A Highly Efficient Procedure for Regeneration of Carbonyl Groups from their Corresponding Oxathioacetals and Dithioacetals Using Sodium Nitrite and Acetyl Chloride in Dichloromethane

Abu T. Khan,* Ejabul Mondal, Priti R. Sahu

Department of Chemistry, Indian Institute of Technology, North Guwahati, Guwahati-781039, Assam, India
Fax +91(361)2690762; E-mail: atk@postmark.net

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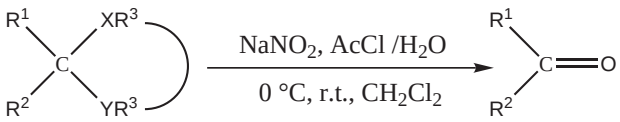
Abstract: A wide variety of oxathioacetals **1** as well as dithioacetals **2** can be chemoselectively deprotected to the corresponding carbonyl compounds **3** in good yields by employing $NaNO_2$–AcCl and H_2O in CH_2Cl_2 at 0 °C to room temperature. Some of the major advantages of this procedure are: mild conditions, easy to handle, highly chemoselective and efficient, high yields and inexpensive reagents. In addition, no acetylation occurs at the hydroxyl group nor chlorination takes place at the double bond.

Key words: deprotection, oxathioacetals, dithioacetals, sodium nitrite, acetyl chloride

The protection-deprotection strategy is a common practice in multistep organic synthesis. Among the various functional groups, protection of carbonyl groups as oxathioacetals and dithioacetals has attracted much attention due to their robustness under mild acidic or basic reaction conditions. They also serve as acyl carbanion equivalents for carbon-carbon bond forming reactions.[1] The most remarkable application is the use of chiral oxathioacetals for the synthesis of optically active tertiary alcohols possessing a carbonyl functionality at the α-position, first demonstrated by Eliel and Lynch.[2] Later on, the utility of oxathioacetals was further shown by Utimoto and his group in organic synthesis.[3] In contrast to many methods available for deprotection of dithioacetals, a few methods are known for oxathioacetals.[4] Consequently, there is a need to find out a better alternative for deprotection of oxathioacetals, which might work under mild conditions. The existing procedures for the deprotection of oxathioacetals are as follows: i) use of isoamyl nitrite[5a] and chloramine T,[5b] ii) treatment with TMSOTf alone,[6a] iii) or with TMSOTf in the presence of *p*-nitrobenzaldehyde,[6b,c] or polymer supported *p*-nitro-benzaldehyde,[6d] iv) use of halonium ion sources in the presence of expensive silver salts[7] or reaction with NBS in acetone.[8] Unfortunately, some of the procedures have serious drawbacks such as the removal of the by-product oxathioacetal derived from *p*-nitrobenzaldehyde[6b,c] or the use of an expensive polymer supported reagent[6d] and sometimes failure to deprotect non-benzylic oxathioacetals.[6a] They also require long reaction times.[6d] Other drawbacks related to halonium ion sources include the need for a large excess in expensive reagents such as silver salts[7] and require long reaction times.[8] Recently, another method was reported[9] by Kirihara et al. using a catalytic amount of trichloroxyvanadium, which also requires drastic reaction conditions. We have also demonstrated some new methodologies based on bromonium ion sources for deprotection of various oxathioacetals[10a–c] and dithioacetals,[10d–f] which involve expensive organic ammonium tribromides[10b,e] and require relatively long reaction times. Very recently one more method was reported[11] using $CeCl_3 \cdot 7H_2O$–NaI, which require long reaction times as well as expensive reagents. Though a large number of methods have already been reported in the literature[12] for deprotection of dithioacetals to the corresponding carbonyl compounds, still there is a need to develop a mild methodology. The usual standard procedure for cleavage of dithioacetals involves mainly a suitable electrophile, which is captured by a soft nucleophilic sulfur atom followed by hydrolysis with water. We decided to test NO^+ as electrophilic species for regeneration of carbonyl compounds from the corresponding protected derivative. Sodium nitrite in combination with trifluoroacetic acid,[13] isoamyl nitrite[5a] and a mixture of oxides of nitrogen[14] have already been used for deprotection of dithioacetals to the carbonyl compounds. However, these procedures have some drawbacks such as incompatibility with other protecting group like TBS ethers due to the use of a large excess of trifluoroacetic acid, drastic reaction conditions and long reaction times,[5a] and provide a low yield for enolizable ketones.[14] In this communication, we wish to report that sodium nitrite in combination with acetyl chloride is a useful reagent for the cleavage of both oxthioacetals and dithioacetals (Scheme 1) under mild reaction conditions.

