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Methods of Deprotection of 1, 3-Dithianes and 1,3-Dithiolanes to the Corresponding Carbonyl Compounds: A Review

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ABSTRACT

Cyclic S,S-acetals, such as 1,3-Dithianes and 1,3-dithiolanes are useful carbonyl protecting groups under acidic as well as basic conditions. Because of the central importance of carbonyl compounds in organic synthesis and utilization of 1,3-dithianes in umpolung-based synthetic strategies, regeneration of carbonyl compounds from these procarbonyl compounds has engaged the attention of chemists over the years. This paper describes recent methods of deprotection of 1,3-Dithianes and 1,3-dithiolanes to the corresponding carbonyl compounds with focus on selectivity and green chemistry features.

KEY WORDS: Dethioacetalization, 1,3-Dithianes, 1,3-dithiolanes, cleavage, carbonyl compounds.

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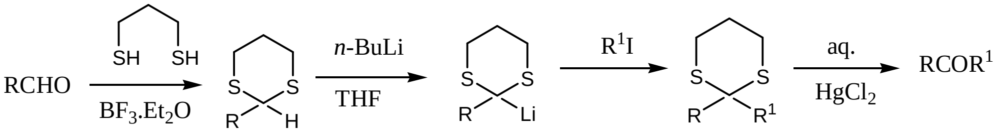
INTRODUCTION

1,3-Dithianes and 1,3-dithiolanes are procarbonyl compounds that are widely used in synthetic sequences and synthesis of natural products. Numerous synthetic operations have been performed that involve the 2-acyl-1,3-dithiane moiety, including extension of carbon chains, the masking and unmasking of carbonyl groups, blocking and unblocking of activated methylene groups, nucleophilic acylation of carboxylic acid derivatives[1,2], reduction of carbonyl groups to methylene groups, and interchange[3] of a carbonyl group with an adjacent methylene group. Temporary inversion of the electrophilic reactivity of the aldehydic carbonyl group permits the synthesis of carbonyl compounds by the coupling of a nucleophilic aldehyde derivative with electrophiles. A useful reaction sequence[1,2] for accomplishing this synthetic sequence involving conversion of the aldehyde to the 1,3-dithiane derivative, metallation of this derivative with n-butyllithium in tetrahydrofuran, reaction of the 2-lithio-1,3-dithiane derivative with an electrophile source, such as R^1I and cleavage of the resulting 1,3-dithiane derivative to the carbonyl compound with mercuric chloride (Scheme 1).

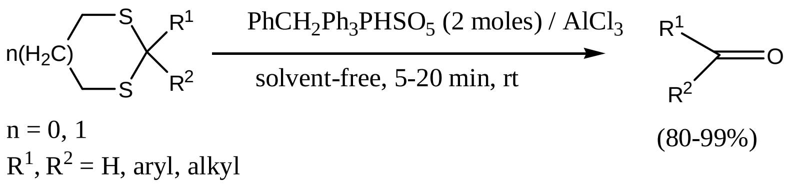


Scheme 1

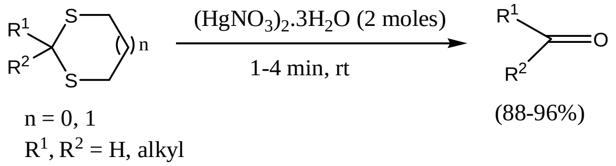
However, regeneration of parent carbonyl compounds is not always a facile and straightforward process. Therefore, development of dethioacetalization protocols has engaged the attention of organic chemists over the years and plethora of methods are documented in the literature. A good number of methods documented in the literature involve toxic metal ions and environmentally hazardous reagents, such as $HgCl_2$[4], $Tl(NO_3)_3$[5], $Tl(OCOCF_3)_3$[6], SeO_2[7], CH_3I[8], $(PhSeO)_2O$[9]. Some of the reagent systems require long reaction times and often lack generality i.e they are not applicable for all varieties of protecting groups, such as 1,3-dithianes and 1,3-dithiolanes, S,S-acetals and ketals.

