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$Yb(OTf)_3$-CATALYZED MICHAEL ADDITION REACTIONS OF β-KETOESTERS ON SILICA GEL SUPPORTS AND AT HIGH PRESSURE[1]

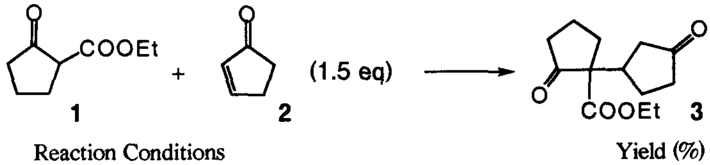
Hiyoshizo Kotsuki* and Koji Arimura

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

Abstract: Michael addition reactions of β-ketoesters with a variety of α,β-unsaturated carbonyl compounds proceed efficiently using a $Yb(OTf)_3$ catalyst either on a silica gel support or at high pressure. © 1997 Elsevier Science Ltd.

The Michael addition reaction is widely recognized as one of the most important carbon-carbon bond forming reactions in organic synthesis. Several reagent systems for this reaction have been developed to date.[2] Instead of traditionally used strong bases, considerable attention has recently been focused on the use of lanthanide(III) trifluoromethanesulfonates [lanthanide triflates, $Ln(OTf)_3$] as water-tolerant Lewis acids.[3] For example, Keller and Feringa found that $Yb(OTf)_3$ could serve as an efficient catalyst for Michael addition reactions of β-ketoesters in water as solvent.[4] Although this method has its own synthetic value, there are some limitations for the available Michael acceptors. For example, no reaction was observed for acrylic esters or cycloalkenones. In our continuing efforts to develop novel organic reactions at high pressure and also on silica gel supports,[1, 5] we explored the feasibility of the $Yb(OTf)_3$ method for these inaccessible Michael addition reactions. In this paper we describe our original findings.

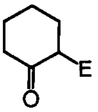
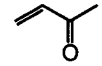
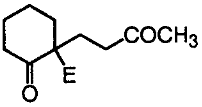
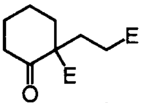
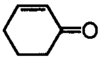
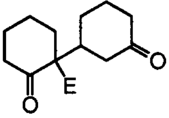
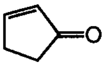
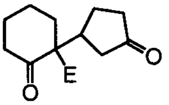
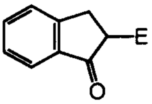
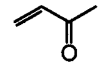
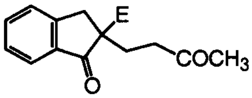
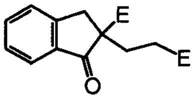
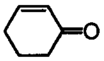
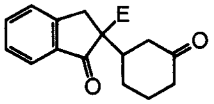
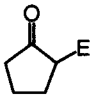
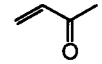
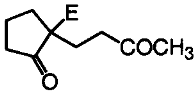
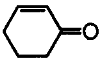
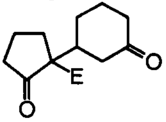
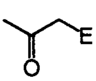
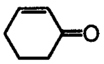
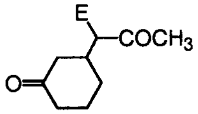
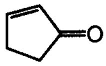
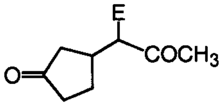
We first examined the reaction of β-ketoester **1** with 2-cyclopentenone (**2**) to determine the optimum conditions (Scheme 1), since these substrates are completely unreactive under Feringa's conditions.[4] An



Reaction Conditions	Yield (%)
$Yb(OTf)_3$ (0.1 eq), H_2O, rt, 5 days	NR (ref 4)
$Yb(OTf)_3$ (0.1 eq), CH_3CN, 8 kbar, 60 °C, 1 day	62
$Yb(OTf)_3$ (0.1 eq), H_2O (0.1 eq), CH_3CN, 8 kbar, 60 °C, 1 day	73
$Yb(OTf)_3$ (0.06 eq) - SiO_2, rt, 6 days	87

