Trimethylsilyl Chloride Promoted Selective Desulfurization of Thiocarbonyls to Carbonyls with Hydrogen Peroxide

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Received 23 August 2010; revised 8 September 2010

Abstract: In the presence of hydrogen peroxide and trimethylsilyl chloride, thiocarbonyls desulfurize to the corresponding carbonyls. The safe, operationally simple, general reaction gives excellent yields in short reaction times with no side reactions and excellent regioselectivity, which makes this process an attractive, environmentally benign alternative for the desulfurization of thiocarbonyls.

Key words: protecting groups, thiocarbonyls, desulfurization, trimethylsilyl chloride, hydrogen peroxide

Protecting groups are important tools in organic synthesis, and they have found extensive use in many different areas of complex syntheses of natural products, biomolecules, and materials.¹ Crucial features of protecting groups are their ease of preparation and removal as well as their relative stability toward different reaction conditions.

The conversion of thiocarbonyls into carbonyls has attracted the interest of organic chemists since the early 19th century, first for the quantitative determination of compounds containing the thiocarbonyl moiety and, later, for synthetic and mechanistic studies.

A variety of methods for C=S \rightarrow C=O conversion have been developed, including oxidative procedures with inorganic² and organic³ reagents, and hydrolytic procedures, of which those catalyzed by metal ions⁴ are the most widely used.

However, many of these approaches suffer from limitations such as high toxicity, vigorous reaction conditions, unsatisfactory yields, tedious work up, or use of a large excess of reagents. Thus, a practical, efficient, and greener alternative for this important transformation is desirable.

In oxidation processes, the use of a number of non-environmental oxidants (for example, heavy metals or peracids) is very common, although other compounds have been sought that are not detrimental to the environment. In this context, the application of hydrogen peroxide (H_2O_2) as an oxidant is useful because water is the sole expected by-product. Furthermore, hydrogen peroxide is a safe, readily available, and cheap reagent.

It is well known that trimethylsilyl chloride (TMSCl) is an efficient Lewis acid, however, although it has found wide-

spread use as a catalyst in organic transformations,^{5–7} to the best of our knowledge, there are no reports on TMSCI-mediated selective desulfurization of thiocarbonyls.

As part of an ongoing program directed towards the development of efficient reagents for use under mild conditions, and following our recent interest in the use of hydrogen peroxide in organic synthesis,⁸ we report an environmentally sound, reasonably simple and efficient method that enables thiocarbonyls to be economically desulfurised to their oxo-analogues using H_2O_2 in the presence of TMSC1, in excellent yields (Scheme 1).

$$\begin{array}{c} S \\ R^{1}-\overset{O}{U}-R^{2} \end{array} \xrightarrow[EtOH, 25 \ ^{\circ}C]{} SC \end{array} \xrightarrow[R^{1}-\overset{O}{U}-R^{2}]{} R^{1}-\overset{O}{U}-R^{2} \\ R^{1}= alkyl, aryl \\ R^{2}= alkyl, aryl, aryl-NH, H, Ph-NMe, piperidyl \end{array}$$

Scheme 1 Reagents and conditions: H_2O_2 (2 mmol), TMSCl (1 mmol), EtOH, 25 °C.

To choose the most appropriate medium for this transformation, we examined the reaction of *N*-phenyl benzothioamide as a model compound in a range of solvents, such as acetonitrile, ethanol, chloroform, diethyl ether, and ethyl acetate. Ethanol and acetonitrile were found to be the most efficient solvents in terms of reaction times and product yields. To optimize the reaction conditions further, the effects of changing the amount of H_2O_2 and TMSCl were examined with *N*-phenyl benzothioamide in ethanol at room temperature. As shown in Table 1, the

Table 1 Effect of the Amount of H_2O_2 and TMSCl on the Desulfurization of N-Phenyl Benzothioamide^a



^a Reaction conditions: *N*-phenyl benzothioamide (1 mmol), 2 min, 25 °C.

^b Isolated yield.

SYNTHESIS 2010, No. 24, pp 4282–4286 Advanced online publication: 05.10.2010 DOI: 10.1055/s-0030-1258283; Art ID: Z21310SS © Georg Thieme Verlag Stuttgart · New York

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best result (96% yield) was obtained by carrying out the reaction with a 1:2 molar ratio of thioamide to H_2O_2 in the presence of 1 mmol TMSCl for two minutes. It should be noted that the use of TMSCl is essential for the success of the reaction, because H_2O_2 alone oxidized the thioamides rather slowly (Table 1, entry 1).

As a control reaction, the desulfurization of N-phenyl benzothioamide to the corresponding amide with TMSCl (1 mmol) was found to proceed extremely slowly (98% of the thioamide was recovered), thus, TMSCl is only effective in the presence of H_2O_2 (Table 1, entry 4).

With the optimized conditions in hand, we investigated the scope and generality of this transformation with various thioamides. The results are shown in Table 2. All the reactions proceeded smoothly and rapidly to give the corresponding amides in excellent yields. Both electron-rich and electron-deficient thioamides worked well, with most leading to excellent yields of products.

