March 2009 *Volume 5 Issue 1*

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Microreview

OCAIJ, 5(1), 2009 [111-116]

Selective hydrolysis of terminal isopropylidene ketals: An overview

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Received: 22nd January, 2009 ; Accepted: 27th January, 2009

ABSTRACT

Selective hydrolysis of isopropylidene ketals have been extensively used in the synthetic organic chemistry for synthesis of 1, 2 and 1, 3-diols. The selective hydrolysis of a terminal isopropylidene ketal in the presence of an internal isopropylidene ketal is a challenge and has immense importance in organic synthesis. The present review focuses on delineating various reagents scattered in the literature for the selective hydrolysis of terminal isopropylidene ketals. The literature in this review is covered until December 2008.

KEYWORDS

Isopropylidene ketals;
Acetonides;
Regioselectivity;
Carbohydrates;
Deprotection;
Hydrolysis.

INTRODUCTION

Isopropylidene ketals, commonly called as acetonides, have been extensively used in carbohydrate chemistry for the protection of 1, 2 and 1, 3-diols[1]. The selective hydrolysis of one acetonide over the other particularly in case of substrates having multiple acetonide protecting groups is of great interest in multistep synthesis of organic molecules. For example, the selective hydrolysis of terminal isopropylidene ketal group in the presence of an internal isopropylidene ketal group not only address the selectivity issue but also gives an ample scope to a synthetic chemist to build molecules at that particular position. Often two types of reagents have been used for these transformations; they are Brønsted and Lewis acids apart from some miscellaneous reagents.

The terminal isopropylidene group being sterically less crowded than an internal one, the rate of hydrolysis of the terminal one should be higher than the internal one and therefore removable selectively (Figure 1).

Towards the regioselective removal of terminal isopropylidene ketals, several reagents have been used. The reagents available in the literature for this objective can be broadly classified under two categories: (1) Bronsted acid reagents, (2) Lewis acid reagents. Reagents not falling under these categories have been assembled under the miscellaneous heading in this review.

In the Bronsted acid class, aq HCl[2], aq HBr[3], aq AcOH[4], 0.8% H_2SO_4 in MeOH[5] and Dowex-H^+ in MeOH:H_2O (9:1)[6] have been the frequent choice of reagents. In contrast to this, the use of Lewis acid reagents has been scarce and limited to $FeCl_3.6H_2O$/SiO_2[7], $CuCl_2.2H_2O$ in ethanol[8], $CeCl_3.7H_2O$[9] and

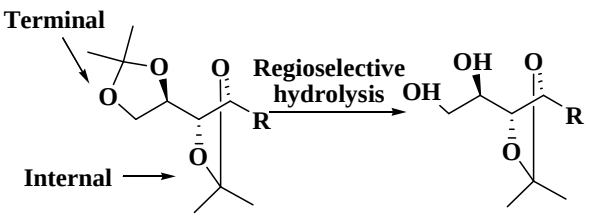


Figure 1

$Zn(NO_3)_2.6H_2O$[10] or $Yb(OTf)_3.H_2O$ in acetonitrile[11]. While using a Brønsted acid, strict control of the reaction parameters like the pH of the medium and reaction period becomes extremely crucial for high regioselectivity. Any negligence in reaction period leads to further hydrolysis and subsequent problems with purification and diminished yield. In the case of Lewis acids, the situation is better. Besides the Lewis acidity of the metal ions, apparent *in situ* hydrolysis of the salt also provides the necessary protic medium for a valuable and useful synergistic effect at least in the case of cupric[8] and zinc ions[10].

