



Environmentally benign deprotection of dithioacetals using 30% hydrogen peroxide catalyzed by Fe(acac)₃ and sodium iodide



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ABSTRACT

The reaction of dithioacetals with 30% hydrogen peroxide in the presence of catalytic amounts of iron(III) acetylacetonate and sodium iodide efficiently produced the corresponding carbonyl compounds in high yields.

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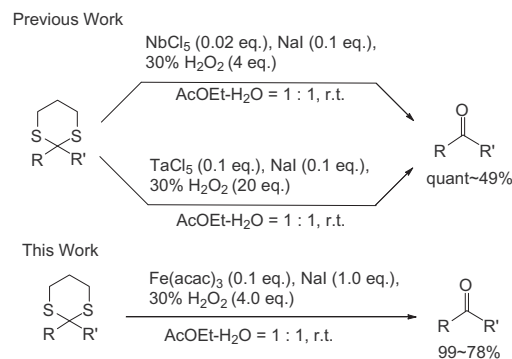
Dithioacetals are widely used as carbonyl protecting groups¹ or as acyl anion equivalents² in organic synthesis. However deprotection of dithioacetals to regenerate the carbonyl functionality^{1,3} is not particularly easy because dithioacetals are quite stable under a variety of reaction conditions including acid or base catalyzed hydrolysis. Although many procedures for dedithioacetalization have been developed, most of them have serious disadvantages. The most reliable and 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 necessity of an excess amount of reagents, and the requirement of expensive silver salts in the case of olefinic compounds.

Environmentally-benign methods for dithioacetal-deprotection mediated by hydrogen peroxide (H₂O₂) have been developed recently by several research groups, in which nontoxic water is the sole waste product of these reactions.⁵

We have been exploring the use of these reactions for organic syntheses,⁶ and have found that dithioacetal deprotection can be achieved smoothly by reaction with 30% H₂O₂ catalyzed by tantalum(V) chloride (TaCl₅)–sodium iodide (NaI)^{7,8} or niobium(V) chloride (NbCl₅)–NaI.⁷ Although, this procedure efficiently provides the

desired carbonyl compounds, the catalysts (TaCl₅ and NbCl₅) are expensive. To remedy this limitation, in this Letter, much more inexpensive iron(III) acetylacetonate [Fe(acac)₃]–NaI is shown to effectively catalyze the deprotection of dithioacetals with 30% H₂O₂ to produce carbonyl compounds (Scheme 1).

First, a dithioacetal was prepared for use as the substrate from 2-acetonaphthone and 1,3-propanedithiol according to the literature,⁹ and various iron catalysts were investigated (Table 1). The substrate was treated with 0.1 equiv of the iron compound, 0.2 equiv of sodium iodide, and 4.0 equiv of 30% H₂O₂ (Table 1). All of the iron compounds tested, except for ferrocene, exhibited catalytic activity, and the desired 2-acetonaphthone was obtained

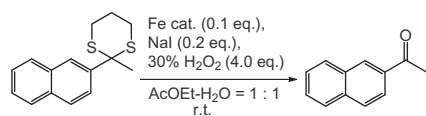


Scheme 1.

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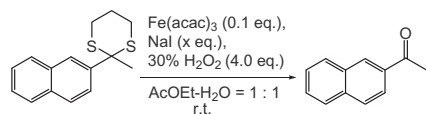
E-mail address: kirihara@ms.sist.ac.jp (M. Kirihara).

Table 1



Run	Catalyst	Time	Yield (%)
1	FeCl ₃	0.6 h	90
2	FeCl ₂ ·4H ₂ O	0.3 h	88
3	Fe(OAc) ₂	0.4 h	92
4	Fe(acac) ₃	1.0 h	91
5	Cp ₂ Fe (ferrocene)	2 days	NR

Table 2



Run	NaI (equiv)	Time (h)	Yield (%)
1	0.1	7.7	5
2	0.2	1.0	91
3	0.4	0.3	89
4	1.0	0.4	93
5	2.0	7.0	25
6	4.0	7.0	5

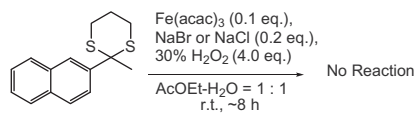
in high yield (runs 1–4). With iron(III) chloride (FeCl₃), iron(II) chloride (FeCl₂), and iron(II) acetate [Fe(OAc)₂], the reaction solution became acidic, whereas it was effectively neutral (slightly weak acidic) in the presence of iron(III) acetylacetonate [Fe(acac)₃]. It is preferable to carry out the deprotection under a milder condition, therefore, Fe(acac)₃ was used as the iron-catalyst for the further investigation.

