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Ytterbium(III) Triflate-Catalyzed Selective Methanolysis of Methoxyacetates: A New Deprotective Method

Takeshi Hanamoto, Yuichi Sugimoto,
Yasuo Yokoyama, and Junji Inanaga*

*Institute for Molecular Science, Myodaiji,
Okazaki 444, Japan, and Institute for Fundamental
Research of Organic Chemistry (IFOC), Kyushu University,
Hakozaki, Fukuoka 812-81, Japan*

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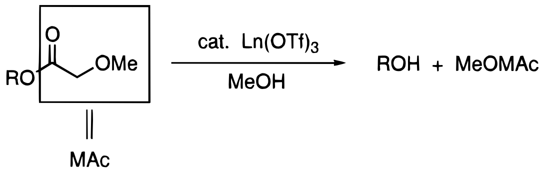
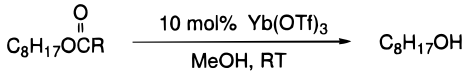
The methoxyacetyl (MAc) group was introduced as a useful protective group for the hydroxy function of nucleoside derivatives in which the cleavage of a methoxyacetate in methanolic ammonia was reported to proceed 20 times faster than the corresponding acetate.[1] Since then, however, it has not found widespread use in organic synthesis probably because of the lack of efficient deprotective methods which would favor use of the methoxyacetyl group.[2] Recently, we introduced the 1-*O*-methoxyacetyl sugar as a new glycosyl donor which can be effectively activated by lanthanide(III) triflate [Ln(OTf)$_3$][3,4] through the strong interaction between the Ln 3+ ion and the methoxyacetyl moiety, thus offering a useful glycosylation method.[5−7] This type of activation prompted us to examine the possibility of the Ln(OTf)$_3$-catalyzed alcoholysis of methoxyacetates under nonbasic conditions. In this paper, we report a new method for the selective deprotection of the methoxyacetyl group in the presence of other protective groups for the hydroxy functionality under mild conditions (eq 1).



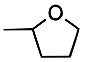
(1)

Screening of a series of lanthanide(III) triflates as catalysts for the methanolysis of benzyl methoxyacetate has revealed that some heavy-lanthanide(III) triflates such as Er(OTf)$_3$, Tm(OTf)$_3$, Yb(OTf)$_3$, and Lu(OTf)$_3$ are superior to light-lanthanide(III) triflates.[8] Among the four heavy-lanthanide(III) triflates, we selected Yb(OTf)$_3$ as an economical catalyst and compared the susceptibility of various acyl derivatives of 1-octanol to methanolysis (Table 1).

Table 1. Yb(III)-Catalyzed Methanolysis of Various Esters



$$C_8H_{17}O\overset{O}{\overset{\|}{C}}R \xrightarrow[\text{MeOH, RT}]{\text{10 mol\% Yb(OTf)}_3} C_8H_{17}OH$$

entry	R	time, h	yield,[a] %
1	- CH_2OMe	0.5	>99
2[b]	"	1	>99
3[c]	"	10	>99
4		4	99
5	- CH_2OPh	5	>99
6	- Me	30	80
7	- $(CH_2)_2OMe$	126	79
8	- CMe_2OMe	126	19
9	- $(CH_2)_2Me$	126	11

[a] Determined by ^{1}H NMR analysis. [b] 1 mol % of the catalyst was used. [c] 0.1 mol % of the catalyst was used.

Among the seven esters examined, octyl methoxyacetate was cleaved most rapidly. For example, its methanolysis is more than 300 times faster than that of the corresponding acetate (Table 1, entries 3 vs 6). Semiempirical calculations of the related compounds strongly suggest that the selective activation of the methoxyacetyl group with a metal ion would be affected by the formation of the five-membered chelate.[6] The reactions of other esters bearing an ethereal oxygen at their α carbons such as 2-tetrahydrofuranylacetate (Table 1, entry 4), phenoxyacetate (Table 1, entry 5), and α-methoxy-α-methylpropionate (Table 1, entry 8) proceeded rather slowly although the ytterbium-involved five-membered chelate formation seems to be possible. The *β*-methoxypropionate (Table 1, entry 7), which might produce the six-membered chelate, reacted more slowly than the acetate (Table 1, entry 6). These results indicate that not only the chelate formation but also steric factors influence the rate of the catalytic alcoholysis.

