Facile Conversion of Dithioesters into Carboxylic Acids or Esters Using Alkaline Hydrogen Peroxide

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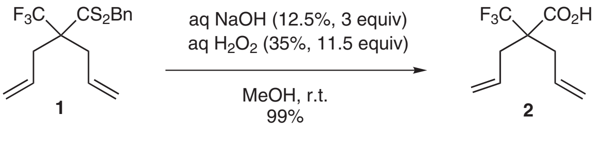
Abstract: Simple, mild, and environmentally friendly procedures for the direct conversion of dithioesters into either carboxylic acids or esters using hydrogen peroxide under alkaline conditions are described.

Key words: desulfurization, oxidation, peroxides, carboxylic acids, esters

Several methods have been reported for the conversion of thiocarbonyl compounds into their oxo analogues, including oxidative procedures involving inorganic or organic reagents and hydrolytic procedures with or without metal ions.[1] However, most of the studies have been carried out on thioamide and/or thione derivatives;[1] only a few have been successfully applied to dithioesters despite the high potential of this functional group. Dithioesters are an easy class of compounds to work with as several synthetic methods available for their preparation[2] and they represent potential precursors of not only the corresponding thiolesters, but also of thionoesters, esters, or acids. Thiolesters have been prepared from dithioesters in variable yields using benzeneseleninic anhydride,[3] *N*-nitrosamine,[4] nitrile oxide,[5] selenium oxide,[6] or tellurium species[7] as oxidants or by hydrolysis using sodium hydroxide under phase-transfer conditions.[8] Thionoesters were accessed by treatment of dithioesters with metal alkoxides.[9] Methyl esters were prepared by reaction with copper-[10] or mercury-containing agents,[10d,11] the latter still being the reagents of choice despite their toxicity. Finally, direct preparation of acids from dithioesters have been only reported for two examples, either by hydrolysis under harsh alkaline conditions[12] or using 1,4-dioxane–dibromine complex.[13] Alternatively, acids have been prepared in two steps, via preliminary transformation of dithioesters into esters using a mercury salt followed by their hydrolysis.[11d]

We recently described the preparation of various α,α-bis(allylic)-α-trifluoromethyl dithioesters[14] via a three-step domino reaction involving a thio-Claisen rearrangement; these compounds were expected to be precursors of the corresponding carboxylic acids.[15] Unfortunately, no reactions were observed when treating the fluorinated dithioester **1** under alkaline conditions (aqueous or solid NaOH or KOH, MeOH, r.t. or reflux, for days). These disappointing results prompted us to search for an alternative method for the conversion of this dithioester **1** into acid **2**. During our investigations we discovered that the simultaneous addition of an aqueous solution of sodium hydroxide and an aqueous solution of hydrogen peroxide[16] allowed the instantaneous transformation of dithioester **1** into acid **2**, which was then cleanly isolated in quantitative yield by simple acid-base workup (Scheme 1). Besides acid **2**, only dibenzyl disulfide was observed as a byproduct[17] and it was easily removed during workup.



Scheme 1 Hydrogen peroxide promoted conversion of trifluoromethylated dithioester **1** into carboxylic acid **2**

Although the conversion of various thioketones and thioamides into their oxygenated analogues with hydrogen peroxide is well known,[1] to our knowledge no reports deal with dithioesters. In this context, we examined this reaction in detail.

We first revisited the reaction conditions of the hydrogen peroxide promoted conversion of the dithioester into a carboxylic acid using benzyl dithiobenzoate (**3**) as a model substrate (Table 1). With use of the previous conditions [NaOH (3 equiv), H_2O_2 (11.5 equiv)], conversion of **3** into benzoic acid (**4**) was completed within two minutes of stirring and pure acid **4** was isolated in high yield after workup (95% yield) (entry 1). Interestingly, the amount of hydrogen peroxide could be reduced to two equivalents without increasing the time of the reaction or lowering the yield (entry 2).[18] However, using only one equivalent of base and one equivalent of oxidant, a complex mixture containing a fair amount of starting dithiobenzoate **3** was obtained after 15 hours of stirring, whereas using two equivalents of each led to the desired acid **4** in quite good yield despite the presence of a small amount of ester **5** (entries 3 and 4). In the absence of a base, after a sluggish start, methyl ester **5** and thiolester **6** were formed in equal quantities (entry 5). Finally, in the absence of an oxidizing reagent, thionoester **7** was isolated in very good yield (82%) and phenylmethanethiol instead of dibenzyl disulfide was formed as a byproduct (entry 6).

