$Yb(OTf)_3 \cdot H_2O$: A Novel Reagent for the Chemoselective Hydrolysis of Isopropylidene Acetals

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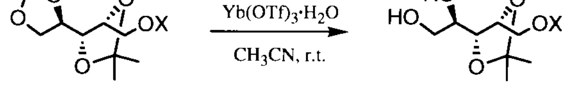
A facile chemoselective hydrolysis of terminal isopropylidene acetals has been achieved using a catalytic amount of $Yb(OTf)_3 \cdot H_2O$ in acetonitrile at ambient temperature.

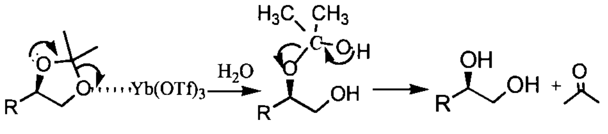
Performing chemoselective transformations of polyfunctional compounds are a challenging problem in organic synthesis especially in cases where similar structural features limit reagent choice. Cyclic isopropylidene acetals, known as acetonides, are widely used for the protection of 1,2- and 1,3-diols in carbohydrate chemistry.[1] Subsequently the hydrolysis of terminal isopropylidene acetals in the presence of internal one is often required in a multi-step synthetic sequence. As a result, several methods are reported for the hydrolysis of isopropylidene acetals, which include protic acid catalyzed aqueous hydrolysis[2–4] as well as Lewis acid catalyzed[5] nonaqueous hydrolysis. Due to the strong acidity, presence of free protons, it is necessary to control the reaction pH, temperature and reaction time while performing reactions with protic acids. Other reagents[6] like thiourea and zinc nitrate are also found to effect this transformation under mild conditions. However, inspite of their potential utility, these methods often encounter some disadvantages including incompatibility with other functional groups, longer reaction times, unsatisfactory yields and the use of stoichiometric amount of catalysts. Therefore, the development of new reagents that are more efficient and lead to convenient procedures and better yields is desirable. The use of lanthanide triflates as Lewis acids in organic synthesis has gained more popularity[7] due to their high catalytic nature, low toxicity, ease of handling, water stability, reusability, noncorrosiveness and greater selectivity. These special properties inherent to lanthanide triflates prompted us to explore these catalysts for the selective hydrolysis of isopropylidene acetals under mild conditions.

In this report we wish to introduce $Yb(OTf)_3 \cdot H_2O$ as a mild and versatile catalyst for the selective hydrolysis of terminal isopropylidene acetals over a wide range of functional groups (Scheme 1).



Scheme 1

The cleavage was effected by catalytic amount of $Yb(OTf)_3 \cdot H_2O$ in acetonitrile at ambient temperature.[8] The reactions proceeded smoothly at room temperature to give the corresponding 1,2-diols in high yields. The catalyst $Yb(OTf)_3 \cdot H_2O$ selectively deprotected terminal isopropylidene acetals leaving other functional groups intact. The procedure is highly chemoselective to deprotect terminal acetals in the presence of other acid sensitive functional groups. Such selectivity can be applied in synthetic sequences in which two different types of acetals must be unmasked at different stages of the synthesis. The cleavage required relatively longer reaction times with anhydrous $Yb(OTf)_3$ to afford comparable yields than those obtained by hydrated ytterbium triflate. The terminal isopropylidene acetals are deprotected in high yields within 2–4 h of reaction time. The reaction conditions are compatible with various functional groups like ethers, esters, sulfonates and olefins present in the molecule. There are many advantages in the use of $Yb(OTf)_3 \cdot H_2O$ for this cleavage which include the selective hydrolysis of 5,6-*O*-isopropylidene acetals in the presence of other acid sensitive protecting groups such as TBDPS, PMB, OAc, OBz, O-allyl and MOM ethers. The procedure failed to differentiate isopropylidene acetals from tetrahydropyranyl and TBDMS ethers. The cleavage may be effected by the coordination of $Yb(OTf)_3$ with dioxolane oxygen to form oxonium ion that is attacked by water to give 1,2-diols.

