

# Highly Efficient One-Pot Three-Component Mannich Reaction in Water Catalyzed by Heteropoly Acids

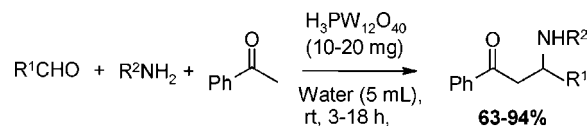
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## ABSTRACT



Heteropoly acids efficiently catalyzed the one-pot, three-component Mannich reaction of ketones with aromatic aldehydes and different amines in water at ambient temperature and afforded the corresponding  $\beta$ -amino carbonyl compounds in good to excellent yields and with moderate diastereoselectivity. This method provides a novel and improved modification of the three-component Mannich reaction in terms of mild reaction conditions and clean reaction profiles, using very a small quantity of catalyst and a simple workup procedure.

Carrying out organic reactions in water has become highly desirable in recent years to meet environmental considerations.<sup>1</sup> The use of water as a sole medium for organic reactions would greatly contribute to the development of environmentally friendly processes. Indeed, industry prefers to use water as a solvent rather than toxic organic solvents. In this context, in recent years, much attention has been focused on Lewis acid catalyzed organic reactions in water.

Heteropoly acids (HPAs) are environmentally benign and economically feasible solid catalysts that offer several advantages.<sup>2</sup> Therefore, organic reactions that exploit heteropoly acid catalysts in water could prove ideal for industrial synthetic organic chemistry applications, provided that the catalysts show high catalytic activity in water.

Mannich reactions are among the most important carbon–carbon bond forming reactions in organic synthesis.<sup>3</sup> They

provide  $\beta$ -amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals and natural products.<sup>4</sup> The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen-containing compounds in drugs and natural products.<sup>5</sup>

However, the classical Mannich reaction is plagued by a number of serious disadvantages and has limited applications. Therefore, numerous modern versions of the Mannich reaction have been developed to overcome the drawbacks of the classical method. In general, the improved methodology relies on the two-component system using preformed electrophiles, such as imines, and stable nucleophiles, such as enolates, enol ethers, and enamines.<sup>6</sup> But the preferable route is the use of a one-pot three-component strategy that allows for a wide range of structural variations. In this context, recent developments of asymmetric synthesis, using

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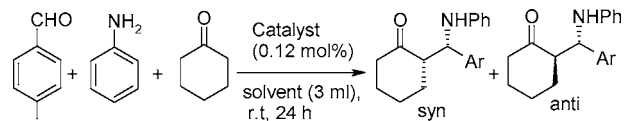
a three-component protocol, have made the Mannich reaction very valuable.<sup>7</sup> However, despite the diverse synthetic routes so far developed for the asymmetric Mannich reaction, only a few one-pot procedures on the use of unmodified aldehydes or ketones in water have been reported in the literature. Furthermore, most of the reported Mannich reactions in water have been carried out in the presence of surfactants such as SDS. Unfortunately, normal-phase separation is difficult during workup due to the formation of emulsions because of the SDS.<sup>8</sup>

There is increasing interest in developing environmentally benign reactions and atom-economic catalytic processes that employ unmodified ketones, amines, and aldehydes for Mannich-type reaction in recent years. In continuation of our studies on the new variants, of one-pot, three-component Mannich-type reactions for aminoalkylation of aldehydes with different nucleophiles,<sup>9</sup> and our ongoing green organic chemistry program that uses water as a reaction medium, performs organic transformations under solvent-free conditions,<sup>10</sup> herein we describe a mild, convenient, and simple procedure for effecting the one-pot, three-component reaction of an aldehyde, an amine, and a ketone for the preparation of  $\beta$ -amino carbonyl compounds in water using a heteropoly acid catalyst.

Initially, the three-component Mannich reaction of 4-chlorobenzaldehyde (3.0 mmol), aniline (3.1 mmol), and the cyclohexanone (5 mmol) was examined (Scheme 1).

