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Highly efficient and chemoselective interchange of 1,3-oxathioacetals and dithioacetals to acetals promoted by *N*-halosuccinimide

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Abstract—Highly efficient interconversion of a range of 1,3-oxathiolanes, 1,3-dithiolanes and 1,3-dithianes to their acetals at ambient temperature using *N*-bromosuccinimide or *N*-chlorosuccinimide and different types of alcohols and diols was investigated. © 2002 Published by Elsevier Science Ltd.

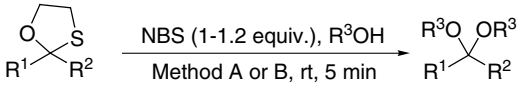
1. Introduction

The protection of carbonyl compounds as acetals or their sulfur analogs is one of the most widely used and versatile transformations in organic synthesis, as testified by a large number of reagents and methods that have been devised to accomplish this functional group interconversion.[1] Among the carbonyl protective groups, 1,3-oxathioacetals and 1,3-dithioacetals have an especial place in organic chemistry. 1,3-Oxathioacetals are considerably more stable than the corresponding *O*,*O*-acetals under acidic conditions, but compared with the *S*,*S*-acetals are more easily deprotected. Among this, both oxathioacetals and dithioacetals are also of importance because they can be used as precursors for acyl anion equivalent displaying reactivity umpolung.[2,3] A major problem during many multi-step syntheses is how to protect a carbonyl group from various types of reagents and reaction conditions. One way to attain this goal is the direct interchange between two chemically different carbonyl-protecting groups without going through the free carbonyl compound. Such a direct interchange, as previously described by Corey and Hase[4a] can remove interference by the original protecting group.[4] For example, replacement of thioacetal by acetal could permit an oxidation or halogenation process not possible in the presence of a sulfur-containing group.[5]

2. Results and discussion

A literature search shows that, although, there are some rare examples of conversion of dithioacetals to the corresponding *O*,*O*-acetals using methyl-fluorosulfonate.[4] There are, to our knowledge, no report presenting the interconversion of oxathioacetals to their acetals. Consequently, the developments of new and general methods for this purpose are being pursued. In our development of new methods for functional group transformation, we are especially interested in exploring the potential use of *N*-bromosuccinimide (NBS) as a relatively neutral and mild catalyst in organic chemistry.[6] In continuation of these studies, herein, we wish to report a new protocol for the mild and rapid transformation of a variety of 1,3-oxathiolanes and their *S*,*S*-analogs to the corresponding cyclic and open-chain *O*,*O*-acetals using NBS or *N*-chlorosuccinimide (NCS) (Scheme 1).

As shown in Table 1, in the presence of NBS (1 equiv.), different types of 1,3-oxathiolanes of aldehydes were rapidly and efficiently converted to the corresponding 1,3-dioxanes or 1,3-dioxolanes upon treatment with dry 1,3-propanediol (3 equiv.) or dry 1,2-ethanediol (2.5 equiv.), respectively, under mild reaction conditions (Method A) (Table 1, entries 1–9). The method can also effectively conducts interchange of 1,3-oxathiolanes of aliphatic as well as aromatic ketones under nearly similar reaction conditions (Table 1, entries 10–19).



Method A = CH_2Cl_2, diol (3 equiv.)
Method B = Absolute MeOH or EtOH
R^3 = Me, Et, -$(CH_2)_2$- or -$(CH_2)_3$-

Scheme 1.

Keywords: protecting groups; 1,3-oxathioacetals; 1,3-dithioacetals; *N*-halosuccinimide; acetals.

