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One-Pot Three-Component Mannich-Type Reaction Catalyzed by Trifluoromethanesulfonic Acid in Water[1]

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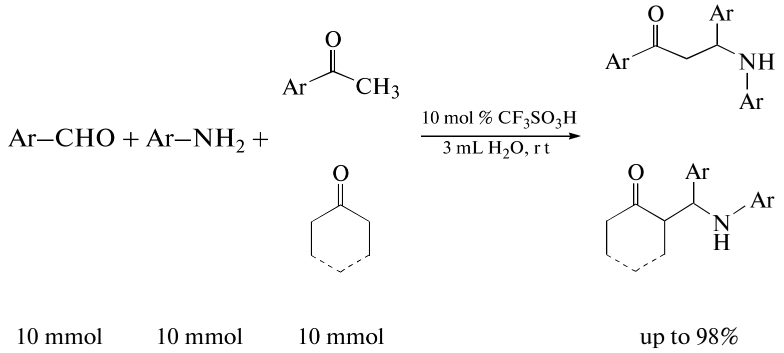
Abstract—One-pot three-component Mannich-type reaction of ketones, aldehydes and amines was efficiently catalyzed by liquid trifluoromethanesulfonic acid in water at ambient temperature. The high yield of corresponding β-amino ketones compounds were achieved. The proposed method is mild, green, simple and efficient.



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Organic reactions using water as a medium instead of noxious organic solvents are a hot study field in the recent years for several reasons [1–5]. First, in comparison with organic solvents often used in organic chemical reaction, water is a green, safe and economical solvent. Second, generally, water's unique physical and chemical properties lead to special reactivity and selectivity of organic reaction, which cannot be attained in organic solvents. Third, organic reactions in water do not require to use expensive anhydrous reactants and reagents. Finally, the work-up procedure is simple. The organic products which are insoluble in water can be obtained by simple filtration or separatory funnel.

The Mannich-type reaction is one of the most essential and fundamental carbon–carbon bond-forming organic reactions because product β-amino carbonyl compounds are crucial intermediates in numerous pharmaceuticals and natural products synthesis [6–9]. Mannich-type reactions have been widely applied in organic chemical industry over the past decades. Up to now, many protocols of Mannich-type reaction have been reported in a number of publications [10–18]. Conventional three-component Mannich-type reactions of aldehydes, amines and ketones are carried out in organic solvents. One of the most conspicuous disadvantages of these methods is to use large number of noxious organic solvents, which pollute the environment and augment operation hazard. To overcome these disadvantages, the three-component Mannich-type reactions in water or aqueous solvent have been developed in the recent years [19–24].

Trifluoromethanesulfonic acid (TfOH) is an important liquid superacid, which has been used to catalyze many organic reactions [25–31]. Ishimaru and Kojima reported TfOH-catalyzed Mannich-type reaction of silyloxydiene in ether [32, 33], but the preparation of nucleophilic silylenolate used in the literature was troublesome. To our knowledge, TfOH-catalyzed one-pot three-component Mannich-type reaction of ketones, aldehydes and amines in water has not yet been reported in the open literature. In this paper, we report that such reactions under mild condition were efficiently catalyzed by TfOH to give the corresponding β-amino ketones compounds in good to excellent yields.

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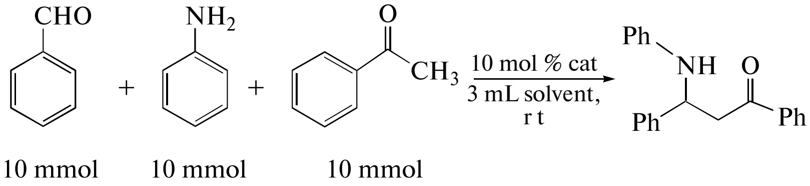
[1] The article is published in the original.

Table 1. Direct three-component Mannich reaction catalyzed by different Brønsted acid



Entry	Catalyst	Solvent	Time, h	Yield, %
1	CF_3SO_3H	H_2O	18	93
2	H_2SO_4	H_2O	24	0
3	CH_3SO_3H	H_2O	24	11
4	CF_3SO_3H	EtOH	18	85
5	CF_3SO_3H	DCE*	18	72
6	CF_3SO_3H	H_2O	18	84 (first recycle)
7	CF_3SO_3H	H_2O	18	57 (second recycle)

* Dichlorethane.

EXPERIMENT

Materials and Methods

All the chemicals and reagents used are of analytical grade and were used without further purification. The structure and *syn*/*anti* ratio of products were determined by IR and ^1H NMR. IR spectra were recorded on a Bruker AM-400 spectrometer using KBr discs. ^1H NMR spectra were obtained from solution in $CDCl_3$ with TMS as internal standard using a Varian Scimitar Series 800 (400 MHz) spectrometer.

