S-Alkyl Chlorothioformates from Xanthates

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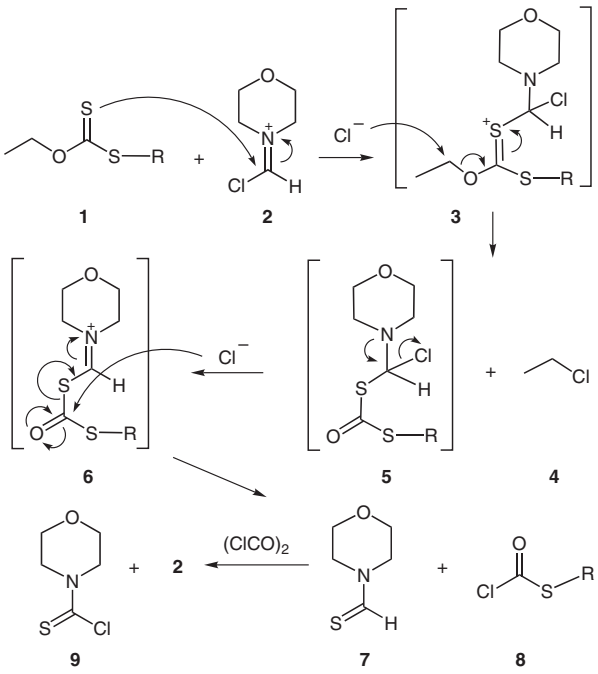
Abstract: Reaction of *S*-alkyl *O*-ethyl xanthates (*S*-alkyl *O*-ethyl dithiocarbonates) with catalytic Vilsmeier reagent generated in situ from *N*-formylmorpholine (morpholine-4-carbaldehyde) gives *S*-alkyl chlorothioformates in good yields.

Key words: halogenation, desulfurization, Vilsmeier reagent, chlorothioformates, dithiocarbonates

S-Alkyl chlorothioformates are useful intermediates for the preparation of thioesters,[1–4] thiocarbamates,[5,6] and thiocarbonates.[7–9] The typical preparation of *S*-alkyl chlorothioformates involves the reaction of a thiol with phosgene.[10,11] This method suffers from two problems, namely, the thiol and the phosgene. While triphosgene is a reasonable substitute for phosgene,[1] working with thiols is problematic. Not only do they produce a stench, but they also undergo oxidation to form disulfides. If the thiol precursor must be prepared as well, then the overall preparation of the *S*-alkyl chlorothioformate will likely involve three steps. Thiols usually are prepared by first alkylating a sulfur nucleophile, such as thioacetate, then releasing the thiol in a deprotection step.[12] Xanthate salts are also good sulfur nucleophiles.[13] The desired alkanethiol is generated by reaction of the *S*-alkylated xanthate with a base, such as 2-aminoethanol.[14] In this paper, we describe a preparation of *S*-alkyl chlorothioformates that circumvents the generation of the corresponding thiol.

S-Alkyl chlorothioformates **8**[15–17] were prepared by the reaction of the corresponding *S*-alkyl *O*-ethyl xanthates **1** with catalytic Vilsmeier reagent **2**, generated in situ from *N*-formylmorpholine (Scheme 1 and Table 1). *O*-Ethyl xanthates were used simply for convenience and because of the commercial availability of potassium ethyl xanthate. The choice of reagent **2** was to minimize the reaction time and to assist in the isolation of chlorothioformates **8** from the product mixture of **8** and **7** in the extraction and washing steps. This Vilsmeier reagent is known to be more reactive than the more common *N*,*N*-dimethylchloromethaniminium chloride derived from *N*,*N*-dimethylformamide.[18,19] Acetonitrile was chosen as the solvent in order to maximize the solubility of **2**. Oxalyl chloride (50% excess relative to **1**) was used to regenerate **2** from *N*-thioformylmorpholine (**7**). The reaction required one-third equivalent of *N*-formylmorpholine. Using less that this amount sometimes gave incomplete conversion because of the undesired side reaction of **7** with oxalyl chloride to give chloro-substituted derivative **9**. A separate NMR spectroscopic experiment showed that treating **7** (in CD_3CN) independently with threefold excess oxalyl chloride gave **2** and **9** in a ratio of 88:12. Most of the yields of **8** were around 80% for a representative range of alkyl group types (Table 1). The reaction of the *S*-*tert*-butyl xanthate gave the lowest yield. The product **8e** decomposed slowly to *tert*-butyl chloride under the reaction conditions and the yield dropped to 20% over 24 hours. The reported yield was for a three-hour reaction.



Scheme 1 Proposed mechanism for the preparation of *S*-alkyl chlorothioformates

The proposed mechanism for the transformation is indicated in Scheme 1. The Vilsmeier reagent **2** was necessary for the reaction to go to completion rapidly (ca. 3 h). Other common chlorinating agents [e.g. $SOCl_2$, $(ClCO)_2$, $POCl_3$, and PCl_5] either gave no reaction or much slower conversion. In fact, only phosphorus pentachloride (PCl_5) gave greater than 10% conversion over one day, and its conversion was still incomplete (ca. 75%) after 18 hours. Indeed, Zard and Tournier have reported the generation of a chloride from an alcohol using PCl_5 without affecting an adjacent xanthate.[20] Sulfuryl chloride (SO_2Cl_2) is known

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to react with xanthates to give the net addition of chlorine (Cl_2) across the thiocarbonyl group.[21,22] To see if the presence of any of the proposed intermediates **3**, **5**, or **6** could be detected, the reaction was conducted in NMR spectroscopic tubes using a slight stoichiometric excess of **2**. Other than the reactants and final products, only ethyl chloride (**4**) was observed. In contrast, the adduct of a primary *O*-alkyl xanthate anion and **2** could be observed by NMR spectroscopy.[23] This adduct is isomeric with **6**, but it has a thiocarbonyl instead of a carbonyl group. We speculate that the greater reactivity of the carbonyl group in **6** prevented its buildup to detectable quantities.

