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Mannich-Type Reactions of Aldehydes, Amines, and Ketones in a Colloidal Dispersion System Created by a Brønsted Acid–Surfactant-Combined Catalyst in Water

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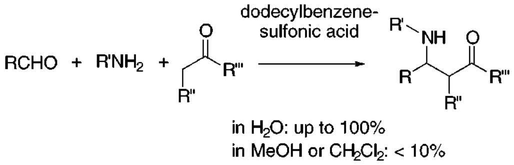
ABSTRACT



Three-component Mannich-type reactions of aldehydes, amines, and ketones were efficiently catalyzed by dodecylbenzenesulfonic acid at ambient temperature in water to give various *β*-amino ketones in good yields. The same reactions proceeded sluggishly in organic solvents.

Recently, organic synthesis in water has received much attention, not only because unique reactivity and selectivity are often exhibited in water but also because it is an economical and environmentally benign solvent.[1] However, one major disadvantage in the use of water as a solvent is that most organic compounds are insoluble in water and, as a result, most reactions are slowed. To circumvent this disadvantage, surfactants, which solubilize organic materials or form colloidal dispersion with them in water, have been used. However, only a limited number of practical examples of surfactant-aided organic reactions have been reported to date.[2] On the other hand, we have recently developed surfactant-aided Lewis or Brønsted acid-catalyzed reactions in water.[3] In these reactions, a catalytic amount of a Lewis acid−surfactant-combined catalyst (LASC) such as scandium tris(dodecyl sulfate)[3c−f] or a Brønsted acid-surfactant-combined catalyst (BASC) such as dodecylbenzenesulfonic acid (DBSA)[3g] acts both as an acid catalyst to activate a substrate and as a surfactant to form stable colloidal dispersion with water-insoluble substrates. These catalysts have been successfully applied to aldol,[3c−f] allylation,[3f] and Mannich-type reactions.[3g]

Mannich and related reactions provide one of the most basic and useful methods for the synthesis of *β*-amino

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[2] (a) Fendler, J. H.; Fendler, E. J. *Catalysis in Micellar and Macromolecular Systems*; Academic Press: London, 1975. (b) *Mixed Surfactant Systems*; Holland, P. M., Rubingh, D. N., Eds.; American Chemical Society: Washington, DC, 1992.

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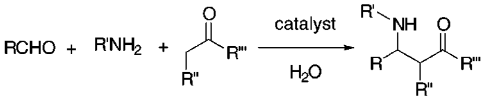
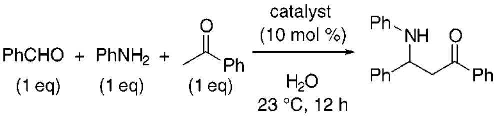
carbonyl compounds, which constitute various pharmaceuticals, natural products, and versatile synthetic intermediates.[4] Conventional protocols for three-component Mannich-type reactions of aldehydes, amines, and ketones in organic solvents include some severe side reactions and have some substrate limitations, especially for enolizable aliphatic aldehydes. Our previous DBSA-catalyzed three-component Mannich-type reactions in colloidal dispersion systems,[3g] in which silyl enolates instead of ketones are used as nucleophilic components,[5] have extended the substrate applicability and avoided the use of organic solvents. However, there is still a drawback in that the silyl enolates have to be prepared from the corresponding carbonyl compounds usually under anhydrous conditions. From atom economical and environmental points of view, therefore, it is desirable to develop a new efficient system for Mannich-type reactions in which the parent carbonyl compounds are directly used[6] and water is used as a solvent (Scheme 1). These three-component reactions would be also useful for the synthesis of β-amino ketone libraries.[7] Here we report DBSA-catalyzed three-component Mannich-type reactions in a colloidal dispersion system using ketones as nucleophilic components.

Scheme 1



The reaction of benzaldehyde, aniline, and acetophenone in the presence of an acid catalyst in water was selected as a model reaction. Among the Brønsted and Lewis acid catalysts tested, DBSA[8] catalyzed the reaction most efficiently (Table 1, entry 1). Interestingly, this efficient catalysis was not observed in the reactions carried out in organic solvents such as MeOH and CH_2Cl_2. This solvent effect shows the unique property of water to induce hydrophobic interactions between the substrates and the catalyst. Scandium tris(dodecyl sulfate), a representative LASC, was less effective than DBSA (entry 2). It should be noted that *p*-toluenesulfonic acid (TsOH) did not afford the desired product (entry 3). DBSA formed a white turbid reaction mixture, while TsOH formed two immiscible layers. This result indicates that the long alkyl chain of DBSA is necessary for formation of the colloidal dispersion which leads to efficient catalysis. In fact, a combination of TsOH and sodium dodecyl sulfate (SDS), which formed a colloidal dispersion in the presence of the substrates, afforded the adduct in a modest yield (entry 5), while SDS alone gave the adduct in a very low yield (entry 4). The reaction proceeds through the imine formation of the aldehyde and the amine, protonation of the imine, and the attack of the enol derived from the ketone to the protonated imine. This dehydrative imine formation in water is a characteristic feature of our colloidal dispersion system for reactions of imines.

Table 1. Three-Component Mannich-Type Reactions in Water



entry	catalyst	yield (%)
1	DBSA	69 (9[a],4[b])
2	$Sc(O_3SOC_{12}H_{25})_3$	54
3	TsOH	0
4	SDS	5
5	TsOH + SDS	56

[a] In MeOH. [b] In CH_2Cl_2.