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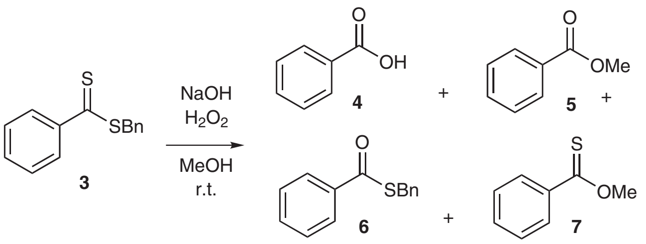
Table 1 Optimization Study Using Benzyl Dithiobenzoate (**3**) as a Model Substrate



Entry	H_2O_2[a] (equiv)	NaOH[b] (equiv)	Time	Yield or Ratio (%)				
				3[c]	**4**[d]	**5**[c]	**6**[c]	**7**[d,e]
1	11.5	3	<2 min		95			
2	2	3	<2 min		96			
3	1	1	15 h	40	40	10	trace	
4	2	2	15 h		79	21		
5	2	0	48 h			50	50	
6	0	3	1 h					82

[a] 35% aq H_2O_2 soln.

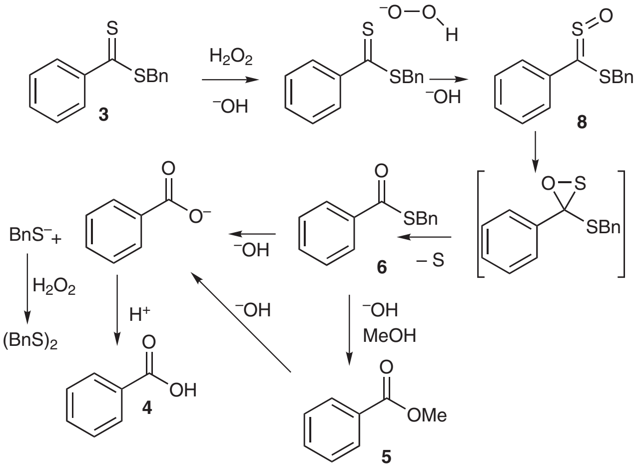
[b] 12.5% aq NaOH soln.

[c] Ratio determined by ^{1}H NMR of the crude reaction mixture (organic layer).

[d] Isolated yield.

[e] Purified by chromatography on silica gel.

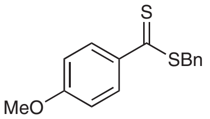
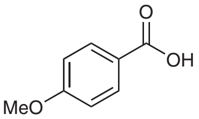
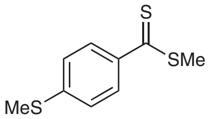
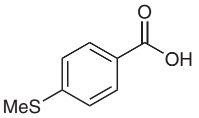
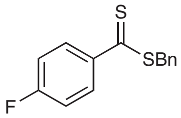
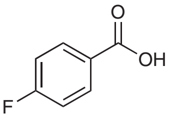
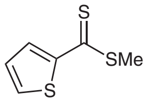
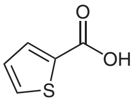
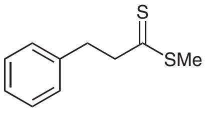
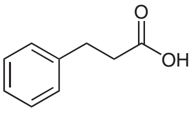
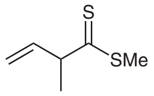
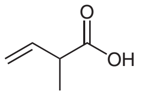
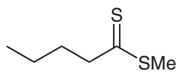
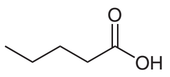
In order to define the mechanism of this reaction, attempts to identify intermediates have been carried out by monitoring aliquots by GC/MS.[19] It appeared that dithioester **3** is first oxidized into the intermediate sulfine (dithioester *S*-oxide) **8** by nucleophilic attack of HOO^- on the electrophilic sulfur atom.[20] Sulfine **8** is then converted into thiolester **6**. Although the direct conversion of sulfines into thiolesters was mentioned only once under ultraviolet irradiation,[21] desulfurization might occur by a rearrangement involving electrocyclization of the sulfine to give an oxathiirane[22] as analogous intermediates have been previously highlighted.[23] Finally, thiolester **6** is hydrolyzed to the carboxylate of **4** either directly or through ester **5**, and the thiolate moiety is oxidized to the disulfide[17] (Scheme 2).