Since the amount of NaI to dithioacetal is a crucial factor in obtaining the desired carbonyl compound in NbCl₅–NaI catalyzed dedithioacetalization with 30% hydrogen peroxide,⁸ reactions with varying several amounts of NaI were examined (Table 2).

The dedithioacetalization efficiently proceeded to afford the desired 2-acetonaphthone in high yields with between 0.2 and 1.0 equiv of NaI. Conversely, the reaction proceeded very slow and the ketone was obtained in poor yields in the presence of 0.1 equiv or more than 2.0 equiv of NaI. These results are similar to those of NbCl₅–NaI catalyzed dedithioacetalization with 30% hydrogen peroxide.⁸

Variation of the halogen anion in the catalysts was then examined. The dedithioacetalization did not proceed at all in the presence of either NaBr or NaCl-containing catalysts (Scheme 2).

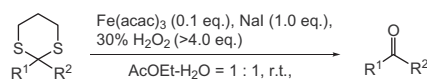
Based on these results, several dithioacetals prepared from ketones were reacted with 30% hydrogen peroxide in the presence of 0.1 equiv of Fe(acac)₃ and 1.0 equiv of NaI in AcOEt/H₂O (1:1, v/v) at room temperature (Table 3).¹⁰ The results are similar to those of the deprotections catalyzed by TaCl₅–NaI^{7,8} or NbCl₅–NaI.⁸ The corresponding ketones were obtained in high yields in all cases. The aromatic ring (entries 3–11), the double bond (entry 5), the acetoxy group (entry 7), and the silyloxy group (entry 8) were inert to the deprotection. The dithioacetal having a tetrahydropyranyl (acetal) group afforded the desired ketone in only 43% yield accompanied by the ketone lacking the acetal moiety. Fortunately, the desired compound was quantitatively obtained when a phosphate buffer (pH 7.2) was used instead of water as part of the solvent (entry 9).



Scheme 2.

The deprotection of several dithioacetals derived from aldehydes was then examined under the same reaction conditions (Table 4). The reactions proceeded much more slowly than those involving dithioacetals derived from ketones. In addition, large amounts of H₂O₂ were required to complete the reaction, because simple decomposition of H₂O₂ predominates over the deprotection of the dithioacetals.

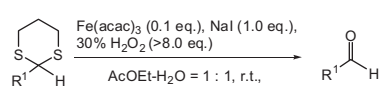
Table 3







Entry	Substance	30% H ₂ O ₂ (equiv)	Time (h)	Yield (%)
1		4.0	3.6	99
2		8.0	2.8	97
3		4.0	0.3	93
4		8.0	20	97
5		4.0	0.2	95
6		4.0	0.3	90
7		8.0	20.4	90
8		4.0	0.5	97
9		8.0 8.0	1.6 0.3	43 93 ^a
10		8.0	18.4	92
11		8.0	18.4	99

^a Phosphate buffer (pH 7.2) was used instead of water.

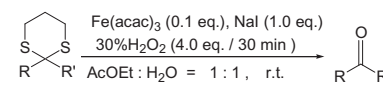
Table 4










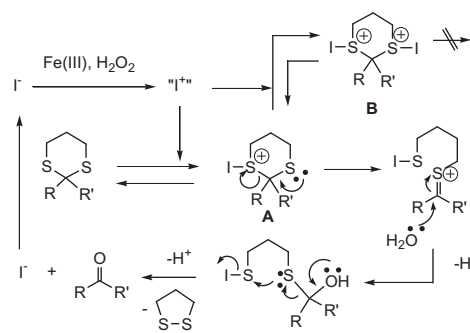
Entry	Substance	30% H ₂ O ₂ (equiv)	Time (h)	Yield (%)
1		8.0	20.6	93
2		8.0	48.3	94
3		12.0	27.5	81
4		16.0	77.3	62

In contrast, the deprotection of dithioacetals prepared from aldehydes proceeded more rapidly when the 30% H₂O₂ was slowly added to the reaction mixture using a syringe pump (4 equiv over 30 min) (Table 5, entries 1–3).¹¹ This procedure is also effective for the dithioacetals prepared from ketones. The dithioacetals which were deprotected rather slowly in Table 3 (entries 4, 7, 10, and 11) rapidly reacted to produce the corresponding ketones (Table 5, entries 4–7).