Next, we have prepared a wide variety of structurally different oxathioacetals **1a**–**n** by following our reported pro-



1 or 2 **3**

1: X = O, Y = S; R^1 = alkyl/aryl; R^2 = H, alkyl, aryl; R^3 = -$(CH_2)_2$
2: X = Y = S; R^1 = alkyl/aryl/sugar residue; R^2 = H, alkyl, aryl; R^3 = Et, -$(CH_2)_2$, $(CH_2)_3$

Scheme 1

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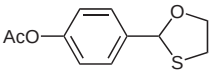
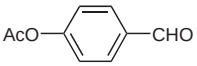
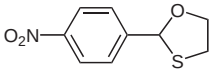
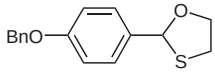
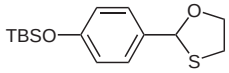
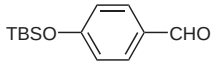
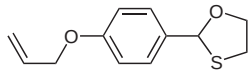
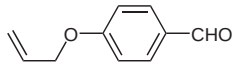
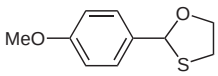
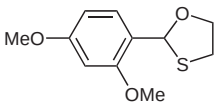
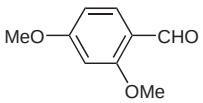
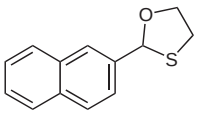
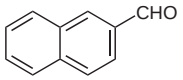
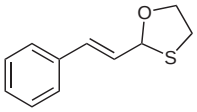
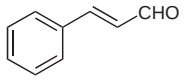
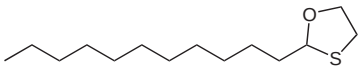
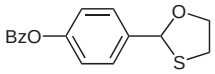
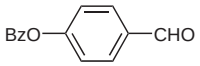
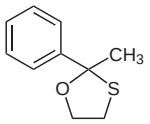
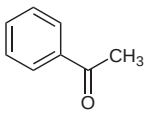
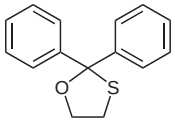
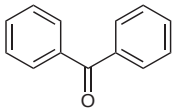
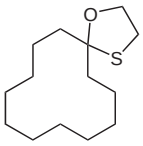
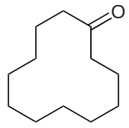
cedure.[10a] The substrate 2-(*p*-acetoxyphenyl)-1,3-oxathiolane (**1a**) was smoothly converted to *p*-acetoxybenzaldehyde (**3a**) by adding **1a** to a stirring solution of $NaNO_2$–AcCl (1:1) at 0–5 °C, followed by addition of water after 10 minutes of stirring. The reaction was completed at the same temperature by additional 15 minutes of stirring. By following the typical procedure described above,[15] various oxathioacetals **1b**–**n** were easily transformed to the parent carbonyl compounds **3b**–**n** in very good yields (Table 1). It is important to mention that other

Table 1 Cleavage of Various Oxathioacetals Using $NaNO_2$–AcCl–H_2O in CH_2Cl_2

Entry	Substrate **1**	Time (min)	Product **3**[a]	Yield (%)[b]
a		25		82
b		40		85
c		35		90
d		25		84
e		30		90
f		35		90
g		30		95
h		25		84
i		35		70
j		25	$CH_3(CH_2)_{10}CHO$	84
k		25		97
l		30		82
m		25		80
n		25		95

[a] Products have been characterized by co-IR with authentic compounds, ^1H NMR, ^{13}C NMR and elemental analyses of the samples.
[b] Isolated yields.

protecting groups such as OBn, OBz, TBS and allyl (for entries **1c**, **1k**, **1d and 1e**) were unaffected under the experimental conditions. Deprotection of compound **1f** requires longer time[5a] compared to our method. All deprotected compounds were fully characterized[16] by IR, ^{1}H NMR, ^{13}C NMR spectroscopy by comparison with authentic samples.

