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Oxidation of Long-Chain and Related Alcohols to Carbonyls by Dimethyl Sulfoxide "Activated" by Oxalyl Chloride[1]

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Dimethyl sulfoxide "activated" by oxalyl chloride at low temperatures in methylene chloride reacts rapidly with alcohols to give alkoxysulfonium salts, convertible to carbonyls in high to quantitative yields upon addition of triethylamine. Oxalyl chloride is the most efficient and generally useful Me_2SO "activator" thus far reported. The mild, high yield oxidation of long-chain saturated, unsaturated, acetylenic, and steroidal alcohols to carbonyls utilizing Me_2SO "activated" by oxalyl chloride is described.

Long-chain aldehydes (in masked form) are of importance in biological systems, such as plasmalogens, found in many organs of the body, e.g., heart, muscle, liver, kidney, pituitary gland, and cerebellum white and gray matter.[2] In the synthesis of plasmalogens, long-chain saturated and unsaturated aldehydes are necessary intermediates.

No satisfactory and universally applicable method for the preparation of long-chain carbonyls by the mild, selective oxidation of the corresponding long-chain saturated and unsaturated alcohols has been reported. Earlier work[3] involved the preparation of a sulfonate ester (mesylate or tosylate) of the alcohol followed by reaction with dimethyl sulfoxide (Me_2SO) at 160 °C for 5–10 min in the presence of sodium bicarbonate (yields 60–72%). The use of Me_2SO–acetic anhydride or Me_2SO–sodium bicarbonate at room temperature with the sulfonate esters was unsuccessful.

The oxidation of long-chain primary alcohols to aldehydes by the dipyridine–chromic anhydride complex was recently reported[4] but a sixfold excess of oxidant to alcohol is required. Yields are good, however, and range from 83–94%. No evidence (by infrared) of cis–trans isomerization of double bonds was observed in the preparation of mono-, di-, or triunsaturated aldehydes. Isomerization of double bonds is observed when more acidic oxidizing agents are employed.[5–8]

"Activated" Me_2SO has been used extensively by us to oxidize many classes of alcohols to carbonyls in excellent yields under mild conditions via the intermediate alkoxysulfonium salts.[9–11] In this paper we report our studies of "activated" Me_2SO as an oxidant for the mild, high-yield oxidation of long-chain saturated, unsaturated, acetylenic, and steroidal alcohols at low temperatures to carbonyls utilizing the newly discovered and most successful "activator" developed in our laboratory, namely, oxalyl chloride.[11] The results were compared with those obtained at room temperature with pyridinium chlorochromate[7] and pyridine–SO_3–Me_2SO,[12] two other well-known oxidants, and Me_2SO "activated" by trifluoroacetic anhydride (TFAA).[9,10]

Results and Discussion

Oxalyl chloride reacts violently and exothermically with Me_2SO at room temperature; therefore successful "activation" of Me_2SO by oxalyl chloride requires the use of low temperatures (−60 °C) to form intermediate **1**. The structure of intermediate **1** from oxalyl chloride and Me_2SO is unknown; intermediates **1a** and **1b** are both possible. Intermediate **1b**

$$(Me_2\overset{+}{S}OC(=O)-C(=O)Cl)\ Cl^- \xrightarrow{-CO_2,\ CO} [Me_2\overset{+}{S}Cl]\ Cl^-$$

1a **1b**

is the same as that reported by Corey and Kim for the low-temperature reaction of dimethyl sulfide with chlorine (Me_2S–Cl_2),[6] also a useful intermediate in alcohol oxidations.

The oxidation of long-chain saturated and unsaturated alcohols by Me_2SO "activated" by oxalyl chloride is summarized in Table I, acetylenic alcohols are summarized in Table II, and steroidal alcohols are summarized in Table III. The TFAA "activated" Me_2SO oxidation of several long-chain saturated alcohols is summarized in Table IV.