Table 5



Entry	Substance	Total amount of 30% H ₂ O ₂ (equiv)	Time (h)	Yield (%)
1		8.0	1.3	98
2		8.0	1.3	98
3		16.0	2.6	78
4		12.0	3.0	89
5		4.0	0.75	90
6		12.0	2.0	91
7		8.0	2.0	Quant

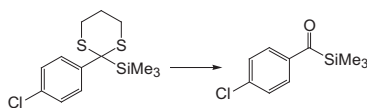


Scheme 3.

A plausible reaction mechanism is shown in Scheme 3. Fe(acac)₃ catalyzes the hydrogen peroxide oxidation of I⁻ to the I⁺ equivalent, and the reactive I⁺ equivalent then reacts with the dithioacetal to form an iodosulfonium complex (A), which is finally hydrolyzed by water to generate the carbonyl compound. When an excess of I⁻ is present, an iodosulfonium complex further reacts with the I⁺ equivalent to form a bisiodosulfonium complex (B), which is inactive toward hydrolysis.

This reaction is applicable for a preparation of an acylsilane which is easily oxidized. In the case of syntheses of 4-chlorophenyl trimethylsilyl ketone from dedithioacetalization of 2-(4-chlorophenyl)-2-(trimethylsilyl)-1,3-dithiane, other methods (for example, HgCl₂,¹² N-bromosuccinimide,¹² or 30% H₂O₂ catalyzed by NbCl₅-NaI¹³) provide the desired acylsilane in low yields accompanied with the corresponding carboxylic acid as a by-product. In contrast, the reaction of 2-(4-chlorophenyl)-2-(trimethylsilyl)-

Table 6



Run	Reaction condition	Yield (%)
1	HgCl ₂ , H ₂ O	25 ¹²
2	NBS, H ₂ O	27 ¹²
3	NbCl ₅ (0.1 equiv), NaI (0.1 equiv) 30% H ₂ O ₂ (20 equiv)	0 ^{a,13}
4	Fe(acac) ₃ (0.1 equiv), NaI (1 equiv) 30% H ₂ O ₂ (50 equiv)	90

^a The corresponding carboxylic acid (4-chlorobenzoic acid) was obtained in 75% yield.

1,3-dithiane with 30% H₂O₂ catalyzed by Fe(acac)₃–NaI produced the desired acylsilane in high yield (Table 6).

In conclusion, a combination of Fe(acac)₃ and NaI is the ideal inexpensive, environmentally-benign catalyst for the deprotection of dithioacetals using 30% H₂O₂. Further details and applications of this reaction for syntheses of acylsilanes are currently under investigation.

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- General procedure for the deprotection of dithioacetals with 30% H₂O₂ catalyzed by Fe(acac)₃–NaI*: A mixture of a dithioacetal (2.0 mmol), Fe(acac)₃ (70.6 mg, 0.20 mmol), sodium iodide (300 mg, 2.0 mmol), and 30% hydrogen peroxide (0.91 ml, 8.0 mmol) in ethyl acetate (6 ml) and water (6 ml) was stirred at room temperature. The reaction progress was monitored via thin layer chromatography (TLC). After the dithioacetal disappeared from the TLC, saturated aqueous sodium thiosulfate (4 ml), was added to the reaction mixture. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (10 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.
- General procedure for the deprotection of dithioacetals with 30% H₂O₂ (the slow addition using a syringe pump) catalyzed by Fe(acac)₃–NaI*: A mixture of a dithioacetal (2.0 mmol), Fe(acac)₃ (70.6 mg, 0.20 mmol) and sodium iodide (300 mg, 2.0 mmol) in ethyl acetate (6 ml) and water (6 ml) was stirred at room temperature. To this mixture, 30% H₂O₂ was added slowly using a syringe pump (4 ml/30 min). The reaction was monitored by thin layer chromatography via TLC. After the dithioacetal disappeared from the TLC, saturated aqueous sodium thiosulfate (4 ml), was added to the reaction mixture. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (10 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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