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Table 1. Interconversion of 1,3-oxathiolanes to *O*,*O*-acetals using NBS at room temperature

Entry	R^1	R^2	R^3	Substrate/alcohol/NBS (ratio)	Method	Yield[a] (%)
1	Ph	H	$-(CH_2)_3-$	1:3:1	A	97
2	Ph	H	$-(CH_2)_2-$	1:2.5:1	A	95
3	4-ClC_6H_4	H	$-(CH_2)_3-$	1:3:1	A	89
4	4-ClC_6H_4	H	$-(CH_2)_2-$	1:2.5:1		95
5	4-(MeO)C_6H_4	H	$-(CH_2)_3-$	1:3:1	A	94
6	4-$(NO_2)C_6H_4$	H	$-(CH_2)_3-$	1:3:1	A[b]	90
7	4-$(NO_2)C_6H_4$	H	$-(CH_2)_2-$	1:3:1	A[b]	93
8	PhCH=CH	H	$-(CH_2)_3-$	1:3:1	A	92
9	$PhCH_2$	H	$-(CH_2)_2-$	1:2.5:1	A	85
10	Ph	CH_3	$-(CH_2)_3-$	1:4:1.2	A	91
11	Ph	CH_3	$-(CH_2)_2-$	1:3:1.2	A	95
12	4-ClC_6H_4	CH_3	$-(CH_2)_3-$	1:4:1.2	A	89
13	4-(Ph)C_6H_4	CH_3	$-(CH_2)_3-$	1:4:1.2	A	86
14	4-$(NO_2)C_6H_4$	CH_3	$-(CH_2)_3-$	1:4:1.3	A[b]	77
15	4-$(NO_2)C_6H_4$	CH_3	$-(CH_2)_2-$	1:4:1.3	A[b]	89
16	Ph	Ph	$-(CH_2)_3-$	1:3:1.2	A	92
17	$PhCH_2CH_2$	CH_3	$-(CH_2)_3-$	1:4:1.3	A	88
18	$PhCH_2CH_2$	CH_3	$-(CH_2)_2-$	1:4:1.3	A	92
19			$-(CH_2)_3-$	1:4:1.3	A	91
20	Ph	H	Me	1:3 mL:1	B[b]	92
21	Ph	H	Et	1:3 mL:1	B[b]	98
22	PhCH=CH	H	Et	1:5 mL:1.1	B[b]	95
23	Ph	CH_3	Et	1:5 mL:1.2	B[b]	98
24	4-$(NO_2)C_6H_4$	CH_3	Et	1:5 mL:1.3	B[b]	92
25	$PhCH_2CH_2$	CH_3	Et	1:5 mL:1.3	B[b]	89

Method A: CH_2Cl_2, rt. Method B: absolute ethanol or methanol was used as solvent, reaction time: 5 min unless otherwise stated.
[a] Isolated yields.
[b] The reactions were completed after 10 min.

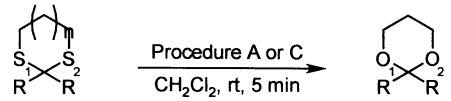
Using this study, we have also discovered that the reaction of various types of 1,3-oxathiolanes in the presence of absolute ethanol and methanol as solvent (3–5 mL) furnished the corresponding diethyl and dimethyl acetals, respectively, in good to excellent yields (Table 1, entries 20–25). It is worth mentioning that the presence of electron withdrawing substituents on aromatic rings of 1,3-oxathiolanes does not affect the efficacy of the transformation (Table 1, entries 6, 7, 14, 15, 24). Among different solvents such as THF, CH_3CN, $CHCl_3$ and CH_2Cl_2, dichloromethane turned out to be a suitable solvent for this transformation.

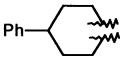
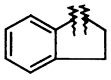
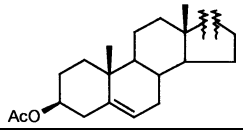
Furthermore, although there are a variety of procedures for conversion of acetals to the corresponding dithioacetals,[7] less attention has been paid to the reverse transformation.[4,5] We hypothesized that the present protocol might also equally applied for interconversion of 1,3-dithioacetals to their *O*,*O*-acetals. As can be seen in Table 2, 1,3-dithiane and 1,3-dithiolanes of aldehydes were effectively and rapidly converted to the corresponding 1,3-dioxanes using NBS (1.0 equiv.) in the presence of 3 equivalents of 1,3-propanediol (entries 1–7).[7]

