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Aluminium Dodecatungstophosphate ($AlPW_{12}O_{40}$)—An Efficient Catalyst for Three-Component *Mannich* Reaction in Water[1]

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Abstract—One-pot, three-component *Mannich* reactions of ketones, aldehydes and amines were efficiently catalyzed by $AlPW_{12}O_{40}$ in water at ambient temperature to give the corresponding β-amino ketones in good to excellent yields. The method has the following merits: Firstly, Catalyst $AlPW_{12}O_{40}$ is non-corrosive and environmentally benign; Secondly, loading amount of catalyst is very low, less than 1 mol %; Thirdly, water as solvent is green and safe.

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Organic reactions in water are a hot study field in recent years because water used as reaction medium has several advantages [1–3]. Firstly, in comparison with organic solvent often used in organic chemical reaction, water is a green and safe solvent. Risk in production process greatly decreases; Secondly, water's unique physical and chemical properties lead to unique reactivity and selectivity of organic reaction in water, which cannot be attained in organic solvents; Thirdly, water is cheap and organic reactions in water do not require to use expensive anhydrous reactants and reagents. So, the cost of product evidently decreases. Finally, the operation after reaction is simple. The organic product which is insoluble in water can be separated from water by simple filtration or separatory funnel.

Mannich reaction is one of the most important multicomponent carbon–carbon bond-forming reactions in organic synthesis and one of the most fundamental and classical routes to prepare (β-amino ketones and their derivatives, which are versatile synthetic intermediates for various pharmaceuticals, natural products and biologically active compounds [4, 5]. The ubiquitous nature of nitrogen-containing compounds including proteins, nucleic acids and most biologically active compounds arouses an increasing interest in *Mannich* reaction. *Mannich* reaction can happen using either two-component system or three-component system. However, the preferable route is one-pot three-component *Mannich* reaction of ketone, aldehyde, and amine. Up to now, many protocols for three-component *Mannich* reaction have been reported in open literatures [6–9]. Various catalysts including Lewis acids [10], Lewis bases [11], Brønsted acids [12, 13], rare metal salts [14], and organic small molecules have been used to promote the *Mannich* reaction [15]. However, most of these are plagued by several evident drawbacks, for example toxicity, corrosivity, expensive catalysts or using organic solvents. Hence, there is high interest in pursuing an efficient, green method for *Mannich* reaction.

Heteropoly acids and its salts as highly active and environmentally benign solid acids have been used to catalyze many organic reations such as esterifications [16–18], Friedel–Crafts [19, 20] and Diels–Alder reactions [21]. *Mannich* reaction catalyzed by heteropoly acids have been also covered in several literatures [22–24]. $AlPW_{12}O_{40}$ as a water stable, highly active non-corrosive and environmentally benign salt have been used to catalyze several organic reactions [25–27], while *Mannich* reaction catalyzed by $AlPW_{12}O_{40}$ is not reported in open literatures so far. In this paper, we describe that one-pot three-component *Mannich* reactions of ketones, aldehydes and amines in water at room temperature were efficiently catalyzed by $AlPW_{12}O_{40}$ to give the corresponding β-amino ketones in good to excellent yields.

EXPERIMENTAL

Materials and Methods

All the chemicals and reagents used were of analytical grade and were used without further purification. The structure and syn/anti ratio of products were determined by IR, ^{1}H NMR. IR spectra were recorded on a Bruker AM-400 spectrometer using KBr discs.

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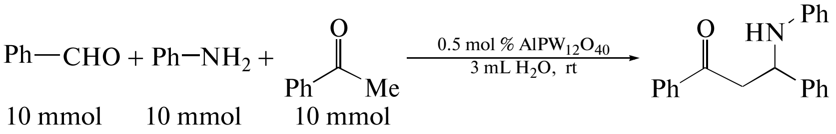
[1] The article is published in the original.