Next, we carefully examined the Yb(OTf)$_3$-catalyzed methanolysis of dodecanediol monomethoxyacetates hav-

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[†] To whom correspondence should be addressed at IFOC, Kyushu University.

(1) Reese, C. B.; Stewart, J. C. M. *Tetrahedron Lett.* **1968**, 4273−4276.

(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; pp 10−142.

(3) (a) Thom, K. F. U.S. Patent 3615169, 1971; *Chem. Abstr.* **1972**, *76*, 5436a. (b) Almasio, M. C.; Arnaud-Neu, F.; Schwing-Weill, M. J. *Helv. Chim. Acta* **1983**, *66*, 1296−1306. (c) Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017−1021.

(4) We thank the Shin-Etsu Chemical Co., Ltd., and the Central Glass Co., Ltd., for providing lanthanoid oxides and triflic acid, respectively, which are starting substrates for Ln(OTf)$_3$.

(5) For the lanthanide(III) triflate-catalyzed glycosylation of 1-*O*-methoxyacetyl sugars, see: Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *Tetrahedron Lett.* **1993**, *34*, 2791−2794. See also: Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1090−1091.

(6) For a MNDO-PM3 study on the selective activation of 1-methoxyacetyl sugars by zinc(II) ion, see: Inanaga, J.; Yokoyama, Y.; Sugimoto, Y.; Hanamoto, T. *Mem. Fac. Sci., Kyushu Univ. Ser. C, Chem.* **1993**, *19*, 29−32.

(7) For other recent reports concerning Ln(OTf)$_3$-catalyzed reactions, see: (a) Hosono, S.; Kim, W.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4−5. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423−424. (c) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413−4414. (d) Fukuzawa, S.; Tsuchimoto, T.; Kanai, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2227−2232. (e) Kobayashi, S. *Synlett.* **1994**, 689−701. (f) Aspinall, H. C.; Browning, A. F.; Greeves, N.; Ravenscroft, P. *Tetrahedron Lett.* **1994**, *35*, 4639−4640. (g) Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827−830. (h) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433−436. (i) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597−2601.

(8) The reactions were performed using methanol-d_4 as a solvent, and the catalytic activities of 14 Ln(OTf)$_3$ were evaluated from the NMR yield of the obtained benzyl alcohol: La(OTf)$_3$ (21%), Pr(OTf)$_3$ (62%), Nd(OTf)$_3$ (46%), Sm(OTf)$_3$ (62%), Eu(OTf)$_3$ (53%), Gd(OTf)$_3$ (55%), Tb(OTf)$_3$ (56%), Dy(OTf)$_3$ (58%), Ho(OTf)$_3$ (58%), Er(OTf)$_3$ (94%), Tm(OTf)$_3$ (90%), Yb(OTf)$_3$ (99%), and Lu(OTf)$_3$ (99%).

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Table 2. Yb(III)-Catalyzed Selective Cleavage of the Methoxyacetyl Group

$$RO(CH_2)_{12}OMAc \xrightarrow[\text{MeOH}]{\text{30 mol\% Yb(OTf)}_3} RO(CH_2)_{12}OH$$

entry	R	temp, °C	time, h	yield,[a] %
1	Ac	0	2	93 (7)
2[b]	Ac	25	13	98 (2)
3	Bz	0	3	95 (1)
4	THP	0	2	92 (3)
5	TBDMS	0	1.5	94 (3)
6	TBDPS	0	2	99 (0)
7	MEM	25	0.5	99 (0)

[a] Isolated yield. In parentheses are shown the yields of 1,12-dodecanediol. [b] Ethanol was used instead of methanol.