In the cases that absolute ethanol or methanol were used as solvent (5 mL), the corresponding diethyl acetals or dimethyl acetals were formed, respectively, in excellent yields under similar reaction conditions (Table 2, Method A, entries 6 and 7). Interestingly, attempted interconversion of dithioacetals of ketones under similar reaction conditions of Method A failed to provide the corresponding *O*,*O*-acetals in satisfactory yield and a mixture of products were formed. We therefore researched another protocol that would allow such a transformation. During this study we discovered that different types of 1,3-dithianes and 1,3-dithiolanes derived from the corresponding ketones using 1,3-propanediol (7 equiv.) upon the slow and portionwise addition of NCS (1.2 equiv.) or NBS (1.2–1.4 equiv.) were converted to their 1,3-dioxanes in good yields (Method C) (Table 2, entries 9–11 and 14–18). Nevertheless, even under this condition, interchanging of dithioacetals of aromatic ketones bearing electron withdrawing groups, affording the corresponding acetals in low yields (Table 2, entries 12 and 13).

The chemical transformations would be of more practical importance if they were accompanied with high degree of chemoselectivity. In our previous report on the new applications of NBS, we observed that the cleavage of 1,3-oxathiolanes is much faster than 1,3-dioxolanes and 1,3-dioxanes. Moreover, we have observed that the presence of a molar excess of organic bases such as DABCO or pyridine in the reaction medium, does not affect considerably the rate of cleavage of 1,3-oxathiolanes, but does completely retard the deprotection of *O*,*O*-acetals (Scheme 2). Based on these observations, it seemed plausible that the described system could promote chemoselective interchange of 1,3-oxathiolanes and 1,3-dithioacetals in the presence of acid-sensitive substrates such as *O*,*O*-acetals. Indeed, 2-phenyl-1,3-oxathiolane were converted to the corresponding 1,3-dioxane in the presence of 2-phenyl-1,3-dioxolane with almost complete chemoselectivity (Scheme 2). The method even tolerates more

Table 2. Conversion of dithioacetals to the corresponding acetals using NBS or NCS under mild reaction conditions

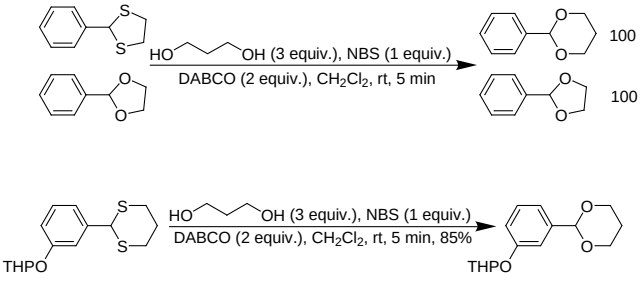


Entry	R^1	R^2	Method	n	Yield[a] (%)
1	Ph	H	A	0	95
2	Ph	H	A	1	90
3	4-$(CH_3)C_6H_4$	H	A	1	93
4	4-$(MeO)C_6H_4$	H	A	1	96
5	PhCH=CH	H	A	1	80
6	Ph	H	A[b]	0	92
7	Ph	H	A[c]	0	86
8	Ph	Ph	A	1	89
9	Ph	CH_3	C[d]	1	92
10	4-$(Cl)C_6H_4$	CH_3	C	1	93
11	4-$(Ph)C_6H_4$	CH_3	C	1	87
12	4-$(NO_2)C_6H_4$	CH_3	C	0	60[e]
13	4-$(NO_2)C_6H_4$	CH_3	C	1	30[e]
14	$PhCH_2CH_2$	CH_3	C	1	90
15			C	0	78
16			C	0	89
17			C	0	70
18			C	0	91

[a] Yields refer to isolated products unless otherwise stated.
[b] Reactions were performed in absolute 5 mL EtOH as solvent without 1,3-propanediol.
[c] Reactions were performed in 5 mL absolute MeOH as solvent in the absence of 1,3-propanediol.
[d] Method C: diol (7 equiv.) and NBS or NCS (1.2–1.4 equiv); catalyst was added portionwise to the reaction mixture.
[e] A complex mixture of products was formed.

acid-sensitive functional groups such as THP ethers (Scheme 2).

