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A Novel Simple Dethioacetalization of Thioacetals and Thioketals with *t*-Butyl Thionitrite

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ABSTRACT

Thioacetals and thioketals were readily cleaved to carbonyl compounds in excellent yields by treatment with t-butyl thionitrite at ca. 0°C in acetonitrile under mild conditions. The conversion of thioketals to the ketones appears to be initiated via nitrosation on two sulfur atoms of the thioketals, followed by intramolecular transfer of nitroso oxygen.

INTRODUCTION

Thioacetals and thioketals have been quite well recognized as protecting groups and also as synthons of carbonyl compounds in organic synthesis [1]. Since thioacetals are more stable than acetals under both acidic and basic conditions, they have been used only to a limited extent due mainly to some difficulty in regenerating the carbonyl compounds. The dithioacetal function was successfully used for some complex substrates as a protecting group of carbonyl compounds [2].

Due to their stability toward acids and bases, the deprotection to obtain the parent carbonyl compounds has stimulated extensive research. As a result, a number of methods has been developed for such a conversion: hydrolytic cleavage through alkylation with methylfluorosulfonate [3] or triethyloxonium tetrafluoroborate [4], through halogenation with chloramine-T [5], bromodimethylsulfonium bromide [6], or P_2I_4 [8], and through oxidation with bis(trifluoroacetoxy)iodobenzene [7].

Oxidative cleavage of thioketals using nitrosating reagents such as isoamyl nitrite [9], clayfen, claycop [10], and nitrosonium tetrafluoroborate [11] were also reported.

Previously we reported that *t*-butyl thionitrite could readily be prepared quantitatively by mixing the thiols and dinitrogen tetroxide and is stable enough to be used for organic synthesis through nitrosation [12]. Our interest in the use of electrophilic reagents, such as *t*-butyl thionitrite (*t*-BuSNO) [12] and *t*-butyl thionitrate (*t*-$BuSNO_2$) [13], to bring about nitrosation [14] under neutral conditions in organic solvents prompted us to explore the possibility of using other electrophilic nitrosating reagents for the dethioacetalization.

RESULTS AND DISCUSSION

We have now found that various thioacetals or thioketals readily react with *t*-butyl thionitrite under mild conditions in acetonitrile without using aqueous media to afford the corresponding parent carbonyl compounds in excellent yields, together

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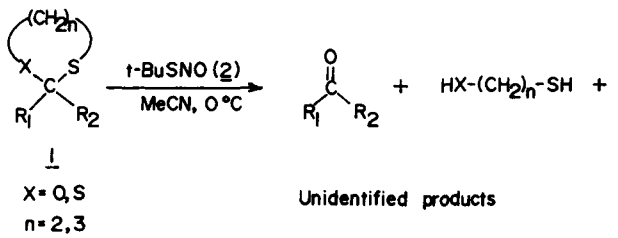


SCHEME 1

with a dithiol or 2-mercaptoethanol and other unidentified products (Scheme 1).

The results obtained are summarized in Table 1.

The amount of **2** for the dethioacetalization was controlled depending on the number of sulfur atoms of the substrates. In the cases of a 1,3-dithian or a 1,3-dithiolan, where more than two equivalents of **2** were used, the maximum yield of the carbonyl compound was achieved. A 1,3-oxathiolan containing one sulfur atom reacted with one equivalent of **2** to give the carbonyl compound in quantitative yield. Most of the known methods for the dethioacetalization have been considered to proceed through hydrolytic cleavage in aqueous media [3–7, 10]. However, our new procedures to cleave 1,3-dithians, 1,3-dithiolans, and 1,3-oxathiolans have been performed in organic solvents, such as anhydrous acetonitrile. A question arises here as to where the oxygen of the carbonyl group comes from. In order to see whether the oxygen of the carbonyl group originates from water or from *t*-butyl thionitrite, 1,3-dithiolan, and 1,3-oxathiolan have been treated with **2** in the presence of ^{18}O-labeled water (^{18}O content = 97 atom%).

