REVIEWS

Umpolung of the Reactivity of Carbonyl Compounds Through Sulfur-Containing Reagents

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The synthetic usefulness of the umpolung of the reactivity of carbonyl compounds by reaction of sulfur-containing reagents is discussed. Firstly, hydrolysis and other reactions of *S,S*-acetals (mainly 1,3-dithianes) and vinyl sulfides are described. The second part is concerned with the reactions of other sulfur-containing reagents such as derivatives of vinyl sulfides, ketene *S,S*-acetals and derivatives, etc. Finally the applications of the methods to the syntheses of natural products are briefly mentioned.

Es wird die Umpolung der Reaktivität von Carbonyl-Verbindungen durch Umsetzung von schwefelhaltigen Reagenzien diskutiert. Der erste Teil beschreibt die Hydrolyse und andere Reaktionen von *S,S*-Acetalen (hauptsächlich 1,3-Dithianen) und Vinyl-sulfiden. Der zweite Teil behandelt Reaktionen anderer schwefelhaltiger Reagenzien wie z. B. von Vinyl-sulfid- und Keten-*S,S*-acetal-Derivaten. Zum Abschluß wird der Einsatz dieser Methoden für die Synthese von Naturstoffen kurz erwähnt.

1. Introduction

Several years ago we described[1] in a review article a method which uses lithiated 1,3-dithianes and 1,3,5-trithianes as nucleophilic acylating agents[2,3,4,5]. This procedure allows the normal reactivity of acyl carbon atoms, which combine only with nucleophiles *(Nu)*, to be reversed. As shown in column 1 of Table 1, the same reactivity at C-3, C-5 ... C-(2n + 1) in the skeleton of a carbonyl compound is found while the alternate carbon atoms [C-2, C-4 ... C-(2n)] react with electrophiles *(E)*; as a notation for this affinity pattern we proposed[6-8] the use of the terms $N^{1,3}$...- and $E^{2,4}$...-reactivity, respectively. Reversal in each of these cases leads to the pattern shown in the second column of Table 1, where nucleophilic acyla-

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[1] D. Seebach, *Synthesis* **1969**, 17.

[2] D. Seebach, *Angew. Chem.* **81**, 690 (1969); *Angew. Chem. Int. Ed. Engl.* **8**, 639 (1969).

[3] E. J. Corey, D. Seebach, *Angew. Chem.* **77**, 1134, 1135 (1965); *Angew. Chem. Int. Ed. Engl.* **4**, 1075, 1077 (1965). D. Orth, *Merck Kontakte* **1**, 29 (1973).

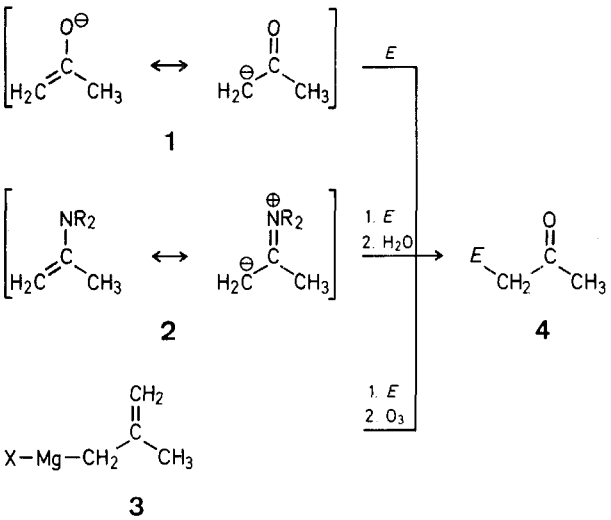
[4] D. Seebach, E. J. Corey, A. K. Beck, *Chem. Ber.* **107**, 367 (1974).

[5] D. Seebach, E. J. Corey, *J. Org. Chem.* **40**, 231 (1975).

[6] First used at a lecture, given in the University of Hamburg, July 7, 1972; see als ref. 2 and D. Seebach, M. Kolb, *Justus Liebigs Ann. Chem.* **1977**, in press.

[7] D. Seebach, K. H. Geiß, *J. Organometal. Chem.* Library 1, D. Seyferth, Ed., Elsevier, Amsterdam, 1976, p. 1–92.

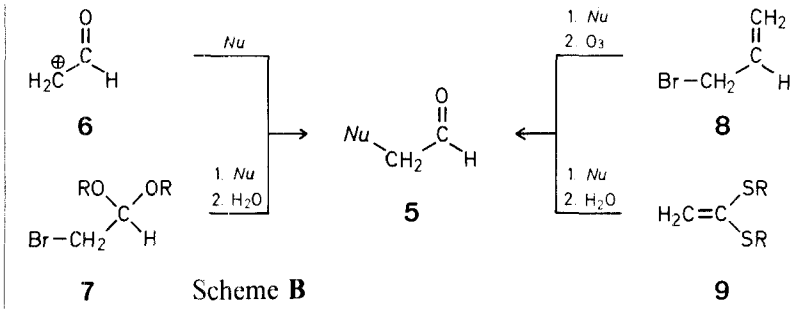
tion (E^1-reactivity) is only the first case of a homologous series of alternating reactivity along the carbon chain. The first examples of N^2- and E^3-reactivity were reported in our previous account[1]. We have proposed[2,5–8] the use of the term *Umpolung* for this inversion of reactivity. This term[9] has also been accepted for use in English[10,11,12]. It is clear that species with reactivity umpolung such as acyl anions (E^1), enolate cations (N^2, electrophilic enolates), and homoenolate anions (E^3) are not generally available as such. Disguised forms are used for which the words *potential*, *protected*, *modified*, *activated*, *masked*, *blocked*, *hidden*, and *latent* appear in the literature.



