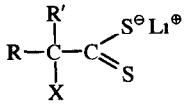
Tetrahedron. Vol. 32, pp. 2507 to 2512. Pergamon Press 1976. Printed in Great Britain

α-ANIONS—VIII

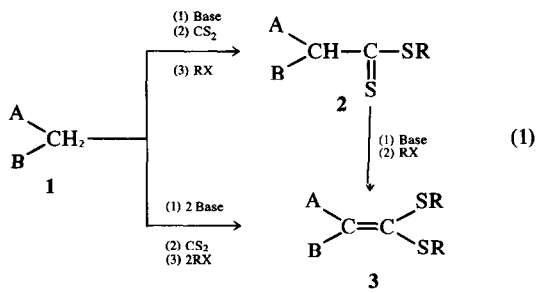
DITHIOESTERS AND KETENE MERCAPTALS FROM ALIPHATIC ACIDS AND ESTERS†

D. A. KONEN,* P. E. PFEFFER and L. S. SILBERT
Eastern Regional Research Center, ‡ Philadelphia, PA 19118, U.S.A.

(*Received in the USA 23 January 1976; Received in the UK for publication 29 March 1976*)

Abstract—Carbon disulfide reacts with the α-anions of carboxylate salts and esters to form intermediate salts,  , where X = $CO_2^{\ominus}Li^{\oplus}$, CO_2Me, R = alkyl and R′ = CH_3 or H. Selective treatment of these salts provides a new pathway to two classes of compounds: dithioesters and ketene mercaptals. The reaction produced the first carboxylated derivatives of dithioesters and ketene mercaptals. Examples of 2-carboxylated dithioesters and ketene mercaptals as well as their decarboxylated derivatives have been prepared and characterized.

Dithioesters **2** and ketene mercaptals **3** are commonly produced through the condensation of activated methylene compounds **1** with carbon disulfide in the presence of base followed by alkylation[1–5] (eqn 1). In the preparation of dithioesters, yields ranged from 20 to 60%



(1)

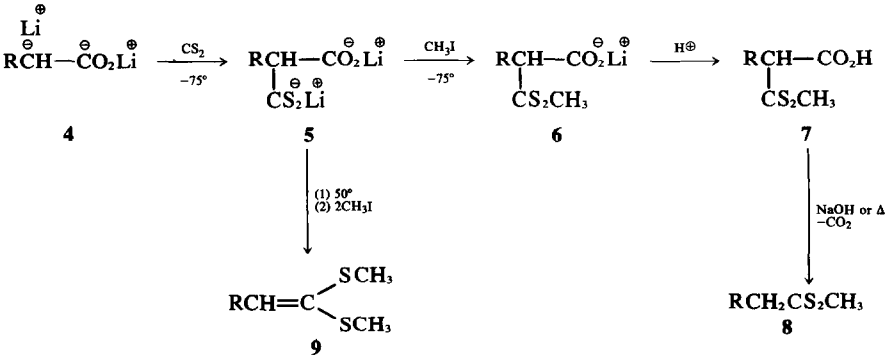
for the aromatic derivatives but were less than 10% for alkyldithioesters such as dithioacetate or dithiopropionate.[5] Dithioesters have also been prepared by the reaction of iminothioethers and hydrogen sulfide, or thioamides and a thiol.[4,6] Similarly, immonium chlorides have been used to produce thiocarbamates, thiolesters, or dithioesters, depending upon the reactants.[5a,7]

Ketene mercaptals are prepared by alkylation of dithioesters in the presence of base or directly from activated methylene compounds with additional base and alkyl halide[2–12] (eqn 1). In either case, both A and B must be strongly• activating groups such as RSO,[9] φ,[4] φC(=O),[3,7b,c,10–12] and/or CN.[8,11] Use of less activated compounds like aliphatic aldehydes or ketones resulted in drastically reduced yields (10–25%).[2,10b] Thioacetals containing labile groups in the α or β position can also be used as intermediates in the preparation of alkyl ketene mercaptals, although the preparation of these precursors is often inconvenient or difficult.[13] Shahak and Sasson[14] obtained low yields (20–45%) of ketene mercaptals from unactivated ketones by use of sodium hydride. Extension of this procedure to simple esters, however, gave large amounts of Claisen condensation products and low conversions to the desired ketene mercaptals.