Scheme 2 Postulated mechanism for the conversion of dithioester **3** into acid **4**

To illustrate the scope of this reaction, a range of aromatic, heteroaromatic and aliphatic dithioesters were examined. Results are depicted in Table 2. The transformations were quantitative within five minutes of stirring, except for the conversion of methyl 4-(methylsulfanyl)dithiobenzoate (**11**) into the corresponding acid **12**, which required several hours due to the very low solubility of this dithioester in methanol. All pure carboxylic acids were isolated in very high yields after workup, no additional purifications were necessary.

Table 2 Hydrogen Peroxide Promoted Conversion of Aromatic, Heteroaromatic, and Aliphatic Dithioesters into Carboxylic Acids[a]

Dithioester		Acid		Yield (%)
	**9**		**10**	91
	**11**		**12**	86
	**13**		**14**	94
	**15**		**16**	92
	**17**		**18**	99
	**19**		**20**	91
	**21**		**22**	89

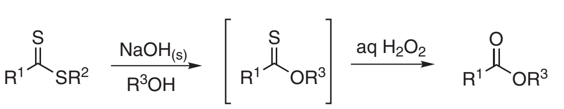
[a] Standard conditions: 12.5% aq NaOH soln (3 equiv), 35% aq H_2O_2 soln (2 equiv), MeOH, r.t.

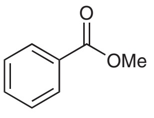
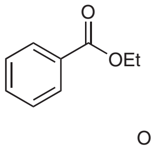
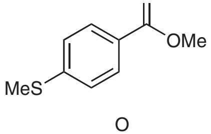
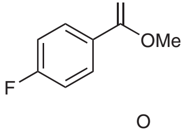
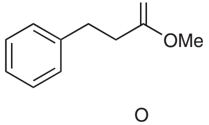
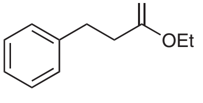
On the basis of the previous study and of the postulated mechanism (Table 1 and Scheme 2), we then attempted to devise a new method to convert directly dithioesters into esters by fine tuning the reaction conditions.

By comparing the data collected in Table 1, we expected that lowering the amount of base would increase the yield of ester **5** (entries 4, 5). Unfortunately, whatever the conditions attempted, ester **5** was always contaminated with variable amounts of starting dithioester **3**, acid **4**, and/or thiolester **6**. Having previously shown that dithioester **3** could be cleanly converted into thionoester **7** under methanolic alkaline conditions (Table 1, entry 6) we thus envisaged a 'one-pot' stepwise procedure via thionoester **7** instead of thiolester **6**. A variety of methods has been reported for the conversion of thionoesters into esters[1] including the use of tellurium,[7,24] chromate,[25] mercury,[26] or copper[27] species, hypochlorite,[28] peracid,[29] or Oxone[30] as reagents.

Optimized conditions for the conversion of dithioester **3** into methyl thionoester **7** required three equivalents of solid sodium hydroxide.[31] After the complete disappearance of the starting dithioester **3** (reaction monitored by TLC), the addition of two equivalents of an aqueous solution of hydrogen peroxide[32] led immediately to the desired ester **5** and dibenzyl disulfide.[17] Methyl ester **5** was then purified by chromatography on silica gel. Notably, this reaction is very versatile as not only methyl benzoate (**5**) could be prepared but also ethyl benzoate (**23**) by simply replacing methanol by ethanol. The results are collected in Table 3. In spite of the slightly slower formation of intermediate ethyl thionoesters than methyl thionoesters, both ethyl and methyl esters were obtained in very good yields.

Table 3 One-Pot Transformation of Dithioesters into Esters[a]



Dithioester	Solvent	Time (1st step)	Ester		Yield (%)
3	MeOH	1 h		**5**	86
3	EtOH	2 h		**23**	83
11	MeOH	15 min		**24**	89
13	MeOH	10 min		**25**	75
21	MeOH	15 min		**26**	88
21	EtOH	2 h		**27**	85

[a] Standard conditions: (1) NaOH solid (3 equiv), solvent, r.t., stirring until complete disappearance of the starting dithioester (by TLC); then (2) 35% aq H_2O_2 (2 equiv), r.t., 2 min.

By analogy to the previously postulated mechanism for the conversion of dithioesters into acids (Scheme 2), the transformation probably proceeds through the oxidation of the intermediate thionoester with hydrogen peroxide, leading to the corresponding sulfine (thionoester *S*-oxide), which is then desulfurized into the ester via the intermediate formation of an oxathiirane.[29]

In summary, we reported a simple process for the direct conversion of dithioesters into either carboxylic acids or esters using a inexpensive and environmentally friendly oxidant, hydrogen peroxide, under alkaline conditions. In particular, this procedure is an interesting alternative to those involving heavy metals.