RESULTS AND DISCUSSION

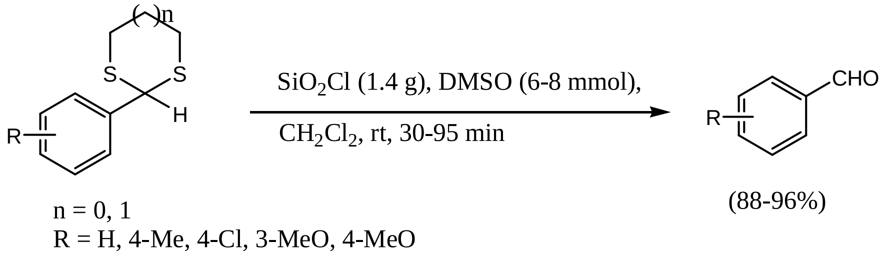
Use of benzyltriphenylphosphonium peroxymonosulfate in the presence of aluminium chloride under solvent free condition for the cleavage of 1,3-dithianes and 1,3-dithiolanes has been recently reported[10].



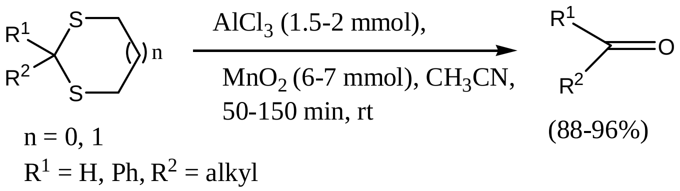
A variety of 1,3-dithianes and 1,3-dithiolanes are also deprotected in the solid-state to the corresponding parent carbonyl compounds in excellent yields using mercury (II) nitrate trihydrate[11] in a mild, efficient and fast method.



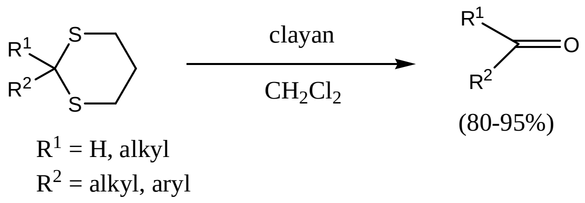
Cyclic thioacetals *viz.* 1,3-dithianes and 1,3-dithiolanes of aromatic aldehydes were cleanly converted into parent aldehydes in excellent yields using solid silica chloride (SiO_2Cl)[12] in the presence of dry DMSO.



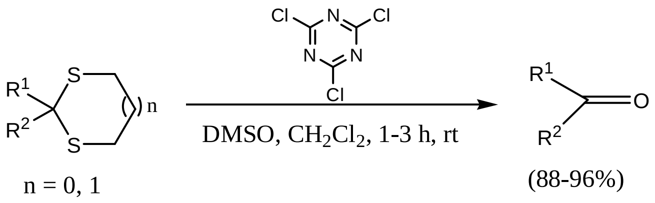
A new efficient and non-hydrolytic method for the deprotection of 1,3-dithianes and 1,3-dithiolanes derived from aldehydes and non-enolizable ketones using dry MnO_2, $BaMnO_4$ and $KMnO_4$ as nucleophiles in the presence of anhydrous $AlCl_3$ and $FeCl_3$ in dry acetonitrile[13] has also been developed.



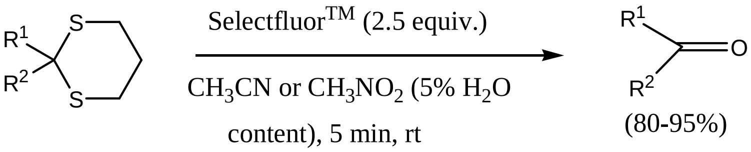
An environment-friendly approach of cleavage of 1,3-dithianes employing “clayan” (clay-supported aluminium nitrate)[14] in dichloromethane has been developed.



Deprotection of 1,3-dithianes and 1,3-dithiolanes to the corresponding carbonyl compounds has been achieved using a combination of 2,4,6-trichloro-1,3,5-triazine TT) and dimethyl sulfoxide[15] at room temperature.

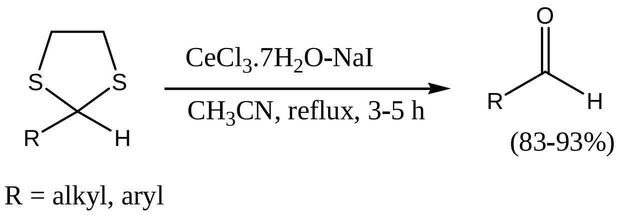


Selectfluor™ [(1-chloromethyl-4-fluro-1,4-diazoniabiclo[2,2,2]octane bis(tetrafluoroborate)] has recently been introduced commercially as a user-friendly electrophilic fluorinating reagent and also been used for the cleavage of 1,3-dithianes protecting groups. [16]

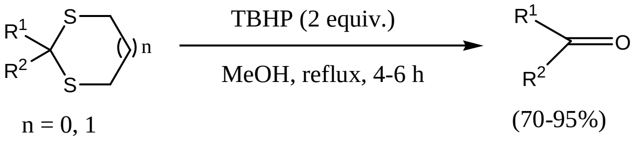


Since selectfluor™ is very soluble in water, a simple aqueous work-up is enough to remove most by-products. Beside this, it is non-toxic and relatively inexpensive compared to other electrophilic fluorinating reagents.