The results obtained are summarized in Table 2.

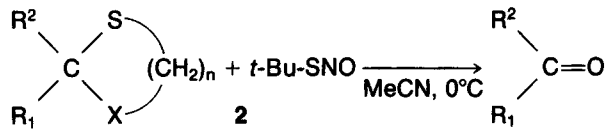
The cleavage reaction in aqueous acetonitrile is much slower than that in anhydrous acetonitrile (see Run 2 in Table 1: reaction time: 1.5 h, 90%; Run 1 in Table 2: reaction time: 24 h, 8%). Incorporation of ^{18}O into the carbonyl group was observed in the longer reaction time. However, the ratio of $C = {}^{16}O/C = {}^{18}O$ in the short reaction time was 22/1 in Run 3 in Table 2.

The incorporation of ^{18}O into the carbonyl group from $H_2{}^{18}O$ can be explained on the basis that oxygen exchange occurs under the reaction conditions and that an equilibrium between the carbonyl products and $H_2{}^{18}O$ exists.

When phenylacetone was treated with two equivalents of $H_2{}^{18}O$ in acetonitrile in the presence of **2** (1 equivalent) and in the absence of **2** at 0°C for 18 h, ^{18}O incorporations into phenylacetone were confirmed, respectively, as shown below.

These results seem to indicate clearly that the conversion of thioketals to the ketones involves an

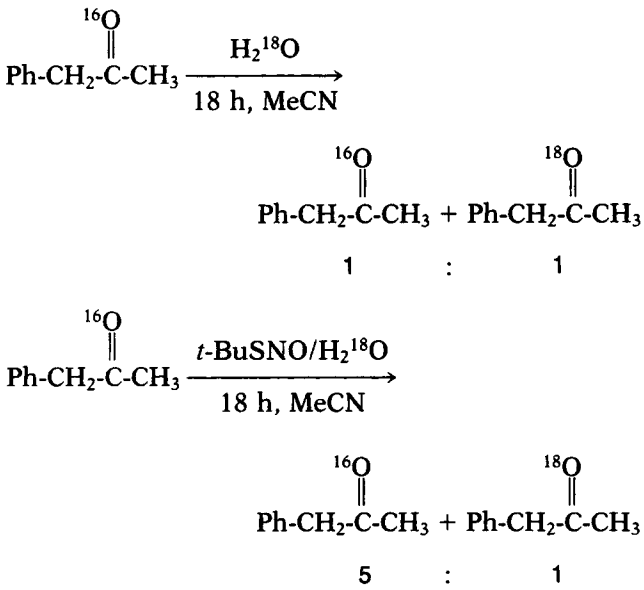
TABLE 1 Cleavage of thioketals with *t*-Bu-SNO



1

Run	R_1	R_2	*X*	*n*	**2** (Eq.)	*Time* (h)	*Yields* (%)[a]
1	Ph	H	S	3	4	0.05	98[b]
2	*p*-Cl-Ph	Me	S	2	2	1.5	90
3	Ph	Ph	S	2	3	3	95
4			S	2	3	0.3	90
5			S	2	3	0.6	85
6	Me	Et	S	2	3	1	73[c]
7	*o*-Cl-Ph	H	O	2	1.2	0.6	95
8	*p*-NO_2-Ph	Me	O	2	1.2	0.6	98
9	*o*-Br-Ph	H	O	2	1.2	0.3	93

[a] Isolated yields.
[b] Determined by ^1H NMR.
[c] Determined by gas chromatography.



intramolecular cleavage of the ring intermediate (**4**): namely, the oxygen of the carbonyl group originates from the nitroso group of **2**, as illustrated in the mechanistic path (Scheme 2), as in the case of desulfurization of thioamide derivatives [15].