Scheme 1

Table 1. Yb(OTf)$_3$-Catalyzed Michael Addition Reaction of β-Keto Esters

Entry	Donor (E = COOEt)	Acceptor (1.5 eq)	Method[a]	Time (d)	Product (E = COOEt)	Yield, %[b]
1			**A**	1		50
2			**B**	2		95
3			**A**	1		81
4			**B**	12		0
5			**A**	1		45[c]
6			**B**	6		79[c]
7			**A**	2		53[c]
8			**B**	5		86[c]
9			**A**	1		67 (5)[d]
10			**B**	1		82
11			**A**	1		88
12			**B**	7		0
13			**A**	1		42 (13)[c,d]
14			**B**	2		71[c]
15			**A**	1		71
16			**B**	1.5		93
17			**A**	1		66[c]
18			**B**	6		79[c]
19			**A**	0.5[e]		39[c,f]
20			**B**	1		89[c]
21			**A**	0.5		68[c]
22			**B**	1.5		78[c]

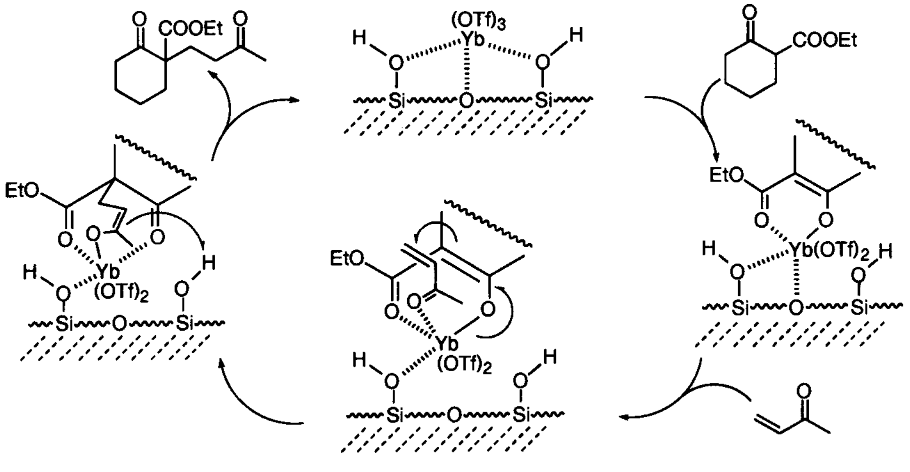
[a] **Method A**: Yb(OTf)$_3$ + H$_2$O in CH$_3$CN, 8 kbar, 60 °C; **Method B**: Yb(OTf)$_3$-SiO$_2$, 1 atm, rt, unless otherwise noted. [b] Isolated yield. Yields in parentheses are recovery. [c] 1 : 1 mixture of diastereomers. [d] Prolonged reactions could not improve the product yields. [e] At 40 °C. [f] Complex mixture of products was obtained.

efficient Michael addition reaction between **1** and **2** (1.5 eq) was accomplished at high pressure with the addition of a small amount of water.[6] The reaction yields were most satisfactory (62 → 73%), consistent with our previous observations.[1]

As an alternative method, we further examined the reaction on silica gel surface under solvent-free conditions.[7] Although the use of silica gel for several organic transformations is well-documented,[8] there is no precedent for lanthanides as catalysts supported on silica gel.[9] The catalytic system of $Yb(OTf)_3$ dispersed on chromatography silica gel (Wakogel C-300) was prepared by simple mixing of both reagents in acetonitrile followed by complete removal of the solvent.[10] Addition of **1** and **2** to this catalyst resulted in a clean reaction at room temperature and, after 6 days, the desired Michael adduct **3** was obtained in 87% yield as a 1 : 1 diastereomeric mixture. Although the reaction on silica gel was relatively slow compared with the high pressure reaction, this method possesses a tremendous advantage due to its mildness and convenience.[11] The recovered silica gel catalyst could be reused, but its catalytic activity was considerably reduced due to complexation of $Yb(OTf)_3$ during the work-up procedure used.

