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Catalytic and chemoselective deprotection of *S*,*S*- and *S*,*O*-acetals and ketals in the presence of their *O*,*O*-analogs with electrophilic halogens under neutral conditions

Nasser Iranpoor,* Habib Firouzabadi* and Hamid Reza Shaterian

Chemistry Department, College of Sciences, Shiraz University, Shiraz 7146713565, Iran

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Abstract—A novel and catalytic method is described for the selective deprotection of *S*,*S*- and *S*,*O*-acetals and ketals in the presence of their *O*,*O*-analogs to their corresponding carbonyl compounds based on the use of *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), 2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one (TABCO), trichlorocyanuric acid (TCCA) or molecular bromine as sources of electrophilic halogens in the presence of DMSO as the source of oxygen in $CHCl_3$.

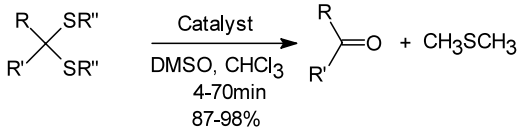
Thioacetals and ketals are important intermediates in multistep natural product synthesis[1,2] and are stable compounds in both acidic and basic conditions and their deprotection to carbonyl groups, especially under mild reaction conditions, is considered an important transformation reaction in organic synthesis.

The methods employed for the deprotection of *S*,*S*-acetals include: (a) hydrolysis in the presence of different transition-metal ions;[3–10] (b) oxidation of sulfur to a higher oxidation state;[11–18] (c) hydrolysis[19–21] and (d) use of alkylating agents.[21b,22] Although some of the reported methods in the literature can be applied for the chemoselective deprotection of the more reactive *O*,*O*-acetals and ketals in the presence of less reactive *S*,*S*- and *S*,*O*-analogs, to the best of our knowledge, there is no report available in the literature concerning the reverse chemoselectivity.

In this paper, we report a novel catalytic and selective protocol for the deprotection of *S*,*S*- and *S*,*O*-acetals and ketals in the presence of their *O*,*O*-analogs. In this method, *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (TABCO), trichlorocyanuric acid (TCCA) as sources of electrophilic halogens and also bromine are used in a catalytic cycle in the presence of DMSO. Here, DMSO acts as a source of oxygen and the ease of halogenation of the sulfur atom in *S*,*S*- and *S*,*O*-acetals and ketals in comparison with the oxygen in their *O*,*O*-analogs, allows the reaction to occur with high chemoselectivity for the deprotection of *S*,*S*- and *S*,*O*-acetals and ketals at room temperature (Scheme 1).

To optimize the reaction conditions, we studied the conversion of 2-phenyl-1,3-dithiane to benzaldehyde in the presence of the above mentioned catalysts. The results obtained are presented in Table 1.

2-Phenyl-1,3-dithiolane was quantitatively converted to benzaldehyde in the presence of 0.05–0.2 equimolar amounts of these catalysts and DMSO in chloroform within 5–75 min at room temperature (Table 1). Although the reactions with NBS and TABCO (Table 1, entries 1–4) are slightly faster than those with NCS



Catalyst = NBS, TABCO, Br_2 (0.1-0.2 mmol)
R, R' = H, Aryl and alkyl carrying no enolizable hydrogen
R''= Ph, Alkyl, $-(CH_2)_n-$ [n=2, 3]

Scheme 1.

* Corresponding authors. E-mail: iranpoor@chem.susc.ac.ir; firouzabadi@chem.susc.ac.ir

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Table 1. Conversion of 2-phenyl-1,3-dithiane (1.0 mmol) to benzaldehyde with various catalysts (NBS, NCS, TABCO, TCCA, Br_2 and I_2) in the presence of DMSO[a] in chloroform at room temperature

Entry	Catalyst (molar equiv.)	Time (min)	Yield[b] (%)
1	NBS (0.05)	45	94
2	NBS (0.2)	5	98
3	TABCO (0.05)	60	93
4	TABCO (0.2)	7	95
5	NCS (0.05)	75	93
6	NCS (0.2)	10	97
7	TCCA (0.1)	60	95
8	TCCA (0.2)	30	95
9	Br_2 (0.1)	10	98
10	Br_2 (0.2)	5	95
11	I_2 (0.2)	24 h	35

[a] The molar ratio of DMSO/2-phenyl-1,3-dithiane is 5/1.
[b] Isolated yield.

and TCCA (Table 1, entries 4–8), the yields are more or less the same. We also examined the possibility of using molecular bromine and iodine as catalyst for this reaction (Table 1, entries 9–11). Our findings showed that the conversion of 2-phenyl-1,3-dithiane to benzaldehyde with catalytic amounts of bromine occurs in a similar manner to those reactions using NBS and TABCO as catalyst (Table 1, entries 9, 10). However, the reaction with iodine is very slow and was not completed (Table 1, entry 11).