The oxalyl chloride "activated" Me_2SO oxidation of long-chain saturated alcohols to the corresponding aldehydes proceeds virtually quantitatively (Table I) and is limited only by the solubility of the alcohol in the solvent system

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Table I. Oxidation of Long-Chain Alcohols with Me_2SO–$(COCl)_2$[f]

Alcohol	Registry no.	Conditions[a]	Carbonyl yield, % 2,4-DNP	GLC >C=O	GLC >CHOH	Registry no. of >C=O deriv
1-Undecanol	112-42-5	A	99	100	0	112-44-7
1-Dodecanol	122-53-8	A	99	100	0	112-54-9
1-Dodecanol		D	98	98	0.2	
1-Tetradecanol	112-72-1	A	26	23	76	124-25-4
1-Tetradecanol		D	97	96	4	
1-Pentadecanol	629-76-5	A	25	24	75	2765-11-9
1-Pentadecanol		D	95	99	0.2	
1-Hexadecanol	36653-82-4	A (−35 °C)	79	80[b]	20[b]	629-80-1
1-Octadecanol	112-92-5	D	84	86[b]	4[b]	638-66-4
Oleyl (cis)	143-28-2	A	97	98[b]	2[b]	2423-10-1
Elaidyl (trans)	506-42-3	A	97	98[b]	2[b]	10009-79-7
Linoleyl	506-43-4	D	98	98[b]	1.9[b]	2941-61-9
Methyl ricinoleate	141-24-2	D	oil	79[b]	20[b]	3047-65-2
Citronellol	106-22-9	A	83	85	14	106-23-0
Geraniol	106-24-7	A	94	95	5	141-27-5
Farnesol	4602-84-0	D	88	92	8	19317-11-4
1,12-Dodecanediol	5675-51-4	A	98[c,d]	99[c,d]	1	38279-34-4
4-Hydroxystearic acid	2858-39-1	D	80[e]			
12-Hydroxystearic acid	106-14-9	D	75[e]			

[a] See Experimental Section. [b] Relative ratios. [c] Dialdehyde. [d] 1 molar equiv of Me_2SO–$(COCl)_2$ per hydroxy function. [e] Isolated keto acid. [f] Registry No.—Me_2SO, 67-68-5; $(COCl)_2$, 79-37-8.

Table II. Oxidation of Acetylenic Alcohols with DMSO–$(COCl)_2$, TEA, −60 °C

Alcohol	Registry no.	Carbonyl yield, % 2,4-DNP	GLC >C=O	GLC >CHOH
$HC{\equiv}C(CH_2)_2CH_2OH$	5390-04-5	99.6	99.8[a]	0.2
$CH_3C{\equiv}CCH_2C(OH)HCH_3$	19780-36-4			
$CH_3(CH_2)_3C{\equiv}CCH_2OH$	1002-36-4	79	98.3[b]	1.7
$CH_3(CH_2)_2C{\equiv}C(CH_2)_2OH$	14916-79-1			90
$CH_3(CH_2)_4C{\equiv}CCH_2OH$	20739-58-6	93	95[c]	5
$CH_3(CH_2)_4C(OH)HC{\equiv}CH$	818-72-4			

[a] Registry no. 18498-59-4. [b] Registry no. 1846-67-9. [c] Registry no. 1846-68-0.

Table III. Oxidation of Steroidal Alcohols with Me_2SO–$(COCl)_2$, TEA, −10 °C

Alcohol	Registry no.	Carbonyl yield, %[a]	Registry no.
Dihydrocholesterol (cholestanol)	80-97-7	96	566-88-1
Cholesterol (5-ene)	57-88-5	95	601-54-7
Stigmasterol (5,22-diene)	83-48-7	95	51529-12-5
11α-Hydroxyprogesterone	80-75-1	99	516-15-4
Testosterone	58-22-0	99	63-05-8

[a] Isolated carbonyl.

Table IV. Oxidation of Long-Chain Alcohols with Me_2SO–TFAA (Procedure C)

Alcohol	Base	Carbonyl yield, %, 2,4-DNP
1-Tetradecanol	TEA	72
	DIPEA	85
1-Pentadecanol	TEA	66
1-Octadecanol	DIPEA	84

(CH_2Cl_2–Me_2SO) at low temperatures. As the solubility decreases at the lower temperature (−60 °C) and with increasing chain length it is necessary to conduct the oxidation at −10 °C, the upper limit for the addition of the alcohol to **1**. High yields of carbonyls are obtained, however, when a 100% excess of oxalyl chloride "activated" Me_2SO is used to ensure that the alkoxysulfonium salt of the alcohol forms at −10 °C even though a considerable amount of intermediate **1** is sacrificed. The longest straight-chain alcohol examined was 1-octadecanol (C-18). The oxalyl chloride–Me_2SO route to carbonyls is superior to TFAA–Me_2SO (Table IV), even when diisopropylethylamine is used with the latter reagent.