All reagents were purchased from commercial sources. Commercially available analytical grade MeOH and abs EtOH were used as solvent. Silica gel Merck 9385 (40–63 μm) was used for flash chromatography. TLC using precoated Al backed plates (Merck Kieselgel 60 F254) were visualized by UV light and/or by a soln of $KMnO_4$. GC/MS analyses were performed with a reversed-phase capillary column (30 m × 0.25 mm i.d. × 0.25 μm; from 50 °C to 250 °C, 10 °C/min) and a spectrometer using a chemical ionization (NH_3 g) detection on a Finnigan trace 2000 series apparatus. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a 250 MHz spectrometer in $CDCl_3$ or MeOH-d_4. Chemical shift are reported relative to TMS (for ^1H and ^{13}C NMR). ^{19}F NMR chemical shift were determined relative to internal $CFCl_3$. HRMS (ESI$^+$) were recorded on a spectrometer using an electrospray source in negative or positive mode. Melting points were determined on a Tottoli apparatus and were uncorrected. The analytical data of known acids and esters were in accord with literature values.

CF_3-dithioester **1** was prepared as previously reported by our group.[14] Other dithioesters were prepared from CS_2 and the suitable Grignard reagents.[33]

Carboxylic Acids; General Procedure

To a soln of dithioester (1 mmol) in MeOH (10 mL) were added dropwise 35% aq H_2O_2 soln (2 mmol, 2 equiv) and 12.5% aq NaOH (3 mmol, 3 equiv). The mixture was vigorously stirred for 5 min. CH_2Cl_2 and H_2O were then added. The aqueous layer was separated, extracted with CH_2Cl_2 (2 ×) and then acidified with HCl. The aqueous layer was extracted with CH_2Cl_2 (3 ×). The latter combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the carboxylic acid.

2,2-Diallyl-3,3,3-trifluoropropanoic Acid (2)

To a soln of dithioester **1** (330 mg, 1 mmol) in MeOH (10 mL) were added dropwise 35% aq H_2O_2 soln (1 mL, 11.5 mmol, 11.5 equiv) and 12.5% aq NaOH (960 μL, 3 mmol, 3 equiv). After 5 min of stirring and workup, **2** (206 mg, 99%) was obtained as colorless liquid.

^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.63$ (d, $J = 7.5$ Hz, 4 H), 5.17 (d, $J = 9.5$ Hz, 2 H), 5.21 (d, $J = 17.0$ Hz, 2 H), 5.78 (m, 2 H), 9.27 (br s, 1 H).

^{13}C NMR (62.8 MHz, $CDCl_3$): $\delta = 36.1$, 56.0 (q, $J = 23.5$ Hz), 120.0, 125.6 (q, $J = 285.0$ Hz), 131.5, 174.8.

^{19}F NMR (235.2 MHz, $CDCl_3$): $\delta = -68.6$ (s).

HRMS: *m/z* [M – H]$^-$ calcd for $C_9H_{10}F_3O_2$: 207.0633; found: 207.0640.

Esters; General Procedure

A soln of dithioester (1 mmol) and NaOH (3 mmol, 3 equiv) in alcohol (10 mL) was vigorously stirred. When the reaction was complete, 35% aq H_2O_2 soln (2 mmol, 2 equiv) was added dropwise to the mixture and vigorous stirring was continued for 2 min. The mixture was then diluted with CH_2Cl_2 and washed with brine and water. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified on silica gel to afford the ester.

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(18) Aqueous hydrogen peroxide could be replaced by solid urea–hydrogen peroxide adduct (UHP). Under these conditions, acid **4** was isolated in 88% yield.

(19) All aliquots were acidified before analysis by GC/MS. Intermediates were identified by comparison of analytical data (t_R, MS peaks) with those of authentic samples of dithioester **3**, acid **4**, ester **5**, thiolester **6**, thionoester **7**, sulfine **8**, and dibenzyl disulfide.

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(31) Despite the fact that only 1 equiv of base is required, using a larger amount reduced the reaction time (1 h instead of 15 h).

(32) Aqueous hydrogen peroxide could be replaced by solid urea–hydrogen peroxide adduct (UHP). Under these conditions, ester **5** was isolated in 50% yield.

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