We therefore chose TABCO, NBS, and Br_2 and continued our study on the deprotection of different dithioacetals and also 1,3-oxathioacetals derived from carbonyl compounds carrying no enolizable hydrogen. The results obtained are presented in Table 2. Thioacetals and 1,3-oxathioacetals derived from enolizable carbonyl compounds under similar reaction conditions were converted to their ring-expanded-brominated products and are currently under further investigation.

In Scheme 2, the suggested mechanism for dethioacetalization using TABCO as catalyst is shown. Bromination of **I** occurs to produce the intermediate **II**, which then reacts with DMSO to give the sulfenyl bromide intermediate **III**. This is in equilibrium with sulfonium and bromide ions in polar solvents[23] and produces the corresponding carbonyl compound and 1,2-dithiacyclopentane **IV** together with the formation of intermediate **V**. In this reaction, the formation of Br_2 possibly through the reaction of intermediate **III** and **V** was also observed and which could also be incorporated in the continuation of the catalytic cycle. The easily polymerizable 1,2-dithiacyclopentane **IV**, which must be handled only in dilute solution, was isolated from the reaction mixture and identified by the comparison of its UV absorption band at 330 μm (ε 147), and ^1H and ^{13}C NMR spectral data with those reported in the literature.[23–25] In addition, its spectral data and GC retention time were also compared with that of a sample obtained from intramolecular coupling of 1,3-propandithiol.[25] In the work-up, due to the polymerization of this compound, it can be easily removed from the reaction mixture by chromatography.

We also studied selective dethioacetalization in the presence of different protected carbonyl groups using TABCO, NBS or Br_2 as catalysts. All the catalysts showed similar results and high to excellent selectivity was observed. The results of selective deprotection of dithioacetals and 1,3-oxathiolanes in the presence of acyclic acetals, cyclic acetals and diacetates (acylals) in 1:1 mixtures using NBS as a representative catalyst are shown in Table 3.

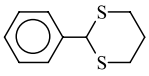
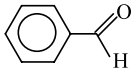
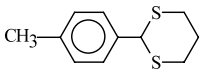
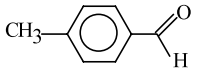
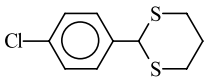
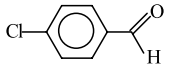
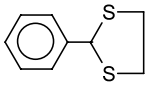
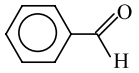
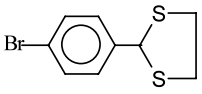
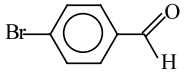
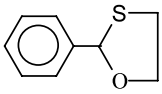
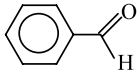
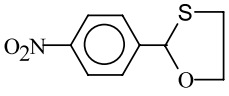
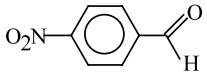
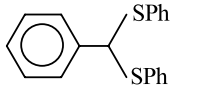
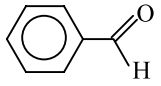
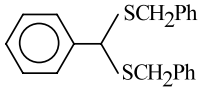
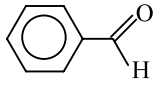
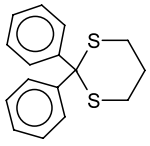
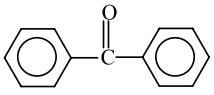
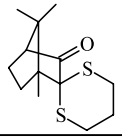
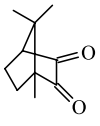
Using this method, 2-phenyl-1,3-dithiane was deprotected in the presence of benzaldehyde dimethyl acetal with a ratio of 100/5 (Table 3, entry 1). When 2-phenyl-1,3-dioxane was used which is more stable than benzaldehyde dimethyl acetal, again excellent chemoselectivity was observed with a ratio of 100/2 (Table 3, entry 2). 2-Phenyl-1,3-oxathiolane was deprotected in the presence of 2-(4-nitrophenyl)-1,3-dioxane with high chemoselectivity of 100/17 (Table 3, entry 3). 2-Phenyl 1,3-dithiolane was also deprotected in the presence of 4-methyl-benzyl diacetate with a ratio of 100/23 (Table 3, entry 4). The same reaction in the presence of 4-nitro benzyldiacetate occurred with a high selectivity ratio of 100/5 (Table 3, entry 5).

In conclusion, in this method, the use of electrophilic halogens provides an efficient, novel and mild procedure for the deprotection reactions of cyclic and acyclic dithioacetals and ketals and also 1,3-oxathioacetals. In addition to the selectivity of the method for the deprotection of *S*,*S*- and *S*,*O*-acetals in the presence of *O*,*O*-analogs, the low cost and availability of the reagents, simplicity of the method, short reaction times, and excellent yields can also be considered as strong points for this method.