Next, we have turned our attention to the deprotection of various dithioacetals, which were prepared following our procedure using catalytic amount of 70% $HClO_4$.[17] When compound **2a** was treated with 2 equivalents of $NaNO_2$–CH_3COCl (1:1) at 0–5 °C, it was smoothly converted to **3a** in good yield. Similarly, **2b** gave compound **3b** in good yield without acetylation of the hydroxyl group. Likewise, various acyclic and cyclic dithioacetals **2c**–**u** were also cleaved chemoselectively to the parent carbonyl compounds without affecting other protecting groups. Moreover, by using our protocol the open chain aldehydic sugars **3v** and **3w** were prepared from the corresponding compounds **2v** and **2w** (Table 2).[18]

Table 2 Cleavage of Various Dithioacetals Using $NaNO_2$–AcCl/H_2O in CH_2Cl_2

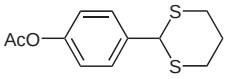
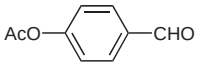
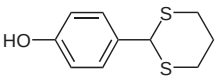
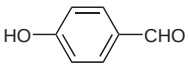
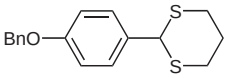
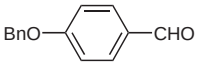
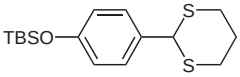
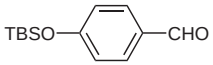
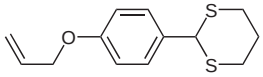
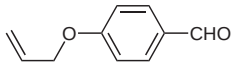
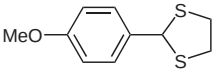
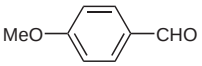
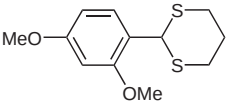
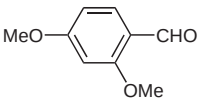
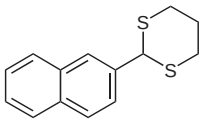
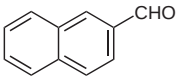
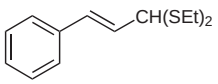
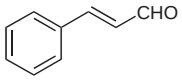
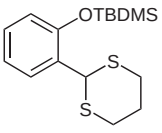
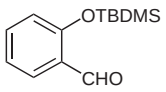
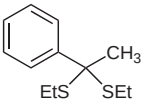
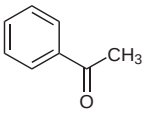
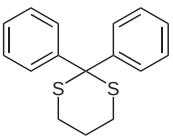
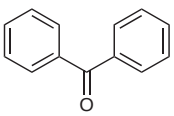
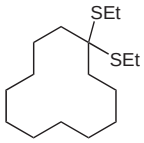
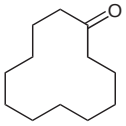
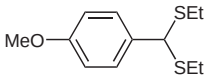
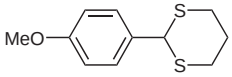
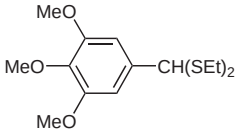
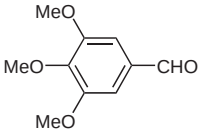
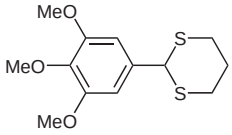
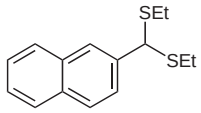
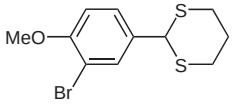
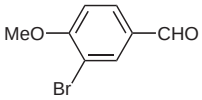
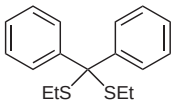
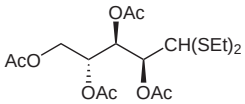
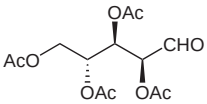
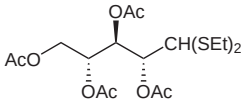
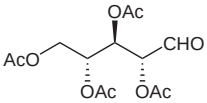
Entry	Substrate **2**	Time (min)	Product **3**[a]	Yield (%)[b]
a		225		85
b		15		90[c]
c		45		97
d		70		85
e		40		97
f		30		95
g		45		97
h		45		96
i		30		95
j	$CH_3(CH_2)_{10}CH(SEt)_2$	70	$CH_3(CH_2)_{10}CHO$	82
k		45		94
l		70		90
m		45		90