A direct pathway to dithioesters and ketene mercaptals from aliphatic carboxylic acids has previously not been investigated. In this report, we describe a method for preparing ketene mercaptals, dithioesters, and their carboxylated derivatives through the agency of a common intermediate prepared from the addition of carbon disulfide to the α-anion of carboxylate salts or ester enolates.

†Presented in part at the 9th Middle Atlantic Regional Meeting, ACS Meeting (25 April 1974).

‡Agricultural Research Service, U.S. Department of Agriculture.



4 **5** **6** **7** **8** **9**

Scheme 1.

Dithioesters. The addition of carbon disulfide to the dianions of alkylcarboxylic acids **4** (Scheme 1) proceeded smoothly and rapidly at −75°, producing the dithiocarboxylate salt **5**, which was subsequently alkylated at low temperature to give methyl 2-carboxydithioester **7** (Table 1, Products 1, 4 and 7). Unlike stable malonic acid derivatives formed by addition of CO_2 to dianions,[15] the thiolated analogs upon neutralization decarboxylated to the corresponding dithioacids.† However, alkylation on sulfur stabilized the carboxylic function making isolation of **7** possible. This reaction represents the first synthetic pathway to 2-carboxydithioesters. Efforts of previous workers to prepare 2-carboxydithioesters through alkaline hydrolysis of 2-carboethoxydithioesters resulted in decarboxylation to dithioesters.[16]

Exploiting the instability of 2-carboxydithioesters in alkaline media, we readily prepared methyl dithioesters **8** through neutralization of **7**. Decarboxylation of **7** to **8** was also thermally induced at elevated temperatures. As a preparative method, distillation of the crude product **7** gave pure **8** (Table 1, Products 2, 5 and 8). The progress of decarboxylation was monitored by NMR using the proton resonances of the methyl thioester group of both **7** at δ 2.73 and its decarboxylated product **8** at δ 2.66 (Table 2). The first order decarboxylation rate constants for methyl 2-carboxydithiohexadecanoate and methyl 2-carboxydithiononanoate at 75° were 1.3 and 2.0×10^{-4} sec^{-1}, respectively.

Paralleling the carboxylate dianion reaction, the enolate ester **11** rapidly reacted with carbon disulfide at −75° to form the dithiosalt **12** (Scheme 2). Alkylation at the low temperature produced the stable methyl 2-carbomethoxydithioester **13** as the primary product (Table 1, Products 3 and 6). Attempts to obtain the methyl 2-carbomethoxydithioester **13** by diazomethane treatment of 2-carboxydithioester **7** produced a complex mixture of products that included the 2-carbomethoxy ketene mercaptal **14** in addition to **13**. Product **14** is presumably formed by the reaction of diazomethane with **13'**, the tautomeric form of **13** (eqn 3).

Compounds **13** and **14** were identified by their characteristic NMR resonances which are presented in Tables 2 and 3.‡

Table 1. Preparation of dithioesters[a]: $R-\underset{\displaystyle X}{\overset{\displaystyle R'}{\underset{|}{\overset{|}{C}}}}-CS_2CH_3$

	Starting material	Product R	R'	X	% Yield	B.P.
1.	Nonanoic acid	C_7H_{15}	H	CO_2H	88[b]	decarboxylates
2.	Nonanoic acid	C_7H_{15}	H	H	65[c,d]	90°/0.3 mm
3.	Methyl nonanoate	C_7H_{15}	H	CO_2CH_3	85[b]	
4.	2-Methylnonanoic acid	C_7H_{15}	CH_3	CO_2H	77[b]	decarboxylates
5.	2-Methylnonanoic acid	C_7H_{15}	CH_3	H	69[c,d]	85°/0.05 mm
6.	Methyl 2-methylnonanoate	C_7H_{15}	CH_3	CO_2CH_3	75[c]	117°/0.04 mm
7.	Hexadecanoic acid	$C_{14}H_{29}$	H	CO_2H	84[b](73)[c]	—[e]
8.	Hexadecanoic acid	$C_{14}H_{29}$	H	H	70[d]	

[a] All compounds gave satisfactory elemental analysis.