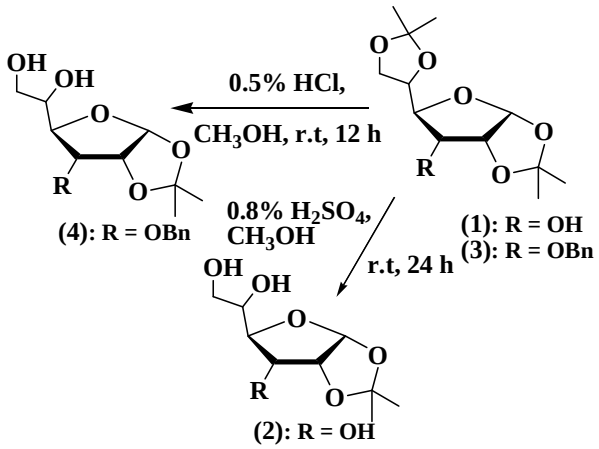
1. Bronsted acid reagents

A dilute solution of sulphuric acid[5] or hydrochloric acid[2] in methanol were used to hydrolyze only the terminal isopropylidene ketals in compound **(1)** and **(3)** (SCHEME 1), intended to be elaborated into either long chain fatty acids or deoxynojirimycin.

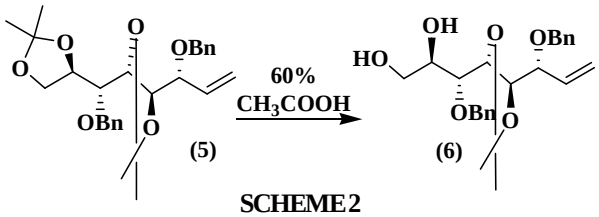
In a project aimed at the synthesis of a carbasugar, the selective removal of the terminal isopropylidene group in the di-O-isopropylidene derivative **(5)** of mannose was essential (SCHEME 2). Shing et al. used a 60% aqueous solution of acetic acid for the selective hydrolysis of the terminal isopropylidene ketal protecting group[12]. Clean reaction afforded the diol, **(6)**. The diol obtained was not isolated and was subsequently elaborated into a carbasugar.

In a synthesis aimed at (+)-castenospermine, Gerspacher and Rapoport developed an efficient methodology to selectively hydrolyze the terminal isopropylidene ketal-protecting group[3]. During the synthetic plan to construct a five membered ring **(11)** by addition of hydrobromic acid to the vinyl ketone **(7)**, a partial deprotection of the 5, 6-O-isopropylidene group was observed (SCHEME 3), due to the presence of moisture in the reaction mixture. Complete deprotection of the terminal isopropylidene group was achieved by addition of 200-mol% of water to the reaction mixture. Clean reaction afforded the diol **(8)** in 70% yield.

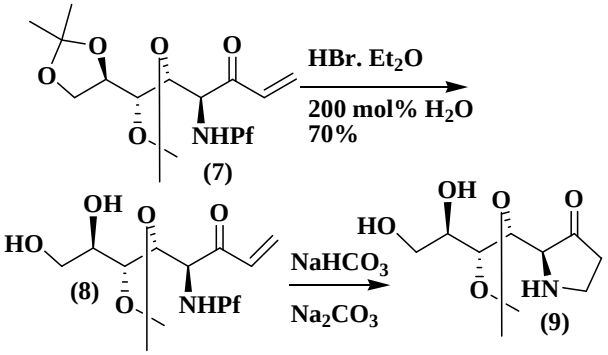
Wu and Wu demonstrated the use of a hydrate form of periodic acid for selective hydrolytic cleavage of a terminal isopropylidene ketal group[13]. In a typical experiment, the reaction of compounds **(10a-d)**, (SCHEME 4) with periodic acid (3 equiv.) in ether gave



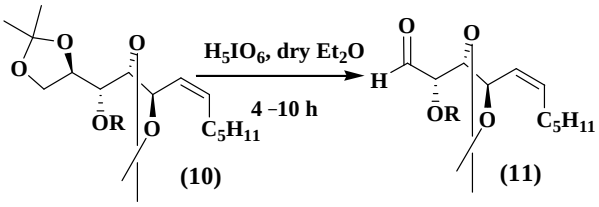
SCHEME 1



SCHEME 2



SCHEME 3

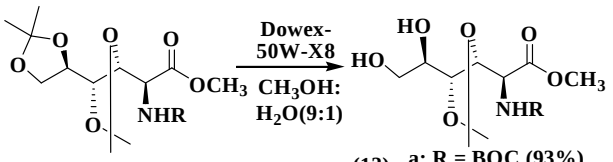


SCHEME 4

the aldehydes **(11a-d)** in very good yields.

