Mannich-Type Reactions Catalyzed by Neutral Salts in Water

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Abstract: Mannich-type reactions of imines with silicon enolates were found to be catalyzed by neutral salts such as sodium triflate in water as a suspension medium. Unusual kinetic behavior indicates that the presence of the Mannich adduct facilitates the rate of its formation.

Keywords: β-amino acid; aqueous media; imine; ketene silyl acetal; Mannich reaction

Mannich-type reactions are useful methods to synthesize various β-amino carbonyl compounds, which constitute many natural products, biologically active compounds, and other functional materials.[1] Among the Mannich-type reactions, addition of silicon enolates to imines has been developed to afford the adducts under mild conditions.[2] Generally, Lewis acids or Brϕnsted acids are used to promote these reactions. Recently, organic reactions in aqueous media have attracted a great deal of attention,[3] not only because these reactions eliminate the necessity of vigorous drying of solvents and substrates, but also because unique reactivity and selectivity are often observed in aqueous reactions. Safety and low cost of water are also regarded as beneficial aspects. Along these lines, Mannich-type reactions in aqueous media have been investigated, and several acid catalysts which work well in water have emerged.[4] On the other hand, we have found, quite recently, that aza-Diels–Alder reactions of imines with Danishefsky's diene are effectively catalyzed by neutral salts such as sodium trifluoromethanesulfonate (NaOTf) in water as a suspension medium.[5] The reactions did not require the use of acid catalysts and proceeded smoothly under mild conditions to give the desired dihydro-4-pyridones in good yields. These results prompted us to investigate neutral salt-catalyzed Mannich-type reactions of imines with silicon enolates derived from esters in water. These reactions would provide a unique and useful method for the construction of β-amino acid skeletons. Here we report that this type of reactions indeed proceeds in the presence of a neutral salt in water, and that kinetic studies have revealed the effect of the Mannich adducts to accelerate the reactions.

First, we investigated the effect of added salts in a model reaction of *N*-benzylideneaniline with the silicon enolate (**1**)[6] derived from phenyl propionate in water as a suspension medium. The results are summarized in Table 1. As shown in entry 1, the reaction did not proceed without catalysts. On the other hand, neutral salts such as NaOTf and NaI effectively promoted the reaction to give the corresponding Mannich adduct in good yields (entries 2 and 3). It is intriguing that the reaction was catalyzed without using acid catalysts, which have been used in the previous examples of the Mannich-type reactions in water. Sodium dodecyl sulfate (SDS) was less effective (entry 4). The reaction in the presence of tetrabutylammonium iodide did not afford **2** (entry 5), suggesting that the metal cation plays a pivotal role in the present catalysis. The effect of the neutral salts was also observed in a two-solvent system where an organic solvent such as dichloromethane was used as a cosolvent (entry 6). The reaction was completely inhibited by 10 mol % [2.2.2]cryptand (**3**) (entry 7), suggesting again the importance of sodium cation for the catalysis.

We next applied this catalytic system to three-component reactions of various aldehydes, amines, and silicon enolates in water. A merit of the three-component reactions is that the reactions can be done without a separate step for imine preparation prior to the Mannich-type reactions,[7] and that adducts from unstable imines such as those derived from aliphatic aldehydes are obtained in high yields. As shown in Table 2, not only aromatic aldehydes but also α,β-unsaturated and aliphatic aldehydes gave the corresponding adducts in good yields (entries 1–7). As for amines, substituted anilines could also be used (entries 8 and 9). When the silicon enolate derived from methyl isobutyrate was used, NaOTf gave the adduct in modest yield (entry 10), but the yield was improved by replacing NaOTf with SDS (entry 11).

To elucidate the mechanism of the present catalytic reactions, we carried out kinetic studies. However, the reaction was found to be more complicated than expected. Fig. 1 shows the reaction profile of the NaOTf-catalyzed Mannich-type reaction of *N*-benzylideneaniline with **1** in water. To our surprise, the yield of **2** drastically increased after 300 min, indicating that formation of **2** was further accelerated as the reaction proceeded. From this result, we assumed that the

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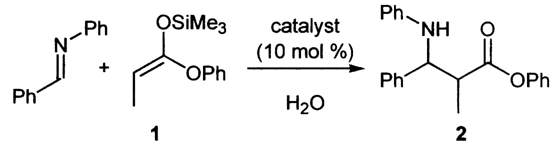
Table 1. The effect of salts in Mannich-type reactions in water.[a]



Entry	Catalyst	Yield (%)[b]
1	-	0
2	NaOTf	81
3	NaI	79
4	SDS	15
5	Bu_4NI	0
6[c]	NaOTf	91
7[c]	NaOTf + **3**[d]	0

[a] Conditions: imine (0.30 mmol), **1** (0.45 mmol), catalyst (0.030 mmol), H_2O (0.60 mL), 20 °C, 7 h.

[b] Determined by ^1H NMR analysis with fluorene as an internal standard.

[c] H_2O (0.15 mL) and CH_2Cl_2 (0.45 mL) were used as solvents.

[d] [2.2.2]Cryptand.

