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Chemoselective hydrolysis of terminal isopropylidene acetals in acetonitrile using molecular iodine as a mild and efficient catalyst

J. S. Yadav,* M. Satyanarayana, S. Raghavendra and E. Balanarsaiah

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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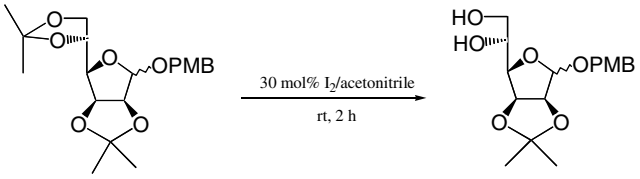
Abstract—A simple, mild and efficient method for deprotection of acetonides in the presence of molecular iodine is described. Acid labile protecting groups such as PMB, OMe, OBn, allyl and propargyl are compatible with the reaction conditions, while TBS, TBDPS, TMS and THP ethers were unstable under the same conditions.

Protection of 1,2- and 1,3-diols in the form of acetonides and their subsequent deprotection is an extremely useful strategy in organic synthesis. Chemoselective deprotection of terminal isopropylidene acetals in the presence of other protecting groups is often needed in total synthesis.[1] Glucose and mannose diacetonides are versatile chiral pool starting materials for the synthesis of several biologically active natural products in the chiron approach.[2] The use of 5,6-dihydroxy glycosides have been explored for the total synthesis of some important targets.[3] 5,6-Acetonide cleavage is frequently employed to access 5,6-dihydroxy glycosides in synthetic strategies towards natural products. Several catalysts have been reported to bring about this conversion. Protic reagents such as aq HCl,[4a] aq HBr,[4b] aq AcOH,[4c] 0.8% H_2SO_4 in MeOH,[4d] Dowex-H^+ in MeOH–H_2O (9:1)[4e] and Lewis acid based reagents, $FeCl_3{\cdot}6H_2O/SiO_2$,[5a] $CuCl_2{\cdot}2H_2O$ in ethanol,[5b] $Zn(NO_3)_2{\cdot}6H_2O$,[5c] $CeCl_3{\cdot}7H_2O/(COOH)_2$[5d] and $BiCl_3$[5e] have all been reported to cleave terminal acetonides. Many of these methods suffer from disadvantages such as strongly acidic conditions, low yields, the need for stoichiometric amounts of reagents and long reaction times. Iodine in methanol has also been reported for the deprotection of acetonides, but without chemoselectivity.[6] Therefore, it is necessary to introduce new reagents and use convenient procedures for acetonide cleavage to afford products in high yields.



Scheme 1.

Iodine has been used as a Lewis acid catalyst for various organic transformations in organic synthesis.[7] In continuation of our efforts to develop new methods using molecular iodine as the catalyst for different organic conversions,[8] herein we report a mild and convenient method for the chemoselective hydrolysis of acetonides (Scheme 1).

The reaction proceeds with 30 mol % of elemental iodine in acetonitrile as solvent by addition of 40 μL water to the reaction mixture. The hydrolysis of acetonides took place within 2–3 h at ambient temperature to give the corresponding diols in excellent yields. No reaction was observed in the absence of either iodine or water. A systematic study was carried out to check the generality of this catalyst (Table 1). Experiments were carried out using 30 and 10 mol % of iodine. Hydrolysis of acetonides was observed within 4–5 h even for 10 mol % of iodine. It is evident from Table 1 that acid sensitive groups such as OMe, MOM, PMB, OAc, OBn, allyl and propargyl were tolerant to the reaction conditions. A previous report describes the cleavage of PMB ethers leaving benzyl ethers intact using iodine in methanol in a given molecule.[9] However, when using I_2 in

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* Corresponding author. Fax: +91 40 7160387; e-mail: yadavpub@iict.res.in

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Table 1. Iodine catalysed hydrolysis of acetonides in acetonitrile at room temperature