As a preliminary study, several Lewis acids and solvents were screened in the model reaction. The results of extensive Lewis acid and solvent screening and optimization are shown

**Scheme 1.** Direct Mannich Reaction Catalyzed by Heteropoly Acids in Different Solvents



in a table in the Supporting Information. Heteropoly acids (HPAs) catalyze Mannich reactions in organic solvents such as acetonitrile, 1,2-dichloroethane, methanol, ethanol, toluene and mixtures of toluene/water and gave the desired products in low yield with the formation of aldol side products. Among the screened solvent systems, water was the solvent of choice, since in this solvent the Mannich-type reactions proceeded smoothly and afforded the desired adducts in high yields at room temperature. Consequently, we conclude that the HPAs are much more reactive in water than in other organic solvents. At room temperature, the Mannich reaction proceeded to completion affording the Mannich adduct in good to excellent yield and relatively good diastereoselectivity. Addition of surfactants such as sodium dodecyl sulfate (SDS) or cetyltrimethylammonium bromide (CTAB) was not effective, and they did not improve diastereoselectivity. The reaction in pure water without using any catalyst gave a low yield of the product. Furthermore, we were excited to find that only 0.12 mol % of the catalyst gave good yields at room temperature. In the some cases, even 0.06 mol % of HPA was sufficient for the completion of the reaction. Furthermore, simple workup in water opened the route for an entirely green highly efficient one-pot Mannich reaction in water. In addition,  $H_3PMO_{12}O_{40}$  has been compared with  $H_3PW_{12}O_{40}$ , and we found the same results for both heteropoly acids in this reaction in water.

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we used various aldehydes and amines and the results. Table 2 clearly demonstrates that HPAs are excellent catalysts for Mannich reactions in water. Thus, a variety of aromatic aldehydes, including electron-withdrawing and electron-donating groups, were tested using our new method in water in the presence of  $H_3PW_{12}O_{40}$  or  $H_3PMO_{12}O_{40}$ . The results are shown in Table 2. Generally, excellent yields of  $\alpha$ -amino ketones were obtained for a variety of aldehydes including those bearing an electron-withdrawing group. Furthermore, several electron-rich aromatic aldehydes led to the desired products in good yield. However, under the same reaction conditions aliphatic aldehydes, such as isobutyraldehyde, gave a mixture, due to enamine formation; the desired product was obtained in low yield (Table 2, entry 22). The scope of our method was extended to other amines. In the case of amines having an electron-donating group, such as 4-isopropylaniline, the corresponding amino ketones were obtained in good yields. Furthermore, amines with electron-withdrawing groups, such as 4-chloroaniline and 3,4-dichloroaniline, gave the desired product in good yields.

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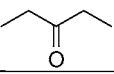

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The high yield, simple reaction protocol, and originality of this novel process prompted us to use other ketones under these conditions (Table 1). Thus, the three-component

**Table 1.** HPA-Catalyzed Three-Component Mannich Reaction<sup>a</sup>

entry	aldehyde (R <sup>1</sup> )	amines (R <sup>2</sup> )	yields (%) <sup>b</sup>	
				
1	Ph	Ph	70 (48:52) <sup>c,d</sup>	76
2	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	68 (45:55)	68
3	4-BrC <sub>6</sub> H <sub>4</sub>	Ph	72 (48:52)	74
4	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	68 (45:55)	80
5	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	63 (44:56)	64
6	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	80 (50:50)	82
7	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	78 (48:52)	78
8	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	75 (49:51)	74

<sup>a</sup> Reaction conditions: aldehyde (3 mmol), amine (3.1 mmol), 2-butanone (5 mmol), acetophenone (3 mmol), and H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> (0.02 g). <sup>b</sup> Yield of isolated products. <sup>c</sup> Syn/anti ratio. <sup>d</sup> Syn/anti ratio was determined by <sup>1</sup>H NMR analysis of crude products.

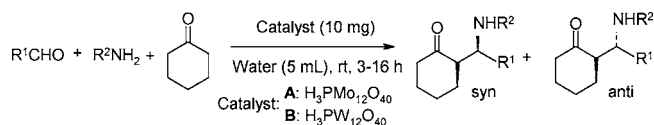
coupling reactions were carried out with acyclic ketones such as 2-butanone and acetophenone. The expected products were obtained in moderate yields under these conditions. Acyclic ketones were less reactive than cyclohexanone and needed much more catalyst to afford the desired products (Table 1).

The regioselectivity was determined by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and by comparison with known compounds reported in the literature.<sup>8</sup> In general, anti selectivity was observed in the reaction of cyclohexanone and 2-butanone.