Table 1. Direct three-component *Mannich* reaction catalyzed by different metal salts in water



Entry	Catalyst	Amount of Cat, mol %	Time, h	Yield, %
1	$AlCl_3$	10	24	0
2	$Al_2(SO_4)_3$	10	24	0
3	$Al(SO_3CH_3)_3$	5	24	24
4	$Al(SO_3C_6H_4CH_3\text{-}p)_3$	5	24	63
5	$AlPW_{12}O_{40}$	0.5	16	93
6	$Na_3PW_{12}O_{40}$	2	24	0
7	$Mg_3(PW_{12}O_{40})_2$	5	24	21
8	$Zn_3(PW_{12}O_{40})_2$	5	24	72
9	$LnPW_{12}O_{40}$	5	24	86

^1H NMR spectra were obtained from solution in $CDCl_3$ with TMS as internal standard using a Varian Scimitar Series 800 (400 MHz) spectrometer. Melting points were determined in open capillaries.

General Procedure for Mannich Reaction Catalyzed by $AlPW_{12}O_{40}$ in Water

Aldehyde (10 mmol), amine (10 mmol) and ketone (10 mmol) were added to a solution of $AlPW_{12}O_{40}$ in water (3 mL) placed in a 50 mL one-necked round-bottom flask. Then, the reaction mixture was stirred (500 rts/min) vigorously with a magnetic stirrer at ambient temperature for the mentioned time. After reaction completion, the crude mixture was either purified by silica gel chromatography (ethyl acetate/petroleum ether mixtures) or recrystallization from ethanol or ethanol-acetone (v/v = 1 : 1) to afford the corresponding compound.

RESULTS AND DISCUSSION

Catalytic Activities of Various Metal Salts in Esterification

Initially, we selected *Mannich* reaction of an equimolar amount of benzaldehyde, aniline, and acetophenone as a model reaction to screen catalysis activities of various usual metal salts for one-pot three-component *Mannich* reaction in water at room temperature. As shown in Table 1, among these catalysts used, $AlPW_{12}O_{40}$ was the most efficient catalyst for the *Mannich* reaction in water at ambient temperature. Only 0.5 mol % of $AlPW_{12}O_{40}$ was enough to efficiently catalyze *Mannich* reaction in an excellent yield 93% (entry 5). Comparatively, other aluminum salts ($AlCl_3$ and $Al_2(SO_4)_3$) had not catalysis towards *Mannich* reaction in water (entries 1, 2). $Al(SO_3CH_3)_3$ and $Al(SO_3C_6H_4CH_3\text{-}p)_3$ could catalyze *Mannich* reaction under the same condition (entries 3, 4), but they were much inferior to $AlPW_{12}O_{40}$. Other phosphotungstate salts were also used to catalyze the model *Mannich* reaction under the same condition, activity of $Mg_3(PW_{12}O_{40})_2$ and $Na_3PW_{12}O_{40}$ were very low, even nought (entries 6, 7). $Zn_3(PW_{12}O_{40})_2$ and $LnPW_{12}O_{40}$ could smoothly catalyze *Mannich* reaction in water (entries 8, 9), but their activities were lower than that of $AlPW_{12}O_{40}$. These results demonstrated that both cation Al^{3+} as a benign Lewis acid and $PW_{12}O_{40}^{3-}$ as a felicitous anion were integrant factors to catalyze efficiently three-component *Mannich* reaction in water.

$AlPW_{12}O_{40}$-Catalyzed Mannich Reaction of Aromatic Ketones

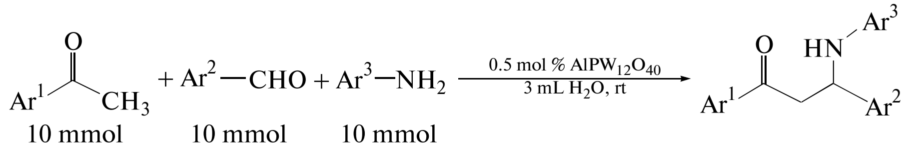
Encouraged by the remarkable results, we explored the generality and scope of $AlPW_{12}O_{40}$-catalyzed one-pot three-component *Mannich* reaction in water, the reaction was examined with various structurally ketones, aldehydes and amines under the same condition.