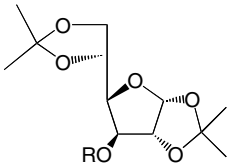
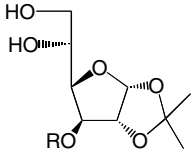
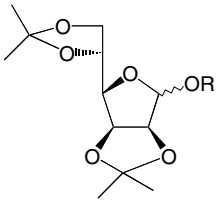
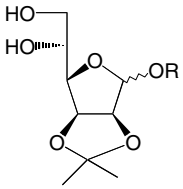
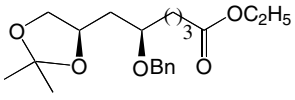
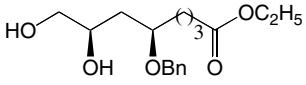
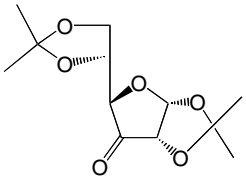
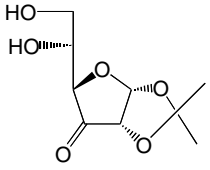
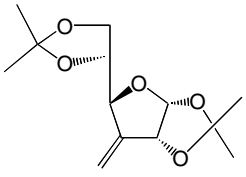
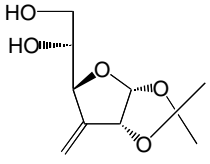
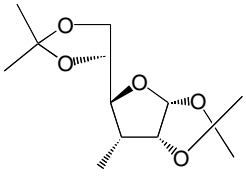
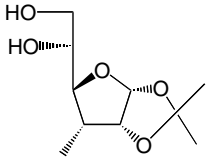
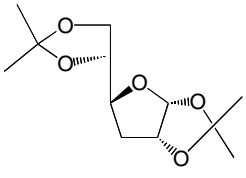
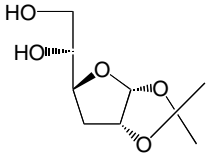
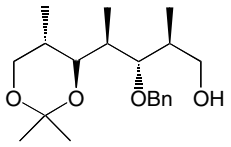
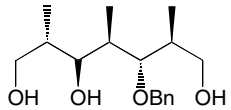
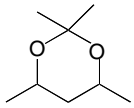
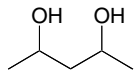
Entry	Substrate	Product[a]	Reaction time (h)		Yield (%)[b]
			30 mol %	10 mol %	
					
a	R = Ac	R = Ac	2	4	92[12a]
b	R = Bn	R = Bn	2.5	4.5	95[12b]
c	R = PMB	R = PMB	2	3.5	94[12c]
d	R = allyl	R = allyl	2	4	90[12d]
e	R = propargyl	R = propargyl	1.5	3.5	90
f	R = MOM	R = MOM	1.5	4	93
g	R = Me	R = Me	2	5	90
h	R = H	R = H	2	4.5	92[12e]
					
i	R = Bn	R = Bn	2	4	93[13a]
j	R = MOM	R = MOM	2.5	4.5	91
k	R = propargyl	R = propargyl	2	4	90
l	R = allyl	R = allyl	2.5	4	94
m	R = Ac	R = Ac	3	4.5	92[5c]
n	R = PMB	R = PMB	2	3.5	90
o			2	4.5	90
p			2.5	4	95[13b]
q			2	4	92
r			2	4.5	94
s			2.5	4	94[4d]

Table 1 (*continued*)

Entry	Substrate	Product[a]	Reaction time (h)		Yield (%)[b]
			30 mol %	10 mol %	
t			2	3	92
u			2	3.5	90

[a] All products were characterised by ^{1}H NMR and mass spectroscopy.
[b] Yield of isolated product.

acetonitrile PMB ethers were found to be stable. From these observations it is apparent that the solvent is playing a key role in the chemoselective cleavage.

Unfortunately all our efforts to improve upon the modest selectivity of acetonide cleavage in the presence of silyl ethers were unsuccessful. Silyl ethers such as TBS, TBDPS and TMS underwent cleavage faster than acetonides. Cleavage of aliphatic silyl ethers, in particular *tert*-butyldimethylsilyl derivatives over aryl silyl ethers was reported using a small percentage of I_2 in methanol at room temperature. TBDPS and TIPS ethers were unaffected using this method.[10] Rapid hydrolysis of THP and acetonide functionalities was observed leading to the formation of the corresponding triol as in the case of the I_2 in methanol system.[11]

The cleavage of TBS, TBDPS, TMS and THP ethers may be attributed to the formation of the corresponding silyl iodide in the presence of HI, which may be produced in the reaction medium.

