HCl-Catalyzed Stereoselective Mannich Reaction in H_2O–SDS System

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Abstract: HCl-catalyzed Mannich reaction of cyclic ketone, aromatic aldehyde, and aromatic amine proceeded smoothly in water in the presence of SDS to afford the corresponding β-amino ketone with high *anti* selectivity.

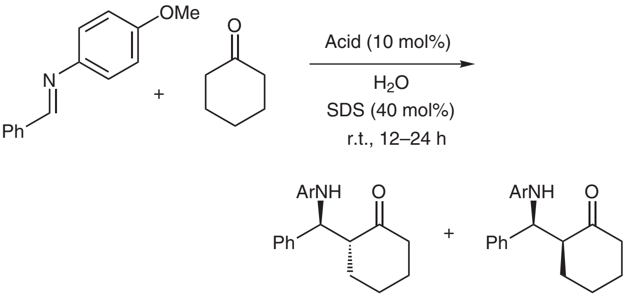
Key words: Mannich reactions, Brønsted acid, water, amines, surfactant

Organic reactions in aqueous media have attracted much attention of synthetic organic chemists lately not only because water is one of the most abundant, cheapest, and environmentally friendly solvent, but also because water exhibits unique reactivity and selectivity different from those in conventional organic solvents.[1,2] Development of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is, thus, one of the challenging goals of aqueous chemistry.

Mannich and related reactions constitute useful reactions for the preparation of β-amino carbonyl compounds, which are important intermediates for the synthesis of biologically active nitrogen containing compounds.[3] We have already reported that the Mannich-type reaction of silyl enolate with aldimines proceeded smoothly under the influence of HBF_4 as a Brønsted acid in aqueous organic solvent to give β-amino carbonyl compounds in good to excellent yields.[4] Furthermore, the HBF_4-catalyzed Mannich-type reaction proceeded smoothly in water in the presence of SDS (sodium dodecylsulfate).[5] It is noted that the *syn*/*anti* selectivity of the Brønsted acid-catalyzed Mannich-type reaction is highly dependent on the solvent system; aqueous organic solvent and H_2O–SDS system exhibited different selectivity.[6,7] We report herein that excellent to good *anti* selectivity was observed in HCl-catalyzed direct Mannich reaction[8] of cyclic ketone and aldimine in water in the coexistence of SDS.[9–11]

At the outset, we carried out Mannich reaction of cyclohexanone with an aldimine derived from benzaldehyde and *p*-anisidine and the effect of Brønsted acid was examined (Table 1). High *anti* selectivity was observed by means of Brønsted acid. Because HCl exhibited excellent *anti* selectivity (entry 1) and is easy to handle, we selected HCl as a Brønsted acid for the present reaction.

Table 1 Effect of Brønsted Acid



Entry	Acid	Yield (%)	*anti*:*syn*
1	HCl	87	99:1
2	Camphorsulfonic acid	89	99:1
3	HBF_4	91	97:3
4	CF_3CO_2H	79	96:4
5	Montmorillonite	61	93:7

The HCl-catalyzed Mannich reaction was examined in several kinds of solvent system (Table 2). Interestingly, present Mannich reaction exhibited intriguing solvent effect; excellent *anti* selectivity was observed in water in the coexistence of SDS, whereas the reaction in aqueous organic solvent or organic solvent showed low stereoselectivity.

The HCl-catalyzed Mannich reaction was examined with a number of aldimines and cyclic ketones (Table 3). Cyclohexanone showed good to high *anti* selectivities. Cycloheptanone gave β-amino ketone with modest *anti* selectivity (entry 6).

Next we studied the three-component synthesis starting from aldehyde, amine, and ketone (Table 4).[12] High *anti* selectivity was observed in the reaction with cyclohexanone. Tetrahydro-4-pyrone and tetrahydro-4-thiopyrone also furnished the Mannich adducts with high yields and high *anti* selectivity. Acetophenone derivatives also gave adducts in good yields.[13]

In summary, we have found that good to high *anti* selectivity was observed in the HCl-catalyzed Mannich-type reaction of cyclic ketone and aromatic aldimines in a water–SDS system.

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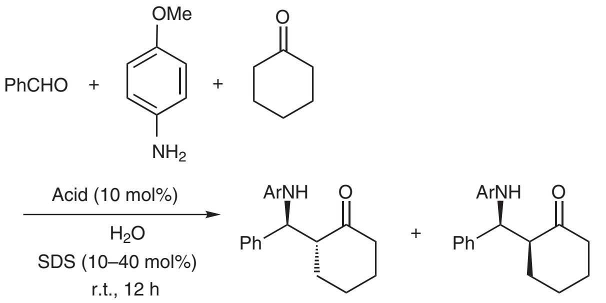
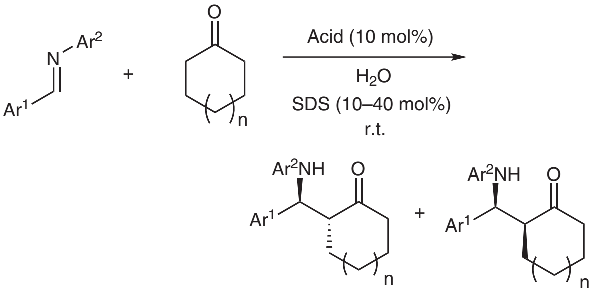
Table 2 Effect of Solvent System



