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An Efficient and Selective Method for Hydrolysis of Acetonides

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Abstract: Acetonide was selectively and efficiently cleaved with cerium (III) chloride heptahydrate and oxalic acid in acetonitrile. This method was found to be of good functionalities compatibility with such acid sensitive groups as Tr, PMB, TBDMS, TBDPS, OAc, OBz, OTs, OTf.

Key words: cerium (III) chloride, oxalic acid, acetonides, diols

The protective groups in organic synthesis, particularly in multi-step synthesis of structurally complicated natural products, are very important. Many syntheses failed just because the protective groups selected were unable to be cleaved at the appropriate step.¹ Acetonide is one of the most commonly used protective groups to mask the hydroxy groups in polyhydroxy natural products, nucleosides and oligosaccharides.²

Over the past years a number of methods have been developed and reviewed for the hydrolysis of acetonide.³ However, the development of new selective methods which have good compatibility with other protecting groups is still entailing.⁴ Recently, in the course of our studies directed toward the total synthesis of macrolactin A, we found that selective removal of acetonide group in 1 giving deprotected product 2 and leaving the TBDPS group intact (Scheme 1) was unsatisfactory with CF₃COOH⁵, CSA⁶ and *p*-TsOH.⁷

Herein we wish to report an efficient and selective method for the cleavage of the acetonide group using cerium (III) chloride heptahydrate with a catalytic amount of oxalic acid in acetonitrile at ambient temperature. This method does not need expensive reagents and special operations to exclude the moisture and oxygen from the reaction medium. It has also proved that this method can achieve high chemo- and regioselectivity with good to excellent yields.



Scheme 1

It is evident from the Table that acid labile protective groups such as Tr, TBDMS, TBDPS, PMB ethers and OAc, OBz, OTs, OTf esters are all left intact under the reaction conditions. The acetonide group in **1** was selectively cleaved obtaining 2 with good yield (86%, entry i). In substrates which have more than one acetonide group, regioselectivity could be achieved as well by cleavage of the least hindered one (entry j). Further experiments were also conducted in determining whether the present method had influence on the stereochemistry of the chiral acetonide. The results (entry a) showed that the stereochemistry of the product was retained during deprotection. The value of specific optical rotation of the resulting diol is the same as that of the deprotected product obtained by using p-TsOH in MeOH.

The amounts of CeCl₃•7H₂O and oxalic acid used in the reaction were tested and optimized. Neither cerium (III) chloride nor oxalic acid alone could effect the hydrolysis of the acetonide even after 48 h. It was found that the amount of CeCl₃•7H₂O was decisive for completion of hydrolysis of acetonides. When less than one equivalent of CeCl₃•7H₂O was used, the hydrolysis proceeded rather slowly. The optimal molar ratio of substrates, CeCl₃•7H₂O and (COOH)₂ is 1:2:0.05.⁸

In this reaction we suppose that the Brønsted acidity of oxalic acid, the Lewis acidity and oxyphilicity of cerium (III) ion generate together a synergic effect on removing the acetonide.⁹ Thus, a possible mechanism is envisioned in Scheme 2, in which cerium (III) ion first coordinates with the least hindered oxygen and then an α -chloro ether is formed which undergoes acid catalyzed hydrolysis to furnish the deprotected diol.





In conclusion, we have developed a novel and efficient method for the selective hydrolysis of acetonide group by $CeCl_3 \cdot 7H_2O$ -(COOH)₂ system. This method offers several advantages like easy handling, good compatibility with other acid sensitive functional groups, low costs of the reagents and high yields of the diols.⁸

Entry	Substrate	Product ^a	Reaction time (h)	Yield (%) ^b
a	Yo COOE		2	98
b		но но ормв	1.5	97
с	↓0 ○↓ ○OTr	HO HO OTr	0.5	64
d	OAc	HO HO OAc	2	98
e	40 OVTS	HO HO	2	97
f	40 OVTf	HO HO OTf	2.5	93
g	40 OBz	HO HO	2	97
h	+0 OTE		s ^{0.7}	70
i		HO OH BDPS HO	S 1	86
j	of of		0.5	76

Table Selective Hydrolysis of Acetonide by CeCl₃•7H₂O-(COOH)₂ in Acetonitrile

^a All products show satisfactory ¹H NMR data.⁸ ^b Isolated yields after purification.

