Mild and eco-friendly oxidative cleavage of 1,3-dithianes and 1,3-dithiolanes with a catalytic amount of hydrobromic acid and hydrogen peroxide: synergetic effect of bromonium ion equivalent and hydrogen peroxide

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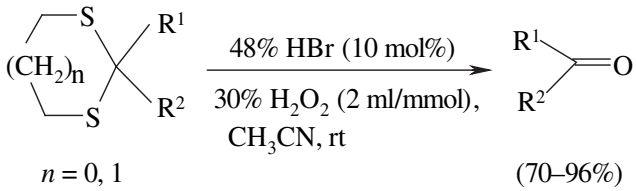
A combination of a catalytic amount hydrobromic acid (10 mol%) and an excess of hydrogen peroxide is found to be an effective reagent for expeditious regeneration of carbonyl compounds from their 1,3-dithiane as well as 1,3–dithiolane derivatives. Absence of nuclear bromination of aromatic substrates and overoxidation of regenerated oxidation–prone aromatic aldehydes, compatibility with a number of functional groups, such as amino, hydroxy, acetoxy, methylenedioxy and useful phenol-protecting allyl, benzyl and TBDMS ethers, benzoate esters and amino-protecting Cbz carbamate and *N*-benzylamine (NHBn) moieties are the advantageous features of this protocol.

Keywords: 1,3-dithianes, 1,3-dithiolanes, hydrobromic acid, hydrogen peroxide, cleavage

Conversion into cyclic *S*,*S*-acetals *viz*. 1,3-dithianes and 1,3–dithiolanes is considered to be a very useful method of protecting carbonyl groups against addition of nucleophiles including organometallic reagents. These derivatives are easy to prepare and remarkably stable under basic and acidic conditions.[1] 1,3-Dithianes of aldehydes are particularly important as precursors of nucleophilic aldehydes through metallation (*umpolung*) allowing carbon–carbon bond formation with electrophiles.[2] However, regeneration of carbonyl compounds from these derivatives is not always straightforward and facile. Therefore a search for newer protocols of cleavage aiming at improved efficiency, selectivity, operational simplicity and atom economy has continued over the years attesting to its great synthetic importance.[1,3] Reagents that provide halonium ion, such as Pyr.HBr.Br_2 along with Bu_4NBr in CH_2Cl_2–pyridine,[4] I_2 in DMSO at 90ºC[5], NBS / NCS (4–9 mol equiv.), Br_2 (2–4 mol equiv.)[6a,b] and, more recently, electrophilic halogens in the presence of DMSO[6c] and hypervalent iodine (V) reagent represented by *o*-iodoxybenzoic acid (IBX)[6d,e] have been effectively utilised as cleaving agents. Apart from operational and environmental hazards associated with the use of elemental bromine in halogenated solvents, such as carbon tetrachloride and dichloromethane,[7a] all these methods require an excess of reagents leading to low utilisation of halogens and concomitant side reactions, such as nuclear halogenation of aromatic aldehydes and ketones, α-halogenation and oxidation of divalent sulfides to sulfoxides. It was our interest to utilise this approach and find environmentally acceptable conditions of cleavage that avoid use of excess halogens and halogenated solvents thereby circumventing the possibility of side reactions and resulting in better atom utilisation. To this aim, the combination of a catalytic amount of HBr and an excess of H_2O_2 in acetonitrile was envisaged to be an ideal candidate because it generates Br^+ or its equivalent as a soft electrophile by complete oxidation of HBr with H_2O_2, an excess of which can act as a nucleophile as well. Another green feature[8] of the use of H_2O_2 as a terminal oxidant is that it minimises waste at source by providing water as the only byproduct. Use of HBr and H_2O_2 has been reported for bromination of aromatics,[7b] olefins and alkynes[7c] with full utilisation of bromine. Herein, we report the results of deprotection of a wide variety of cyclic *S*,*S*-acetals (Table 1) employing catalytic amounts of 48% HBr (10 mol%) and an excess of 30% H_2O_2.