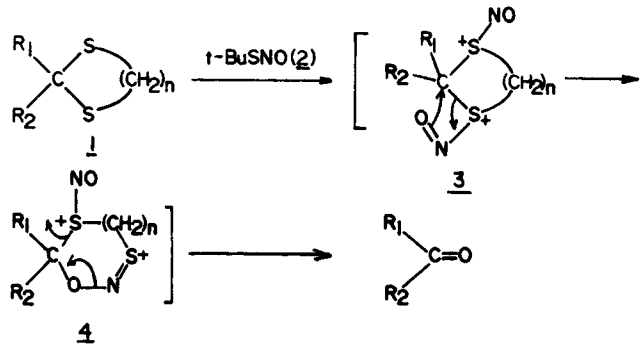
Since the dethioacetalization requires more than two equivalents of **2** for the maximum yield, the reaction seems to be initiated by nitrosations on the two sulfur atoms, with subsequent ring cleavage.

Although the detailed mechanism of this reaction is not clear, **2** is considered to be an excellent reagent for the dethioacetalization under mild and neutral conditions.

EXPERIMENTAL

Preparation of t-*Butyl Thionitrite*

A solution of dinitrogen tetroxide (N_2O_4, 20 mmol) in CCl_4 (5 mL) at ca. −20°C was carefully added to a



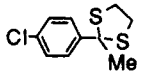
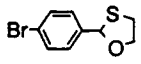
SCHEME 2

solution of the *t*-butyl mercaptan (20 mmol) in dried diethyl ether (50 mL) at −20°C with vigorous stirring in the dark. Immediately the mixture became dark green, characteristic of *t*-butyl thiontrite (*t*-BuSNO). After having been stirred for 20 min, the reaction mixture was washed with cold $NaHCO_3$ solution and then with water to remove unchanged N_2O_4 and nitric acid formed. The organic layer was separated from the aqueous layer and dried over anhydrous magnesium sulfate. The ethereal solution was evaporated in vacuo at 0°C and can be used for further reaction over several months if it is kept at −20°C over molecular sieves; bp 40–42°C/55 mmHg, infrared (IR) (neat); 1490 (NO), 1360, 1298 cm^{-1}, ^1H NMR (CCl_4); δ 1.85 (s) [12].

Reaction of 2,2-Diphenyl-1,3-Dithiolan with t-*Butyl Thionitrite*

To a solution of 2,2-diphenyl-1,3-dithiolan (129 mg, 0.5 mmol) in acetonitrile (3 mL) and THF (1 mL) was added *t*-butyl thionitrite solution (1.5 mmol, in THF: 240 μL). The reaction mixture was stirred for 3 h at 0°C and then, after addition of a 5% solution of $NaHCO_3$, extracted with methylene chloride (10 mL × 3). The organic layer was concentrated to

TABLE 2 ^{18}O-Isotope Experiments

Run	*Substrate*	*$H_2{}^{18}O$ (Eq.)*[c]	*Time* (h)	*Yield* (%)[a]	*C=^{16}O : C=^{18}O*[b]
1		1	24	8	3 : 1
2		3	48	10	1 : 3
3		1.8	1	87	22 : 1

[a] Isolated yield.
[b] Determined by mass spectroscopy.
[c] 97.2 atom% ^{18}O.

afford a mixture of benzophenone and *t*-butyl disulfide, the dithiol, and other unidentified products. The benzophenone product was purified (86 mg, 95%) by preparative tlc on silicagel (Merck, Kieselgel 60 GF_{254}, CH_2Cl_2/*n*-hexane = 1/1) and then identified by the comparison of mp, IR, and ^1H nuclear magnetic resonance (NMR) spectra with those from the authentic sample. The formation of *t*-butyl disulfide, the dithiol, and unidentified products originated from the dithiol was observed by ^1H NMR spectra. Other dethioacetalizations were carried out in the same way as described above.

Acknowledgment

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