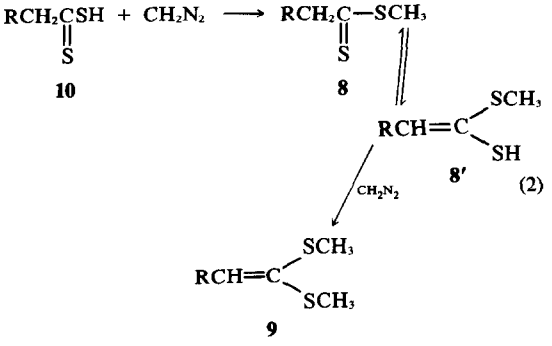
[b] Percent conversion based on both glc and nmr analysis.

[c] Percent isolated yield.

[d] Obtained from the decarboxylation of the corresponding 2-carboxy derivative.

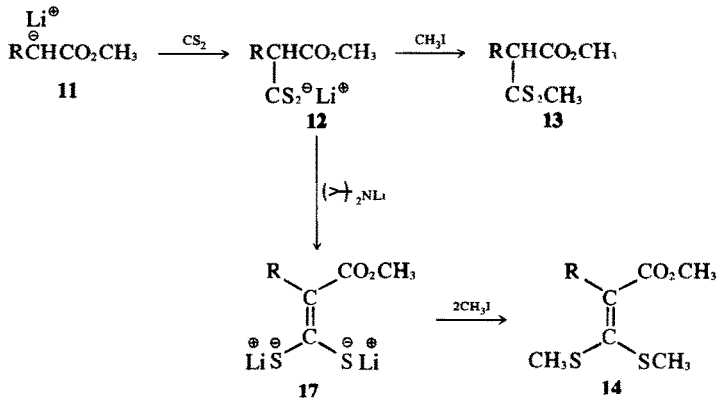
[e] Solid, m.p. 67-72°, decarboxylates.

†The unstable dithioacids **10** were not isolated. Esterification of the crude dithioacid product with ethereal diazomethane produced both dithioester **8** and ketene mercaptal **9** (eqn 2).



The products were readily differentiated by NMR analysis. The amounts of ketene mercaptal increased with additional diazomethane as indicated by eqn (2). Isolation of **9** was unsuccessful owing to its subsequent hydrolysis by the presence of water in the diazomethane reagent to its corresponding thiolester.

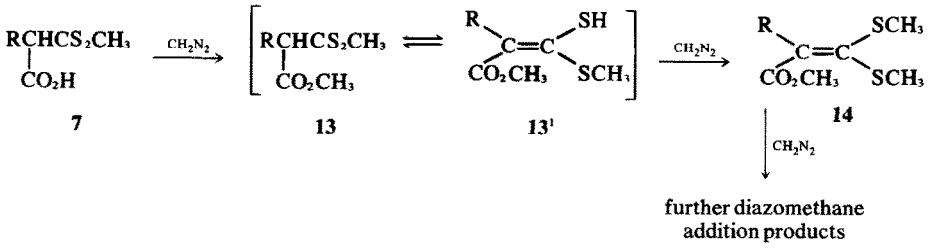
‡Further addition products are formed by reaction of diazomethane with the ketene mercaptal **14**. These are presumably the cyclopropane and pyrazoline derivatives which were also observed when diazomethane was added to pure **13** and **14**. Cyclopropane and pyrazoline derivatives have previously been reported as side products in the diazomethane esterification of unsaturated malonic acid derivatives.[15b]



Scheme 2.

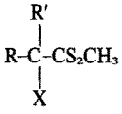
Ketene mercaptals. Small quantities of ketene mercaptal products **9** (Scheme 1) and **14** (Scheme 2) were present in the dithioester preparations. Since **9** and **14** presumably originated from the reaction of the enolic form of the carbon disulfide addition products **5** and **12**, it seemed likely that ketene mercaptals could be obtained under conditions favoring enolization.