Regeneration of aromatic aldehydes from their dithianes and dithiolanes proceeds efficiently without overoxidation with a catalytic amount (10 mol%) of 48% HBr along with an excess of 30% H_2O_2 (2 ml per mmol of substrate) in CH_3CN at room temperature. Cleavage of dithianes was marginally faster than dithiolanes, as observed with other oxidative cleavage methods.[9] The degree of electron availability at C-2 is a crucial factor that determines the rate of cleavage and this is manifest in the relatively slower demasking of derivatives of 2-acetoxybenzaldehyde (entry 6) and 4-nitrobenzaldehyde (entries 7, 8). On the other hand, the presence of electron-releasing groups, such as hydroxy, methoxy and methylenedioxy facilitates the cleavage process. This also accounts for the longer cleavage times required for non-activated dithianes and dithiolanes (entries 16, 17) in comparison with those where stabilisation of the incipient carbocation at benzylic and allylic centres is possible. In our case, success of cleavage with a catalytic amount of HBr seems to be partially related to the presence of H_2OBr^+ generated *in situ* as the brominating species in the acidic aqueous solution which has more pronounced electrophilicity[10] than molecular bromine. An excess of 30% H_2O_2 (2 ml per mmol of substrate) along with 10 mol% of HBr were found to be the optimised conditions of cleavage catalysed by HBr. We also evaluated the stoichiometric version of cleavage with one mole equivalent of HBr and an identical excess of 30% H_2O_2. The cleavage process was substantially accelerated under these conditions. However, this produces a molar equivalent of waste bromide and, therefore, is not as eco-friendly as it could be. Gratifyingly, successful cleavages were observed without overoxidation, even for oxidation-prone aromatic aldehydes and an α-hydroxyketone (entry 10) under catalytic as well as stoichiometric conditions. The turnover of the catalytic cycle of oxidation of HBr with 30% H_2O_2 is low, thereby requiring longer reaction times, and it is particularly sluggish and, therefore, less attractive from practical point of view for sterically hindered and unactivated substrates (entries 15, 16, 17). Addition of a catalytic amount of Mo(VI) in the form of ammonium molybdate (5 mol%) which is effective in activating H_2O_2 as an oxidant particularly at low pH[11] was found to expedite cleavage and is another green option for reluctant substrates (entries 7, 8). Use of an excess of H_2O_2 is crucially important for bromine utilisation as well as the absence of side reactions, such as sulfoxidation of



n = 0, 1 (70–96%)

