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CONVERSION OF α-CHLOROSULFENYL CHLORIDES TO KETONES VIA α-CHLOROSULFENAMIDES. USE OF THIONYL CHLORIDE FOR OXIDATION OF ACTIVE METHYLENE COMPOUNDS

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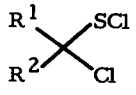
The current literature[1a-d] shows clearly that the substitution reaction of excess thionyl chloride with active methylene compounds gives α-chlorosulfenyl chlorides. This communication deals with the chemical conversion of α-chlorosulfenyl moieties into carbonyl groups, and shows that thionyl chloride oxidation is an useful method for the preparation of ketones, especially α-diketones, under remarkably mild conditions.

Simple hydrolysis under neutral, acidic, and basic conditions of the α-chlorosulfenyl chlorides 1a-e, prepared from the corresponding active methylene compounds (see Table I), regenerated the original methylene compounds by the extrusion of hydrogen chloride and sulfur dioxide.[3] To overcome this difficulty, we chose secondary sulfenamides, especially morpholides 2a-e, as the key intermediates for the desired hydrolysis.[4] The requisite morpholides were prepared in high yields, almost quantitatively, by the reaction of the sulfenyl chlorides 1a-e with the theoretical or a slight excess amount of morpholine. All sulfenamides described were fairly stable materials and identified as assigned structures by spectroscopic analyses (for instance, 2b; m/e M^+ = 285 (16%); NMR (C_6D_6) δ 2.10 (s, CH_3), 2.78 and 3.24 (m, 2 NCH_2CH_2O), 7.10 (m, m- and p-H_3), 8.42 (m, o-H_2); ir (neat) 1672 (C=O)).

It is well precedented in sulfur chemistry that the α-chloro thioethers form carbonium ions



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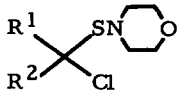
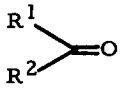


2

	R^1	R^2
a	Ph	PhCO
b	Me	PhCO
c	Ph	COCl for 1c; CON⟨⟩O for 2c, 3c
d	COOEt	COOEt



3

$PhCOCHClCH_3$

4

e

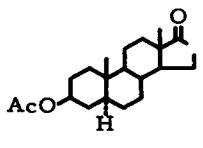


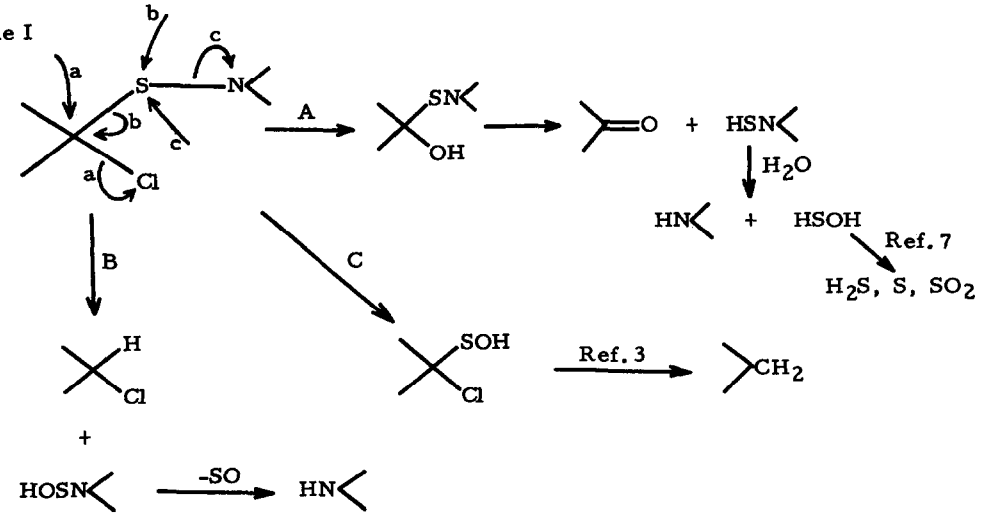
Table I Synthesis of α-chlorosulfenyl chlorides from active methylene compounds

Substrate	Condition[a]	Product	Yield %[b]	ir (neat) C=O
Benzyl phenyl ketone[c]	reflux, 15 min	1a	97	1659, 1690
Propiophenone	room temp., 5 hr	1b	85	1660, 1689
Phenylacetic acid[d]	reflux, 1.5 hr	1c	92	1780, 1810
Diethyl malonate[c]	reflux, 3 hr	1d	96	1723, 1760
Epiandrosterone acetate	reflux, 30 min	1e	not isolated[e]	———

(a) All reactions were carried out in 10-15 mol. eq. $SOCl_2$ in the presence of 0.01-0.03 mol. eq. pyridine. (b) Isolated yield after silica gel column chromatography. (c) Thiirane and olefin synthesis from benzyl phenyl ketone and diethyl malonate, respectively, with equimolar amount of $SOCl_2$ has been reported (Ref. 2). (d) In an earlier synthesis of 1c, a large amount of pyridine (0.35 mol. eq.) was used (Ref. 1d). (e) Chromatography caused the product to decompose.

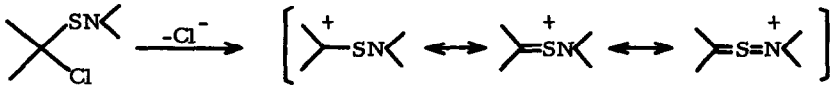
stabilized by resonance with sulfur[5] and that the β-oxo thioethers are desulfenylated by a nucleophile (R_1R_2NH, etc.).[6] However, it was possible that the electron-withdrawing effect of the chlorine on sulfur in α-chlorosulfenyl chlorides 1a-e shift the nature of reaction from those to a simple substitution on sulfur atom. Thus the simple hydrolysis of 1a-e[3] and the preparation of α-chlorosulfenamides 2a-e were explained reasonably. Such α-chloro-β-oxosulfenamides 2a-e, which may have some of the characteristics of α-chloro thioethers, β-oxo thioethers, and α-chloro-β-oxosulfenyl chlorides 1a-e, have never been used for the purpose of hydrolysis. In the acid-catalyzed hydrolysis of 2a-e, the following C-S and S-N bond fissions have to be considered.