General Procedure for the TfOH-Catalyzed Mannich Reaction in Water

Aldehyde (10 mmol), amine (10 mmol) and ketone (10 mmol) were added usualy to a solution of TfOH (10 mmol) in water (3 mL) placed in a 50 mL one-necked round-bottom flask. Then, the reaction mixture was stirred vigorously (400 rpm) with a magnetic stirrer at room temperature (rt) for the mentioned time. After reaction completion, the crude mixture is 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 compounds.

RESULTS AND DISCUSSION

Initially, we selected the reaction of an equal amount of benzaldehyde, aniline, and acetophenone as a typical Mannich reaction to investigate the influence of various catalysts and solvents on the reaction as shown in Table 1. To our surprise, among Brønsted acid catalysts used, liquid superacid TfOH can more efficiently catalyze the Mannich reaction in water at ambient temperature to give the corresponding product in an excellent yield 93% (entry 1). However, common Brønsted acid H_2SO_4 and CH_3SO_3H were hardly active for the Mannich reaction in water under the same condition (entries 2, 3). The Mannich reaction catalyzed by TfOH was also carried out in organic solvents, such as alcohol and dichlorethane, but its catalysis activity in organic solvent was less than that in water (entries 4, 5). Notwithstanding the solubility of substrates and TfOH are completely different, the Mannich reaction in water can be still catalyzed efficiently by TfOH at room temperature. The reaction should happen at the interface of organic substrates-water in the heterogeneous system because the experiment results indicated that vigorous stirring was imperative for the smooth progress of the reactions. The recycling performance of TfOH-catalyzed Mannich reaction was also investigated under the same condition. After the separation of the crude products by simple filtration, the catalyst-containing filtrate was reused in the next run without further treatment. The results show that the yield of product gradually decreases in recycling process (entries 6, 7) and the phenomenon should attribute to the loss of catalyst because of adsorption of TfOH to alkalic product (β-amino ketones).

To explore the generality and scope of the TfOH-catalyzed one-pot three-component Mannich-type reaction in water, the reaction was examined with a series of various ketones, aldehydes and amines under the same condition as shown in Table 2. These Mannich-type reactions of various substrates catalyzed by TfOH reveal the following characteristics.

(1) TfOH can catalyze Mannich-reactions of equal mole amount of ketones, aldehydes and amines in water. For Mannich reactions of cyclohexanone, 2-pentone with aldehydes and amines, polyaminoalkylations were not found in products.

Table 2. One-pot three-component Mannich-type reaction catalyzed by TfOH in water

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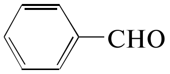
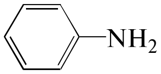
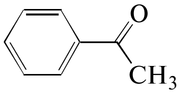
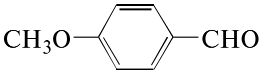
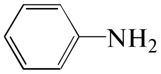
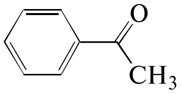
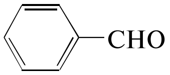
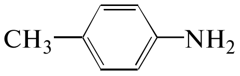
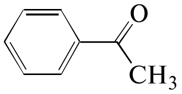
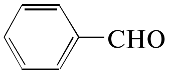
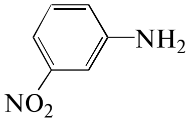
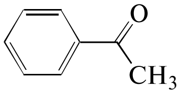
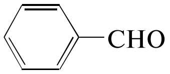
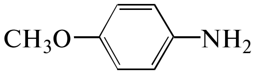
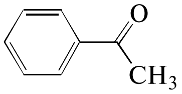
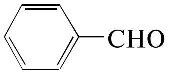
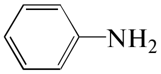
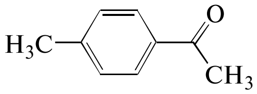
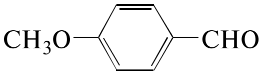
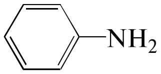
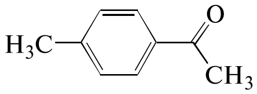
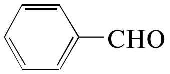
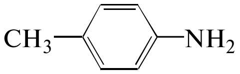
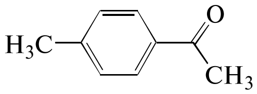
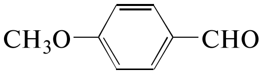
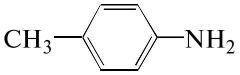
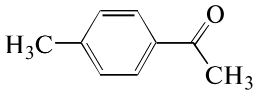
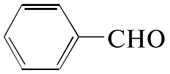
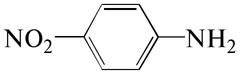
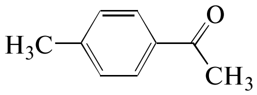
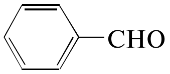
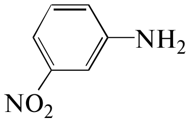
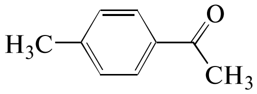
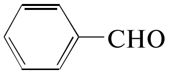
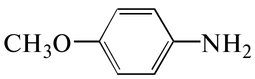
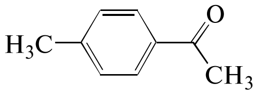
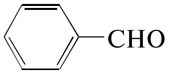
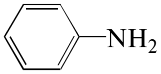
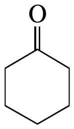
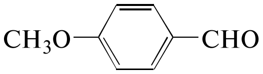
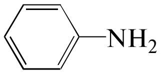
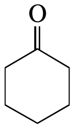
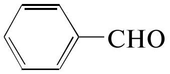
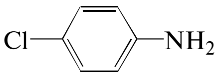
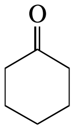
1				18	93	
2				18	73	
3				16	98	
4				16	94	
5				18	93	
6				18	72	
7				18	68	
8				8	84	
9				18	61	
10				18	70	
11				8	81	
12				17	53	
13				1	92[c]	48 : 52
14				14	85	49 : 51
15				8	96	39 : 61