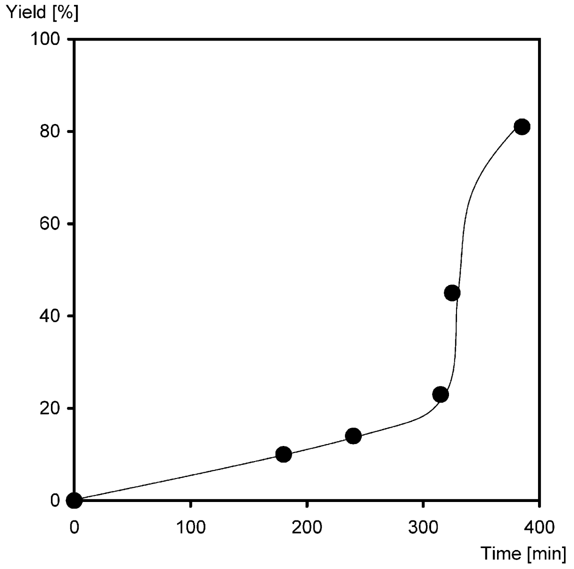
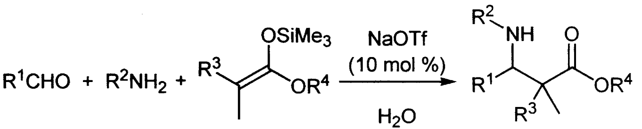


Figure 1. Reaction profile of the Mannich-type reaction in water. Conditions: benzylideneaniline:**1** = 1:1.5 in H_2O at 30 °C in the presence of NaOTf (10 mol %).

Table 2. Three-component Mannich-type reactions in water.[a]



Entry	R^1	R^2	R^3	R^4	Yield (%)[b]	(*syn*:*anti*)[c]
1	Ph	Ph	H	Ph	90	(49:51)
2	*p*-$MeOC_6H_4$	Ph	H	Ph	84	(64:36)
3[d]	*p*-$NO_2C_6H_4$	Ph	H	Ph	50	(58:42)
4	(*E*)-PhCH=CH	Ph	H	Ph	90	(90:10)
5	*c*-C_6H_{11}	Ph	H	Ph	71	(62:38)
6	$PhCH_2CH_2$	Ph	H	Ph	93	(17:83)
7	$(CH_3)_2CHCH_2$	Ph	H	Ph	82	(10:90)
8	Ph	*p*-$MeOC_6H_4$	H	Ph	73	(56:44)
9	Ph	*p*-BrC_6H_4	H	Ph	83	(62:38)
10[e]	Ph	Ph	Me	Me	49	-
11[e,f]	Ph	Ph	Me	Me	90	-

[a] Conditions: aldehyde (0.30 mmol), amine (0.30 mmol), silicon enolate (0.45 mmol), NaOTf (0.030 mmol), H_2O (0.60 mL), 20 °C, 7 h.

[b] Isolated yield.

[c] Determined by ^1H NMR analysis.

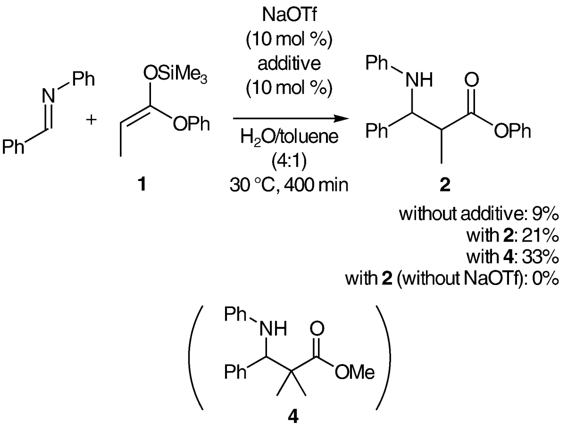
[d] Silicon enolate (0.90 mmol) was used.

[e] 3 h.

[f] SDS instead of NaOTf was used.

presence of a catalytic amount of the Mannich adduct would improve the rate of the NaOTf-catalyzed reaction at the early stage.

To confirm this hypothesis, the reaction in the presence of the Mannich adduct itself as an additive was carried out as shown in Equation (1). Toluene was used as a cosolvent to ensure dissolution of the additive. Under these conditions, the yield was improved in the presence of 10 mol % Mannich adduct **2** (21% vs. 9% yield). Adduct **4** as an additive also promoted the reaction. On the other hand, **2** alone without NaOTf did not give the product. These results indicate that NaOTf and the adduct cooperatively work to promote the formation of the adduct itself. While the precise mechanism is still unclear, this cooperative effect is a characteristic feature of the present catalysis.[8]



without additive: 9%
with **2**: 21%
with **4**: 33%
with **2** (without NaOTf): 0% (1)

In conclusion, we have found that neutral salts such as NaOTf and SDS effectively catalyzed Mannich-type reactions of imines with silicon enolates in water. In contrast to the previous examples of Mannich-type reactions in water, the present system does not need acidic materials as catalysts. In addition, the unique kinetic behavior indicates that the product itself is involved in the catalytic system to promote the neutral salt-catalyzed reaction. The catalysis by the neutral salts described here will open a new avenue for efficient catalytic processes in water.

Experimental Section

General Procedure for the Three-Component Mannich-Type Reactions

To a mixture of an amine (0.30 mmol), an aldehyde (0.30 mmol), and NaOTf (0.030 mmol) in H_2O (0.60 mL) was added a silicon enolate (0.45 mmol). After stirring for 7 h at 20 °C, the reaction mixture was diluted with CH_2Cl_2, and the organic materials were extracted. The organic phases were combined and dried over Na_2SO_4. The crude mixture was purified by preparative TLC (silica gel) affording the corresponding Mannich adduct.

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