The unsaturated lipid alcohols, oleyl (cis), elaidyl (trans), linoleyl (*cis,cis*-9,12-octadecadienol), and methyl ricinoleate, are converted to their corresponding carbonyls in high yield with no cis–trans isomerization of double bonds observed. The terpene alcohols, citronellol, and the two allylic alcohols, geraniol and farnesol, are also oxidized in good yields with no effect on the double bond systems.

The only diol examined gives an almost quantitative yield of dialdehyde when 1 equiv of "activated" Me_2SO per hydroxyl function is used (Table I).

Hydroxy acids can also be successfully oxidized to their corresponding keto acids (Table I).

Acetylenic Alcohols. Although the oxidation of unsaturated and allylic alcohols with the oxalyl chloride–Me_2SO reagent is very successful, oxidation of acetylenic alcohols is complex and the results are neither uniform nor understood (Table II). 1-Octyn-3-ol also fails to give any isolable carbonyl product when oxidized by TFAA–Me_2SO or pyridinium chlorochromate.[7]

Those acetylenic alcohols that can be successfully oxidized by our method can also be oxidized by other methods,[4,7] but

Table V. Oxidation of Long-Chain Alcohols by Pyridinium Chlorochromate[7] and Pyridine–SO_3–Me_2SO[12] at Room Temperature (25 °C)

Alcohol	Oxidant	Carbonyl yield, %
1-Tetradecanol	Py·SO_3·Me_2SO	42[a]
1-Tetradecanol	$PyHCrO_3$·Cl	69
1-Octadecanol	$PyHCrO_3$·Cl	85
Citronellol	$PyHCrO_3$·Cl	82[b]
2-Octyn-1-ol	$PyHCrO_3$·Cl	84[b]

[a] Recovered alcohol (58%). [b] Taken from ref 7.

not in as high yields. The acetylenic alcohols which fail to yield carbonyl by our oxidation procedure have not been reported to yield carbonyls by other methods.

Steroidal Alcohols (Table III). The oxidation of steroidal alcohols by Me_2SO–*N*,*N*-dicyclohexylcarbodiimide (Moffatt oxidation) has been examined extensively[14-16] and will not be discussed further. Oxalyl chloride–Me_2SO gives almost quantitative oxidation of cholesterol and stigma sterol without isomerization (5-en-3-one products). The absence of the 4-en-3-one isomers was confirmed by the absence of the α,β-unsaturated carbonyl band in the infrared spectrum of the products. Ergosterol gives a 90% yield of carbonyl products whose composition is not the same under three sets of presumably identical oxidation conditions. The 4,6-dien-3-one, 4,7-dien-3-one and 5,7-dien-3-one isomerization mixture is known to be light and moisture sensitive and extremely prone to isomerization. The 5,7-dien-3-one is very difficult to obtain regardless of the oxidation method. It has previously been reported in admixture with the 4,7-dien-3-one.[17] The oxalyl chloride–Me_2SO oxidation has been used by us[11] to oxidize β,γ-unsaturated alcohols to the corresponding β,γ-unsaturated carbonyls without isomerization to the α,β-unsaturated carbonyls.

Comparison of Oxidation Methods. We used pyridinium chlorochromate[7] ($PyHCrO_3$·Cl) to oxidize 1-tetradecanol and 1-octadecanol for comparison with the oxalyl chloride–Me_2SO and TFAA–Me_2SO procedures. Unoxidized alcohol is not recovered in this procedure and yields of the carbonyls are comparable but somewhat lower than with oxalyl chloride–Me_2SO. The pyridinium chlorochromate reagent has the advantage of being operable at room temperature, however, but its versatility, scope, and limitations have not been totally explored.[7]

Pyridine–SO_3–Me_2SO[12] at room temperature was also used as an oxidant by us; it does not give as good yields of long-chain carbonyls as does oxalyl chloride–Me_2SO.