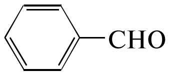
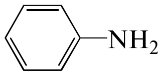
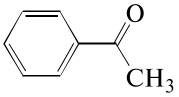
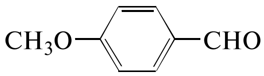
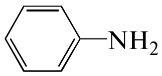
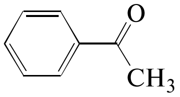
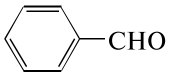
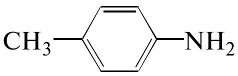
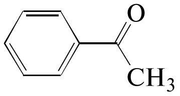
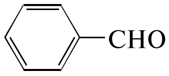
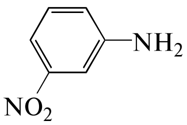
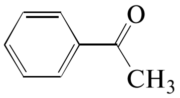
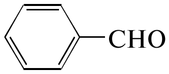
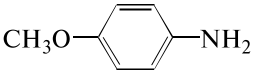
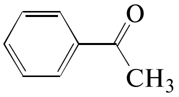
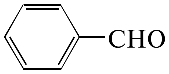
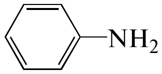
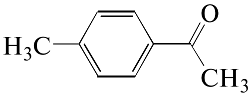
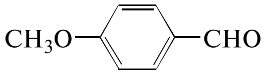
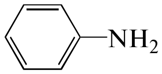
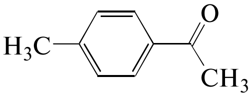
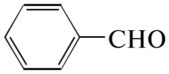
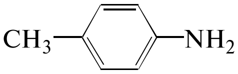
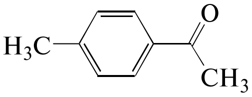
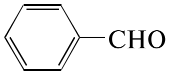
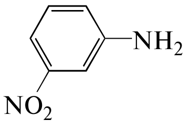
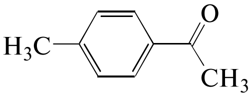
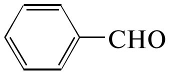
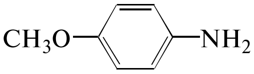
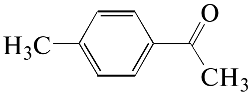
The *Mannich* reaction of aromatic ketones with various aromatic aldehydes and amines could be catalyzed by $AlPW_{12}O_{40}$ in water in good to excellent yields as shown in Table 2. These results revealed the following characters:

(1) When anisaldehyde bearing strong electron-donating methoxy group was used as reaction substrate, yield was distinctly low because electron-donating action of methoxy group decrease electrophilicity of carbonyl carbon atom (entries 2, 7);

(2) It is worthly to say that an excellent yield could also be obtained for reaction of 3-nitroaniline with strong electron-withdrawing nitro group (entries 4, 9);

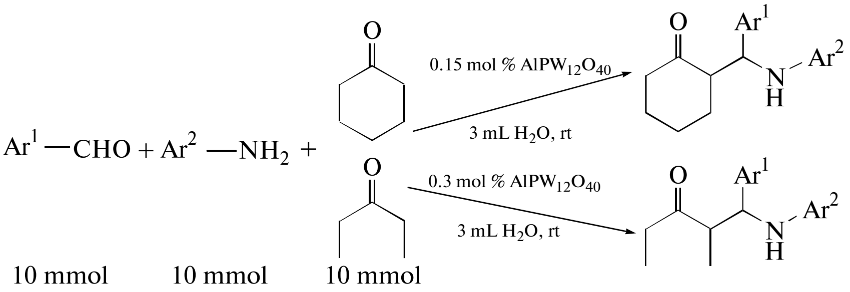
Table 2. $AlPW_{12}O_{40}$-catalyzed three-component *Mannich* reaction of Aromatic Ketones in Water