The reactions of various aldehydes, amines, and ketones were found to be efficiently catalyzed by DBSA at ambient temperature in water (Table 2).[9,12]

The following features are noteworthy in these reactions. (1) A 1:1:1 mixture of benzaldehyde, *p*-anisidine, and acetophenone with 10 mol % of DBSA gave the Mannich adduct in 63% yield (entry 1), in contrast to a 30% yield by a conventional HCl-catalyzed reaction in EtOH (18 h).[6a] (2) In the case of the substrates shown in entries 3, 5, and 6, only 1 mol % of DBSA was sufficient to catalyze the reactions. (3) The reactivity order of the amines is *p*-chloroaniline > aniline > *p*-anisidine, indicating the importance of the electronic nature of the amines. (4) In the reaction of 2-butanone (entry 8), the adduct aminoalkylated at the less substituted α-carbon was formed preferentially. (5) Not only benzaldehyde but also heteroaromatic aldehydes such as 2-furfural and 2-pyridinecarbaldehyde worked well (entries 9 and 10). (6) For enolizable aliphatic aldehydes such

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(5) (a) Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998,** *39*, 323. (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999,** 1045. (c) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426.

(6) HCl-catalyzed three-component Mannich-type reactions of aldehydes, amines, and ketones in EtOH have been reported. (a) Blatt, A. H.; Gross, N. *J. Org. Chem.* **1964**, *29*, 3306. (b) Yi, L.; Zou, J.; Lei, H.; Lin, X.; Zhang, M. *Org. Prep. Proced. Int.* **1991,** *23*, 673.

(7) Multiple-component reactions, which can produce a diversity of compounds, provide one of the most efficient methods for the combinatorial synthesis of compound libraries. For example, see: Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1.

(8) Dodecylbenzenesulfonic acid (soft type) was purchased from Tokyo Kasei Kogyo Co., Ltd., and used without further purification. This is a mixture of several linear alkylbenzenesulfonic acids. Its molecular weight was regarded as 326.50.

(9) All the Mannich adducts in Table 2 were adequately characterized by ^1H and ^{13}C NMR. The adducts in entries 1,[6a] 2,[6a] 3,[6] 5,[6b,10] 7,[11] and 8[6a] have been reported earlier. The spectral data for the other Mannich adducts are included in the Supporting Information.

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(12) **General Reaction Procedure:** To a solution of DBSA (0.0025−0.075 mmol, 1−30 mol %) in H_2O (1.5 mL) were added an amine (0.25 mmol), an aldehyde (0.25 mmol), and a ketone (0.25−1.25 mmol) successively at 23 °C. After stirring at the same temperature for the period of time listed in Table 2, a saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL) were added, and the mixture was extracted with ethyl acetate. Purification by silica gel chromatography gave the desired product. Ten-mmol-scale reactions were also carried out without any difficulties. For example, the reaction of benzaldehyde (10 mmol), aniline (10 mmol), and acetophenone (10 mmol) in the presence of 10 mol % of DBSA afforded the product in 82% yield (24 h).

Table 2. Three-Component Mannich-Type Reactions of Aldehydes, Amines, and Ketones in the Presence of DBSA in Water at 23 °C

entry	aldehyde	amine	ketone (equiv)	DBSA (mol %)	time (h)	yield (%)
1	benzaldehyde	*p*-anisidine	acetophenone (1)	10	24	63
2	benzaldehyde	aniline	acetophenone (1)	10	24	81
3	benzaldehyde	aniline	cyclohexanone (5)	1	1	97[a]
4	benzaldehyde	*p*-anisidine	cyclohexanone (5)	10	12	81[b]
5	benzaldehyde	*p*-chloroaniline	cyclohexanone (5)	1	1	quant[c]
6	benzaldehyde	*p*-anisidine	cycloheptanone (5)	1	12	89[d]
7	benzaldehyde	*p*-chloroaniline	propiophenone (1)	10	47	73[e]
8	benzaldehyde	aniline	2-butanone (5)	10	24	84[f]
9	2-furfural	aniline	cyclohexanone (5)	10	24	87[g]
10	2-pyridinecarbaldehyde	aniline	cyclohexanone (5)	10	12	78[h]
11	isovaleraldehyde	aniline	cyclohexanone (5)	10	12[i]	71[j]
12	isovaleraldehyde	*p*-chloroaniline	cyclohexanone (5)	10	12[i]	66[k]

[a] Diastereomer ratio (dr) = 74/26. [b] dr = 68/32. [c] dr = 70/30. [d] dr = 81/19. [e] dr = 58/42. [f] Regioisomer ratio = 87/13. The dr of the minor regioisomer = 57/43. [g] dr = 67/33. [h] dr = 69/31. [i] The aldehyde was added slowly during 9 h, and then the whole was stirred for 3 h. [j] dr = 65/35. [k] dr = 62/38.

as isovaleraldehyde, the reaction procedure mentioned above afforded a complicated mixture of various compounds probably due to self-condensation of the aldehyde. Therefore, we tried slow addition of the aldehyde to a mixture of an amine, a ketone, and DBSA in water. Indeed, this procedure greatly improved the yields up to 71% (entries 11 and 12). (7) For the reactions of cyclohexanone, cycloheptanone, and 2-butanone, 5 equiv of the ketones was needed to avoid polyaminoalkylation.

In summary, three-component Mannich-type reactions of aldehydes, amines, and ketones are efficiently catalyzed by DBSA in water. Aromatic, heteroaromatic, and aliphatic aldehydes can be successfully used as the aldehyde component. Moreover, these reactions, which proceed sluggishly in organic solvents, attest to the unique property of water as a reaction medium. DBSA forms stable colloidal particles in the presence of the substrates in such a medium, and this colloid formation plays an essential role in acceleration of the reactions. Although organic reactions in water are still at a preliminary stage, the colloidal dispersion systems will provide a promising method for practical synthetic reactions in water.

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Supporting Information Available: Spectral data for the Mannich adducts in entries 4, 6, 9, 10, 11, and 12 in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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