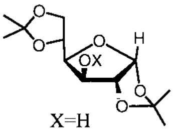
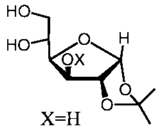
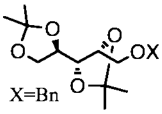
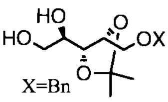
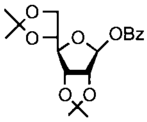
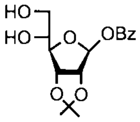
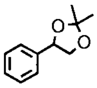
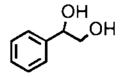


Scheme 2

The cleavage proceeds smoothly in commercial grade acetonitrile containing 1.5% of water that promotes the hydrolysis of acetals. Further, it should be noted that longer reaction times (8–12 h) and the use of large quantity of catalyst (30 mol%), the cleavage of 3,4-*O*-isopropylidene acetals was also observed. The results as summarized in Table 1 clearly reveal the scope and generality of the reaction with respect to various functionalized acetals. The catalyst, $Yb(OTf)_3$ was recovered from aqueous layer during workup and reused for two times without the significant loss of activity.

In conclusion, we have described a mild and highly efficient procedure using $Yb(OTf)_3 \cdot H_2O$ for the chemoselective hydrolysis of terminal isopropylidene acetals in presence of a wide range of functional groups. The method offers several advantages including compatibility with other functional groups, high yields of products, catalytic amount of reagent, greater selectivity, regeneration of the catalyst and experimental simplicity which makes it a useful and attractive addition to the existing ones.

Table 1: Chemoselective hydrolysis of isopropylidene acetals

Entry	Substrate **1**	Time/h	Product^a **2**	Yield^b/%
a	 X=H	3.0	 X=H	88
b	X=Bn	3.5	X=Bn	90
c	X=Allyl	4.0	X=Allyl	81
d	X=Me	3.0	X=Me	91
e	X=Ts	3.5	X=Ts	92
f	X=PMB	2.5	X=PMB	90
g	 X=Bn	2.5	 X=Bn	91
h	X=Allyl	4.0	X=Allyl	80
i	X=Me	3.0	X=Me	87
j	X=Ts	3.5	X=Ts	85
k	X=TBDPS	3.0	X=TBDPS	81
l	X=Ac	2.5	X=Ac	92
m		3.0		89
n		2.0		90

^{a}All the products were characterized by ^{1}H NMR, IR and Mass spectra.

^{b} Isolated and unoptimized yields after purification.

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8 General procedure: A mixture of isopropylidene acetal (5 mmol) and Yb(OTf)$_3$.H$_2$O (0.25 mmol) in acetonitrile(15 mL) was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted twice with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate:hexane, 3:7) to afford pure 1,2-diol. Spectroscopic data for **1f**: ^{1}H NMR (CDCl$_3$): δ 1.30 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 3.80 (s, 3H), 3.95 (m, 2H), 4.05 (m, 2H), 4.30 (m, 1H), 4. 50 (dd, 1H, J = 4.0 and 2.0 Hz), 4.55 (2d, 2H, J = 7.8 Hz), 5.85 (d, 1H, J = 4.0 Hz), 6.85 (d, 2H, J = 7.8 Hz), 7.25 (d, 2H, J = 7.8 Hz). **2f**: ^{1}H NMR (CDCl$_3$): δ 1.30 (s, 3H), 1.45 (s, 3H), 3.65 (m, 1H), 3.80 (s, 3H), 3.95 (m, 1H), 4.05 (m, 2H), 4.45 and 4.65 (2d, 2H, J = 7.8 Hz), 4. 50 (m, 1H), 4.60 (d, 1H, J = 4.0 Hz), 5.90 (d, 1H, J = 4.0 Hz), 6.85 (d, 2H, J = 7.8 Hz), 7.25 (d, 2H, J = 7.8 Hz).

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