For preparations of 2-carbomethoxyketene mercaptals (**14**, Scheme 2) ester enolates were preferred to carboxylate dianions as the starting material. Addition of a second equivalent of n-butyl-lithium to the reaction mixture containing the 2-carbomethoxy dithiolate salt **12** produced the dithiolate dianion **17** which reacted with two equivalents of alkyl halide to generate the carbomethoxy



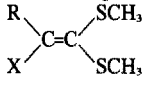
(3)

Table 2. Characteristic NMR absorptions of dithioesters:



Dithioesters	CS_2CH_3 δ, ppm	R′	δ, ppm	X	δ, ppm
Methyl 2-carboxydithiononanoate	2.73	H	4.27	CO_2H	11.42
Methyl dithiononanoate	2.66	H	3.10	H	3.10
Methyl 2-carbomethoxydithiononanoate	2.69	H	4.14	CO_2CH_3	3.70
Methyl 2-methyldithiononanoate	2.63	CH_3	1.35	H	3.24
Methyl 2-carbomethoxy-2-methyl-dithiononanoate	2.68	CH_3	1.65	CO_2CH_3	3.75

Table 3. Characteristic NMR absorptions of ketene mercaptals:



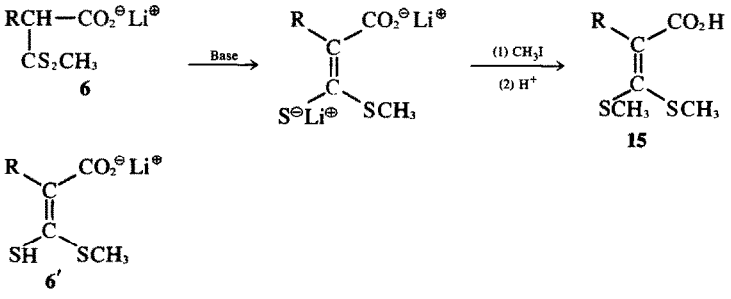
Ketene mercaptals	$(SCH_3)_2$ δ, ppm	X	δ, ppm
1,1-dimethylmercapto-2-carboxynon-1-ene	2.40, 2.37	CO_2H	10.5
1,1-dimethylmercaptonon-1-ene	2.25, 2.21	H	5.92
1,1-dimethylmercapto-2-carbomethoxynon-1-ene	2.35, 2.29	CO_2CH_3	3.80
1,1-dimethylmercapto-2-methylnon-1-ene	2.26	CH_3	2.07

ketene mercaptal **14** (Table 4, Products 3 and 6).† Refluxing **14** in alcoholic sodium hydroxide overnight‡ produced a mixture of 2-carboxyketene mercaptal **15** and its decarboxylated analog **9**. The conversion to **9** was completed by thermal decarboxylation of the mixture.

Various attempts at producing the 2-carboxyketene mercaptal **15** (eqn 4) resulted in low yields of the desired product (Table 4, Product 1).

SUMMARY

Addition products derived from α-anions of carboxylic acids or esters and carbon disulfide are excellent intermediates for the preparation of α-carboxylic and unsubstituted alkyl sulfur compounds. Thermal decarboxylation (50°) of the initially formed addition product of carboxylic acid dianion and carbon disulfide followed by alkylation leads to ketene mercaptals whereas low temperature alkylation of the same addition product prevents decarboxylation and permits isolation of the 2-



(4)

Table 4. Preparation of ketene mercaptals[a]: R–C(X)=C(SCH3)(SCH3)

	Starting material	Product R	Product X	% Yield
1.	Nonanoic acid	C_7H_{15}	CO_2H	40[b]
2.	Nonanoic acid	C_7H_{15}	H	54[b]
3.	Methyl nonanoate	C_7H_{15}	CO_2CH_3	97[b] (78)[c]
4.	2-Methylnonanoic acid	C_7H_{15}	CH_3	66[b] (53)[c]
5.	Hexadecanoic acid	$C_{14}H_{29}$	H	56[b]
6.	Methyl hexadecanoate	$C_{14}H_{29}$	CO_2CH_3	50[b,d]

[a]All compounds gave satisfactory elemental analyses.

[b]Percent conversion based on both glc and nmr analysis.

[c]Isolated yield.

[d]No attempt was made to optimize this yield.

Low temperature addition of one equivalent each of base and alkylating agent to **6** gave a mixture comprised of starting material (33%), methyl 2-carboxydithioester **7** (27%), and the desired 2-carboxy ketene mercaptal **15** (40%). The decarboxylated analog ketene mercaptal **9** (Scheme 1) was obtained by heating the dithiocarboxylate salt **5** with two equivalents of alkylating agent (Table 4, Products 2 and 5).

†Although we had not prepared the ketene mercaptal containing different alkyl substituents, it is evident that by the appropriate choice of R in the alcohol moiety of the ester and in the alkylating agent a wide variety of ketene mercaptals can be synthesized.

