



Pergamon

Tetrahedron Letters 41 (2000) 3107–3111

TETRAHEDRON
LETTERS

Michael reactions in water using Lewis acid–surfactant-combined catalysts

Yuichiro Mori, Kentaro Kakumoto, Kei Manabe and Shū Kobayashi *

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 28 January 2000; revised 15 February 2000; accepted 17 February 2000

Abstract

Michael reactions in water using Lewis acid–surfactant-combined catalysts (LASCs) have been developed. In the presence of a catalytic amount of scandium tris(dodecyl sulfate) (STDS), reactions of various β -ketoesters with enones proceeded smoothly in water without any organic solvents, to afford the corresponding Michael adducts in high yields. The catalytic activity in water was found to be higher than that in organic solvents. Among the Lewis acids tested, STDS was proved to be the most superior Lewis acid catalyst for Michael reactions in water. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Michael reactions; surfactants; micellar systems; scandium and compounds; aqueous reactions.

Michael reactions are one of the most important carbon–carbon bond-forming reactions in organic synthesis. Traditionally, these reactions have been performed under the influence of strong bases such as alkali metal alkoxides or hydroxides.¹ However, the strongly basic conditions are often a limiting factor since they can lead to a number of undesirable side- and subsequent reactions. To address this issue, Lewis acid-catalyzed Michael reactions have been developed, allowing the reactions to be carried out under milder conditions.² On the other hand, while most Michael reactions reported so far are performed in organic solvents, today's environmental concerns require organic reactions in water without using harmful organic solvents.^{3–5} The use of water as a solvent in the Michael reaction of 1,3-diketones was reported under basic conditions,⁶ and quite recently, Michael reactions of β -ketoesters with enones in water were found to be catalyzed by ytterbium triflate ($\text{Yb}(\text{OTf})_3$),^{7,8} which has been developed as a water-stable Lewis acid.⁹ However, the reactions were reported to proceed very slowly and needed a period of three to five days for completion. In this paper, we report much faster Michael reactions in water using an excellent Lewis acid catalyst.

In the course of our investigations to develop new synthetic reactions in aqueous media, we have recently introduced new types of Lewis acids, scandium tris(dodecyl sulfate) (STDS) and scandium

* Corresponding author.

Table 1
Effects of Lewis acid catalysts

Entry	Catalyst (eq.)	Yield (%)
1	Sc(OTf) ₃ (0.1)	7
2	Yb(OTf) ₃ (0.1)	10
3	Cu(OTf) ₂ (0.1)	9
4	Sc(O ₃ SC ₁₂ H ₂₅) ₃ (0.1)	14
5	Yb(O ₃ SC ₁₂ H ₂₅) ₃ (0.1)	19
6	Cu(O ₃ SC ₁₂ H ₂₅) ₂ (0.1)	25
7	Sc(O ₃ SOC ₁₂ H ₂₅) ₃ (STDS, 0.1)	81
8	Yb(O ₃ SOC ₁₂ H ₂₅) ₃ (0.1)	16
9	Cu(O ₃ SOC ₁₂ H ₂₅) ₂ (0.1)	46
10	NaO ₃ SOC ₁₂ H ₂₅ (SDS, 0.3)	4
11	SDS (0.3) + Sc(OTf) ₃ (0.1)	65
12	-	6
13 ^a	STDS (0.1)	57
14 ^b	STDS (0.1)	55
15	SDS (0.3) + HCl (0.1)	14

^aCH₂Cl₂ was used as a solvent.

^bNo solvent was used.

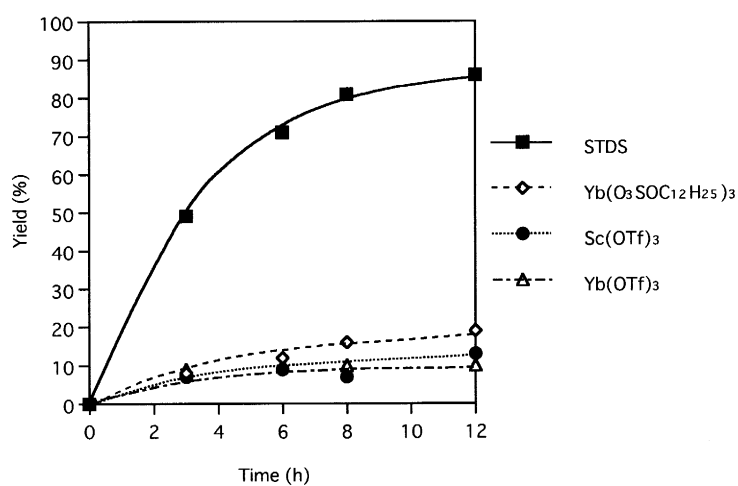


Fig. 1. Plot of isolated yield versus time for Michael reaction of benzyl 2-oxocyclopentanecarboxylate with MVK

tris(dodecanesulfonate).¹⁰ These 'Lewis acid–surfactant-combined catalysts (LASCs)'¹¹ form stable colloidal dispersion systems with organic substrates in water and have been used for Lewis acid-catalyzed reactions such as aldol reactions. It has been suggested that LASCs create hydrophobic reaction fields in water while an active Lewis acidic site is close to the hydrophobic sites.¹⁰ We then intended to use LASCs in Michael reactions of β -ketoesters with enones in water.