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- (8) Typical experimental procedure: To a stirred solution of acetonide protected diol (1mmol) and CeCl₃•7H₂O (745mg, 2mmol) in acetonitrile (5ml) was added (COOH)₂ (6.3mg, 0.05mmol) at ambient temperature. Stirring was continued for the time period as indicated (Table). Upon completion of the reaction, the mixture was cooled to 0 °C, solid sodium bicarbonate was added to neutralize the pH of the reaction mixture, which was then concentrated in vacuo. The residue was treated with ethyl acetate and filtered. The filtrate was then concentrated, and the resulting product was subjected to flash chromatography (silica gel, ethyl acetate) to afford the corresponding diol. ¹H NMR (400MHz, CDCl₃) entry a: δ 6.90 (dd, 1H, *J* = 15.7Hz, 2.4Hz), 6.15 (d, 1H, *J* = 15.7Hz), 4.40-4.45 (m, 1H), 4.20 (q, 2H, J = 7.0Hz), 3.92 (brs, 2H), 3.75-3.81 (m, 2H), 1.31 (t, 3H, *J* = 7.0Hz); entry b: δ 7.22 (dd, 2H, *J* = 6.6Hz, 2.2Hz), 6.86 (dd, 2H, *J* = 6.6Hz, 2.2Hz,), 4.43 (s, 2H), 3.82-3.87 (m, 1H), 3.78 (s, 3H), 3.56-4.22 (m,

2H) 3.22-3.28 (m, 2H), 1.64-1.80 (m, 2H); entry c: δ7.42 (dd, 6H, J = 7.6Hz, 1.1Hz), 7.31 (td, 6H, J = 7.6Hz, 1.1Hz), 7.22 (td, 3H, J = 7.6Hz, 1.1Hz), 3.86-3.92 (m, 1H), 3.42-3.47 (m, 1H), 3.59-3.62 (m, 1H), 3.45-3.50 (m, 1H), 3.37-3.40 (m, 1H), 2.29 (brs, 2H), 1.79-1.87 (m, 2H); entry d: δ 4.25-4.32 (m, 1H), 4.16-4.18 (m, 1H), 3.75-3.80 (m, 1H), 3.61-3.67 (m, 1H), 3.42-3.49 (m, 1H), 3.01 (brs, 2H), 2.05 (s, 3H), 1.69-1.79 (m, 2H); entry e: δ 7.78 (d, 2H, *J* = 7.7Hz), 7.30 (d, 2H, J = 7.7Hz), 4.20-4.28 (m, 1H), 4.10-4.18 (m, 1H), 3.82-3.90 (m, 1H), 3.60-3.66 (m, 1H), 3.40-3.46 (m, 1H), 2.42 (s, 3H), 2.18 (brs, 2H), 1.66-1.82 (m, 2H); entry f: δ 4.48-4.55 (m, 1H), 4.33-4.38 (m, 1H), 3.78-3.83 (m, 1H), 3.62-3.67 (m, 1H),

3.42-3.46 (m, 1H), 2.70 (brs, 2H), 1.76-1.89 (m, 2H); entry g: δ 8.04 (dd, 2H, J = 7.0Hz, 1.1Hz), 7.78 (td, 1H, J = 7.0Hz, 1.1Hz), 7.43 (td, 2H, J = 7.0Hz, 1.1Hz), 4.59-4.62 (m, 1H),

4.39-4.43 (m, 1H), 3.87-3.90 (m, 1H), 3.68-3.72 (m, 1H), 3.50-3.56 (m, 1H), 2.97 (brs, 2H), 1.80-1.93 (m, 2H); entry h: δ 5.67-5.72 (m, 2H), 4.10 (d, 2H, J = 5.1Hz), 3.76-3.79 (m, 1H), 3.42-3.47 (m, 2H), 2.37-2.41 (m, 1H), 2.25-2.30 (m, 1H), 1.85 (brs, 2H), 0.91 (s, 9H), 0.02 (s, 6H); entry i: 87.62-7.67 (m, 4H), 7.26-7.39 (m, 6H), 4.19-4.26 (m, 1H), 4.12-4.17 (m, 1H), 4.00 (brs, 3H), 3.85-3.92 (m, 2H), 3.45-3.64 (m, 2H), 1.70-1.78 (m, 2H), 1.55-1.65 (m, 2H), 1.05 (s, 9H); entry j: δ 4.18-4.22 (m, 1H), 4.00-4.10 (m, 1H), 3.71-3.78 (m, 2H), 1.43 (s, 3H).

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