Selective hydrolysis of the 1,3-dithioacetals has been achieved in high yields using $CeCl_3.7H_2O$-NaI in acetonitrile[17] at reflux temperature under neutral condition. This method is mild and compatible with a wide range of functional groups such as TBDPS, THP, MOM, prenyl and benzyl ethers.

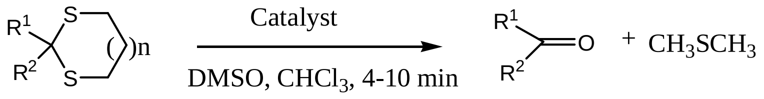


Regeneration of carbonyl compounds from their 1,3-dithianes and 1,3-dithiolanes was achieved using *t*-butyl hydroperoxide[18] (TBHP, aq. 70%) in high yields.



A novel catalytic and selective protocol for the deprotection of S,S-acetals and ketals in the presence of their O,O-analogs to corresponding carbonyl compounds based on the use of N-bromosuccinamide (NBS), N-chlorosuccinimide (NCS), 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one

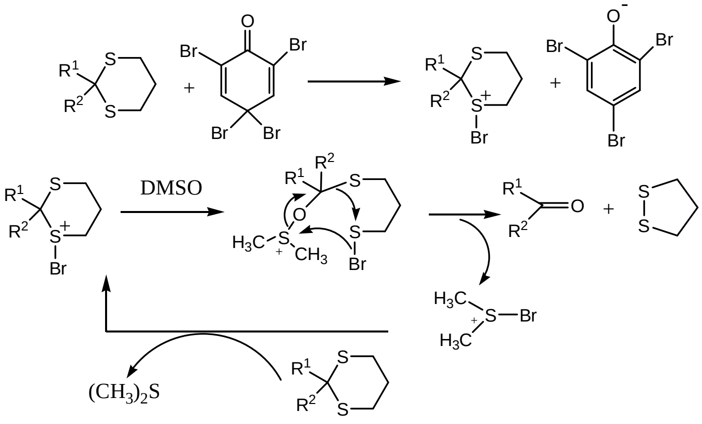
(TABCO), trichlorocynauric acid (TCCA) as sources of electrophilic halogens and also bromine in a catalytic cycle in the presence of DMSO has been reported. [19] DMSO has been used as a source of oxygen and the ease of halogenations of the sulfur atom in S,S-acetals and ketals in comparison with the oxygen in their O,O-analogs, allowed the reaction to occur with high chemoselectivity for the deprotection of S,S-acetals and ketals at room temperature.



n = 0, 1 Catalyst = NBS, TABCO, Br_2 (0.1-0.2 equiv.)

R^1, R^2 = H, aryl and alkyl carrying no enolizable hydrogen

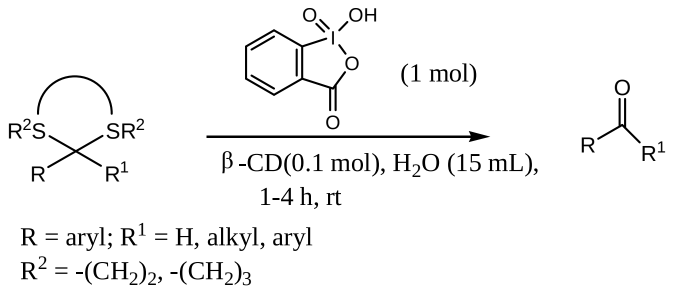
The suggested mechanism for dethioacetalization was shown in scheme 2 using TABCO as catalyst.



Scheme 2. Dethioacetalization using TABCO as catalyst

Use of electrophilic halogens provides an efficient, novel and mild procedure for the deprotection reaction. In adition to the selectivity of the method for the deprotection of S,S-acetals and ketals in the presence of their O,O-analogs, the low cost and availability of the reagents, simplicity of the method, short reaction times and excellent yields are the key advantages of this method.