The acidic resin Dowex-50W-X8 served as an excellent reagent for the specific removal of terminal

acetonide groups in compounds **(12a-d)** having acid-sensitive groups[6]. When acetonide derivatives containing BOC, Pf (9-phenyl fluorenyl), Bz, CBz, alkene, Ts, and ester functionalities were exposed to 110-w/w% of Dowex-50W-X8 in 90% methanol (SCHEME 5), the terminal acetonide groups were selectively hydrolyzed to yield the diols **(13a-d)** in excellent yields.



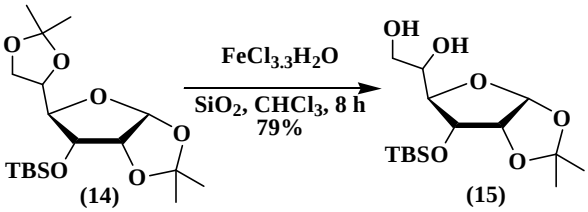
(12) a: R = BOC
b: R = Pf
c: R = CBz
d: R = Ts

(13) a: R = BOC (93%)
b: R = Pf (95%)
c: R = CBz (96%)
d: R = Ts (92%)

SCHEME 5

2. Lewis acid reagents

Unlike the Brønsted acid reagents employing proton sources in aqueous organic medium, only a few Lewis acid reagents have been reported in the literature. Although few in number, they have been fairly successful in selectively removing the terminal isopropylidene ketal functionality in the presence of an internal ketal. A brief review of the use of these reagents is presented in the following paragraphs.

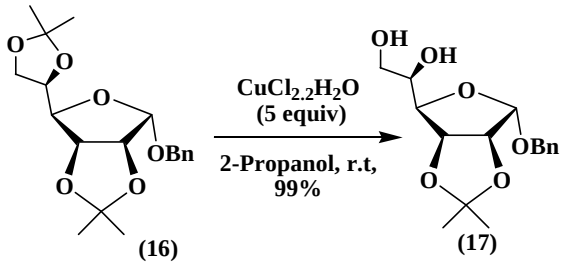


(14) (15)

SCHEME 6

2.1. Ferric chloride adsorbed on silica gel

Treatment of an acetone solution of hydrated ferric chloride with silica gel followed by evaporation of the solvent to dryness afforded a yellow coloured ferric chloride-silica gel reagent[7]. A solution of this reagent in chloroform was found to be efficient in hydrolyzing only the terminal isopropylidene ketal group (SCHEME 6).

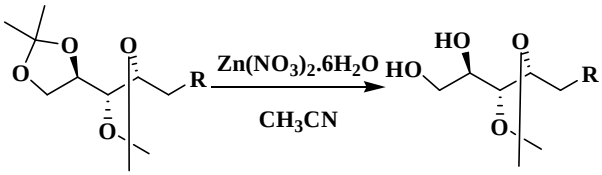


(16) (17)

SCHEME 7

2.2. Copper (II) chloride as a source of lewis acidity

Iwata and Ohrui developed a convenient and efficient method for regioselective removal of a terminal isopropylidene ketal protecting group using copper (II) chloride.[8] Typically, the 5, 6-O-isopropylidene group was selectively hydrolyzed by stirring a mixture of benzyl 2,3:5,6-di-O-isopropylidene-α-D-mannofuranoside **(16)** and five molar equivalents of copper (II) chloride dihydrate in ethanol or 2-propanol at room temperature to afford the diol **(17)** in 99% yield (SCHEME 7). Although the yield of this reaction is attractive, this method was only applied to simple di-O-isopropylidene gluco or manno furanoside derivatives and requires large excess of the reagent. It was also observed that the benzyl group migrates under these acidic conditions.