Entry	Solvent	Yield (%)	*anti*:*syn*
1	H_2O, SDS (10 mol%)	84	96:4
2	MeCN–H_2O, (90:10)[a]	42	65:35
3	MeOH–H_2O, (90:10)[a]	30	70:30
4	MeCN	36	65:35
5	MeOH	12	95:5

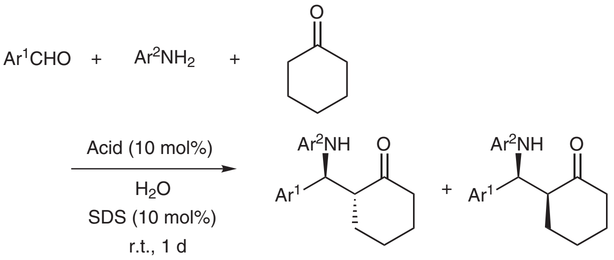
[a] Volume:volume.

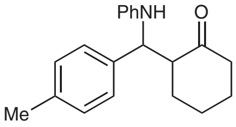
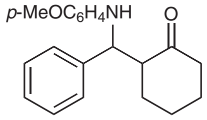
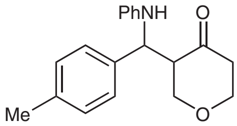
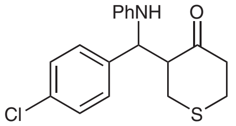
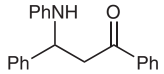
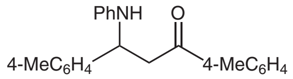
Table 3 Results of the Mannich Reaction



Entry	Ar^1	Ar^2	n	Yield (%)	*anti*:*syn*
1	Ph	4-$MeOC_6H_4$	1	87	99:1
2	Ph	4-ClC_6H_4	1	90	82:18
3	Ph	C_6H_5	1	90	83:17
4	4-MeC_6H_4	4-ClC_6H_4	1	90	96:4
5	4-$MeOC_6H_4$	4-ClC_6H_4	1	90	98:2
6	Ph	4-ClC_6H_4	2	89	77:23

Table 4 Three-Component Mannich Reactions



Entry	Product	Yield (%)	*anti*:*syn*
1		83	94:6
2		84[a]	96:4
3		80	91:9
4		88	>98:<2
5		98	–
6		86	–

[a] 40 mol% of SDS was employed.

A Typical Experimental Procedure for the Mannich Reaction (Table 1, Entry 1).

To a solution of SDS (16.3 mg, 0.0565 mmol) in H_2O (1.0 mL) were successively added *N*-benzylidene *p*-anisidine (39.9 mg, 0.142 mmol) and cyclohexanone (22.0 μL, 0.212 mmol). After 10 min, aq HCl solution (14.2 μL, 0.0143 mmol, 1.01 mol/L solution) was added and the mixture was vigorously stirred at r.t. for 24 h. The reaction was quenched by addition of ion exchange resin (Dowex 50W-X8, 50-100 mesh, Cl^- form) followed by sat. $NaHCO_3$. The resin was removed by filtration over Celite and the filtrate was extracted with EtOAc for 3 times. The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated to dryness. The crude mixture was purified by *p*-TLC (SiO_2, hexane–EtOAc = 4:1, $R_f = 0.3$) to afford the β-amino ketone (38.3 mg) in 87% as a 99:1 *anti*:*syn* mixture.

References

(1) (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley: New York, **1997**. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (d) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (e) *Organic Reactions in Water*; Grieco, P., Ed.; Blackie Academic and Professional: London, **1998**.
(f) *Modern Solvents in Organic Synthesis,* In *Topics in Current Chemistry*, Vol. 206; Knochel, P.; Houk, K. N.; Kessler, H., Eds.; Springer Verlag: Berlin, **1999**.
(g) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751.

(2) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

(3) (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 893. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1045. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(4) (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1045. (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831.

(5) (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426. (b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Adv. Synth. Catal.* **2002**, *344*, 338. (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Synlett* **2002**, 1269.

(6) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **2001**, *42*, 4025.

(7) Recent examples in H_2O–SDS-system, see: (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401. (b) Yonehara, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9381. (c) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358.

(8) Recent examples of direct Mannich reaction, see: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (b) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (c) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(9) HCl-catalyzed Mannich reactions of imine and cyclic ketones, see: (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*, 67.

(10) Brønsted acid-catalyzed Mannich reaction in water, see: (a) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. (b) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537.

(11) Although Brønsted acid-catalyzed Mannich reactions have been reported,[9,10] high stereoselectivity has not been observed.

(12) We have not observed the diaminoalkylation product.

(13) Other acyclic ketones such as 2-butanone and propiophenone did not give the Mannich adduct.