Table 2 Cleavage of Various Dithioacetals Using $NaNO_2$–AcCl/H_2O in CH_2Cl_2 (continued)

Entry	Substrate **2**	Time (min)	Product **3**[a]	Yield (%)[b]
n		45		78
o		90	**3f**	98
p		45	**3f**	90
q		45		96
r		90	**3q**	96
s		60	**3h**	95
t		45		80
u		45	**3m**	87
v		45		75
w		60		72

[a] Products have been characterized by co-IR with authentic compounds, ^1H NMR and elemental analyses of the samples.
[b] Isolated yields.
[c] After addition of the substrate, water is added after 2 min instead of 5 min.

The formation of the parent carbonyl compounds from their corresponding oxathioacetals or dithioacetals can be rationalized as follows. Sodium nitrite reacts with acetyl chloride to form acetyl nitrite, which ultimately generates a highly reactive species NO^+ ion. The NO^+ ion reacts with the sulfur atom of the thioacetal to form a complex,[5a] which is finally hydrolyzed by water to provide the carbonyl compound.

In conclusion, we have presented a mild and easy procedure for deprotection of oxathioacetals and dithioacetals to the parent carbonyl compounds by using a mixture of sodium nitrite and acetyl chloride. In addition, this methodology is compatible with the presence of a large number of other protecting groups such as acetyl, benzyl, benzoyl, TBS ether, allyl and also provide good yield for enolizable ketones.

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(15) **A Typical Procedure for Deprotection of Oxathioacetals**: The mixture of $NaNO_2$ (0.069 g, 1 mmol) and AcCl (71 μL, 1 mmol) in CH_2Cl_2 (3 mL) was stirred for 10 min at 0–5 °C. Then the substrate 2-(*p*-methoxyphenyl)-1,3-oxathiolane **1f** (0.196 g, 1 mmol) in CH_2Cl_2 (2 mL) was added into the above reaction mixture at the same temperature. After stirring for 5 min, water (1 mL) was added and the mixture brought to r.t. The reaction was completed with additional stirring 20 min (TLC). Finally, the reaction mixture was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was washed with water (2 × 20 mL) and dried (Na_2SO_4). Evaporation of the solvent gave the crude residue, which was purified by column chromatography on silica gel (eluent: hexane–EtOAc, 19:1). Product **3f** was obtained as a colourless liquid 0.122 g (90%).
A Typical Procedure for Deprotection of Dithioacetals: The reaction was carried out with compound **2f** as stated above except 2 equiv of $NaNO_2$ and AcCl (1:1) mixture was used. Product **3f** was obtained as a colourless liquid 0.129 g (95%).