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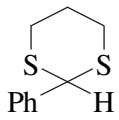
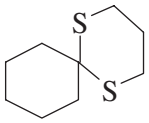
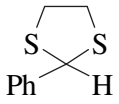
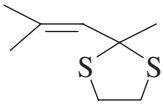
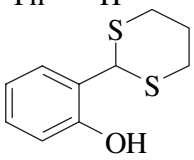
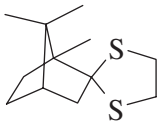
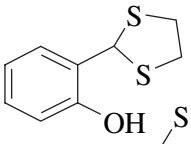
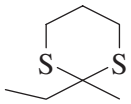
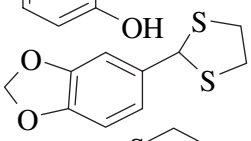
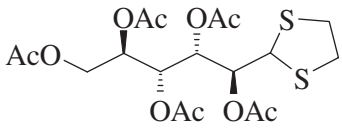
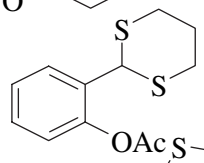
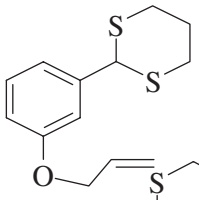
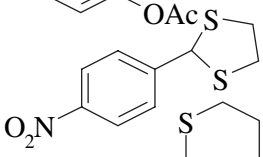
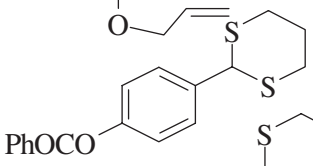
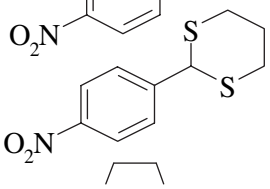
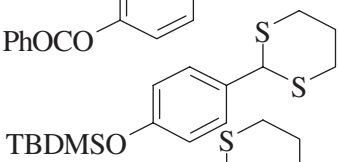
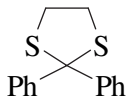
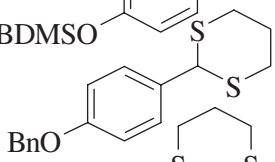
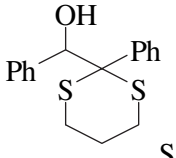
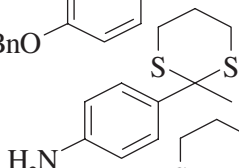
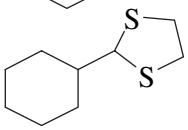
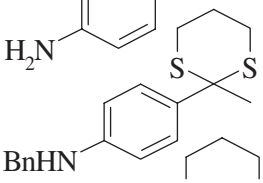
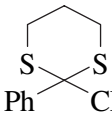
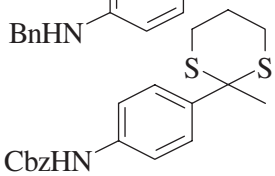
Table 1 Deprotection of 1,3-dithianes and 1,3-dithiolanes using HBr and H_2O_2

Entry	Substrate	Reaction time [Yield/%][a]	Entry	Substrate	Reaction time [Yield/%][a]
1		(a) 3 h [88] (b) 6 min [84]	13		(a) 4 h [96] (b) 5 min [80]
2		(a) 5 h [92] (b) 12 min [85]	14		(a) 5 h [85] (b) 10 min [87]
3		(a) 4 h [88] (b) 5 min [95] (c) 20 min [80]	15		(a) 16 h [70] (b) 50 min [75] (c) 4 h [78]
4		(a) 8 h [80] (b) 10 min [90] (c) 30 min [88]	16		(a) 12 h [90] (b) 23 min [94]
5		(a) 5 h [90] (b) 12 min [96]	17		(a) 12 h [76] (b) 20 min [80]
6		(a) 7 h [98] (b) 15 min [85]	18		(a) 6 h [86] (b) 15 min [83]
7		(a) 12 h [92] (b) 40 min [80] (c) 3h [84]	19		(a) 10 h [88] (b) 20 min [85]
8		(a) 10 h [80] (b) 30 min [84] (c) 4h [82]	20		(a) 8 h [86] (b) 15 min [92]
9		(a) 7.5 h [85] (b) 15 min [90]	21		(a) 5 h [90] (b) 13 min [88]
10		(a) 1 h [90] (b) 5 min [88]	22		(a) 6 h [95] (b) 10 min [90]
11		(a) 5 h [90] (b) 8 min [92]	23		(a) 7 h [94] (b) 12 min [89]
12		(a) 6 h [80] (b) 12 min [87]	24		(a) 7 h [80] (b) 15 min [85]

(a) Reaction conditions :48% HBr (10 mol%), 30% H_2O_2 (2 ml) per mmol of substrate in acetonitrile, rt.
(b) Reaction conditions : 48% HBr (1 mmol), 30% H_2O_2 (2 ml) per mmol of substrate, rt.
(c) Reaction conditions : 48% HBr (1 mmol), 30% H_2O_2 (0.5 ml) per mmol of substrate, rt.
(d) Reaction conditions : 48% HBr (10 mol%), 30% H_2O_2 (2 ml), $(NH_4)_2MoO_4$ (5 mol%).
[a]Yields refer to chromatographically isolated pure products; the identity of the products was confirmed by comparison with authentic samples (m.p./b.p., co-TLC, IR and ^1H NMR).