In summary, we have utilised[14] molecular iodine in acetonitrile as an excellent catalyst for the deprotection of terminal isopropylidene acetals to give the corresponding diols in excellent yields. Apart from silyl and THP ethers, other acid sensitive groups were found to be stable under the reaction conditions. Due to the catalytic nature of the reaction and the non-toxic nature, availability, low cost of the reagent and high yields we believe that this process is a useful addition to the available organic methodologies.

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14. Experimental procedure: Iodine (30 mol %) was added to a solution of glucose diacetonide (0.384 mmol) in acetonitrile (2 mL) and after adding water (40 μL) the reaction was stirred at room temperature for 2–3 h. After complete conversion, as indicated by TLC, the reaction mixture was diluted with aqueous $Na_2S_2O_3$ (10 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layers were dried over anhydrous Na_2SO_4 and filtered through silica gel (Merck, 100–200 mesh) using hexane–ethyl acetate (7:3) to afford the pure diol. Spectral data: 1,2-*O*-Isopropylidene-3-*O*-*p*-methoxybenzyl-α-D-glucofuranose (**c**): ^{1}H NMR ($CDCl_3$, 200 MHz), δ ppm 1.30 (s, 3H), 1.46 (s, 3H), 3.63–3.75 (m, 2H), 3.80 (s, 3H), 3.91 (m, 1H), 4.0–4.08 (m, 2H), 4.46 (d, $J = 11.1$ Hz, 1H), 4.53 (d, $J = 3.7$ Hz, 1H), 4.65 (d, $J = 11.9$ Hz, 1H), 5.87 (d, $J = 3.7$ Hz, 1H), 6.86 (d, $J = 8.9$ Hz, 2H), 7.25 (d, $J = 8.2$ Hz, 2H); 1,2-*O*-Isopropylidene-3-*O*-propargyl-α-D-glucofuranose (**e**): $[\alpha]_D$ −37.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.00 (s, 3H), 1.18 (s, 3H), 2.24 (t, $J = 2.3$ Hz, 1H), 3.28 (br s, 1H), 3.35 (dd, $J = 5.3$ Hz, 1H), 3.47–3.62 (m, 2H), 3.75 (dd, $J = 3.0$ Hz, 1H), 3.85 (d, $J = 3.0$ Hz, 1H), 4.00 (t, $J = 3.7$ Hz, 2H), 4.27 (d, $J = 3.7$ Hz, 1H), 5.55 (d, $J = 3.7$ Hz, 1H). LCMS: *m*/*z* 281 (M^++Na); 1,2-*O*-Isopropylidene-3-*O*-methoxymethyl-α-D-glucofuranose (**f**): $[\alpha]_D$ +79.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.31 (s, 3H), 1.48 (s, 3H), 3.43 (s, 3H), 3.69 (dd, $J = 4.5$ Hz, 1H), 3.79–3.89 (m, 2H), 4.06 (dd, $J = 3.0$ Hz, 1H), 4.20 (d, $J = 3.0$ Hz, 1H), 4.52 (d, $J = 3.8$ Hz, 1H), 4.72 (m, 2H), 5.84 (d, $J = 3.0$ Hz, 1H). LCMS: *m*/*z* 279 (M^++Na); 1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-glucofuranose (**g**): $[\alpha]_D$ −38.75 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.34 (s, 3H), 1.51 (s, 3H), 3.50 (s, 3H), 3.73 (dd, $J = 4.5$ Hz, 1H), 3.80–3.98 (m, 3H), 4.09 (dd, $J = 3.0$ Hz, 1H), 4.57 (d, $J = 3.8$ Hz, 1H), 5.86 (d, $J = 3.8$ Hz, 1H); LCMS: *m*/*z* 257 (M^++Na); 2,3-*O*-Isopropylidene-1-*O*-methoxymethyl-α-D-manofuranose (**j**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.33 (s, 3H), 1.46 (s, 3H), 3.37 (s, 3H), 3.68 (m, 1H), 3.81 (m, 1H), 3.94 (s, 2H), 4.48 (d, $J = 6.0$ Hz, 1H), 4.59 (d, $J = 6.0$ Hz, 1H), 4.81 (m, 2H), 5.19 (s, 1H); LCMS: *m*/*z* 279 (M^++Na); 2,3-*O*-Isopropylidene-1-*O*-propargyl-α-D-manofuranose (**k**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.33 (s, 3H), 1.47 (s, 3H), 2.02 (s, 1H), 3.64–3.95 (m, 4H), 4.15 (m, 2H), 4.57 (d, $J = 5.6$ Hz, 1H), 4.81 (m, 1H), 5.16 (s, 1H); LCMS: *m*/*z* 281 (M^++Na); 1-*O*-Allyl-2,3-*O*-isopropylidene-α-D-manofuranose (**l**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.32 (s, 3H), 1.46 (s, 3H), 3.68–3.80 (m, 2H), 3.93 (m, 3H), 4.09 (m, 1H), 4.58 (d, $J = 6.0$ Hz, 1H), 4.80 (m, 1H), 5.00 (s, 1H), 5.15–5.27 (m, 2H), 5.83 (m, 1H); LCMS: *m*/*z* 283 (M^++Na); 2,3-*O*-Isopropylidene-1-*O*-*p*-methoxybenzyl-α-D-manofuranose (**n**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.36 (s, 3H), 1.53 (s, 3H), 3.64–3.88 (m, 6H), 4.05 (m, 1H), 4.50–4.62 (m, 2H), 4.72–4.83 (m, 3H), 6.84 (d, $J = 8.1$ Hz, 2H), 7.26 (d, $J = 8.9$ Hz, 2H); LCMS: *m*/*z* 363 (M^++Na); Compound (**o**): $[\alpha]_D$ −16.2 (*c* 0.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, $J = 7.4$ Hz, 3H), 1.43–1.58 (m, 2H), 2.52 (t, $J = 6.7$ Hz, 2H), 3.35 (dd, $J_{1,2} = 11.1$ Hz, $J_{2,3} = 5.9$ Hz, 1H), 3.5 (dd, $J_{1,2} = 11.1$ Hz, $J_{2,3} = 5.9$ Hz, 1H), 3.78–3.86 (m, 2H), 4.18 (q, $J = 7.4$ Hz, 2H), 4.46 (d, $J = 11.1$ Hz, 1H), 4.69 (d, $J = 11.1$ Hz, 1H), 5.85 (d, $J = 15.6$ Hz, 1H), 6.98–6.82 (m, 1H), 7.35–7.24 (m, 5H); MS FAB: *m*/*z* 331 (M^++Na), 309 (M^++1); Compound (**q**): $[\alpha]_D$ +101.6 (*c* 1, $CHCl_3$); 1.34 (s, 3H), 1.45 (s, 3H), 3.66 (m, 3H), 4.66 (br s, 1H), 4.82 (d, $J = 4.4$ Hz, 1H), 5.41 (s, 2H), 5.75 (d, $J = 3.7$ Hz, 1H); LCMS: *m*/*z* 239 (M^++Na); Compound (**r**): $[\alpha]_D$ +21.42 (*c* 1, $CHCl_3$); 0.86 (d, $J = 6.8$ Hz, 3H), 1.02 (s, 3H), 1.21 (s, 3H), 1.75 (m, 1H), 3.32–3.50 (m, 4H), 4.22 (t, $J = 4.5$ Hz, 1H), 5.4 (d, $J = 3.77$ Hz, 1H); LCMS: *m*/*z* 241 (M^++Na); Compound (**t**): $[\alpha]_D$ −0.26 (*c* 1, $CHCl_3$); 0.73 (d, $J = 7.1$ Hz, 3H), 0.95 (d, $J = 7.1$ Hz, 3H), 1.12 (d, $J = 7.4$ Hz, 3H), 1.82 (m, 2H), 2.02 (m, 1H), 3.50–3.85 (m, 6H), 4.65 (m, 2H), 7.30 (m, 5H); FABMS: *m*/*z* 297 (M^++1).