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Deprotection of dithioacetals using the tantalum(V) chloride catalyzed oxidation of iodide ion by hydrogen peroxide

Masayuki Kirihara,* Aiko Harano, Hiroyuki Tsukiji, Ryu Takizawa,
Tomoyuki Uchiyama and Akihiko Hatano

Department of Materials and Life Science, Shizuoka Institute of Science and Technology, 2200-2 Toyosawa, Fukuroi, Shizuoka 437-8555, Japan

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Abstract—Dithioacetals can be deprotected to afford carbonyl groups using the tantalum(V) chloride catalyzed oxidation of iodide ion by hydrogen peroxide under mild conditions.

Dithioacetals are widely used as a carbonyl protecting group in organic synthesis due to their stability under both acidic and basic conditions.[1] Moreover, a cyclic dithioacetal, such as 1,3-dithiane, is an important synthetic reagent as an acyl anion equivalent.[2] Although many procedures have been developed for regeneration of the carbonyl functionality,[1,3] most of them have serious disadvantage. The most frequently used deprotection procedures involve using a stoichiometric amount or an excess amount of heavy metals such as mercury.[4] These procedures need to treat highly toxic and expensive reagents, and produce undesirable wastes. Halonium ion sources, such as *N*-bromosuccinimide, are also utilized to deprotect dithioacetals,[5] however, these methods have drawbacks such as the use of an excess amount of reagents, and require expensive silver salts in the case of olefinic compounds.

Khan and co-workers recently developed dethioacetalization by employing the vanadium pentoxide (V_2O_5) catalyzed oxidation of ammonium bromide (NH_4Br) by hydrogen peroxide (H_2O_2).[6] The reaction conditions of this method are very mild, and the reaction affords a product in high yield with high chemoselectivity. However, there are still some problems such as the use of a toxic vanadium compound, a stoichiometric amount of bromide, and dichloromethane as the solvent.

We recently found that tantalum(V) chloride ($TaCl_5$)[7] catalyzed the oxidation of bromide ion (Br^-) into the bromonium ion (Br^+) equivalent with H_2O_2 and the reaction can be used for the electrophilic bromination of organic compounds.[8] Iodide ion (I^-) was also oxidized into the iodonium ion (I^+) equivalent with H_2O_2 in the presence of a catalytic amount of $TaCl_5$ (Scheme 1).[9]

The $TaCl_5$ catalyzed oxidation of halogen anions (X^-) into the halogen cation (X^+) equivalents is expected to be used as an environmentally benign dedithioacetalization, because tantalum compounds are less toxic than vanadium compounds. We now report that dithioacetals (**1**) can be deprotected to afford carbonyl groups (**2**) using the $TaCl_5$ catalyzed oxidation of I^- by H_2O_2 in ethyl acetate–water under mild conditions (Scheme 2).

First, the dithioacetal (**1a**) derived from 2-acetonaphthone and 1,3-propanedithiol was used as the substrate, and the reaction conditions were investigated. The substrate (**1a**) was treated with Br^- or I^-, catalytic amounts

$$\mathrm{Br^-} \xrightarrow{\text{cat. } TaCl_5,\ H_2O_2} \text{"}\mathrm{Br^+}\text{"}$$

$$\mathrm{I^-} \xrightarrow{\text{cat. } TaCl_5,\ H_2O_2} \text{"}\mathrm{I^+}\text{"}$$

Scheme 1.

Keywords: Deprotection of dithioacetals; Tantalum(V) chloride; Iodide ion; Hydrogen peroxide.

* Corresponding author. Tel.: +81 538 45 0166; fax: +81 538 45 0110; e-mail: kirihara@ms.sist.ac.jp

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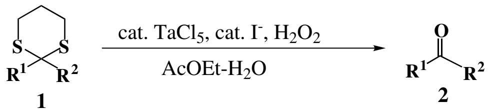
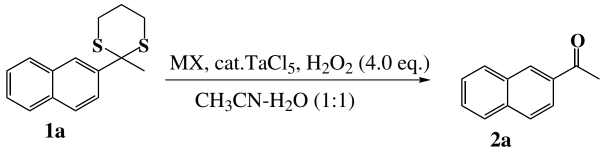


Scheme 2.