Scheme A

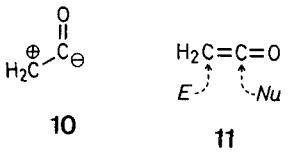
We have used and propose herewith the exclusive use of *masked* for those reagents which provide an *umpolung* of normal reactivity of a functional derivative. Thus, the enamine **2** and the Grignard reagent **3** may be employed as precursors of the product **4** which is normally obtained from an enolate **1**; **2** and **3** are thus *potential* or *latent*[13] enolates (Scheme **A**).

On the other hand, the elusive enolate cation **6**[14] would give the product **5**, which can also be made from the bromoacetal **7**, from allyl bromide **8**, or from the ketene *S,S*-acetal **9** as indicated in Scheme **B**; compounds **7**, **8**, and **9** are thus *masked* electrophilic enolates.

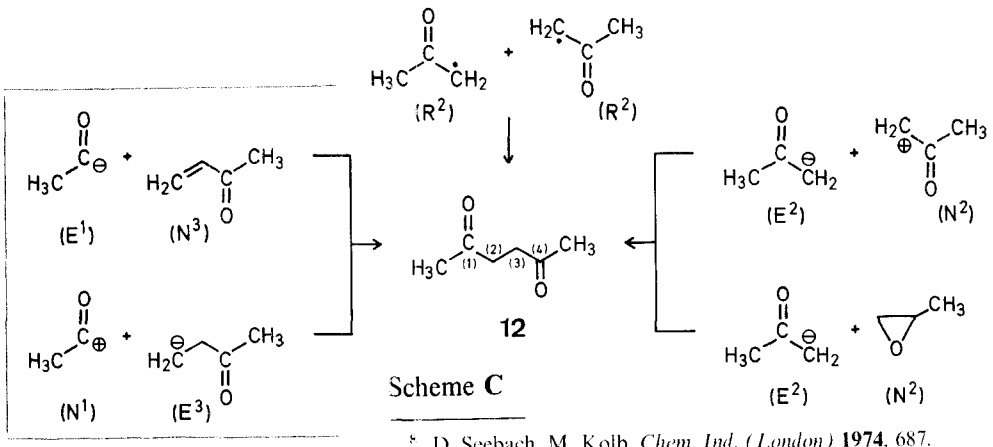


Scheme **B**

As shown by formula **10**, ketene *S,S*-acetal (**9**) can be viewed as an acyl anion at the same time and thus as ketene **11** with umpolung of both carbons (E^1, N^2).



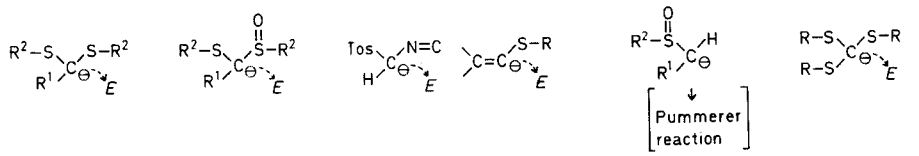
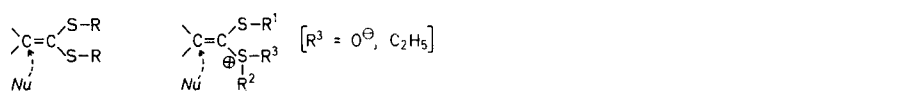
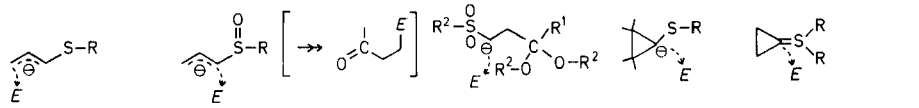
It is important to realize that whenever we want to create a [1,(2n)]-relationship (even) of functional groups in a carbonyl derivative – and this is true for other functionalities as well[15] – we have to use one component with reactivity umpolung. Examples are provided by the several modes of preparation of the 1,4-diketone **12**. This is an important problem for the synthesis of hydroxycyclopentanones and cyclopentenones[16,17]. In addition to the polar processes which use E- and N-affinities, radical type coupling can also be applied[18,19] (Scheme **C**).



Scheme **C**

[8] D. Seebach, M. Kolb, *Chem. Ind. (London)* **1974**, 687.
[9] Annual Survey in *Nachr. Chem. Techn.* **23**, 69 (1975).
[10] Highlights in *Chem. Ind. (London)* **1974**, 910.
[11] E. J. Corey, *Pure Appl. Chem.* **14**, 19 (1967).
[12] D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **7**, 147 (1974).
[13] D. Lednicer, *Advan. Chem.* **8**, 179 (1972).
[14] M. Charpentier-Morize, *Bull. Soc. Chim. Fr.* **1974**, 343.
[15] D. Seebach, D. Enders, *Angew. Chem.* **87**, 1 (1975); *Angew. Chem. Int. Ed. Engl.* **14**, 15 (1975); *New Synthetic Methods* **2**, 65 (1975).