We attribute the success of this transformation to the facile initial electrophilic attack. While the reaction between a neutral xanthate and a neutral chlorinating agent goes slowly at best, the positively charged Vilsmeier reagent is a strong enough electrophile to react with the weakly nucleophilic xanthate. The first proposed intermediate **3** is a triheteroatom-substituted carbocation. A similar cation is formed when xanthates react with a sulfenyl chloride. These cations are reported to suffer nucleophilic attack by chloride ion resulting in cleavage of the carbon–oxygen bond and generation of a carbonyl group and an alkyl chloride.[5,24] Cleavage of the carbon–sulfur bond is not observed. Likewise, in the reaction of **1** with **2** the carbon–oxygen bond is cleaved in overwhelming preference to the carbon–sulfur bond. The only exception was in the reaction of **1e**. Analysis of the crude reaction product from **1e** showed that the formation of *O*-ethyl chlorothioformate was 0.9% relative to **8e**. All of the other xanthates gave undetectable amounts of this side product (Table 1). In the reaction of **1a** with PCl_5, this side product was much more pronounced (6% relative to **8a**).

In conclusion, *S*-alkyl chlorothioformates can be prepared directly from xanthates without having to prepare and isolate the corresponding thiol.

Xanthates **1a–c** and **1f**,**g** were prepared by the standard method of nucleophilic substitution of the appropriate alkyl bromide with potassium ethyl xanthate.[13,25–27] Two equivalents of iodocyclohexane were used for the preparation of **1d**.[28] Zinc xanthate was used for the preparation of **1e**.[29–31] All xanthates were purified by vacuum distillation and checked by GC/MS before use. NMR spectroscopy was performed on a Varian VX-400 spectrometer, with TMS as an internal standard.

S-Alkyl Chlorothioformates 8; General Procedure

Oxalyl chloride (4.77 g, 37.5 mmol) was added dropwise with stirring to a solution of morpholine-4-carbaldehyde (0.96 g, 8.3 mmol) in MeCN (25 mL) cooled in an ice bath. The mixture was stirred for an additional 15 min before adding *S*-alkyl *O*-ethyl dithiocarbonate **1** (25 mmol). The ice bath was removed, and the mixture was stirred for at least 6 h over which time it became very dark. The mixture was then extracted with PE (3 × 150 mL). The combined organic extracts were washed with ice-water (2 × 150 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The *S*-alkyl chlorothioformates were distilled under reduced pressure (see Table 1). The purity of the distilled products was greater than 98% by GC/MS.

8a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (t, *J* = 7.3 Hz, 2 H), 1.66 (tt, *J* = 7.7, 7.3 Hz, 2 H), 1.42 (tq, *J* = 7.7, 7.3 Hz, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.10, 33.89, 30.95, 21.91, 13.66.

8b

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.96 (t, *J* = 7.7 Hz, 2 H), 1.66 (nonet, *J* = 6.6 Hz, 1 H), 1.56 (dt, *J* = 7.7, 6.6 Hz, 2 H), 0.93 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.09, 37.65, 32.32, 27.60, 22.29.

8c

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.49 (sext, *J* = 6.9 Hz, 1 H), 1.67 (dq, *J* = 7.4, 6.9 Hz, 2 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 1.00 (t, *J* = 7.4 Hz, 3 H).

Table 1 Preparation of *S*-Alkyl Chlorothioformates from Xanthates

Compound	R	Yield (%)	Formation of EtO(CS)Cl relative to **8** (%)	Bp (°C/14 mmHg)	Lit. bp (°C/mmHg)	Ref.
8a	Bu	75	<0.1	66–67	76–78 (18)	15,16
8b	isopentyl	80	<0.1	76–77	85 (22)	17
8c	*s*-Bu	80	<0.1	57–58	89–90 (60)	17
8d	Cy	93	<0.1	104–106	[a]	16
8e	*t*-Bu	55[b]	0.9	48–49	50 (16)	17
8f	All	64	<0.1	45–47	60–61 (91)	16,17
8g	Bn	76	<0.1	130–134[c,d]	65–70 (0.001)	16,17

[a] Not reported.
[b] After 3 h and 97% conversion.
[c] Slightly decomposes at these temperatures.
[d] Bp 57–60 °C/0.3 mmHg.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.47, 46.78, 28.99, 20.24, 11.49.

8d

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55–3.46 (m, 1 H), 2.04–1.97 (m, 2 H), 1.78–1.70 (m, 2 H), 1.64–1.56 (m, 1 H), 1.54–1.35 (m, 4 H), 1.34–1.23 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.26, 47.88, 32.29, 25.80, 25.45.

8e

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.94, 52.66, 29.50.

8f

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddt, *J* = 16.8, 10.0, 7.0 Hz, 1 H), 5.32 (d, *J* = 16.8 Hz, 1 H), 5.23 (d, *J* = 10.0 Hz, 1 H), 3.59 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.38, 130.74, 120.30, 36.82.

8g

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H), 4.15 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.65, 134.83, 129.09, 129.07, 128.28, 38.37.

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