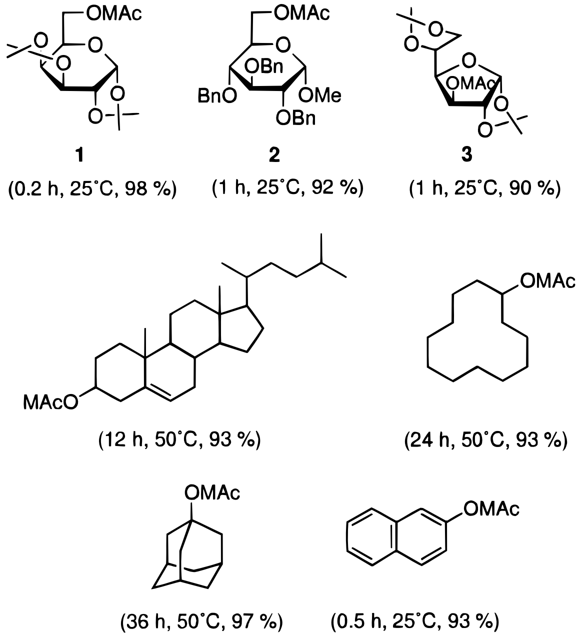

Figure 1. Yb(OTf)$_3$-catalyzed methanolysis of methoxyacetates.

ing different protective groups for the other hydroxy function (Table 2). As expected, the methoxyacetyl group was removed selectively in the presence of not only ester moieties such as acetate and benzoate but also such acid-labile ethereal protective groups as THP, TBDMS, *tert*-butyldiphenylsilyl (TBDPS), and MEM ethers.

As shown in Figure 1, various substrates such as sugar derivatives (**1**–**3**), secondary and tertiary esters, and an aromatic ester were all cleaved cleanly under nonbasic conditions to give the corresponding alcohols in excellent yields.

In conclusion, we have developed a new method for the deprotection of the methoxyacetyl group, in which Yb(OTf)$_3$ acted as a Lewis acid catalyst in methanol to effectively promote the transesterification.[9] With the present new deprotective method, the methoxyacetyl group should receive further evaluation and should be more widely used in organic synthesis as a unique acyl-type protective group which can be selectively removed under nonbasic conditions. It should also be noted that the catalyst can be recovered easily and reused without serious loss of catalytic activity.[10]

Experimental Section

The following experimental procedures are representative:

Cleavage of Methoxyacetate 1 by Yb(OTf)$_3$ in Methanol. To a solution of 1,2:3,4-di-*O*-isopropylidene-6-*O*-(methoxyacetyl)-α-D-galactopyranose[11] (**1**, 19.9 mg, 0.051 mmol) in dry methanol (0.5 mL) was added a solution of Yb(OTf)$_3$ (9.5 mg, 30 mol %) in dry methanol (1 mL), and the mixture was stirred for 12 min at 25 °C. To the reaction mixture was added a drop of water, and then the solvent was evaporated under vacuum. Purification of the crude product by preparative TLC on silica gel afforded the desired alcohol (13.0 mg, 98%) as a colorless oil.

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[9] It was also found that Yb(OTf)$_3$ acts as an effective catalyst for the esterification of methoxyacetic acid with alcohols. For example, 1-octyl methoxyacetate and 1-adamantyl methoxyacetate were prepared in quantitative and 79% yield, respectively, by treating the corresponding alcohols with methoxyacetic acid (1.1 equiv) and 10 mol % of the catalyst. Preliminary results were presented at the 65th meeting of the Chemical Society of Japan, Tokyo, March 1993, symposium paper II, p 474. For a recent report on the Sc(OTf)$_3$, catalyzed acylation of alcohols, see ref 7c.

[10] For example, the methanolysis of benzyl methoxyacetate with the recovered catalyst under the same conditions afforded benzyl alcohol in 91% isolated yield.

[11] Prepared from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and methoxyacetyl chloride according to the standard esterification procedure.