Table 1. Reactivity of Carbonyl Compounds towards Nucleophiles (N^n) and Electrophiles (E^n)

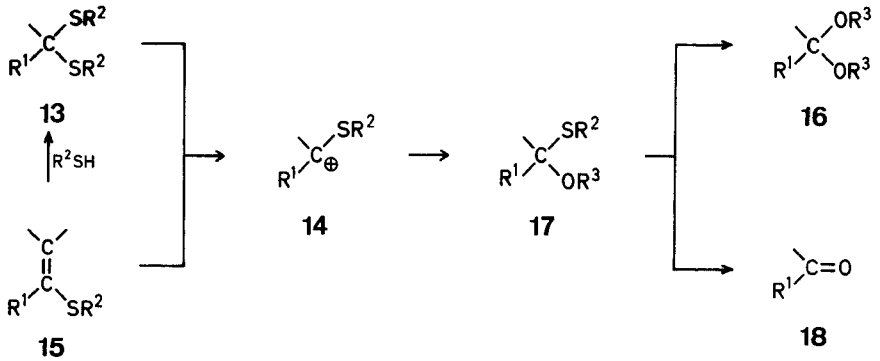
Normal reactivity	Reactivity with Umpolung	Sulfur-Containing Reagents with Carbonyl Reactivity Umpolung
N^1	E^1	
E^2	N^2	
N^3	E^3	
E^4	N^4	
N^5	E^5	

The versatile chemistry of sulfur compounds is well suited to provide masked reagents with carbonyl umpolung (Table 1, middle column). The possibilites are listed in the right-hand column and will be the subject of the following sections. The progress in this field since our last reviews[1,2] is so vast that the present report cannot cover all the work done. We have recently given a brief account including carbonyl umpolung with non-sulfur-reagents[8]. The general usefulness of sulfur compounds in organic synthesis was outlined in special reviews[20,21,22] and the exploitation of sulfur-heterocycles in an excellent book[23]. A summary on the subject "α-neutral hetero-atom-substituted organometallic compounds" covering the literature until June 1971 has also appeared[24].

2. Hydrolysis of *S,S*-Acetal and Vinyl Sulfide Derivatives and other Desulfurization Reactions

As can be seen from the types of reagents employed for carbonyl umpolung in Table 1, most methods require the hydrolysis of an *S,S*-acetal derivative or a vinyl sulfide to give the carbonyl product. This step was, and partially still is, a crucial one in the minds of many chemists; we therefore devote a large section to this topic. Other desulfurizations are included because the α-sulfur anions used are such excellent nucleophiles in carbon-carbon-bond forming reactions that they are now widely used even when the synthetic target is not a carbonyl compound.

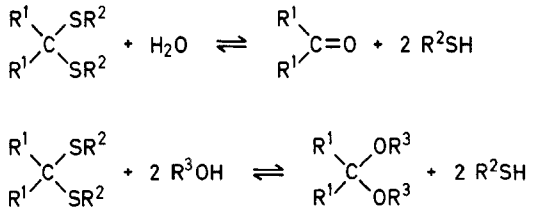
In both the *S,S*-acetal **13** and the vinyl sulfide **15** solvolysis, a hemiacetal or *O,S*-acetal **17** is formed through the carbenium ion **14** (Scheme **D**).



Scheme **D**

[16] R. A. Ellison, *Synthesis* **1973**, 397.
[17] T.-L. Ho, *Synth. Commun.* **4**, 265 (1974).
[18] M. S. Kharasch, H. C. McBay, W. A. Urry, *J. Am. Chem. Soc.* **70**, 1269 (1948).
[19] F. Beck, *Elektroorganische Chemie*, Verlag Chemie, Weinheim, 1974, p. 241–242.
D. Koch, H. Schäfer, E. Steckhan, *Chem. Ber.* **107**, 3640 (1974).
[20] E. Block, *J. Chem. Educ.* **48**, 814 (1971).
[21] J. M. Brown, *Chem. Ind. (London)* **1972**, 454.

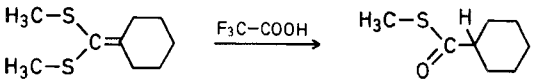
The desired final products are acetals **16** (formed especially instead of free aldehydes in alcoholic solvents) or carbonyl compounds **18** (water). The problem is that the equilibria shown in the Scheme **E** lie far to the left.