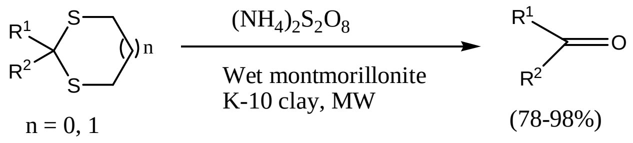
An efficient and user-friendly procedure has been developed for the cleavage of 1,3-Dithianes and 1,3-dithiolanes to corresponding carbonyl compounds in impressive yields with *o*-iodobenzoic acid (IBX) in presence of *β*-cyclodextrin (β-CD) in water under neutral conditions[20] at room temperature.



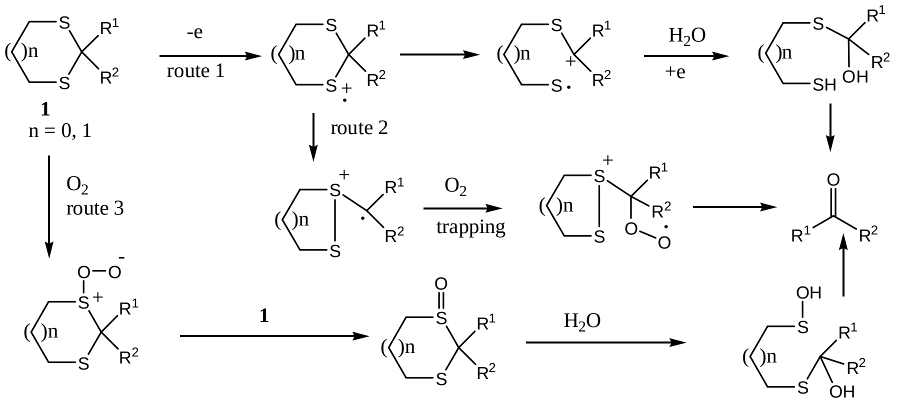
R = aryl; R^1 = H, alkyl, aryl
R^2 = $-(CH_2)_2$, $-(CH_2)_3$

Amongst various oxidizing agents, *o*-iodobenzoic acid (IBX) has attractive features due to its low toxicity, high selectivity and eco-friendly nature. [21] Use of IBX and DMSO[13] as solvent has also been reported earlier. Use of IBX in water is particularly ecofriendly.

Solid-state microwave-assisted oxidative deprotection of 1,3-Dithianes and 1,3-dithiolanes of aromatic aldehydes and ketones, cyclic ketones, α,β-unsaturated aldehydes and aliphatic aldehydes and ketones has been accomplished using ammonium persulfate on wet montmorillonite K-10 clay. [22]

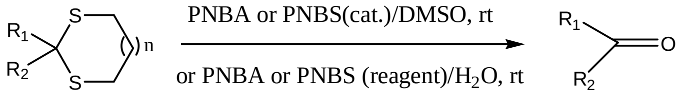


Mechanistically, the oxidative cleavage of cyclic thioacetals presumably involves cation-radical intermediates in view of the propensity of cyclic thioethers to undergo single-electron transfer (SET) oxidations[23-25](Scheme 3; route 1). Since microwave-assisted hydrolysis of ammonium persulfate on activated moist acidic clay surface is reported[26] to generate molecular oxygen another two routes are also suggested by the authors where oxygen trapping occurs (Scheme 3; route 2 and route 3).



Scheme 3

An efficient chemoselective method for the deprotection of 1,3-Dithianes and 1,3-dithiolanes using cross-linked poly(N-bromoacrylamide) (PNBA) and poly(N-bromosuccinimide) (PNBS) in the presence of DMSO and water as oxidant has been achieved recently.[27] These polymeric reagents have the advantage of being heterogeneous which resulted in easy isolation of them from the reaction mixture. In a system in which DMSO is applied as an oxidant, PNBA or PNBS is used catalytically. However, when the reactions are performed in water, PNBA or PNBS would be employed as a reagent.



n = 0, 1
R_1 = alkyl, phenyl or H
R_2 = alkyl, phenyl

CONCLUSION

Regeneration of carbonyl compounds from 1,3-Dithianes and 1,3-dithiolanes has engaged attention of organic chemistry over the years and numerous reagents have been employed for this purpose. Each reagent represents a different balance of yield, toxicity, cost efficiency, selectivity and operational convenience. I hope this review to be a method of choice for cleavage of 1,3-Dithianes and 1,3-dithiolanes, particularly for high throughput chemistry.

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