General procedure for the deprotection of dithioacetals and 1,3-oxathioacetals to their parent carbonyl compounds:

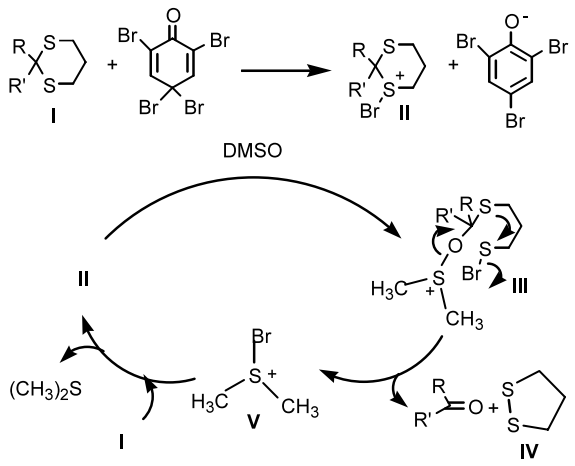
Dithioacetal or 1,3-oxathioacetal (1.0 mmol) was added to a stirred solution of 0.05–0.3 mmol of catalyst (NBS, TABCO, or Br_2) in 3 ml of chloroform (Table 2). Dimethyl sulfoxide (5 mmol) was then added to this mixture. The reaction was monitored by thin layer chromatography (silica-gel/*n*-hexane) and GC analysis. Upon completion of the reaction, 25 ml of chloroform was added to the reaction mixture. The solution was washed with cold 5% NaOH (20 ml) followed with brine solution (10 ml) and water (2×10 ml). The organic phase was separated and dried with

Table 2. Deprotection of *S*,*S*- and *S*,*O*-acetals and ketals with TABCO (A), NBS (B), and also Br_2 (C) as the catalysts in the presence of DMSO (5 mmol) in $CHCl_3$ at room temperature

Entry	Substrate	Product	Sub./Cat. (ratio)	Time (min)	Yield %[a]
1			1/0.2(A) 1/0.2(B) 1/0.1(C)	7 5 10	93 95 96
2			1/0.2(A) 1/0.2(B) 1/0.1(C)	5 4 8	95 94 95
3			1/0.2(A) 1/0.2(B) 1/0.1(C)	10 8 15	93 96 97
4			1/0.2(A) 1/0.2(B) 1/0.1(C)	8 5 10	95 96 97
5			1/0.2(A) 1/0.2(B) 1/0.2(C)	10 7 4	94 96 97
6			1/0.2(A) 1/0.2(B) 1/0.1(C)	9 7 5	92 94 96
7			1/0.2(A) 1/0.2(B) 1/0.2(C)	12 7 4	94 95 98
8			1/0.2(A) 1/0.2(B) 1/0.1(C)	8 5 7	94 93 96
9			1/0.2(A) 1/0.2(B) 1/0.1(C)	10 7 8	91 93 96
10			1/0.3(A) 1/0.3(B) 1/0.2(C)	50 40 30	89 90 92
11			1/0.3(A) 1/0.3(B) 1/0.2(C)	70 55 45	87 88 89

a) Isolated yield.

anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica-gel using *n*-hexane as eluent to give the pure carbonyl compound(s) in excellent yield(s). The products were characterized by comparison of their physical data (mp or bp), IR, and ^1H NMR spectra with those of known aldehydes and ketones.



Scheme 2.

References

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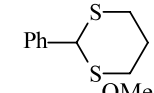
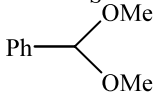
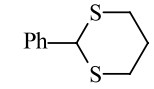
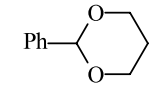
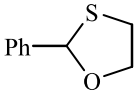
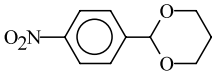
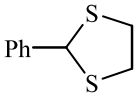
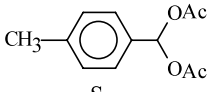
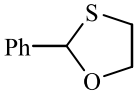
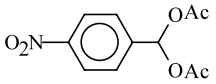
2. (a) Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643–7677; (b) Guanti, G.; Banfi, L.; Brusco, S.; Riva, R. *Tetrahedron Lett*. **1993**, *34*, 8549–8552.
3. (a) Toshima, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 1281–1283; (b) Vedejs, E.; Fuchs, P. L. *J. Org. Chem*. **1971**, *36*, 366–367; (c) Uemura, M.; Nishimura, H.; Minami, T.; Hayashi, Y. *J. Am. Chem. Soc*. **1991**, *113*, 5402–5410.

Table 3. Selective deprotection of dithioacetals and 1,3-oxathiolanes with *N*-bromosuccinimide (NBS) as the catalyst in the presence of DMSO (5 mmol) in $CHCl_3$ at room temperature

Entry	Substrate1 Substrate 2	Product 1 Product 2	Sub 1/Sub 2/ NBS (ratio)	Time (min)	Yield [a] (%)
1		PhCHO	1/1/0.2	5	100
		PhCHO			5[b]
2		PhCHO	1/1/0.2	5	100
		PhCHO			2[b]
3		PhCHO	1/1/0.2	5	100
		$O_2NC_6H_4CHO$			17
4		PhCHO	1/1/0.2	5	100
		$CH_3C_6H_4CHO$			23
5		PhCHO	1/1/0.2	10	100
		$O_2NC_6H_4CHO$			5[b]

a) Yields based on NMR and GC analysis (*n*-heptane was used as internal standard).

b) Yield was based on the amount of unreacted starting material.

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