(16) **Spectroscopic Data for Compound 1d, 1e, 3d and 3e: For 1d:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.20 (s, 6 H, $SiCH_3$), 0.97 [s, 9 H, $SiC(CH_3)_3$], 3.19 (m, 1 H, -CHS-), 3.27 (m, 1 H, -CHS-), 3.94 (m, 1 H, -OCH-), 4.52 (m, 1 H, -OCH-), 5.99 (s, 1 H, OCHS-), 6.81 (d, 2 H, *J* = 8.5 Hz, ArH), 7.35 (d, 2 H, *J* = 8.5 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.45(2 C), 18.17, 25.64 (3 C), 34.03, 61.20, 87.01, 119.98 (2 C), 128.18 (2 C), 131.46, 156.07. Anal. Calcd for $C_{15}H_{24}O_2SSi$: C, 60.76; H, 8.16; S, 10.81. Found: C, 60.57; H, 8.10; S, 10.68. **For 1e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.18 (m, 1 H, -CHS-), 3.28 (m, 1 H, -CHS-), 3.91 (m, 1 H, -OCH-), 4.51 (m, 3 H, $-OCH_2$-, OCH-), 5.28 (dd, 1 H, *J* = 1.5 Hz, *J* = 10.5 Hz, OCH_2CH=CH_2), 5.40 (dd, 1 H, *J* = 1.5 Hz, *J* = 17.3 Hz, OCH_2CH=CH_2), 5.99 (s, 1 H, OCHS-), 6.05 (m, 1 H, OCH_2CH=CH_2) 6.95 (d, 2 H, *J* = 8.7 Hz, ArH), 7.40 (d, 2 H, *J* = 8.7 Hz, ArH). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 16.22. Found: C, 64.61; H, 6.30; S, 16.10. **For 3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $SiCH_3$), 0.79 [s, 9 H, $SiC(CH_3)_3$], 6.70 (d, 2 H, *J* = 8.6 Hz, ArH) 7.54 (d, 2 H, *J* = 8.6 Hz, ArH), 9.94 (s, 1 H, CHO). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.69; H, 9.57. **For 3e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.63 (m, 2 H, -OCH_2-CH=CH_2), 5.34 (dd, 1 H, *J* = 1.5 Hz, *J* = 10.5 Hz, OCH_2CH=CH_2), 5.44 (dd, 1 H, *J* = 1.5 Hz, *J* = 17.3 Hz, OCH_2CH=CH_2), 6.06 (m, 1 H, OCH_2CH=CH_2) 7.02 (d, 2 H, *J* = 8.8 Hz, ArH), 7.84 (d, 2 H, *J* = 8.7 Hz, ArH), 9.88 (s, 1 H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.95, 114.94 (2 C), 118.34, 129.94, 131.94 (2 C), 132.21, 163.55, 190.81. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.95; H, 6.15.

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(18) **Spectroscopic Data for Compound 3v and 3w: For 3v**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (s, 9 H, $COCH_3$), 2.20 (s, 3 H, $COCH_3$), 4.19 (dd, 1 H, *J* = 4.6 Hz, *J* = 12.6 Hz, H-5′), 4.33 (dd, 1 H, *J* = 2.6 Hz, *J* = 12.6 Hz, H-5), 5.27 (m, 1 H, H-4), 5.39 (d, 1 H, *J* = 2.2 Hz, H-2), 5.69 (dd, 1 H, *J* = 2.1 Hz, *J* = 8.8 Hz, H-3), 9.48 (s, 1 H, CHO). Anal. Calcd for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70. Found: C, 48.88; H, 5.63. **For 3w**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.97 (s, 3 H, $COCH_3$), 2.06 (s, 3 H, $COCH_3$), 2.09 (s, 3 H, $COCH_3$), 2.19 (s, 3 H, $COCH_3$), 4.17 (dd, 1 H, *J* = 4.3 Hz, *J* = 12.6 Hz, H-5′), 4.37 (dd, 1 H, *J* = 2.6 Hz, *J* = 12.6 Hz, H-5), 5.31 (m, 1 H, H-4), 5.45 (d, 1 H, *J* = 2.5 Hz, H-2), 5.61 (dd, 1 H, *J* = 2.5 Hz, *J* = 8.8 Hz, H-3), 9.50 (s, 1 H, CHO). Anal. Calcd for $C_{13}H_{18}O_9$: C,49.06; H, 5.70. Found: C, 48.82; H, 5.74.