(18): R = OTs
(19): R = CO-Ph

(20) a: R = OTs
b: R = CO-Ph

SCHEME 8

2.3. $Zn(NO_3)_2.6H_2O$ in acetonitrile

Vijayasaradhi et al. reported an efficient and selective hydrolysis of a terminal isopropylidene ketal protecting group by $Zn(NO_3)_2.6H_2O$ in acetonitrile[10]. Treatment of 1 mmol of 3,4:5,6-Di-O-isopropylidene-1-C-phenyl-hexose **(18)** with 5 equivalent of $Zn(NO_3)_2.6H_2O$ in acetonitrile (5 ml) at 50^0C, resulted in the selective cleavage of the terminal isopropylidene group to furnish the product **(20b)** in 8 hours with 87% yield (SCHEME 8).

2.4. Ceric ammonium nitrate-pyridine reagent

Recently, Barone et al. reported the use of ceric ammonium nitrate and pyridine, which offers an optimum pH of 4.4, as effective in hydrolyzing only a terminal isopropylidene ketal protecting group[14]. Under these conditions, the Lewis acidity of cerium was found

to play a prominent role in the selective removal of the terminal isopropylidene ketal protecting group of several acetonides in the presence of other commonly used hydroxyl-protecting groups(SCHEME 9).

2.5. $Yb(OTf)_3.H_2O$ in acetonitrile

A catalytic amount of $Yb(OTf)_3.H_2O$ [0.25 mmol is required for 5 mmol of the starting substrate] in acetonitrile served as a mild and efficient reagent for selective hydrolysis of a terminal isopropylidene ketal protecting group (SCHEME 10) in the presence of a wide range of functional groups **(23a-e)**[15].

2.6. $La(NO_3)_3.6H_2O$ in acetonitrile

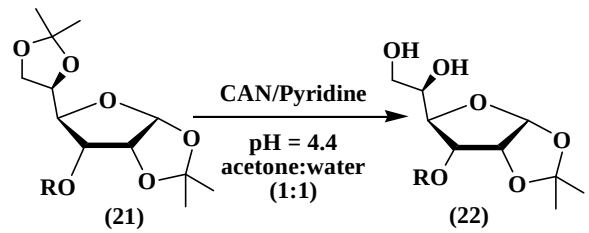
Acetonides are hydrolyzed selectively and efficiently with $La(NO_3)_3.6H_2O$ in acetonitrile[16]. This method is compatible with other sensitive hydroxyl protecting groups like TBDMS **(25c)**, THP **(25d)**, OAc **(25e)**, OBz **(25f)** and OBn **(25g)**. A primary acetonide group is selectively hydrolyzed in the presence of a secondary acetonide as well as other hydroxyl protecting groups (SCHEME 11).

2.7. Cd^{2+}, Co^{2+} and In^{3+} catalyzed hydrolysis of isopropylidene acetals

In our own lab we screened Cd^{2+}, Co^{2+} and In^{3+} salts for the selective hydrolysis of isopropylidene ketals[17]. A simple and efficient protocol is described for the regioselective hydrolysis of terminal isopro pylidene ketal group in carbohydrate derivatives. It uses either $CoCl_2 \cdot 2H_2O$ in acetonitrile or $InCl_3$ in methanol at temperatures ranging from 50 to 60^{0}C. The low cost of $CoCl_2 \cdot 2H_2O$ along with its requirement in catalytic quantities offers a great advantage for the multi-gram scale reactions (SCHEME 12).

2.8. Micro wave assisted $Er(OTf)_3$ catalyzed hydrolysis of isopropylidene acetals

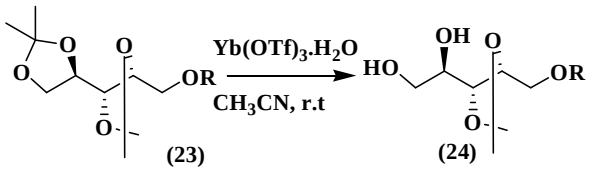
Recently, Antonio Procopio et al. reported the erbium (III) triouoromethane sulfonate as a very gentle Lewis acid catalyst in a MW-assisted chemoselective method for the cleavage of isopropylidene acetals in awkward substrates by using pure water as the solvent[18]. Under normal condition with $Er(OTf)_3$ the diacetone glucofuranose **(1)** gave mixture of both mono- and di- isopropylidene hydrolyzed products **(29)** and **(31)** but under micro wave condition a quantitative di-