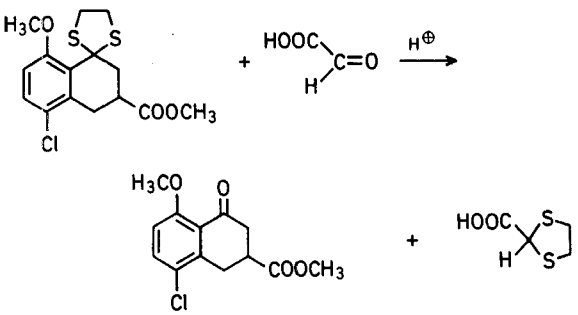
Scheme **E**

Therefore, only irreversible removal of the thiol or of the solvolysis products can push it to the right[25]; the same is true for the vinyl derivatives **15**, the acidic hydrolysis[26] of which should actually lead to 50% carbonyl compound and 50% *S,S*-acetal[27]; likewise, ketene *S,S*-acetals (**15**, $R^1 = SR^2$) and trithorthocarboxylates (**13**, $R^1 = SR^2$) do not easily hydrolyze to sulfur-free compounds under acidic conditions[28] (the hydrolysis normally stops at the *S*-ester[26i, 29]). The irreversible removal of thiol in these hydrolyses can be brought about by one of the following methods: blowing away of volatile, low molecular weight thiols (CH_3SH, C_2H_5SH)[30], transacetalization to a highly reactive carbonyl derivative, formation of a transition metal thiolate (Ti, Cu, Ag, Cd, Hg), oxidation to a higher oxidation state of sulfur, and alkylation to a sulfide. Most of these tricks go back to E. Fischer[31] who used 5% HCl, $HgCl_2$, $AgNO_3$, Br_2, and HNO_2 on his sugar ethyl *S,S*-acetals and to Holmberg[32, 33] who introduced $CdSO_4$, J_2, and the mercaptan transfer to formaldehyde and glyoxylic acid.

2.1. Acidic Hydrolysis and Transacetalization



Acid Hydrolysis of Ketene *S,S*-Acetals[29c]:
Procedure: see *Synthesis* **1975** (7), 461.



5-Chloro-8-methoxy-3-methoxycarbonyl-1-tetralone from its Ethanediyl *S,S*-Acetal[25b]:
Procedure: see *Synthesis* **1976** (10), 695.

2.2. The Transition Metal-Induced Hydrolysis

Among the metals mentioned above, mercury is still used most. Since 1969[1] many papers have been published which demonstrate that this method is compatible with sensitive groups such as those of acyloin, aldol, α,β-unsaturated carbonyl, olefinic double bond, three- and four-membered ring, and enol ether moieties. Table 2 contains examples with leading references to *S,S*-acetal and vinyl sulfide[74] hydrolyses involving mercury(II). We would like to mention a few points about this hydrolysis which are often not taken into account by various workers.

(a) During the hydrolyses the reaction mixture becomes acidic[34b, 75].

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22 L. Field, *Synthesis* **1972**, 101.
P. Neumann, F. Vögtle, *Chem. Ztg.* **98**, 138 (1974); **99**, 308 (1975).

23 A. I. Meyer, *Heterocycles in Organic Synthesis*, J. Wiley & Sons, New York, 1974.

24 D. J. Peterson, *Organometal. Chem. Rev. Sect. A* **7**, (1972) 295.

25 B. K. Koe, W. D. Celmer, *J. Med. Chem.* **7**, 705 (1964).

26 (a) S. Bernstein, L. Dorfman, *J. Am. Chem. Soc.* **68**, 1152 (1946).
(b) G. Rosenkranz, S. Kaufmann, J. Romo, *J. Am. Chem. Soc.* **71**, 3689 (1949).
(c) J. Romo, M. Romero, C. Djerassi, G. Rosenkranz, *J. Am. Chem. Soc.* **73**, 1528 (1951).
(d) G. Wittig, M. Schlosser, *Chem. Ber.* **94**, 1373 (1961).
(e) R. F. Church, R. E. Ireland, J. A. Marshall, *J. Org. Chem.* **27**, 1118 (1962).
(f) R. L. Clarke, *J. Org. Chem.* **28**, 2626 (1963).
(g) B. S. Kupin, A. A. Petrov, *Zh. Org. Khim.* **3**, 975 (1967); *C. A.* **67**, 99786 (1967).
(h) T. Mukaiyama, S. Fukuyama, T. Kumamoto, *Tetrahedron Lett.* **1968**, 3787.
(i) G. A. Russel, L. A. Ochrymowycz, *J. Org. Chem.* **35**, 764 (1970).
(j) E. J. Corey, B. W. Erickson, R. Noyori, *J. Am. Chem. Soc.* **93**, 1724 (1971).

27 Cf. the ready addition of a thiol **15**→**13**.
(a) M. M. Campos, H. Hauptmann, *J. Am. Chem. Soc.* **74**, 2962 (1952).
(b) K.-H. Geiß, B. Seuring, R. Pieter, D. Seebach, *Angew. Chem.* **86**, 484 (1974); *Angew. Chem. Int. Ed. Engl.* **13**, 479 (1974).
K.-H. Geiß, B. Seuring, D. Seebach, *Chem. Ber.* in press.
(c) A. J. Mura, G. Majetich, P. A. Grieco, T. Cohen, *Tetrahedron Lett.* **1975**, 4437.

28 (a) I. Shahak, Y. Sasson, *Tetrahedron Lett.* **1973**, 4207.
(b) P. F. Juby, W. R. Goodwin, T. W. Hudyma, *U.S. Patent* 3717661; *C. A.* **79** 18493 (1973).

29 (a) G. L. Hekkert, W. Drenth, *Recl. Trav. Chim. Pays-Bas* **80**, 1285 (1961).
(b) J. A. Marshall, J. L. Belletire, *Tetrahedron Lett.* **1971**, 871.
(c) D. Seebach, R. Bürstinghaus, *Synthesis* **1975**, 461.