Table 1.

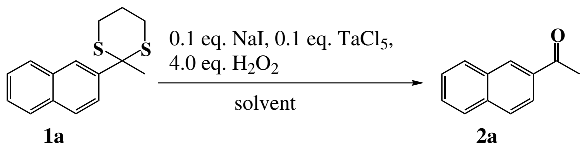


Run	MX (equiv)	Catalyst (equiv)	Time (h)	Yield (%)
1	KBr (1.0)	$TaCl_5$ (0.05)	48	42
2	KBr (1.0)	$TaCl_5$ (0.1)	19.5	80
3	NaI (1.0)	$TaCl_5$ (0.05)	25	82
4	**NaI (0.1)**	**$TaCl_5$ (0.1)**	**20**	**93**
5	NaI (1.0)	—	90	No reaction
6	—	$TaCl_5$ (0.1)	20	No reaction

of $TaCl_5$, and 4.0 equiv of H_2O_2 in water containing acetonitrile (Table 1). The dithioacetal (**1a**) was efficiently deprotected to afford 2-acetonaphthone in high yields. Sodium iodide (NaI) is an excellent halogen anion source, and only 0.1 equiv of the reagent was enough to complete the reaction (run 4). In the absence of $TaCl_5$, the dedithioacetalization did not proceed at all (run 5). The reaction also did not occur in the absence of halogen anions (run 6). These results mean that both a halogen anion and $TaCl_5$ catalyst are essential for the dedithioacetalization to occur.

We then examined the dedithioacetalization of **1** with 0.1 equiv of NaI, 0.1 equiv of $TaCl_5$, and 4.0 equiv of H_2O_2 in several solvent systems (Table 2). The best result was obtained in a two-phase system using ethyl acetate and water (AcOEt–H_2O) (run 4). The product was obtained in a high yield with a shorter reaction time. It is notable that ethyl acetate is more environmentally benign than a chlorinated hydrocarbon such as dichloromethane or chloroform. We also found that the reaction with 20.0 equiv of H_2O_2 quantitatively provided the desired compound within a shorter time (run 5).

Table 2.

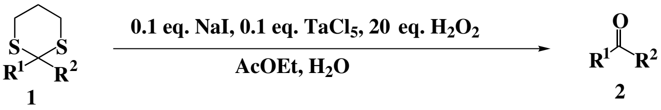


Run	Solvent	Time	Yield (%)
1	$CH_3CN–H_2O$ (1:1)	19 h	96
2	$CH_3OH–H_2O$ (1:1)	17.5 h	90
3	Acetone–H_2O (1:1)	3 days	81
4	AcOEt–H_2O	2 h	85
5[a]	**AcOEt–H_2O**	**1 h**	**Quant.**
6	$CHCl_3–H_2O$	9 days	24
7	$CH_2Cl_2–H_2O$	2 days	74

[a] 20.0 equiv H_2O_2 was used.

Several kinds of dithioacetals were treated with 0.1 equiv of NaI, 0.1 equiv of $TaCl_5$ and 20.0 equiv of H_2O_2 in AcOEt–H_2O. These results are summarized in Table 3. Most of the substrates quantitatively provided the carbonyl compounds. We observed that the aromatic ring (entries 3–9), the double bond (entry 5), the acetoxy group (entry 6), and the silyloxy group (entry 7) were inert under the given reaction conditions. The dithioacetal (**1j**) having the tetrahydropyranyl (acetal) group afforded the ketone in 56% yield accompanied with the ketone lacking an acetal moiety, however, the desired compound was quantitatively obtained when

Table 3.