cyclic *S*, *S*- acetals which is the dominant process with NBS in anhydrous Ch_3OH.[6b] This is substantiated by the observations that the use of a lesser amount of H_2O_2 (0.5 ml) in combination with HBr (1 mmol) resulted in substantially slower cleavages in the cases of 2-(2-hydroxyphenyl)-1,3-dithiane (entry 3) and the corresponding dithiolane (entry 4). The synergetic effect accruing from the generation of strongly electrophilic species in the form of H_2OBr^+ and nucleophilic assistance[12] towards ring opening by an excess of H_2O_2 make the cleavage the predominant, if not exclusive, process – a novel feature absent in earlier methods of dethioacetalisation based on halogenium ions. Gratifyingly, no α-bromination was observed in the case of regenerated acetophenone (entry 12) under both conditions, although it has been reported[7b] at elevated temperature in dioxane with the same reagent. Phenolic hydroxy, acetoxy, methylenedioxy and oxidation-prone α-hydroxyketone functions (entry 10) are found to remain intact under the conditions of cleavage. Significantly, compatibility with a number of useful phenol and amino protective groups, such as allyl, benzyl and TBDMS ethers, benzoate ester and Cbz carbamate and NHBn enhances the synthetic utility of this protocol. The absence of nuclear bromination for activated aromatics, particularly for the stoichiometric method, is surprising in view of the readiness with which phenols and anilines are brominated in aqueous acid; the use of a mole equivalent or less of HBr and full utilisation of the liberated bromine in the fast cleavage process seems to explain this.

In conclusion an efficient oxidative hydrolysis of 1,3-dithianes and 1,3-dithiolanes of a wide variety of aldehydes and ketones has been accomplished utilising inexpensive rack reagents *viz*. 48% hydrobromic acid and an excess of 30% hydrogen peroxide. The catalytic and the faster stoichiometric versions of the cleavage process have been evaluated employing 10 mol% and one mole equivalent of aqueous hydrobromic acid respectively. The generality, the manipulative simplicity, mildness, compatibility with a number of common functional groups and useful protective groups, absence of side reactions, high yields and, very importantly, its environmentally benign nature will hopefully make this protocol a method of choice to organic chemists.

Experimental

CAUTION: Hydrobromic acid is a corrosive acid; 30% H_2O_2 is a corrosive oxidiser. However, we did not encounter any difficulty while handling catalytic/nonexcess stoichiometric amount of 48% HBr and 30% H_2O_2 (used in excess) on a 1–2 millimolar scale.

(a) *General procedure for the cleavage of 1,3-dithianes and 1,3–dithiolanes (catalytic method)*: To a thoroughly stirred solution of substrate (2 mmol) in a minimum amount of acetonitrile (2 ml) at 0–5 °C was added dropwise 30% H_2O_2[13] (4 ml) followed by 48% HBr[13] (20 mol%). After completion of the reaction at room temperature (25 °C) for the specified time, the reaction mixture was extracted with ethyl acetate, (3 × 3 ml) washed with sodium bisulfite solution (0.5 ml), brine (2 ml) and dried (Na_2SO_4). Removal of solvent from the organic extract yielded the crude product which upon chromatographic purification (usually filtration) over silica gel, yielded the anticipated carbonyl compound[13] uncontaminated with any byproduct.

(b) *Representative procedure for the oxidative hydrolysis of 1,3-dithianes and 1,3–dithiolanes (stoichiometric method)*: To a stirred solution of 2-phenyl-1,3-dithiolane (entry 2) (330 mg, 1.81 mmol) in acetonitrile (1.5 ml) at 0–5 °C was added 30% hydrogen peroxide (3.6 ml) and then 48% hydrobromic acid (0.3 ml, 1.8 mmol) over 1 minute. The reaction mixture was allowed to warm to room temperature (25 °C) and stirred for 12 min until complete consumption of starting material was observed by TLC. The reaction mixture was extracted with ethyl acetate (2 × 4 ml), washed with sodium bisulfite solution, water, brine and dried (Na_2SO_4). Concentration of the organic extract under water suction and chromatography on silica gel (60–120 mesh) gave benzaldehyde (165 mg, 85%) from the light petrol (b.p. 60–80°) eluates.