30 See 26a, 26d, 26g, 26h, 26i, 26j, 28a, 29c.

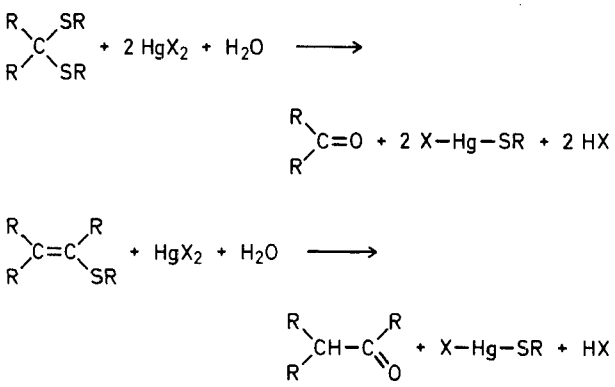
31 E. Fischer, *Ber. Dtsch. Chem. Ges.* **27**, 673 (1894).

32 B. Holmberg, *J. Prakt. Chem.* **135**, 57 (1932).

33 B. Holmberg, *Ark. Kemi, Mineral. Geol.* **A 15** No 2211 (1942); *C. A.* **38**, 2945 (1944).

34 (a) D. Seebach, M. Kolb, R. Bürstinghaus, B.-T. Gröbel, *Chem. Ber.* in press.
(b) E. J. Corey, B. W. Erickson, *J. Org. Chem.* **36**, 3553 (1971).

35 W. D. Woessner, R. A. Ellison, *Tetrahedron Lett.* **1972**, 3735.



The reactions can be carried out under neutral conditions if the acid formed is removed by use of additives such as calcium carbonate[34,35], barium carbonate[76], cadmium carbonate[77], or mercury(II) oxide[78].

(b) Aldehydes normally give acetals[79] under neutral and acidic conditions even in aqueous alcohols[1,72]; if ketone acetals are the desired products, use of absolute methanol in the presence of some trimethyl orthoformate is advisable[1].

(c) Excess mercury(II) can be disastrous in the presence of double bonds within the substrate molecule (N.B. if insoluble mercury(II) oxide is used for neutralization, soluble mercury(II) salt is formed!); therefore only a slight excess over the 1:1-ratio for Hg(II): SR should be used.

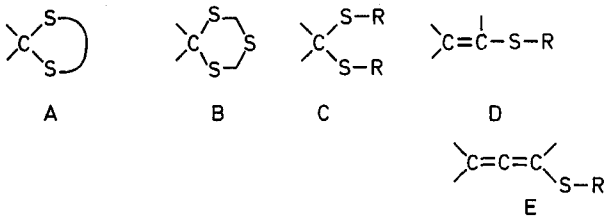
(d) A new procedure[45] which uses mercury(II) oxide/boron trifluoride, is suitable for sensitive substrates.

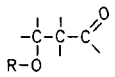
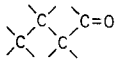
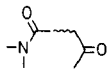
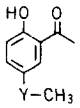
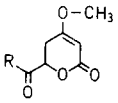
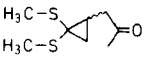
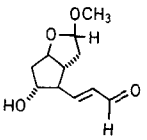
(e) All types of thioacetals can be hydrolyzed by the mercury(II)-method except for 1,2-dicarbonyl derivatives $(RS)_2C(COR)R$[80].

There are only a few examples in which ketene *S,S*-acetals[81,82] and trithiocarbonates[83-86] are reported to have been hydrolyzed by this method. Other metals have the advantage of being less poisonous than mercury. Silver(I) [as nitrate[26k,52,54], perchlorate[87], or oxide[88]] is mainly used for *S,S*-acetals containing double bonds[54,87,88] and vinyl sulfides[26k], copper(II) was applied to *S,S*-acetal[89a-d] and vinyl sulfide hydrolyses[89e,f], and titanium(IV) chloride to the conversion of phenyl[64,90-92] and methyl vinyl sulfides[93].

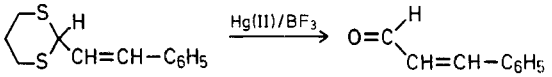
Table 2. Mercury(II) Hydrolyses and Alcoholyses of *S,S*-Acetals, Vinyl Sulfides, and Allenyl Sulfides to give Acid- or Lewis Acid-Sensitive Functional Compounds

Precursors:

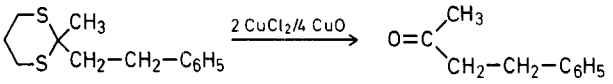


Functionality in hydrolysis product	Precursor	Reference
	A C D	34-38 39 40, 41
	A B C D	35, 37, 38, 44-47 4 39 40, 42, 43
	A D	34, 48, 49, 50 26k, 51, 52, 53, 26b
	A	34, 54, 55
 X = =O X = -OH	A A	34, 56, 57 34, 56, 57
	A	58, 59
	A	60
	A	61, 62
	A C	63 64
	A	65b
	A C	1, 66, 67 68
	A C D	1 69, 70 43, 71, 72
	A	45
	D	73