‡Shorter reflux times (2 hr) resulted in incomplete saponification with concurrent formation of **15** and **9**.

§Caution should be exercised in the use of HMPA since it has recently been implicated as a possible carcinogen (*Science* **190**, 422, 1975).

¶Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.

carboxyalkyldithioesters. Pure 2-carboxyalkyldithioesters may be quantitatively decarboxylated to alkyl dithioesters. Carbon disulfide addition products of ester enolates provide direct routes to the preparation of either pure 2-carbomethoxyketene mercaptals or 2-carbomethoxydithioesters through variations in the molar ratio of base and alkyl halide to the enolate.

EXPERIMENTAL

Materials. Dry, O_2-free THF was obtained by distillation from sodium and benzophenone under N_2 prior to use. HMPA§ was distilled at reduced pressure from Na and stored under N_2. n-BuLi (1.6 M in hexane soln) was obtained from Foote Mineral Company.¶ Diisopropylamine was distilled over calcium hydride and maintained under N_2. Isopropylcyclohexylamine was distilled at reduced pressure. CS_2 was freshly distilled at atmospheric pressure.

Analytical procedures. Conversions of carboxylic acids and esters to their CS_2 derivatives were determined by both GLC analyses and integration of NMR spectra. Analytical GLC was performed with an F & M Model 5750 gas chromatograph using 6'-1/8" stainless steel column with Supelco SP-2100 as the substrate. IR spectra were recorded on a Perkin Elmer 457 grating

spectrophotometer. NMR spectra were recorded on a Jeolco C-60H NMR spectrometer. The composition of the crude mixtures was determined by NMR since all of the compounds had at least one characteristic and unique NMR absorption (Tables 2 and 3). The alkylation of the dithiocarboxylate salt **5** produced four products† after neutralization: **7**, **8**, **9** and **15**. Integration of each of the methyl dithiolate absorptions gives the ratio of the four products. Combining these ratios with the integration of the carboxylic hydrogen gives the percent yield of each of the products. An alternate check of the yield is provided by integration of the α-H's of **7**, **8** and **9**.

I. *Preparation of dithioesters*

(a) *Methyl 2-carboxydithiohexadecanoate.* Anhyd THF (175 ml) and diisopropylamine (2.74 ml, 21 mmol) were added to a dry flask flushed with N_2 and cooled to −50° by means of a dry ice-acetone bath. *n*-BuLi (13.13 ml, 21 mmol) was added followed by hexadecanoic acid (2.56 g, 10 mmol) and HMPA (1.8 ml, 10 mmol) in 25 ml of THF while the temp. was maintained at −50°. Dianion formation was completed by heating the soln to 35° for 30 min. The soln was cooled to −30° and CS_2 (0.665 ml, 11 mmol) was added and allowed to react for 10 min. The soln was cooled to −50° and MeI (0.619 ml, 10 mmol) was added. The temp. of reaction was maintained at −50° for 30 min. The mixture was acidified with dil. HCl at −50° with rapid increase in temp. The water layer was separated and extracted three times with petroleum ether. The combined organic layers were washed with dil. HCl, then H_2O, dried over anhyd Na_2SO_4, and the solvent was removed at ambient temp. by rotary evaporation to give 3.30 g of a yellow solid. Analysis of the NMR spectrum (Table 2) indicated a 75% yield of methyl 2-carboxydithiohexadecanoate. The crude mixture showed, by GLC analysis, hexadecanoic acid (11%), methyl dithiohexadecanoate (84%) (thermal decarboxylation product) and 1,1-dimethylmercaptohexadec-1-ene (3%). The product was crystallized from $CHCl_3$ (20 ml) to give pure methyl 2-carboxydithiohexadecanoate 2.54 g, 73% yield; m.p. 67–72°, (decarboxylates); IR (cm^{-1}, CCl_4): 3400–3000 (OH), 1710 (C=O) 1200–1300; NMR (TMS, CCl_4): δ 2.73 (s, 3, SCH_3), 4.28 (t, 1, αH), 11.40 (br s, 1, OH). (Found: C, 62.60; H, 10.17; S, 17.88. Calc. for $C_{18}H_{34}O_2S_2$: C, 62.43; H, 9.83; S, 18.50%).