Characterisation data of some novel carbonyl compounds isolated as products:

3-Allyloxybenzaldehyde† (*entry* **18**): Viscous oil; FTIR (liquid film) ν_{max}/cm^{-1} 3082 and 3022 (allyl), 2985, 2924, 2851 and 2729 (aldehydic C-H), 1700 (C=O), 1649, 1596, 1568, 1484, 1450, 1424, 1388, 1322, 1286, 1263, 1169, 1146, 1026, 992; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (2H, d, *J* = 5.1 Hz, 1'-CH_2), 5.28–5.45 (2H, m, vinylic 3'-CH_2), 5.98–6.10 (1H, m, H-2'), 7.15–7.21 (1H, m, H-5), 7.38 (1H, d, *J* = 1.8 Hz, H-2), 7.41–7.45 (2H, m, H-4 and H-6), 9.94 (1H, s, CHO).

4-Benzoyloxybenzaldehyde (*entry* **19**): M.p. 92–94 °C; FTIR (KBr) ν_{max}/cm^{-1} 2851, 2923 and 2745 (aldehydic C-H), 2550, 1687 (C=O), 1602, 1583, 1495, 1453, 1423, 1325, 1289, 1185, 1127, 1072, 1026, 934; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.73 (7H, m), 8.12 (2H, d, *J* = 6.8 Hz, H-2 and H-6), 9.48 (1H, bs, CHO); Anal. Calcd. For $C_{14}H_{10}O_3$: C, 74.33; H, 4.42; Found C, 74.30; H, 4.45.

4-t-Butyldimethylsilyloxybenzaldehyde (*entry* **20**)†: Colourless oil; FTIR (liquid film) ν_{max}/cm^{-1} 3066, 2956, 2931, 2887, 2859 and 2733 (aldehydic C-H), 1700 (C=O), 1599, 1576, 1508, 1472, 1464, 1421, 1391, 1362, 1274, 1211, 1156, 1101, 1007, 909; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (6H, s, 2 × CH_3), 0.94 (9H, s, CMe_3), 6.90 (2H, d, *J* = 8.5 Hz, H-3 and H-5), 7.74 (2H, d, *J* = 8.5 Hz, H-2 and H-6), 9.83 (1H, s, CHO).

4-Benzyloxybenzaldehyde (*entry* **21**): M.p. 60–62 °C; FTIR (KBr) ν_{max}/cm^{-1} 3055, 3036, 2958, 2924, 2851, 2830 and 2745 (aldehydic C-H), 1687 (C=O), 1601, 1575, 1509, 1497, 1462, 1425, 1394, 1321, 1301, 1261, 1213, 1165, 1110, 1019; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (2H, s, PhO**C**$\mathbf{H_2}$), 6.86 (2H, d, *J* = 8.7 Hz, H-3 and H-5), 7.09–7.25 (5H, m, C_6H_5), 7.61 (2H, d, *J* = 8.7 Hz, H-2 and H-6), 9.66 (1H, s, CHO); Anal. Calcd. For $C_{14}H_{12}O_2$: C, 79.24; H, 5.66; Found C, 79.19; H, 5.62.

4-N-benzylaminoacetophenone (*entry* **23**))†: Light yellow viscous oil; FTIR (liquid film) ν_{max}/cm^{-1} 3349 (NH), 3061, 3029, 2853, 1652 (C=O), 1597, 1531, 1494, 1453, 1423, 1359, 1309, 1280, 1180, 1129, 1076, 956; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (3H, s, CH_3), 4.33 (2H, s, Ph**C**$\mathbf{H_2}$), 4.64 (1H, s, NH), 6.57 (2H, d, *J* = 8.4 Hz, H-2 and H-6), 7.12–7.27 (5H, m, C_6H_5), 7.74 (2H, d, *J* = 8.4 Hz, H-3 and H-5).

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