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Triethyl- (or Trimethyl-)Silyl Triflate-Catalyzed Reductive Cleavage of Triphenylmethyl (Trityl) Ethers with Triethylsilane

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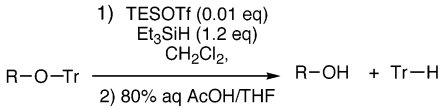
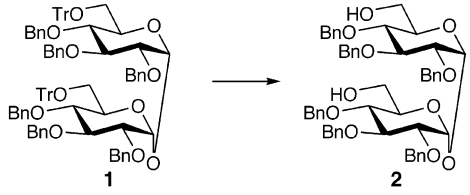
ABSTRACT



A triphenylmethyl (trityl) ether was reductively and instantaneously cleaved by triethylsilane in the presence of a catalytic amount of TES- (or TMS)-triflate. The reaction conditions are mild enough to achieve reduction in the presence of a variety of acid-sensitive functional groups. Upon a mild acidic treatment of the crude product, the corresponding alcohol is obtained in high yield.

A trityl ether is often employed in carbohydrate chemistry due to its usefulness for the selective protection of primary alcohol in the presence of a secondary or tertiary alcohol.[1] However, as rather strong acidic conditions are required for hydrolytic cleavage, some of the acid-sensitive functional groups cannot survive under the reaction conditions. Although several milder processes for the cleavage of a trityl group have been developed recently, more effective procedures are still required.[2−6] During our synthetic study using trehalose derivative **1**, we encountered difficulty in achieving selective cleavage of a trityl group without causing damage to the acid-sensitive 1,1-glycosidic linkage.[7] We examined a reductive condition that was developed for reductive etherification in our group in 1994[8] and found a mild process to achieve novel TES- (or TMS)-triflate-catalyzed reductive cleavage of a trityl ether under neutral conditions with very high chemoselectivity. When the crude product was treated with weak acid (aqueous acetic acid−THF at room temperature),[9] the corresponding alcohol was obtained in excellent yield. The cleavage process of the trityl group is not hydrolysis but reduction and is particularly characteristic in its quick reaction and color change.



The reaction should involve an equilibrium between trityl ether **3** and triethylsilyl ether **4** together with trityl cation **5**. The yellow cation **5** should be quickly reduced to triphenylmethane (**6**) by triethylsilane, and triethylsilyl triflate should be regenerated at the same time to accomplish the catalytic cycle. Since trityl cation **5** is characteristic in its yellow color, the reaction is simply monitored by its disappearance.

(1) Greene, T. W.; Wuts, P. G. M. *Protective Group in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, 1999; pp 102−104.
(2) Wahlstrom, J. L.; Ronald, R. C. *J. Org. Chem.* **1998**, *63*, 6021−6022.
(3) Lu, R. J.; Liu, D.; Giese, R. W. *Tetrahedron Lett.* **2000**, *41*, 2817−2819.
(4) Jones, G. B.; Hynd, G.; Wright. J. M.; Sharma, A. *J. Org. Chem.* **2000**, *65*, 263−265.
(5) Nezhad, A. K.; Almadari, R. F. *Tetrahedron* **2001**, *57*, 6805−6807.
(6) Yadav, J. S.; Reddy, B. V. S. *Carbohydr. Res.* **2000**, *329*, 885−888.

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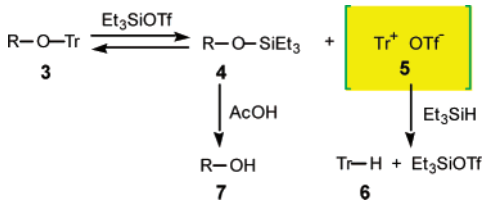
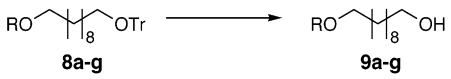
Generally, the reaction is completed very quickly within a few minutes after the addition of TESOTf (or TMSOTf).[9,10]



We were interested in the chemoselectivity of this novel reductive cleavage and prepared a variety of 1,10-decanediol derivatives **8a**−**g**. The acetyl group of **8a** was entirely inert against the reaction conditions, and the reaction of **8a** was completed within 2 min by treatment with 0.02 equiv of TESOTf and 1.2 equiv of Et_3SiH in CH_2Cl_2 at room temperature. The crude extract was treated with 80% aqueous acetic acid in THF at room temperature for 30 min and, following column chromatography on silica gel, afforded diol **9a** in 95% yield (entry 1 of Table 1).[7] Using 0.01 or even

Table 1. TESOTf-Catalyzed Reductive Cleavage of Trityl Ether

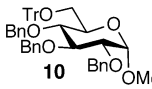
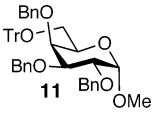
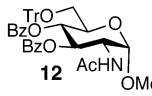
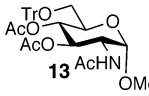
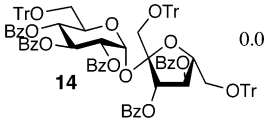
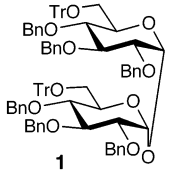


entry	R	TESOTf (equiv)	temp	time[a]	yield (%)[b]
1	Ac (**8a**)	0.02	25	1 min, 10 sec	95
2	Ac (**8a**)	0.01	25	2 min, 28 sec	98
3	Ac (**8a**)	0.005	25	13 min, 00 sec	91
4	Ac (**8a**)[c]	0.005	25	4 min, 30 sec	96
5	Piv (**8b**)[c]	0.02	25	2 min, 00 sec	99
6	Bz (**8c**)	0.01	25	3 min, 30 sec	95
7	Bn (**8d**)	0.01	25	1 min, 20 sec	93
8	MPM (**8e**)	0.01	25	1 min, 16 sec	93
9	TBDPS (**8f**)	0.01	25	4 min, 00 sec	89
10	MOM (**8g**)	0.01	−48	24 min, 00 sec	93[d]

[a] Time until the disappearance of the yellow color. [b] Isolation yield after acidic treatment using 80% AcOH and THF at room temperature for 30 min. [c] Reaction was carried out using TMSOTf instead of TESOTf. [d] Isolation yield after hydrolysis of TES group by using TBAF in THF at room temperature for 1 h.