(b) *Preparation of methyl dithiononanoate.* Methyl 2-carboxydithiononanoate was prepared in a reaction similar to the preparation of methyl 2-carboxydithiohexadecanoate as described in I (a) except the reaction temp. was maintained at −75° throughout. Acidification of the mixture followed by the usual workup procedure gave an orange oil. The NMR spectrum indicated the presence of methyl 2-carboxydithiononanoate (76%), methyl diisopropyldithiocarbamate (13%) and 1,1-dimethylmercapto-2-carboxynon-1-ene (10%).

1. The methyl 2-carboxydithiononanoate was decarboxylated by heating the reaction mixture at 125° for 15 min prior to distillation (90°/0.3 mm) of the methyl dithiononanoate (64% yield based on nonanoic acid) IR (cm^{-1}, CCl_4): 1190, 1230; NMR (TMS, CCl_4): δ 2.66 (s, 3, SCH_3), 3.10 (t, 2, α-CH_2). (Found; C, 59.18; H, 9.88; S, 31.11. Calc. for $C_{10}H_{20}S_2$: C, 58.82; H, 9.80; S, 31.37%).

2. Decarboxylation of methyl 2-carboxydithiononanoate also occurred upon room temp. neutralization of the crude mixture with 0.1 N NaOH. Extraction with petroleum ether followed by drying over Na_2SO_4 and elution through a silicic acid column produced pure methyl dithiononanoate (66% yield).

(c) *Preparation of methyl 2-carbomethoxy-2-methyldithiononanoate.* Isopropyl cyclohexylamine (1.00 ml, 5.5 mmol) and n-BuLi (3.43 ml, 5.5 mmol) was added to THF (50 ml) at −75° followed by addition of methyl 2-methylnonanoate (0.93 g, 5 mmol) and the temp. was maintained for 30 min. CS_2 (0.331 ml, 5.5 mmol) was introduced and, after a reaction time of 30 min at −75°, was followed by the addition of MeI (0.339 ml, 5.5 mmol), while the temp. of the mixture was maintained at −75° for 1 hr. A light yellow ppt formed which was filtered from the mixture. The filtrate was acidified with dil HCl, followed by the usual workup procedure to give a yellow-orange oil, 1.35 g. NMR analysis of the crude mixture indicated complete reaction to the expected product. Distillation of the crude product at 117°/0.04 mm gave methyl 2-carbomethoxy-2-methyldithiononanoate (85% yield), IR (cm^{-1}, CCl_4): 1740 (C=O), 1130–1140, 1230; NMR (TMS, CCl_4): δ 1.65 (s, 3, α-CH_3), 2.68 (s, 3, SCH_3), 3.75 (s, 3, OCH_3). (Found: C, 54.20; H, 9.07; S, 24.20. Calc. for $C_{12}H_{24}O_2S_2$: C, 54.54; H, 9.09; S, 24.24%).

II. *Preparation of dialkyl ketene mercaptals*

(a) *Preparation of 1,1-dimethylmercaptohexadec-1-ene.* The dianion was prepared as described in **1a**. The mixture was cooled to −50° for the addition of CS_2 (0.665 ml, 11 mmol) and then heated to 50° for 2 hr to decarboxylate the intermediate dithiocarboxylate salt. MeI (1.86 ml, 30 mmol) was added at −50° followed by heating to 50° for an additional 2 hr. Acidification of the mixture followed by the usual workup procedure resulted in 3.2 g reddish oil. NMR analysis indicated the mixture to be composed of hexadecanoic acid (7%), methyl 2-carboxydithiohexadecanoate (9%), methyl dithiohexadecanoate (28%), and 1,1-dimethylmercaptohexadec-1-ene (56%).

(b) *Preparation of 1,1-dimethylmercapto-2-carbomethoxynon-1-ene.* Anion formation was completed as in **1c**. CS_2 (0.663 ml, 11 mmol) was added at −75° for 30 min. Additional n-BuLi (6.8 ml, 11 mmol) was added, and the soln was stirred for 15 min, followed by the addition of MeI (1.50 ml, 22 mmol). The soln was stirred for 18 hr at room temp. Work up by acidification and extraction as above gave 2.8 g of crude product. GLC analysis showed 1,1-dimethylmercapto-2-carbomethoxynon-1-ene (97% conversion). Purification was accomplished by elution from a silica gel column with petroleum ether-methylene chloride (50/50) to give a 78% isolated yield of 1,1-dimethylmercapto-2-carbomethoxynon-1-ene. IR (cm^{-1}, CCl_4) 1730 (C=O), 1135, 1270; NMR (TMS, CCl_4) δ 2.30 (s, 3, SCH_3), 2.35 (s, 3, SCH_3), 3.80 (s, 3, OCH_3). (Found: C, 56.46; H, 8.87, S, 23.46. Calc. for $C_{13}H_{24}O_2S_2$: C, 56.52; H, 8.70; S, 23.19%).