In summary, we have introduced a new and efficient method for the interconversion of dithioacetals and oxathioacetals into their *O*,*O*-acetals without going through the free carbonyl compounds. To the best of our knowledge, this is the first example of direct conversion of oxathioacetals to the corresponding acetals without going through their parent carbonyl compounds. Simplicity of the procedures, easy workup of the reaction products, mild reaction conditions and the high yield of the product can be considered as the advantages of the present protocol. Work on other reactions promoted by NBS and related compounds are currently underway in our laboratories.



Scheme 2.

3. Experimental

All yields refer to isolated products unless otherwise stated. The products were purified by column chromatography and the purity determination of the products were accomplished by GLC on a Shimadzu model GC-8A instrument or by TLC on Silica-gel polygram SIL G/UV254 plates. IR spectra were record on a Vector 22 Bruker spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 250 MHz spectrometer in $CDCl_3$ as the solvent and TMS as internal standard. Most of the products are known and all of the isolated products gave satisfactory IR spectra. However, some of the selected spectra are as follows.

3.1. General procedure for interchange of 1,3-oxathiolanes to acetals

To a stirred solution of 1,3-oxathiolane (2 mmol) and diol (5–8 mmol, Procedure A in dry CH_2Cl_2 (15 mL) was added NBS (2–2.6 mmol), and the resulting mixture was stirred for 5 min at room temperature. The progress of the reaction was monitored by TLC or GC. After completion of the reaction, the mixture was diluted with aqueous NaOH (20 mL) and it was extracted with CH_2Cl_2 (3×30 mL^2). The combined organic layers were washed with 10% aqueous NaOH (10 mL) and water (2×25 mL^2) and dried over anhydrous sodium sulfate. The extracts were then concentrated under reduced pressure to afford crude products. Further purification was achieved by chromatography on a silica-gel column to give pure product(s).

3.2. General procedure for interchange of dithioacetals to acetals

To a stirred solution of 1,3-dithiolanes or 1,3-dithianes (2 mmol) and 1,3-propanediol (6 mmol, Procedure A or 14 mmol, Procedure B) in dry CH_2Cl_2 (15 mL) was added NBS (Method A, 2.0 mmol) or NBS (Method C, 2.4–2.8 mmol, portionwise), and the resulting mixture was stirred for 5–10 min at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with aqueous NaOH (20 mL) and it was extracted with CH_2Cl_2 (3×30 mL^2). The combined organic layers were washed with 10% aqueous NaOH (10 mL) and water (2×25 mL^2) and dried over anhydrous sodium sulfate. The extracts were then concentrated under reduced pressure to afford crude products. Further purification was achieved by chromatography on a silica-gel column to give pure product(s).

3.2.1. Benzaldehyde diethyl acetal. ^1H NMR ($CDCl_3$/TMS, 250 MHz): δ=7.40–7.44 (m, 2H), 7.25–7.33 (m, 3H), 5.48 (s, 1H), 3.44–3.55 (m, 4H), 1.19–1.27 (m, 6H); ^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ=138.99, 128.01, 127.91, 126.66, 100.95, 60.28, 15.24.

3.2.2. Acetophenone diethyl acetal. ^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ=7.60–7.61 (m, 2H), 7.25–7.57 (m, 3H), 3.38–3.56 (m, 4H), 1.43 (s, 3H), 1.21–1.28 (m, 6H); ^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ=151.56, 135.62, 135.01, 133.81, 108.87, 64.29, 34.82, 22.66.

3.2.3. 2,2-Diethoxy-4-phenylbutane. ^{1}H NMR ($CDCl_3$/TMS, 250 MHz): δ=7.23–7.37 (m, 5H), 3.52–3.64 (m, 4H), 2.69–2.76 (m, 2H), 1.99–2.06 (m, 2H), 1.51 (s, 3H), 1.23–1.33 (m, 6H); ^{13}C NMR ($CDCl_3$/TMS, 63 MHz): δ=142.62, 128.77, 128.65, 126.17, 101.59, 55.99, 39.56, 31.13, 22.56, 15.94.