(21) a: R = PMB, b: R = TBS, c: R = OAc

(22) a: R = PMB (82%), b: R = TBS (no reaction), c: R = OAc (48%)

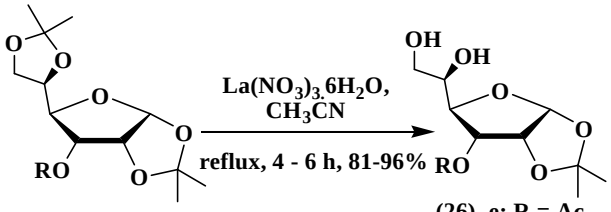
SCHEME 9



(23) a: R = Bn, b: R = Allyl, c: R = Me, d: R = Ts, e: R = TBDMS

(24) a: R = Bn (91%), b: R = Allyl (80%), c: R = Me (87%), d: R = Ts (85%), e: R = TBDMS (81%)

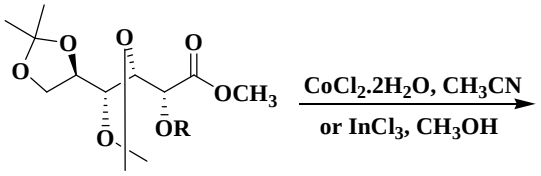
SCHEME 10



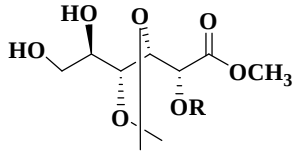
(25) a: R = H, b: R = TMS, c: R = TBDMS, d: R = THP

(26) e: R = Ac, f: R = Bz, g: R = Bn, h: R = Me

SCHEME 11



(27) a: R = H, b: R = TBDPS, c: R = Bn, d: R = Ac

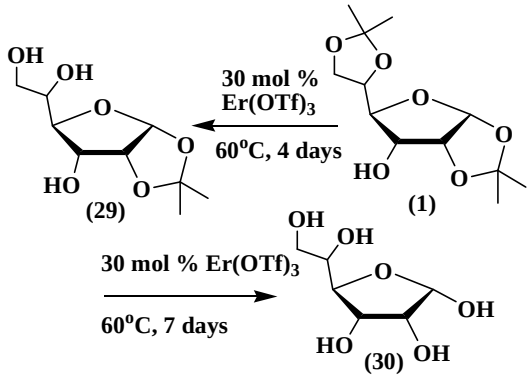


(28) a: R = H, b: R = TBDPS, c: R = Bn, d: R = Ac

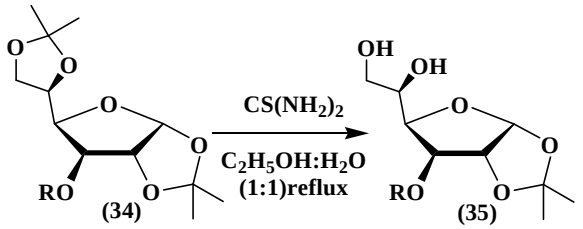
SCHEME 12

isopropylidine cleavage product **(30)** was accomplished in 15 min (SCHEME 13).