Various catalysts were first tested in the model reaction of benzyl 2-oxocyclopentanecarboxylate with methyl vinyl ketone (MVK) in water, and the results are summarized in Table 1. The reaction proceeded very slowly in the presence of scandium, ytterbium, and copper triflates (entries 1–3).¹² The metal dodecansulfonates, which have been used as LASCs, gave slightly better yields than the triflates (entries 4–6). When STDS was used, the reaction was greatly accelerated (entry 7). Although a $\text{Sc}(\text{OTf})_3$ -catalyzed reaction in the presence of a catalytic amount of sodium dodecyl sulfate as a surfactant proceeded smoothly, STDS was more effective (entry 11). In the absence of a Lewis acid catalyst, the reaction proceeded sluggishly (entry 12). It should be noted that STDS worked well in water rather than in dichloromethane or under neat conditions (entries 13 and 14). When a Brønsted acid was used instead of Lewis acids, the yield was low (entry 15). The high catalytic activity of STDS observed in this reaction is supposed to be ascribed to two factors; high Lewis acidity of scandium and high local concentration of the catalyst and the substrates.

The profiles of the reactions catalyzed by $\text{Sc}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, STDS, and $\text{Yb}(\text{O}_3\text{SOC}_{12}\text{H}_{25})_3$ were shown in Fig. 1. STDS was the most effective among the catalysts tested, and the reaction proceeded smoothly to give >80% yield after 8 h.

Several examples of STDS-catalyzed Michael reactions are summarized in Table 2. In all cases, the reactions proceeded smoothly in the presence of a catalytic amount of STDS at 30°C in water, to afford the corresponding Michael adducts in high yields. It should be noted that no bis-Michael adduct was obtained in the reaction of an α -unsubstituted β -ketoester (entry 5). When ethyl acrylate was used, only starting materials were recovered.

A typical experimental procedure for the LASC-catalyzed Michael reactions of β -ketoesters with enones is described: To LASC (0.025 mmol, 0.1 equiv.) in water (1.5 mL) was added a β -ketoester (0.25 mmol) and an enone (0.75 mmol). After stirring for 12–24 h at 30°C, the reaction mixture was diluted with water, and the aqueous layer was extracted with ethyl acetate. To the combined organic layer was added toluene and the solution was concentrated under reduced pressure. The residue was purified by preparative TLC to afford the desired Michael adduct.

In summary, a Lewis acid–surfactant-combined catalyst, STDS, was found to catalyze Michael reactions of β -ketoesters with enones smoothly in water. As far as we know, this is the most active Lewis acid catalyst for Michael reactions in water. Development of efficient synthetic reactions in water using LASCs as catalysts and the application of LASCs to asymmetric Michael reactions are now under investigations.

Acknowledgements

This work was partially supported by a grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. M.Y. thanks the JSPS fellowship for Japanese Junior Scientists.

Table 2
STDS-catalyzed Michael reactions in water^a

Entry	Donor	Acceptor ^b	Time (h)	Product	Yield (%)
1			24		91 (R ¹ = Bn)
2			20		96 (R ¹ = ^t Bu)
3			12		92 (R ² = Me)
4			12		100 (R ² = Et)
5			16		91
6			24		87
7			24		86
8 ^c			35		68

^aThe reactions were carried out in the presence of STDS (0.1 eq.) in H₂O at 30 °C unless otherwise noted.

^bAcceptor (3.0 eq.) was used. When acceptor (1.5 eq.) was used, the reaction proceeded more slowly.

^cSTDS (0.2 eq.).

References

1. (a) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179–555. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp. 1–67.
2. For transition metal catalysis of the Michael reaction of 1,3-dicarbonyl compounds, see: Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259–1266 and references cited therein.
3. *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, 1998.
4. Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035.
5. For a recent example of Michael reactions under solvent-free conditions, see: Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770–3773.

6. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497.
7. (a) Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879–1882. (b) For Yb(OTf)₃-catalyzed Michael reactions of β-nitroesters in water, see: Keller, E.; Feringa, B. L. *Synlett* **1997**, 842–843.
8. Yb(OTf)₃-catalyzed Michael reactions of silyl enol ethers with enones were reported. Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815–6818.
9. Kobayashi, S. *Synlett* **1994**, 689–701.
10. Kobayashi, S.; Wakabayashi, T. *Tetrahedron Lett.* **1998**, *39*, 5389–5392.
11. For other carbon–carbon bond-forming reactions in the presence of various LASCs, see: (a) Manabe, K.; Kobayashi, S. *Synlett* **1999**, 547–548. (b) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **1999**, *55*, 11 203–11 208.
12. Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288.