3.2.4. 2-(4-Chlorophenyl)-1,3-dioxane. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C, TMS): δ=7.40–7.49 (d, J=8.0 Hz, 2H), δ=7.30–7.34 (d, J=8.0 Hz, 2H), δ=5.44 (s, 1H), δ=4.20–4.26 (dd, J=5.0, 11.3 Hz, 2H), δ=3.88–3.98 (*pseudo*-t, J=11.3 Hz, 2H), δ=2.14–2.23 (tq, J=5, 13.2 Hz, 1H), δ=1.37–1.43 (quind, J=1.2, 13.2 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$, 25°C, TMS): δ=137.70, 134.95, 128.81, 127.91, 101.19, 67.78, 26.09.

3.2.5. 2-(4-Nitrophenyl)-1,3-dioxane. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C, TMS): δ=7.98–8.28 (d, J=9.0 Hz, 2H), δ=7.62–7.73 (d, J=9.0 Hz, 2H), 5.54 (s, 1H), δ=4.24–4.51 (dd, J=5, 13.8 Hz, 2H), δ=3.94–4.05 (*pseudo*-t, J=13.8 Hz, 2H), δ=2.13–2.25 (tq, J=5, 13.3 Hz, 1H), δ=1.43–1.50 (quind, J=1.1, 13.3 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$, 25°C, TMS): δ=154.5, 147.05, 132.33, 127.50, 102.52, 67.80, 34.5.

3.2.6. 2-Methyl-2-phenyl-1,3-dioxane. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C, TMS): δ=7.16–7.37 (m, 5H), δ=3.66–3.78 (m, 4H), δ=1.94–2.08 (tq, J=5.4, 12.9 Hz, 1H), δ=1.44 (s, 3H), δ=1.11–1.19 (quind, J=1.2, 12.9 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$, 25°C, TMS): δ=141.63, 129.10, 128.99, 128.24, 100.92, 61.62, 32.84, 25.89.

3.2.7. 2-Methyl-2-(2-phenylethyl)-1,3-dioxane. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C, TMS): δ=6.91–7.38 (m, 5H), δ=3.79–3.89 (m, 4H), δ=2.73–2.79 (m, 2H), δ=1.98–2.05 (m, 2H), δ=1.97–1.73 (m, 1H), δ=1.48–1.68 (m, 1H), δ=1.44 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$, 25°C, TMS): δ=139.01, 129.63, 129.65, 126.02, 100.85, 58.09, 41.50, 34.13, 23.67, 18.27.

3.2.8. 1,5-Dioxa-spiro[5.11]heptadecane. ^{1}H NMR (250 MHz, $CDCl_3$, 25°C, TMS): δ=3.57–3.79 (m, 4H), δ=1.59–1.66 (m, 6H), δ=1.16–1.26 (m, broad, 18H), ^{13}C NMR (63 MHz, $CDCl_3$, 25°C, TMS): δ=100.77, 60.28, 60.03, 40.30 (two peaks), 36.50, 30.29 (seven peaks), 19.25 (two peaks).

3.2.9. 2-[3-(Tetrahydro-pyran-2-yloxy)-phenyl]-[1,3]-dioxane. ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): δ=8.20–8.22 (dd, J=8.4, 1.4 Hz, 2H), 7.61–7.65 (tt, J=7.4, 1.4 Hz, 1H), 7.56–7.59 (d, J=8.4 Hz, 2H), 7.49–7.53 (t, J=7.4 Hz, 2H), 7.23–7.26 (dd, J=8.4, 1.4 Hz, 2H), 5.54 (s, 1H), 4.27–4.30 (dd, J=11.0, 3.6 Hz, 2H), 3.98–4.03 (*pseudo*-t, J=11.0 Hz, 2H), 2.20–2.27 (tq, J=5.0, 13.3 Hz, 1H), 1.44–1.48 (quind, J=1.3, 13.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C, TMS): δ=165.08, 151.29, 136.58, 133.68, 130.25, 129.62, 128.65, 127.38, 121.55, 101.05, 67.45, 25.82.

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