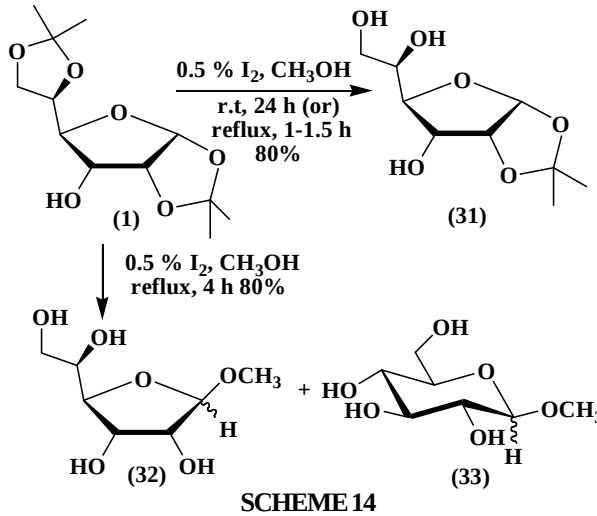
3. Miscellaneous reagents



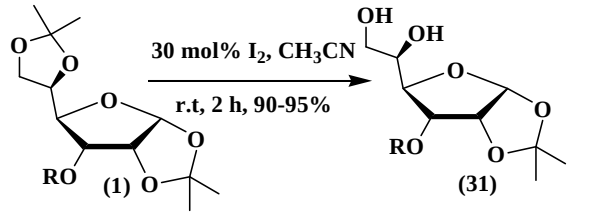
SCHEME 13



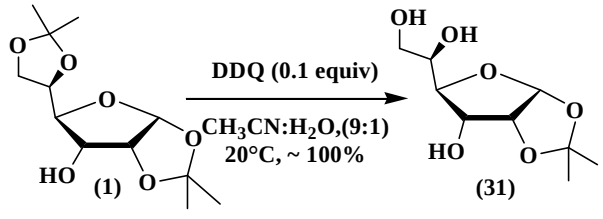
SCHEME 17



SCHEME 14



SCHEME 15



SCHEME 16

Mild reagents which have affinity for the oxygen atom have also been explored. There are three types reagents reported in the literature, which include, (a) 0.5-1% I_2 in methanol, (b) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in $CH_3CN:H_2O$ (9:1), and c) thiourea.

3.1. 0.5-1% Iodine in methanol

Szarek et al. developed a synthetic protocol for the selective as well as complete deprotection of isopropylidene ketals by varying the reaction conditions[19]. The synthetic procedure involves stirring a solution of substrate **(1)** in 0.5-1% iodine in methanol (w/v) at room temperature or at reflux temperature. A temperature dependent hydrolysis yields either the selectively hydrolyzed product **(31)** or the completely deprotected products **(32)** and **(33)** as depicted in the SCHEME 14.

Recently, Yadav and co-workers developed a protocol for chemoselective hydrolysis of terminal isopropylidene acetals using 30 mol% I_2 in acetonitrile (SCHEME 15)[20]. Acid labile protecting groups such as PMB, Bn, allyl and propargyl are compatible with these reaction conditions, while TBS, TBDPS, TMS and THP ethers were unstable under these conditions.

3.2. 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) in $CH_3CN:H_2O$ (9:1)

DDQ, a well-known reagent for the formation of charge-transfer complexes, was explored for the selective removal of terminal isopropylidene ketals. A catalytic amount of DDQ (0.1-0.4 equivalents) in $CH_3CN:H_2O$ (9:1) is sufficient to effect this transformation[21]. Typically reaction of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose **(1)** with 0.1 equivalents of DDQ in $CH_3CN:H_2O$ (9:1) at 20°C for 4 hours resulted in the formation of 1, 2-O-isopropylidene-D-

glucofuranose **(31)** in quantitative yield (SCHEME 16).

3.3. Thiourea in ethanol: water (1:1)

Treatment of the 3-O-protected diacetone-D-glucose derivatives **(34a-e)** with a 0.85 M solution of thiourea in ethanol: water (1:1) mixture under reflux for 18-24 hours afforded the required 5, 6-de-isopropyli denated products **(35a-d)** in 64-93% yields (SCHEME 17)[22]. An iminothiol tautomer of thiourea with an acidic thiol group is possibly involved in the hydrolytic removal of the isopropylidene moiety.

CONCLUSIONS

In conclusion, the review presents an overview of the different developments for the selective hydrolysis of terminal isopropylidene ketal in the presence of an internal isopropylidene ketal. Broadly, there are Bronsted and Lewis acid types of reagents used for this transformations. Apart from this some of the miscellaneous mild reagents have also been explored. Since this transformation is very important for making various synthons for synthesis and preparing carbohydrate based bioactive compounds; this review will be more informative and helpful to the chemist working in the field of carbohydrates and natural products.

ACKNOWLEDGMENTS

The authors thank the Department of Chemistry, IIT-Madras and Sambalpur University for providing necessary facilities for research.

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