

Mannich-type reactions in water using a hydrophobic polymer-supported sulfonic acid catalyst

Shinya Iimura, Daisuke Nobutou, Kei Manabe and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: skobayas@mol.f.u-tokyo.ac.jp

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Three-component Mannich-type reactions were efficiently catalyzed by hydrophobic polystyrene-supported sulfonic acid (PS-SO₃H) in water as the sole solvent under mild conditions.

Organic reactions in water without using harmful organic solvents are of great current interest, especially in relation to today's environmental concerns.¹ On the other hand, organic reactions using reusable solid catalysts have also received much attention because of their practical advantages.^{2,3} Therefore, organic reactions using solid-supported catalysts in water will be an ideal methodology, provided that the catalysts show high catalytic activity in water.⁴ In the course of our investigations to develop efficient catalysts for organic reactions in water, we have recently found that a hydrophobic polystyrene-supported sulfonic acid (PS-SO₃H) is an effective and reusable catalyst for several organic reactions in water.⁵ Contrary to polymer-supported catalysts which swell in water, which have been traditionally used for organic reactions in aqueous media, the hydrophobic PS-SO₃H does not swell in water but is highly effective for the formation of esters, hydrolysis of thioesters, *etc.* in water.

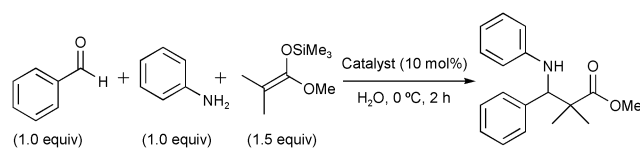
Mannich-type reactions are among the most important carbon-carbon bond-forming reactions in organic synthesis.⁶ They provide β-amino carbonyl compounds, which are important synthetic intermediates for various pharmaceuticals, natural products, *etc.* We have recently reported that a surfactant-type Brønsted acid such as dodecylbenzenesulfonic acid (DBSA) effectively catalyzes three-component Mannich-type reactions of aldehydes, amines, and silicon enolates in water.^{7,8} To develop immobilized catalysts in this reaction, we focused on polymer-supported sulfonic acids. Herein, we disclose our preliminary results on hydrophobic polystyrene-supported sulfonic acids (PS-SO₃H)-catalyzed Mannich-type reactions in water.⁹

The three-component Mannich-type reaction of benzaldehyde (1.0 equiv.), aniline (1.0 equiv.), and the ketene silyl acetal (1.5 equiv.) derived from methyl isobutyrate was selected as a model, and the reaction was conducted in the presence of an acid catalyst (10 mol%) in water at 0 °C for 2 h (Table 1). Although DBSA catalyzed the reaction better than other monomeric catalysts such as TsOH, the yield was moderate (entry 3). On the other hand, the yield was only 4%, when a commercially available polymer-supported catalyst (DOWEX 50W-X2) was used (entry 4).¹⁰ We then used hydrophobic PS-SO₃H, and it was revealed that the Mannich-type reactions proceeded smoothly to afford the desired adducts in high yields (entries 5–7). In general, ketene silyl acetals are known to be easily hydrolyzed in the presence of water. Therefore, these results suggest that the hydrophobic environment created by the catalyst might suppress the hydrolysis of the ketene silyl acetal. It is noteworthy that a remarkable effect of the loading levels on the polystyrene-supported sulfonic acid was observed (entries 4–7). To be precise, the lower the loading, the higher the catalytic activity. In addition, it was exciting to find that only 1 mol% of the catalyst gave almost the same result as 10 mol% of the catalyst did in the case of the lowest loading of PS-SO₃H (entry 7).¹¹

Next, we investigated the three-component Mannich-type reactions in water using various silicon enolates (Table 2).[†] It was revealed that the silicon enolates derived from a ketone, esters, and a thioester reacted with benzaldehyde smoothly to afford the desired Mannich-type adducts in high yields (entries 1–4). As for the aldehydes, aliphatic as well as aromatic aldehydes worked well to give the corresponding β-amino esters in good yields (entries 6 and 7). It should be noted again that only 1 mol% of the catalyst was enough to catalyze the reactions under mild conditions in most cases.

Mannich-type reactions, for which ketones are directly used instead of silyl enol ethers as nucleophilic components, were

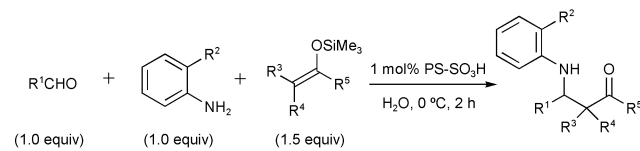
Table 1 Mannich-type reaction in water with various catalysts



Entry	Catalyst	Loading/ mmol g ⁻¹	Yield (%) ^a
1	None	—	3 ^b
2	TsOH	—	30
3	DBSA	—	40
4	DOWEX 50W-X2	4.41	4 ^b
5	PS-SO ₃ H	1.55	41
6	PS-SO ₃ H	0.46	77
7	PS-SO ₃ H	0.12	85 (83) ^c