0.005 equiv of TESOTf completed the reaction within 3 or 13 min, respectively (entries 2 and 3). TMSOTf is also useful for the cleavage of the trityl group and afforded alcohol **9a** in excellent yield (entry 4). The pivaloyl group of **8b** and the benzoyl group of **8c** were also inert and afforded alcohols **9b** and **9c**, respectively, in excellent yields (entries 5 and

Table 2. TESOTf-Catalyzed Reductive Cleavage of Trityl Ether

Substrate	TMSOTf (equiv.)	Time (min)	Yield (%)
 **10**	0.01	11	88
 **11**	0.01	5	89
 **12**	0.01 0.01[a] 0.05[a]	32 65 25	99 92 90
 **13**	0.01	55	87
 **14**	0.01[b]	5	86
 **1**	0.01[c] 0.01[d]	40 25	96 95

[a] TESOTf was employed as the catalyst. [b] Employed 3.6 equiv of Et_3SiH. [c] Employed 2.5 equiv of Et_3SiH. [d] Employed 2.5 equiv of Et_3SiH and 0.01 equiv of Et_3SiOTf.

6). The trityl groups of **8d**−**f** were also cleaved without causing any damage to the benzyl, MPM, and TBDPS protecting groups, respectively, under similar reaction conditions. Selective cleavage of trityl ether in the presence of the MOM group required lower reaction temperatures, and the yellow color disappeared after 24 min at −48 °C. Furthermore, TBAF/THF was required for selective cleavage of the TES group to obtain alcohol **9g** in excellent yield (entry 10). The drying operation[7] is critical for preparing TES ethers **4** in excellent yield since significant quantities of alcohols were detected by using an ordinary reaction system.

Therefore, we applied our procedure to a variety of sugar derivatives by using 0.01 equiv of TMSOTf and 1.2 equiv of Et_3SiH. Sugar derivatives generally required a rather longer reaction period; however, 30 min is sufficient for most cases. The trityl group of tribenzyl methyl glucoside **10** was

(7) (a) Nishizawa, M.; Minagawa, R.; García, D. M.; Hatakeyama, S. *Tetrahedron Lett.* **1994**, *35*, 5891−5894. (b) Nishizawa, M.; García, D. M.; Minagawa, R.; Noguchi, Y.; Imagawa, H.; Yamada, H.; Watanabe, R.; Yoo, Y. C.; Azuma, I. *Synlett* **1996**, 452−454. (c) Watanabe, R.; Yoo, Y. C.; Hata, K.; Mitobe, M.; Koike, Y.; Nishizawa, M.; Garcia, D. M.; Noguchi, Y.; Imagawa, H.; Yamada, H.; Azuma, I. *Vaccine* **1999**, *17*, 1484−1492.

(8) Hatakeyama, S.; Mori, H.; Kitano, K.: Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1994**, *35*, 4367−437.

(9) General procedure is as follows. To the dried solution of trityl ether (0.05 M in CH_2Cl_2) (see ref 8) were added triethylsilane (1.2 equiv) and trimethylsilyl triflate (0.01 equiv) at room temperature. The resulting yellow solution was stirred until the color disappeared, and the reaction was quenched by the addition of water. The crude extract was dissolved in THF and 80% aqueous acetic acid (1:1), and the solution was stirred for 30 min. After neutralization, the organic extract was purified by column chromatography on silica gel using hexane/ethyl acetate as an eluant.

(10) Nishizawa, M.; García, D. M.; Yamada, H. *Synlett* **1992**, 797−799.

cleaved in 11 min and converted to the corresponding primary alcohol in 88% yield after acidic hydrolysis using aqueous AcOH in THF at room temperature for 30 min. Methyl galactoside **11** also afforded the corresponding primary alcohol in 89% yield after 5 min of reaction and acidic hydrolysis. The trityl group of *N*-acetylglucosamine derivative **12** was also selectively cleaved after 32 min by using 0.01 equiv of TMSOTf and the following aqueous hydrolysis. TESOTf can also be applied to the reaction of **12**, but a longer reaction period is required. The corresponding acetate **13** was also smoothly converted to the corresponding primary alcohols in 87% yields. Three trityl groups of sucrose derivative **14** were also selectively cleaved and afforded a triol in 86% yield.[11] Finally, we applied our procedure to a 2 g scale of trehalose derivative **1**, and diol **2** was obtained in 96% yield by 40 min of reaction and the following aqueous hydrolysis.

(11) Khan, R. *Carbohydr. Res.* **1972**, *22*, 441−445.

Therefore, we have established extremely mild conditions to cleave a trityl ether and will now be able to choose trityl protection of alcohols in the presence of a variety of acid-sensitive functional groups. In our synthetic study using trehalose derivative **1**, we have employed an expensive TBDPS group for the selective protection of the primary alcohols of trehalose. Now we can substitute trityl protection in the methodology since the price of trityl chloride is 1/10 of that of TBDPS chloride in commercial catalogs.[10]

Acknowledgment. This work was supported by a Grant-in-Aid for Priority Area (No. 14044111) and (No. 13771348) from the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government. We wish to dedicate this study to Professor Yoshinori Asakawa of Tokushima Bunri University on the occasion of his 61st birthday.

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