Table 2 Selective Desulfurization of Thiocarbonyl Compounds^a Ö

$R^1-\ddot{C}-R^2 \longrightarrow R^1-\ddot{C}-R^2$											
Entry	Substrate	Product	Time (min)	Yield (%) ^b	Mp (°C)	Lit mp (°C)	Ref.				
1	S HN-		2	96	158–162	163	9				
2	S HN-		5	96	155	157–158	9				
3			12	93	195–197	198–199	9				
4			6	93	139	140–143	10				
5	S HN-S		2	90	163–165	164–165	11				
6	O ₂ N- Me	O ₂ N-	10	92	104	106–107	9				
7	HN-Br	HN-Br	5	95	168	168	9				
8	O ₂ N-S	0 ₂ N	4	92	120	122–125	12				
9	S HN-		9	96	82	83–84	13				
10	$N \rightarrow N \rightarrow$		8	92	124	126	14				
11	COOH S	COOH	4	88	132	135	15				

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 Table 2
 Selective Desulfurization of Thiocarbonyl Compounds^a (continued)

ö

$R^{1-C}-R^{2} \longrightarrow R^{1-C}-R^{2}$										
Entry	Substrate	Product	Time (min)	Yield (%) ^b	Mp (°C)	Lit mp (°C)	Ref.			
12	S O		3	95	Oil	Oil	16			
13	X s	Ă,	9	92	179	180–182	14			
14	S S	↓ S	5	93	210	213	17			
15	S S S S S S S S S S S S S S S S S S S		2	91	80	84	14			
16	S S		5	92	50	49	14			

^a The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.

^b Pure isolated product.

Notably, sterically hindered thioamide, such as *N*-methyl-4-nitro-*N*-phenylbenzothioamide, gave the desired amide in excellent yield (Table 2, entry 6). According to the results, primary, secondary, and tertiary thioamides all undergo this reaction with equal efficiency.

Furthermore, we found that this reaction is similarly effective for a range of thioketones and thioesters, yielding the corresponding products in excellent yields (Table 2, entries 11–16). Steric effects did not influence the yield significantly, for example, in the reaction of thiocamphor (Table 2, entry 13) and fluorene-9-thione (Table 2, entry 15), the corresponding products were obtained in 92 and 91% yields, respectively. Surprisingly, several functionalities, such as nitro, carboxyl, sulfur, halide, and pyridine were tolerated under these reaction conditions.

Ho¹⁸ has reported that a combination of TMSCl and hydrogen peroxide gives trimethylsilyl hydroperoxide, which possesses a bonding arrangement similar to that found in percarboxylic acids. Both of these types of compounds are made up of soft acid–soft base pairs with respect to the O–O linkage.

The proposed mechanism for the desulfurization of thioamides is shown in Scheme 2. Nucleophilic attack of H_2O_2 on TMSCl makes the oxygen atom more electrophilic. Thus, the mechanism probably proceeds through a cyclic intermediate that undergoes sulfur extrusion. It is important that the by-product of the oxidant system, trimethylsilyl alcohol, is soluble in water and thus will not contaminate product, i.e, simple extraction or recrystallization of product from a mixture of ethanol and water can remove it easily.



Scheme 2 Proposed mechanism for the desulfurization of thioamides

In conclusion, a practical and efficient desulfurization of thioamides, thioketones, and thioesters has been achieved. Short reaction times, excellent yields, operational simplicity, generality, no side reactions, and excellent regioselectivity make the process attractive for the green synthesis of the target compounds. The thiocarbonyls are either commercially available or were prepared as follows: thioamides from the reaction of the corresponding amides with P_4S_{10} ,¹⁹ thioketones and thioesters from the reaction of the corresponding carbonyl compounds with Lawesson's reagent.²⁰ Melting points were determined in a capillary tube and are not corrected. ¹H NMR and ¹³C NMR spectra were recorded with a Bruker-200 NMR spectrometer using TMS as internal standard.

Desulfurization of Thiocarbonyls to Carbonyls; General Procedure

A mixture of thioamide (2 mmol), 30% H₂O₂ (4 mmol, 0.4 mL) and TMSCl (2 mmol) was stirred in EtOH (10 mL) at 25 °C for the appropriate time (Table 2). A yellow solid (elemental sulfur, mp 120 °C) immediately precipitated. The progress of the reaction was monitored by TLC to determine the necessary reaction times. Upon completion of the reaction, the reaction mixture was filtered to remove the elemental sulfur and the filtrate was poured into H₂O (10 mL), extracted with EtOAc (4 × 5 mL), and the extract was dried with anhydrous MgSO₄. The filtrate was evaporated under vacuum to afford the analytically pure product. An identical procedure was employed using thioketone or thioester (2 mmole), 30% H₂O₂ (4 mmol, 0.4 mL) and TMSCl (2 mmol) for the desulfurization of thioketones or thioesters.

All of products are known compounds, and were characterized by comparison with authentic samples (¹H and ¹³C NMR spectra, and melting point).

Acknowledgment

We are thankful to the Razi University Research Council for partial support of this work.

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