Despite of the low solubility of aldehydes, ketones, and amines in water, the heteropoly acid-catalyzed Mannich reactions still proceed efficiently at ambient temperature. The reaction might take place at the interface of organic materials with water in the heterogeneous system. It was found that vigorous stirring was required for the success of these reactions.

The possibility of recycling the catalyst was examined. For this reason, the reaction of 4-chlorobenzaldehyde, aniline and cyclohexanone in water at room temperature in the presence of H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> was studied. When the reaction was complete, ethyl acetate was added and organic materials were extracted and the aqueous solution was saved for the next reaction. When the same reaction was carried out in this solution, containing the used catalyst, low yields (ca. 60%) of the product were obtained.

**Table 2.** One-Pot, Three-Component Direct Mannich Reaction<sup>a</sup>

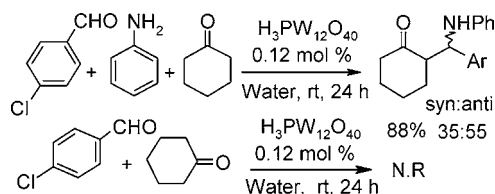


entry	R <sup>1</sup>	R <sup>2</sup>	catalyst	anti/syn <sup>b</sup>	yields <sup>c</sup> (%)
1	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	A	63:37	81
2	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	B	62:38	80
3	Ph	Ph	A	63:37	84
4	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	B	64:35	80
5	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	A	64:36	84
6	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	B	65:35	83
7	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	B	47:53	95
8	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	A	46:54	95
9	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	B	58:42	90
10	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	A	55:45	94
11	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	B	56:44	90
12	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	A	57:43	88
13	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	B	41:59	80
14	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	A	39:61	93
15	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	B	66:34	80
16	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Ph	B	68:32	83
17	2-MeOC <sub>6</sub> H <sub>4</sub>	Ph	B	65:33	60
18	4-MeOC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	B	54:46	70
19	4-OMeC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	B	50:50	72
20	4-MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	Ph	B	72:28	88
21	4-ClC <sub>6</sub> H <sub>4</sub>	4-(i-Pr)C <sub>6</sub> H <sub>4</sub>	B	62:38	80
22	(CH <sub>3</sub> ) <sub>2</sub> CH	Ph	B	-	25
23	2-naphthyl	4-ClC <sub>6</sub> H <sub>4</sub>	B	43:57	85
24	2-thienyl	4-ClC <sub>6</sub> H <sub>4</sub>	B	62:38	87

<sup>a</sup> Reaction conditions: aldehyde (3 mmol), amine (3.1 mmol), and cyclohexanone (5 mmol) were successively added to a solution of catalyst (10 mg) in water (5 mL) placed in a test tube, and the reaction mixture was vigorously stirred at room temperature for 3–16 h. <sup>b</sup> Yields of isolated products. <sup>c</sup> Diastereomeric ratio measured by <sup>1</sup>H NMR spectroscopy analysis of the crude reaction mixture.

Another characteristic feature of the present protocol is the high chemoselectivity of cyclohexanone toward aldimines, prepared in situ from the reaction of aldehydes and amines, in preference to aldehydes as shown in Scheme 2.

**Scheme 2.** Aldole and Mannich Reaction in Water



Although conventional Lewis acids activate aldehydes preferentially, in this media, aldehydes do not undergo aldol reaction by means of HPAs in water. The high chemoselectivity is rationalized by considering the higher basicity of nitrogen over oxygen. A related phenomenon was recently reported in the reactivity between aldimines and aldehydes by the use of proline, HBF<sub>4</sub>, and dibutyltin dimethoxide.<sup>11</sup>

In conclusion, this procedure offers several advantages including low loading of catalyst, improved yields, clean reaction, use of unmodified ketones, which make it a useful and attractive strategy for the multicomponent reactions of combinational chemistry. In addition, a very easy workup has been realized that does not require organic solvents. When the products are solid and insoluble in water, the pure products can be obtained directly by filtration and washing the filtrate with water and by crystallization from ethanol or diethyl ether. No extraction or separation by column chromatography is necessary in some cases. Current efforts in

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our research group are attempting to expand the application of heteropoly acids in water for other reactions.

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**Supporting Information Available:** General experimental procedure and copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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