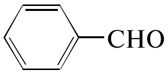
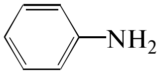
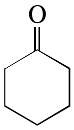
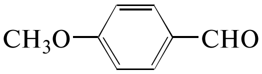
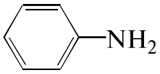
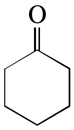
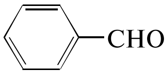
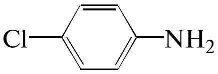
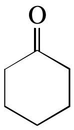
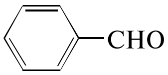
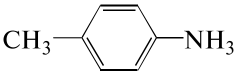
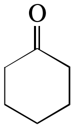
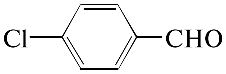
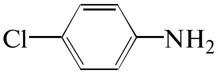
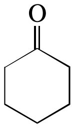
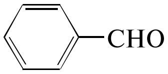
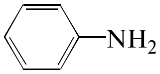
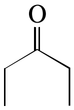
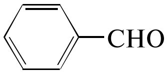
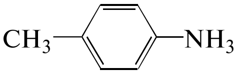
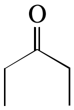
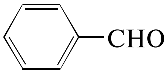
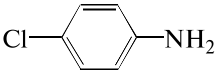
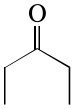
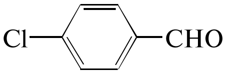
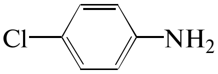
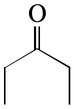


Entry	Aldehyde	Amine	Ketone	Time, h	Yield, % [a]	*T.* mp., °C
1				18	95	167–168
2				20	54	148–150
3				16	93	161–162
4				16	94	144–146
5				20	74	148–150
6				20	80	128–130
7				18	48	142–143
8				15	90	150–151
9				15	83	130–132
10				21	45	128–130

Note: [a] isolated yields (data were obtained according to amount of product purified by gel chromatography or recrystallization).

Table 3. $AlPW_{12}O_{40}$-catalyzed three-component *Mannich* reaction of Aliphatic Ketones in Water



Entry	Aldehyde	Amine	Ketone	Time, h	Yield, %[a]	*syn/anti*[b]	*T*. mp., °C
1				1	95	48/52	136–138
2				15	75	49/51	131–133
3				4	92	39/61	138–140
4				8	91	47/53	116–117
5				8	94	50/50	139–140
6				15	76	53/47	123–125
7				18	82	53/47	103–105
8				10	91	52/48	138–140
9				18	62	51/49	120–122

Note: [a] isolated yields (data were obtained according to amount of product purified by gel chromatography or recrystallization), [b] anti/syn ratio was determined by ^1H NMR spectroscopy analysis of the crude reaction mixture.

(3) In general, the reactivity of *p*-methylacetophenone was a little lower than that of acetophenone.

$AlPW_{12}O_{40}$-*Catalyzed Mannich Reaction of Aliphatic Ketones*

Furthermore, we used $AlPW_{12}O_{40}$ to catalyze *Mannich* reaction of aliphatic ketones such as cyclohexanone and 3-pentanone, as substrate in water. It can be seen from Table 3 that reactivities of aliphatic ketones were obviously superior to those of aromatic ketones. Smaller amount of $AlPW_{12}O_{40}$ could efficiently catalyze *Mannich* reaction of aliphatic ketones. Especially, *Mannich* reaction of cyclohexanone, benzaldehyde and aniline, not only was amount of catalyst $AlPW_{12}O_{40}$ used less, but also reaction rate was very quick. An excellent yield 95% could be obtained in one hour in the present of only 0.15 mol % $AlPW_{12}O_{40}$.

In conclusion, $AlPW_{12}O_{40}$ could highly efficiently catalyze one-pot three-component *Mannich* reaction of an equal mole amount of aldehydes, amines and ketones at ambient temperature to obtain β-amino ketones. The method exhibits several merits: Firstly, as compared with heteropoly acids, $AlPW_{12}O_{40}$ as a water stable salt is non-corrosive and environmentally benign; Secondly, loading amount of catalyst green is very low, less than 1 mol %; Thirdly, water as solvent is green and safe. So, it was an attractive and promising method to synthesize β-amino ketones in laboratory and chemical industry.

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