†In the carboxylic acid reactions (Scheme 1) in which lithium diisopropyl amide is used as the base, CS_2 reacts also with the released amine as well as with the carboxylate dianion. Consequently, the addition of MeI to the mixture generates the methyl diisopropyldithiocarbamate [$(\diagup\!\diagdown)_2N$–CS_2CH_3] as a side product. The carbamate is detected in the NMR spectrum of the crude reaction mixture by the methyl dithioate absorption at δ 2.57 and the diisopropyl absorptions at δ 1.45 and 1.55.

REFERENCES

[1] M. J. Janssen, *The Chemistry of Carboxylic Acids and Esters* (Edited by S. Patai), Chap. XV, pp. 746–764. Wiley-Interscience, New York, (1969).

[2] L. Dalgaard, L. Jensen and S. O. Lawesson, *Tetrahedron* **30**, 93 (1974).

[3] P. Yates, D. R. Moore and T. R. Lynch, *Can. J. Chem.* **49**, 1456 (1971).

[4] F. C. V. Larsson and S. O. Lawesson, *Tetrahedron* **28**, 5341 (1972).

[5a] R. Mayer, S. Scheithauer and D. Kunz, *Chem. Ber.* **99**, 1393 (1966); [b] K. A. Jensen and C. Pedersen, *Acta Chem. Scand.* **15**, 1087 (1961); [c] J. Houben and K. M. L. Schultze, *Ber. Dtsch. Chem. Ges.* **43**, 2481 (1910); [d] J. Houben and K. M. L. Schultze, *Ibid.* **44**, 3226 (1911); [e] J. Houben and H. Pohl, *Ibid.* **40**, 1725 (1907).

[6a] S. A. Karjala and S. M. McElvain, *J. Am. Chem. Soc.* **55**, 2966 (1933); [b] C. S. Marvel, P. deRadzitzky and J. J. Broder, *Ibid.* **77**, 5997 (1955).

[7] H. Eilingsfeld, M. Seefelder and H. Weidinger, *Chem. Ber.* **96**, 2671 (1963).

[8a] A. Thuillier and J. Vialle, *Bull. Soc. Chim. Fr.* 2182 (1962); [b] R. Gompper and T. Werner, *Chem. Ber.* **95**, 2861 (1962); [c] R. Gompper and H. Schaefer, *Ibid.* **100**, 591 (1967).

[9] W. E. Truce, J. E. Tracy and M. L. Gorbaty, *J. Org. Chem.* **36**, 237 (1971).

[10a] A. Thuillier and J. Vialle, *Bull. Soc. Chim. Fr.* 1398 (1959); [b] M. Saquet and A. Thuillier, *Ibid.* 1582 (1966); [c] P. Rioult and J. Vialle, *Ibid.* 4477 (1968).

[11]L. Dalgaard, H. Kolind-Andersen and S. O. Lawesson, *Tetrahedron* **29**, 2077 (1973).
[12a]P. Yates, T. R. Lynch and D. R. Moore, *Can. J. Chem.* **49**, 1467 (1971); [b]P. Yates and T. R. Lynch, *Ibid.* **49**, 1477 (1971).
[13a]E. Rothstein, *J. Chem. Soc.* 1550 (1940); [b]E. Rothstein, *Ibid.* 1553 (1940).
[14]I. Shahak and Y. Sasson, *Tetrahedron Letters No.* **43**, 4207 (1973).
[15a]P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, *J. Org. Chem.* **37**, 451 (1972); [b]D. A. Konen, P. E. Pfeffer and L. S. Silbert, *Ibid.* **40**, 3253 (1975).
[16]P. V. Laakso, *Suomen Kemistilehti* **17B**, 1 (1944).