The results obtained in the oxidation of several long-chain alcohols by $PyHCrO_3$·Cl and Py–SO_3–Me_2SO are summarized in Table V.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. IR spectra were obtained using a Pye Unicam SP1000 spectrometer. A Varian Aerograph Series 2100 gas chromatograph with a flame-ionization detector and a 4 ft × 0.125 in. column packed with 8% SE-30 on Chromosorb P was used in the analysis of oxidations of long-chain alcohols (C_8 or greater; N_2 was the carrier gas). Occasionally a 6 ft × 0.25 in. column packed with 10% FFAP on Chromosorb P in a Varian A-90 P-3 gas chromatograph with a thermal conductivity detector was used; He was the carrier gas. Me_2SO was distilled from calcium hydride under reduced pressure and the heart cut was stored over Linde Molecular Sieves Type 3A in a sealed brown bottle. Purest grades of alcohols were purchased and purified, if necessary; purity exceeded 98% in most cases. Oxalyl chloride and other acid halides for "activation" of Me_2SO were freshly distilled and stored over Linde Molecular Sieves Type 3A in sealed brown bottles under N_2. Trifluoroacetic anhydride, gold label, pyridinium chlorochromate, and pyridine–sulfur trioxide were used as received from Aldrich Chemical Co. Amines were distilled from calcium hydride or sodium, and the heart cuts were retained and stored over Linde Molecular Sieves Type 3A or sodium. Authentic samples of carbonyls were purchased. Methylene chloride was distilled from phosphorus pentoxide and stored over Linde Molecular Sieves Type 4A. Glassware was dried in an oven just before use. A sample of 1-pentyn-5-ol was generously supplied by Dr. Grant R. Krow, Temple University and a sample of linoleyl alcohol was generously supplied by Applied Science Laboratories, State College, Pa.

Oxidation of Alcohols to Carbonyls by Oxalyl Chloride–Me_2SO. Procedure A. General Procedure. A solution of CH_2Cl_2 (25 mL) and oxalyl chloride (1.0 mL, 11 mmol) was placed in a 100-mL four-neck round-bottom flask equipped with an overhead mechanical stirrer, a thermometer, a $CaSO_4$ drying tube, and two pressure-equalizing dropping funnels containing Me_2SO (1.7 mL, 22 mmol) dissolved in CH_2Cl_2 (5 mL) and the alcohol (10 mmol in 10 mL of CH_2Cl_2 or a minimum amount of CH_2Cl_2–Me_2SO to dissolve the alcohol), respectively. The Me_2SO was added to the stirred oxalyl chloride solution at −50 to −60 °C. The reaction mixture was stirred for 2 min and the alcohol was added within 5 min; stirring was continued for an additional 15 min. TEA (7.0 mL, 50 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (50 mL) was then added and the aqueous layer was reextracted with additional $CHCl_2$ (50 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), and dried over anhydrous $MgSO_4$. The filtered solution was concentrated in a rotary evaporator to 25 mL. A 5-mL solution was used for GLC analysis; a 10-mL portion was used for characterization of carbonyls as their 2,4-DNP derivatives. The remaining 10-mL portion was washed successively with dilute HCl (1%), water, dilute Na_2CO_3 (5%), and water and evaporated to dryness to give a slightly colored crude carbonyl which was frequently pure without further workup. IR and NMR spectra of the crude products were identical with those of authentic samples of the carbonyls. Melting points of crude derivatives agreed well with the literature values. In some cases, derivatives and carbonyls were recrystallized.

Procedure D. This procedure is identical to procedure A except (a) $(COCl)_2$ (2 mL, 22 mmol) and Me_2SO (3.4 mL, 48 mmol) were used and (b) the alcohol (10 mmol) was added at −10 °C and the reaction temperature was maintained for 15 min.

Oxidation of Alcohols to Carbonyls by TFAA–Me_2SO. This procedure has already been reported by us.[9,10]

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