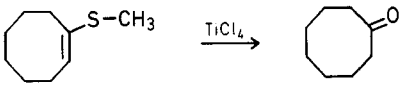
36 J. A. Katzenellenbogen, S. B. Bowlus, *J. Org. Chem.* **38**, 627 (1973).
37 H. Paulsen, H. Redlich, *Chem. Ber.* **107**, 2992 (1974).
38 H. Paulsen, W. Stenzel, *Chem. Ber.* **107**, 3020 (1974).
39 H. Zinner et al., *Chem. Ber.* **92**, 3151 (1959), and literature cited therein.
40 K. Oshima et al., *J. Am. Chem. Soc.* **95**, 2694 (1973).
41 J. H. S. Weiland, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **79**, 1293 (1960).
42 H. J. Bestmann, J. Angerer, *Tetrahedron Lett.* **1969**, 3665.
43 J. M. J. Tronchet, S. Jaccard-Thorndahl, B. Baehler, *Helv. Chim. Acta*, **52**, 817 (1969).
44 J. B. Jones, R. Grayshan, *Can. J. Chem.* **50**, 1414 (1972).
45 E. Vedejs, P. L. Fuchs, *J. Org. Chem.* **36**, 366 (1971).
46 S. Torii, K. Uneyama, M. Isihara, *J. Org. Chem.* **39**, 3645 (1974).
47 S. Rozen, J. Shahak, E. D. Bergmann, *Tetrahedron Lett.* **1972**, 1837.



Mercury(II) Hydrolysis of 1,3-Dithianes; Typical Procedure[45]:
Red mercury(II) oxide (20 mmol), boron trifluoride etherate (20 mmol), and 15% aqueous tetrahydrofuran (23 ml) are stirred vigorously in a three-necked flask fitted with a dropping funnel and a nitrogen inlet tube. The dithiane (2.28 g, 10 mmol), dissolved in the minium amount of tetrahydrofuran, is added via the dropping funnel within 10–15 min under nitrogen and stirring is continued for 10–20 min. During this period, the red mercury(II) oxide gradually dissolves and a white precipitate appears. The hydrolysis is carried out at room temperature. Ether (2 vol) is added, the precipitated salts are filtered, and the ether is washed to pH 10 with saturated sodium carbonate and to neutrality with saturated sodium chloride solutions. After drying over magnesium sulfate, the ether is evaporated in vacuo; crude yield of N.M.R.-homogeneous aldehyde: 86%.



Copper(II) Hydrolysis of 1,3-Dithianes; Typical Procedure[89a]:
A mixture of the dithiane (5 mmol), copper(II) chloride (10 mmol), copper(II) oxide (20 mmol), and aqueous 99% acetone (50 ml) is refluxed for 1 h. The precipitate is filtered off and the filtrate is concentrated under reduced pressure. Ether is added to the residue and the resulting precipitate is filtered off. The filtrate is distilled to give benzylacetone; yield: 93%.



Titanium(IV) Chloride Hydrolysis of 1-Methylthiocyclooctene[93]:
To the yellow solution of titanium(IV) chloride (5.9 g, 30 mmol) in acetic acid (40 ml) is added with stirring from a syringe 1-methylthiocyclooctene (2.34 g, 15 mmol) at room temperature. After 20 min water (1.1 ml, 60 mmol) is added and, after 4 h, chloroform (200 ml) and water (200 ml) are added. The organic layer is separated, washed with sodium hydrogen carbonate and sodium chloride, the solvent distilled off, and the residue distilled to give the ketone; yield: 1.51 g (80%); b.p. 120–125° (bath)/25 torr; m.p. 41°.

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2.3. Oxidative and Alkylative Hydrolysis of *S,S*-Acetals

The principle behind these methods is to render the sulfur moiety in the *S,S*-acetal a better leaving group, e.g. **13**→**19** or **20** (Scheme **F**), and to remove the thiol irreversibly by converting it to other sulfur derivatives. A typical example is the hydrolysis of the *S*-oxide **19** under mild acidic conditions to give the disulfide and the carbonyl compound[94,95]. This

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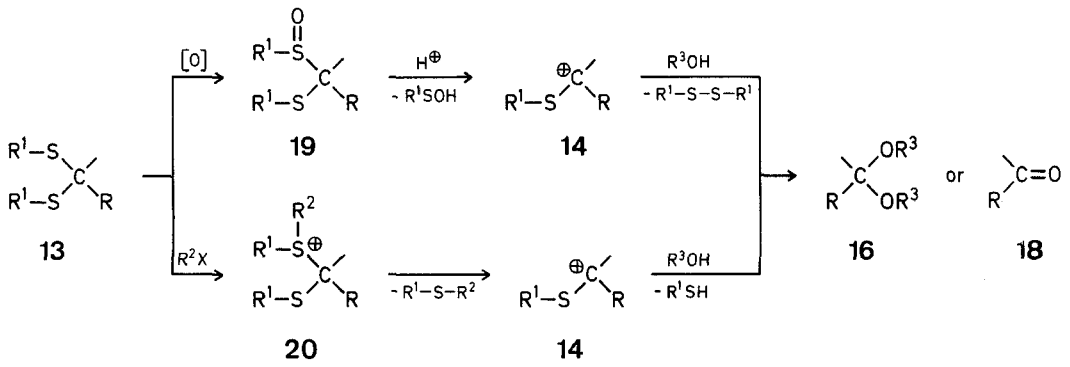
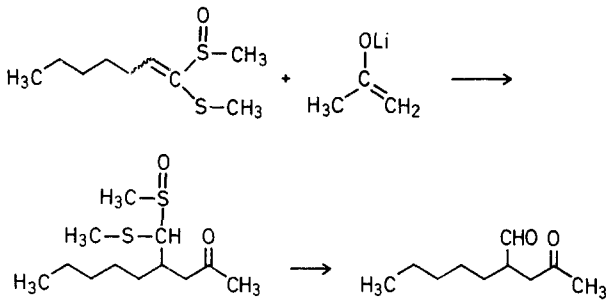


Scheme F

reaction is mechanistically well understood[96]; bis-sulfoxides and sulfones of *S,S*-acetals are stable under these conditions[96], but can be hydrolyzed with base[97].



