combination of the heteropoly acid and [bmim]BF_4 provides a homogeneous system for the reaction; hence, this prompted us to investigate the possibility of recycling the complete system of HPA and ionic liquid. The result was quite fruitful. The entire product could be isolated from the reaction mixture simply by ether extraction, and the system of the catalyst and the ionic liquid could be recovered and recharged with fresh substrates. We screened the system for two subsequent runs; the product was obtained in 83% and 75% yields, respectively.

Table 3. Synthesis of various β-amino ketones via the Mannich reaction, using phosphotungstic acid and employing different aldehydes, ketones, and amines in [bmim]BF_4.

Entry	Aldehyde **1**	Ketone **2**	Product[a] **3**	Yield[b] (%)
1				88
2				78[c]
3				65
4				73[c]
5				56
6				77
7				80
8				72
9				73
10				75
11	$CH_3(CH_2)_6CHO$			23

[a] Representative spectral data of some Mannich bases are given in the experimental section.
[b] Isolated yields.
[c] A *syn*:*anti* ratio of 42:58 for entry 2 and 35:65 for entry 4 was obtained and confirmed by ^{1}H NMR spectroscopic analysis of the crude product.
[d] PMP is *p*-methoxy phenyl.
[e] PHP is *p*-hydroxy phenyl.

Conclusion

We have demonstrated an efficient one-pot methodology for the Mannich reaction using a combination of heteropoly acid and ionic liquid in the syntheses of β-amino carbonyl compounds. Both the catalyst and the ionic liquid could be easily recovered and recycled. The absence of undesirable side-products and ambient reaction conditions also enhanced the synthetic utility of the reaction.

Experimental

General procedure for Mannich reaction

To a mixture of the ionic liquid (2 mL) and phosphotungstic acid (0.1 mmol), an amine (1 mmol) and an aldehyde (1 mmol) were added. This was followed by the addition of a ketone (10 mmol). The resulting mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. The crude product was isolated by extracting the reaction mixture with diethyl ether (4 × 15 mL). The combined ether extractions were dried over Na_2SO_4, concentrated, and purified by CC to obtain the desired β-amino ketones, which were characterized by IR and ^{1}H NMR spectroscopy.

4-(4-methoxyphenylamino)-4-(phenyl)butan-2-one (Table 3, entry 1)

IR ν_{max} (cm^{-1}): 3385, 2899, 1710, 1515, 1033. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (s, 1H, N*H*), 2.17 (s, 3H), 3.31–3.59 (m, 2H), 3.68 (s, 3H), 4.91–4.94 (m, 1H), 6.51 (d, *J* = 8 Hz, 2H), 6.70 (d, *J* = 8 Hz, 2H), 7.33 (t, *J* = 6 Hz, 2H), 7.56 (t, *J* = 6 Hz, 1H), 7.9 (d, *J* = 6 Hz, 2H).

1-(4-methoxyphenylamino)-1-phenyl-2-methylpentan-3-one (Table 3, entry 2)

IR ν_{max} (cm^{-1}): 3394, 2939, 1705, 1518, 1251, 1035. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, *J* = 6 Hz, 3H, CH_3), 1.14 (d, *J* = 6 Hz, 3H, CH_3), 2.24 (q, *J* = 3 Hz, 2H, CH_2), 3.01–3.31 (m, 1H), 3.67 (s, 3H), 4.03 (s, 1H, N*H*), 4.21 (d, 1H, C*H*NH), 6.46 (d, *J* = 8 Hz, 2H), 6.67 (d, *J* = 8 Hz, 2H), 7.25–7.45 (m, 5H).

3-(4-methoxyphenylamino)-1,3-diphenyl-1-propanone (Table 3, entry 3)

IR ν_{max} (cm^{-1}): 3399, 2974, 1672, 1598, 1515, 1295, 1221, 1080, 1026. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.41 (d, 2H), 3.65 (s, 3H), 4.93 (m, 1H), 6.48 (d, 2H), 6.51 (d, *J* = 8 Hz, 2H), 6.70 (d, *J* = 8 Hz, 2H), 7.01–7.24 (m, 3H), 7.21–7.38 (m, 5H).

General procedure for the recyclability of the system of the ionic liquid and heteropoly acids

The system containing the ionic liquid and the catalyst was regenerated from the total reaction mixture by consecutive extractions with diethyl ether, and then it was recharged with the amine, aldehyde, and ketone to carry out the next set of reactions. Then, a similar procedure as the previously mentioned was followed.

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