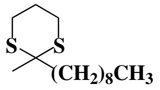
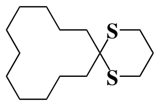
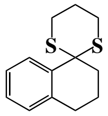
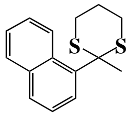
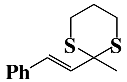
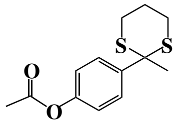
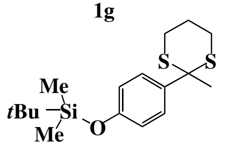
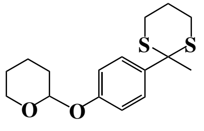
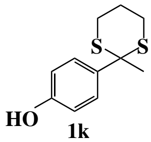
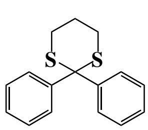
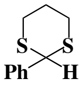
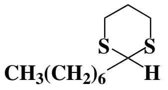
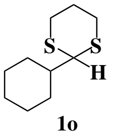
Entry	Starting material	Time	Yield (%)
1	 **1b**	4.5 h	Quant.
2	 **1c**	5 h	89
3	 **1d**	0.3 h	Quant.
4	 **1e**	2.5 h	91
5	 **1f**	0.5 h	Quant.
6	 **1g**	1.5 h	94
7	 **1h**	1.5 h	90
8	 **1j**	0.5 h; 0.5 h	56; quant.[a]

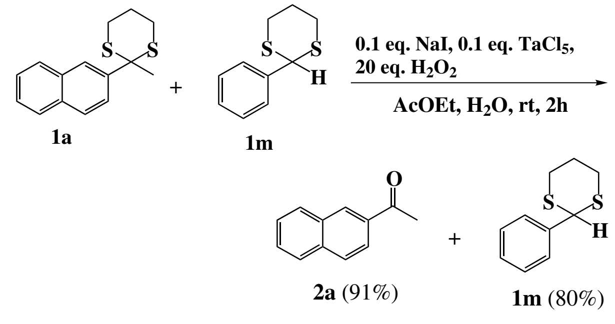
Table 3 (*continued*)

Entry	Starting material	Time	Yield (%)
9	 **1k**	1 h	Quant.
10	 **1l**	1.5 h	95
11	 **1m**	92 h	82
12	 **1n**	68 h	85
13	 **1o**	6 days	81

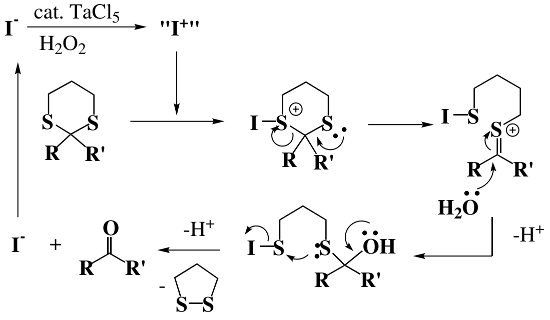
[a] Phosphate buffer (pH = 7.2) was used instead of water.

phosphate buffer (pH 7.2) was used as the part of solvent instead of water (entry 8). Interestingly, the dithioacetals derived from aldehydes (**1m–o**) reacted more slowly than the dithioacetals (**1a–l**) derived from ketones. In the case of the equimolar mixture of **1a** and **1m**, **1a** was chemoselectively deprotected to afford **2a** in 91%, and 80% of **1m** was recovered (Scheme 3). These results are in sharp contrast to the results of the dedithioacetalization with V_2O_5–Br^-–H_2O_2 reported by Khan et al. They reported that the dithioacetals derived from aldehydes quickly reacted to afford the aldehydes.[5]

The plausible reaction mechanisms are as follows. $TaCl_5$ catalyzed the hydrogen peroxide oxidation of I^- to the I^+ equivalent, and the reactive I^+ equivalent then reacts with dithioacetals to form an iodosulfonium complex, which is finally hydrolyzed by water to the carbonyl compound (Scheme 4). Further details of this reaction are currently under investigation.



Scheme 3.



Scheme 4.

The general experimental procedure for the deprotection is as follows: A mixture of **1** (0.5 mmol), tantalum chloride (17.9 mg, 0.05 mmol), sodium iodide (7.5 mg, 0.05 mmol) and 30% hydrogen peroxide (1.15 mL, 10.0 mmol) in ethyl acetate (3 mL) and water (3 mL) was stirred at room temperature. The reaction was monitored by thin layer chromatography (TLC). After **1** disappeared on TLC, saturated aqueous sodium thiosulfate (2 mL) and saturated aqueous sodium bicarbonate (2 mL) were added to the reaction mixture. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and evaporated. Chromatography on silica gel gave a pure product.

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