4-Formyl-2-nonanone from 1-Methylsulfinyl-1-methylthio-1-heptene and Acetone[34a]**:**

Neat acetone (1.68 g, 29 mmol) is added to a stirred solution of lithium diisopropylamide (29 mmol) in tetrahydrofuran (60 ml) and *n*-hexane (20 ml) at −78°. After 30 min a 1:1-mixture of tetrahydrofuran and the ketene *S,S*-acetal *S*-oxide (6.00 g, 90% pure, 26.1 mmol, 5:1-*E*/*Z*-mixture) is added all at once. The reaction mixture is allowed to warm up to room temperature and worked up after 24 h by pouring into a threefold volume of saturated ammonium chloride solution and extracting three times with dichloromethane (3 × 60 ml). The combined extracts are washed once with water and dried (Na_2SO_4). Removal of the solvent on a rotatory evaporator furnishes the crude adduct consisting of several diastereomers (3 centers of chirality!); yield: 6.92 g. The crude mixture is hydrolyzed directly as follows. The product is dissolved in anhydrous acetonitrile (33 ml) and 70% aqueous perchloric acid (1.1 ml) is added at 0° (it is important that the water content of the mixture does not exceed 1.5% and that ~0.3 equivalents of acid catalyst is present). After being stirred at 0° for 2 h, the reaction mixture is poured into twice its volume of water. Three extractions with dichloromethane (3 × 60 ml), washing of the combined extracts once each with 1 molar sodium hydrogen carbonate and saturated sodium chloride solution, drying (Na_2SO_4), and evaporating the solvents gives a yellow oil (5.76) which is distilled; yield of analytically and spectroscopically pure ketoaldehyde: 2.25 g (13.2 mmol, 50% based on ketene *S,S*-acetal monosulfoxide); b.p. 60–65°/0.03 torr.

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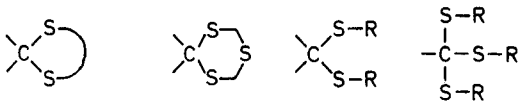
Numerous examples for *S,S*-acetal *S*-oxide hydrolysis will be given in subsequent sections. *S*-Oxides or their derivatives may be intermediates in some of the other oxidative *S,S*-acetal hydrolyses, e.g. the oxidation of sulfides to sulfoxides with chlorine, bromine, iodine, *t*-butyl hypochlorite, *N*-chloro-, and *N*-bromosuccinimide[98–104]. In addition to these oxidants, benzoyl peroxide[105], chloramine-T[106–108], mesitylsulfonylhydroxylamine[50,109], thallium(III) trifluoracetate[110a] lead(IV) acetate[110b], cerium(IV) ammonium nitrate[111], and concentrated sulfuric acid[112] were recently recommended for *S,S*-acetal hydrolysis; examples and references are collected in Table 3. It appears that *N*-bromosuccinimide is especially suitable for *S,S*-acetals of 1,2-dicarbonyl derivatives[1,34,58,69,113,114]. The mildness of neutral mercury(II) hydrolysis is matched among the oxidative procedures by iodine/sodium hydrogen carbonate[115], *N*-chlorosuccinimide/silver nitrate/lutidine[1,36] and mesitylsulfonylhydroxylamine[50,109], the latter is especially useful for liberating α,β-unsaturated aldehydes and ketones.

Table 3. Oxidative and Alkylative Hydrolyses of *S,S*-Acetals

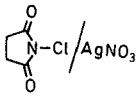
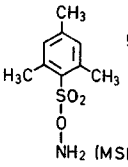
Precursors:



A B C F

Type of carbonyl compound generated by hydrolysis	Precursor	Reagent	References
H>C=O, H	B, C	Cl_2	128
-C(OH)-CHO, Ar-C(=O)-R, -C(=O)-C(=O)-, -C(=O)-C(=O)-C(=O)-, sugar	A, C	Br_2	34, 39, 129–136
Ar-CHO, -C(OH)-CHO, ⌬C=O, >C=C(=O)-C(=O)-, Ar-C(=O)-R, -C(=O)-C(=O)-, -C(=O)-SR	A, B, C, F	J_2	115, 137–140

Table 3. (Continued)