Scheme I



(A) Bond fission proceeds as indicated by the solid arrow a (Scheme I) to give an α-hydroxysulfenamide from which a ketone and a mercaptamine are easily produced. The latter

material might be hydrolyzed into the amine and HSOH which further decomposes.[7] The initial step of this cleavage may involve the formation of carbonium ion stabilized by resonance owing to electron-donating character of nitrogen (eq. 1). (B) Bond fission proceeds as indicated by the solid arrow b to give a monochloride and a sulfenic acid. From the latter the amine is generated by releasing SO which is in equilibrium with free sulfur and SO_2.[8] (C) Bond fission proceeds as indicated by the solid arrow c to give an α-chlorosulfenic acid which further decomposes into original active methylene compound by the extrusion of HCl and SO_2 as in the case of simple hydrolysis of α-chlorosulfenyl chlorides 1a-e.[3]



.....eq. 1

The hydrolysis of 2a, c, and e proceeded smoothly in benzene with 10% hydrochloric acid to afford ketones 3a, c, and e, respectively, in accordance with course A. Hydrogen sulfide, sulfur dioxide, and free sulfur were detected during work up. However, hydrolysis of sulfenamide 2b with hydrochloric acid afforded ketone 3b (38%) and monochloride 4 (45%) in accordance with courses A and B, respectively, but only ketone 3b when the hydrolysis was carried out with sulfuric acid. The sulfenamide 2d was intact throughout these mild conditions at room temperature in benzene, while diethyl malonate (78%) was obtained at elevated temperatures in ethanol in accordance with course C.[9]

For preparative purposes, these consecutive reactions (sulfenylation, amidation, and hydrolysis) described above could be carried out continuously as an one-pot reaction. The

Table II Conversion of α-chlorosulfenyl chlorides to ketones via morpholides

Substrate	Amidation		Hydrolysis		
	Condition[a]	Product (%)[b]	Condition[c]	Product (%)[d] ketone, monochloride, methylene	
1a	5°, 2 min	2a (97)	10% HCl, 10 min	3a (85)	
1b	5°, 2 min	2b (98)	10% HCl, 10 min 10% H_2SO_4, 3 hr	3b (38) 3b (72)	4 (45)
1c	10°, 10 min	2c (95)	10% HCl, 30 min	3c (80)	
1d	20°, 10 min	2d (100)	10% HCl, over night c. HCl-EtOH, reflux, 2 hr	(–)[e]	(78)
1e	10°, 10 min	2e (–)[f]	10% HCl, 20 min	3e (63)[g]	

(a) All reactions were carried out in benzene. (b) Isolated yield based on 1. (c) Benzene was used as solvent at room temperature unless otherwise indicated. (d) Isolated yield based on the active methylene compound without any isolation or purification of the intermediates. (e) Morpholide 2d was recovered quantitatively. (f) Not isolated. (g) mp 185-187° (i-Pr_2O, needles), ir (KBr) 1727, 1754, 1760 (C=O); NMR ($CDCl_3$) δ 0.90, 1.02 (s, 2 CH_3), 2.02 (s, Ac), 4.68 (m, 3α-H). Other materials were identified with authentic samples.

results are summarized in Table II. A typical procedure is as follows.

Benzyl phenyl ketone, 5 g, and pyridine, 20 mg, were dissolved in $SOCl_2$ (bp 78-79°), 20 ml, and the mixture was refluxed until the evolution of HCl and SO_2 ceased (about 15 min). The excess reagent was evaporated in vacuo. The resulting oil (1a) was dissolved in absolute benzene, 30 ml, and the solution of morpholine, 4.5 g, in benzene, 20 ml, was added dropwise under cooling with ice-water. After a few minutes, the mixture was shaken with 10% HCl, 30 ml, for 10 min. The organic layer was dried (Na_2SO_4) and evaporated. Recrystallization from MeOH gave needles (3a), 3.2 g, mp 92-93°, which was identified with authentic sample. Purification of the mother liquor on silica gel column gave the additional pure material, 1.35 g.

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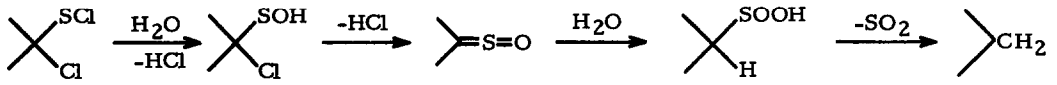
(3) This reductive decomposition has been first observed by Simon et al.[1d] about the hydrolysis of phenylacetic acid derivative. This somewhat curious reaction now seems to be of considerable generality. The reaction course, we suppose, is as follows:



i ii iii

Although the exact nature of these reactions is not known, we believe the electron-withdrawing effect of neighbouring carbonyl group(s) of the present derivatives plays the driving force for both the addition of water to sulfur atom of sulfine ii (for addition of water to carbon atom see the Ref. 7) and the elimination of SO_2 from sulfinic acid iii as in the case of β-ketocarboxylic acid.

(4) For alcoholysis of α-chlorosulfenyl chloride at high temperature for a few days see Ref. 1d.

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(9) Ketone synthesis from 1d via dehydrochlorination of its anilide followed by hydrolysis of resulting phenyliminomalonate will be published elsewhere.