Table 2. (Contd.)

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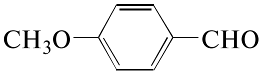
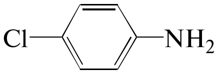
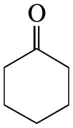
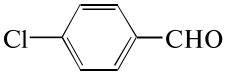
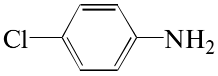
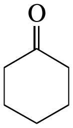
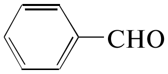
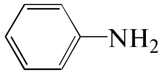
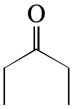
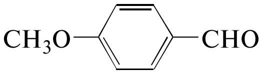
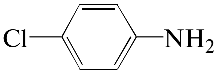
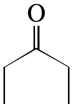
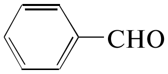
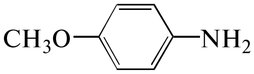
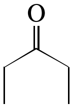
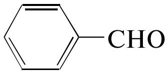
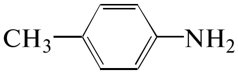
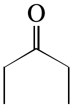
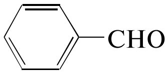
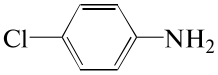
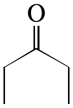
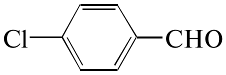
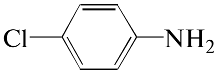
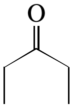
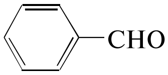
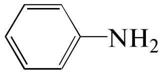
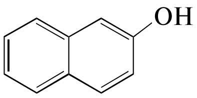
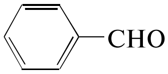
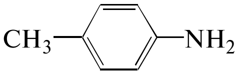
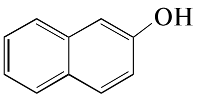
16				1.5	84	47 : 53
17				7	97	50 : 50
18				3	85	53 : 47
19				19	34	51 : 49
20				9	40	52 : 48
21				18	70	53 : 47
22				18	91	52 : 48
23				18	56	51 : 49
24				24	88	
25				24	71	

Note: Reaction conditions: aldehyde—10 mmol, amine—10 mmol, ketones—10 mmol, catalyst—10 mol %, water—3 mL, room temperature.

[a] Isolated yields.

[b] *anti*/*syn* ratio was determined by ^{1}H NMR spectroscopy analysis of the crude reaction mixture.

[c] 1 mol % TfOH.

(2) For aromatic amines with various substitution groups, including nitroaniline bearing strong electron-withdrawing group NO_2, the reaction can happen and give the corresponding β-amino ketones compounds in moderate to excellent yields (entries 4, 10, 11).

(3) Though activity of anisaldehyde bearing strong electron-donating group CH_3O– is lower than that of benzaldehyde, good yields of β-amino ketones can be also obtained.

(4) For Mannich reaction of aliphatic ketone, reactivity of open alkyl chain 2-pentone is less than that of cyclic ketone cyclohexanone because the opening of alkyl chain increases steric effect in the reaction course (entries 13–23).

(5) Only 1 mol % of TfOH is enough to catalyze the Mannich reaction of benzaldehyde, aniline and cyclohexanone (entry 13).

(6) TfOH can also efficiently catalyze Mannich reaction of β-naphthol in water in good yields (entries 24, 25).

The regioselectivity of the reaction products of 2-pentone and cyclohexanone was determined by ^{1}H NMR spectroscopy and comparison with the known compounds reported in the literatures. For the reactions using cyclohexanone as the substrate, *anti*-β-amino ketone isomer is the major product. For the reactions employing 2-pentone as the substrate, *syn*-β-amino ketone isomer is the major product.

So, one-pot three-component Mannich-type reactions of equal molar amounts of aldehydes, amines and ketones can be efficiently catalyzed by TfOH at ambient temperature. The method is applicable to various structural aromatic aldehydes, aromatic amines, aromatic ketones, aliphatic ketones and β-naphthol. The Mannich-type reaction catalyzed by TfOH in water provides a green, mild and simple efficient route to obtain β-amino ketones compounds.

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The authors can provide supplementing supporting information (NMR spectra of the studied compounds) on request to e-mail address: lgorgchem@126.com.

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