The general applicability of these two methods has also been demonstrated for a variety of substrates and the results are summarized in Table 1.[12] As a consequence, the following characteristic features should be mentioned. Yb(III)-catalyzed reactions on silica gel were particularly useful for conjugated enones as Michael acceptors. The only unsuccessful example was ethyl acrylate (entries 4 and 12), although the use of the high pressure technique was highly successful (entries 3 and 11). Enone derivatives, e.g., methyl vinyl ketone, gave lower yields at high pressure compared with silica gel-supported catalysis because of the formation of unidentified by-products under these enforced conditions (compare entries 1 and 2, 9 and 10, and 15 and 16). In spite of our extensive efforts, less reactive substrates such as acrylonitrile, methyl crotonate, methyl propiolate, and methyl cinnamate gave no adducts.[13]

A plausible mechanism to account for the remarkable effect of silica gel is shown in Scheme 2. Silica gel is mildly acidic and must interact favorably with $Yb(OTf)_3$ at its surface. When β-ketoesters and Michael acceptors were introduced, both reagents probably coordinated at a vacant coordination site of Yb-metal. Condensation then took place efficiently by virtue of the anchimeric assistance of silica gel.



Scheme 2

In conclusion, we have succeeded in developing a powerful new method to effect Michael addition reactions of β-ketoesters under Yb(III)-catalyzed conditions.[14] In particular, the reaction on a silica gel support was favorable for conjugated enone systems. At high pressure acrylic esters reacted most successfully. We believe that these two methods are complementary for production of either type of β-ketoester Michael adduct. Further studies to extend the synthetic utility of these novel procedures are now in progress in our laboratories.

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10. No remarkable difference in reactivity was observed after drying at 200 °C for 5 h.
11. As expected, direct treatment of 1 and 2 with an Yb(OTf)$_3$ catalyst was rather drastic to control the reaction, giving 3 in 78% yield after 2 days at rt. We could not recognize the catalytic activity of silica gel itself for the present purpose: a trace amount of 3 was only detected after 1 week at rt.
12. Satisfactory spectral data were obtained for all new compounds.
13. At high pressure the use of acrylonitrile as an acceptor resulted in polymerization.
14. **Preparation of Yb(OTf)$_3$-SiO$_2$ catalyst:** Wakogel C-300 (4.0 g) was added to a solution of Yb(OTf)$_3$ (400 mg, 0.64 mmol) in CH$_3$CN (9 mL) and this suspension was stirred for 24 h at rt. Removal of the solvent under reduced pressure gave a white powder, which was stored under dry conditions. No significant loss of reactivity was observed even after standing for 1 month at rt.

    General procedure for Michael addition reactions. At high pressure (Method A): A solution of donor (1.0 mmol) and acceptor (1.5 mmol) in ca. 1.5 mL of CH$_3$CN containing Yb(OTf)$_3$ (60 mg, 0.1 mmol) and water (1.8 mg, 0.1 mmol) was placed in a Teflon reaction vessel at 8 kbar as indicated in Table 1. The crude product was extracted with AcOEt and purified by silica gel column chromatography to give the desired Michael adduct. **On silica gel supports (Method B):** A mixture of donor (1.0 mmol) and acceptor (1.5 mmol) was mounted on Yb(OTf)$_3$-SiO$_2$ (400 mg, 0.06 mmol as an active Yb(OTf)$_3$ catalyst) and allowed to stand at rt. After completion of the reaction, the catalyst was removed by filtration and rinsed well with CH$_2$Cl$_2$. Evaporation of the solvent gave a crude product, which was purified as above to afford the desired Michael adduct.

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