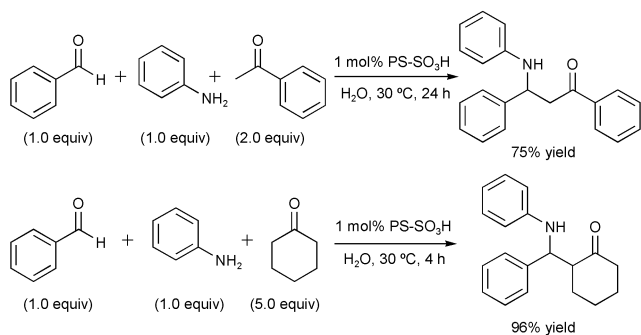
^a Isolated yields. ^b Determined by NMR. ^c PS-SO₃H (1 mol%).

Table 2 PS-SO₃H-catalyzed Mannich-type reactions in water using silicon enolates as nucleophiles



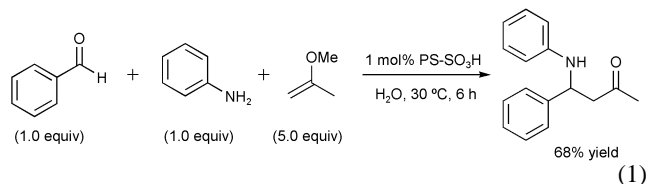
Entry	R ¹	R ²	R ³	R ⁴	R ⁵	Yield (%)
1 ^a	Ph	H	H	H	Ph	91
2	Ph	H	Me	Me	OMe	83
3 ^b	Ph	H	H	Me	OPh	73
4 ^c	Ph	H	H	H	SEt	83
5 ^c	Ph	OMe	H	H	SEt	68
6 ^d	C ₅ H ₁₁	H	Me	Me	OMe	76
7 ^d	Ph(CH ₂) ₂	OMe	Me	Me	OMe	66

^a At 30 °C. For 24 h. ^b PS-SO₃H (5 mol%). For 4 h. ^c At 30 °C. ^d For 0.5 h.

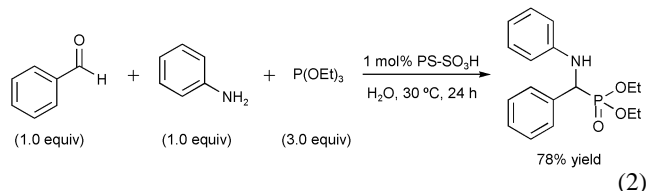


Scheme 1 PS-SO₃H-catalyzed direct Mannich-type reactions in water.

also achieved using this catalytic system in water (Scheme 1).⁷ In addition, it was also found that a vinyl ether reacted with an aldehyde and an amine in the presence of 1 mol% PS-SO₃H in water at 30 °C for 6 h to give the Mannich-type adduct in good yield (eqn. 1), although the direct Mannich-type reaction using acetone as a nucleophile proceeded in 24% yield under the same reaction conditions. It is noted that these three-component reactions are an atom-economical and environmentally friendly synthetic method as well as a useful method for facile synthesis of β-amino ketone libraries.³



Finally, we conducted another three-component Mannich-type reaction in water using a phosphite as a nucleophile (eqn. 2).^{12,13} This type of reaction is also an attractive method to produce α-amino phosphonates, which are not only an important class of biologically active compounds but also structural analogues to α-amino acids.¹⁴ The reaction proceeded smoothly using 1 mol% PS-SO₃H in water to afford the α-amino phosphonate in good yield.



In summary, several types of three-component Mannich-type reactions were efficiently catalyzed by hydrophobic polystyrene-supported sulfonic acid (PS-SO₃H) in water under mild conditions. This is the first example of C-C and C-P bond-forming reactions in water as the sole solvent using this type of catalyst. It should be noted that PS-SO₃H has high catalytic activity in water, and that only 1 mol% of PS-SO₃H is enough to catalyze the reactions in most cases. These results not only provide a new aspect of catalytic organic reactions in water but also extend the utility of hydrophobic PS-SO₃H in organic synthesis in water to lead to environmentally benign processes.

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Notes and references

† A typical experimental procedure is as follows: benzaldehyde (0.25 mmol), aniline (0.25 mmol), and the ketene silyl acetal (0.375 mmol) derived from methyl isobutyrate were successively added to a mixture of PS-SO₃H (0.12 mmol g⁻¹, 0.0025 mmol) in degassed water (1.5 mL) at 0 °C. The reaction mixture was stirred for 2 h at the same temperature, and then quenched with sat. aq. NaHCO₃ (5 mL). The polymer was filtered and washed with water and dichloromethane. The organic layer was dried over Na₂SO₄, and evaporated. The mixture was purified by preparative TLC on silica gel to give the desired product in 83% yield. All experiments were carried out using PS-SO₃H whose loading was 0.12 mmol g⁻¹ except for some experiments shown in Table 1.

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