Type of carbonyl compound generated by hydrolysis	Pre-cursor	Reagent	References
Ar–CHO, –C(=O)–C(OH)–, >C=C–C(=O)–, >C=C–C(=O)–C(=O)–, –C(=O)–C(=O)–, –C(=O)–C(=O)–C(=O)–C(=O)–	A		1, 34, 56, 57, 141-144
R–CHO, R–C(=O)–R′, –C(OH)–C–C(=O)–, –C(=O)–C(=O)–	A, C		1, 34, 58, 69, 113, 114, 145
Ar–CHO, Ar–C(=O)–R, ⌬C=O, fluorenone, R–CHO, >C=C–CHO, >C=C–C(=O)–	A		50, 109
–C(NH2)–C(NH2)–CHO, Ar–C(=O)–R	A	chloramine T	105-108
Ar–CHO, R–C(=O)–R′, ⌬C=O, Ar–C(=O)–R, Ar–C(=O)–C(=O)–R	A	$Tl(OOC-CF_3)_3$	110
Ar–CHO, R–C(=O)–R, ⌬C=O, Ar–C(=O)–R, sugar	A	$Ce(NH_4)_2(NO_3)_6$	111, 146
Ar–CHO, R–C(=O)–R′, ⌬C=O, Ar–C(=O)–R, R–C(=O)–C–C–C(=O)–R′, Ar–C(=O)–C(=O)–R	A	conc. H_2SO_4	112
R–CHO, Ar–CHO, R–C(=O)–R′, ⌬C=O, >C=C–C(=O)–, Ar–C(=O)–R	A	H_3C-J	119-123
R–CHO, Ar–CHO, R–C(=O)–R′, R–C(=O)–R′(+ N-function), ⌬C=O, Ar–C(=O)–R	A	$(H_3C)_3O^{\oplus}$ or $(C_2H_5)_3O^{\oplus}$	116, 117, 118, 124, 125
R–CHO, R–C(=O)–R′(+ N-function), ⌬C=O, Ar–C(=O)–R	A	$F-S(=O)_2-OCH_3$	116, 121, 126

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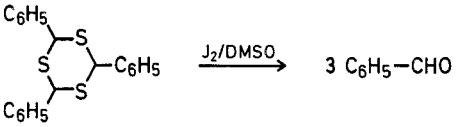

Iodine Hydrolysis of 2,4,6-Triphenyl-1,3,5-trithiane[138]**:**
A mixture of 2,4,6-triphenyl-1,3,5-trithiane (3.66 g, 0.01 mol), iodine (3.81 g = 0.03 g-atom), and dimethyl sulfoxide (20 ml) is heated on a steam bath for 1 h. During the course of the reaction a volatile fraction distilling at 35–38° can be collected and characterized as dimethyl disulphide (1.4 g). The solution is cooled, diluted with cold water (100 ml), and free iodine destroyed by adding a solution of sodium thiosulfate (4 g) in water (15 ml). The aqueous solution is extracted with petroleum ether. Removal of the solvent gives benzaldehyde; yield: 3 g (94%).

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See also T.-L. Ho *Synthesis* **1973**, 347.
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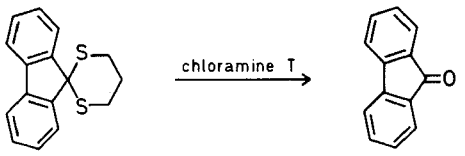
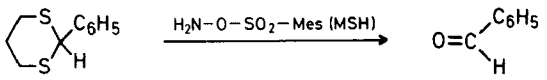
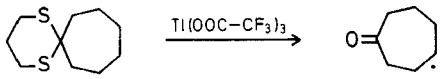


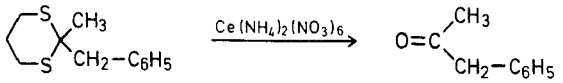
Chloramine T Hydrolysis of 1,3-Dithianes[107]:
An 80% aqueous methanol solution of chloramine T (4-fold excess) is added drop-wise to a stirred solution of the dithiane in acetone. Stirring is continued for 15 min. 10% Aqueous sodium chloride solution is added, the mixture made strongly basic with sodium hydroxide, and extracted with benzene. The solution is dried and evaporated to give the crude ketone. Recrystallization gives the pure fluorenone; yield: 84%.



Hydrolysis of 1-Phenyl-1,3-dithiane with *O*-Mesitylenesulfonylhydroxylamine[109]:
Procedure: see *Synthesis* **1973** (5), 312.

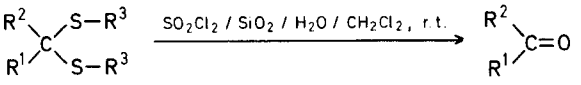


Thallium(III) Trifluoroacetate Hydrolysis of 1,3-Dithianes[110a]:
To a solution of the dithiane (1 mmol) in tetrahydrofuran (2 ml) is added thallium(III) trifluoroacetate (600 mg, 1.1 mmol). The reaction is mildly exothermic as the thallium salt dissolves, and the brownish mixture soon fades to milky white. After 5 min at room temperature, it is poured into water (10 ml) and extracted twice with benzene (2 × 15 ml). The combined extracts are washed with dilute aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated in vacuo. The crude cycloheptanone is purified by passing it through a short neutral alumina column and distilling; yield: 80%; b.p. 173–180°.

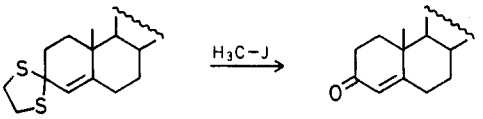


Cerium(IV) Ammonium Nitrate Hydrolysis of 2-Benzyl-2-methyl-1,3-dithiane[111]:
Procedure: see *Synthesis* **1973** (6), 352.

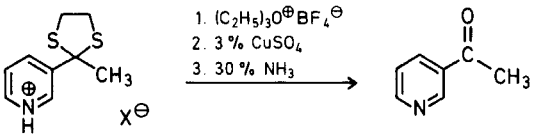
The alkylative hydrolysis occurs via the sulfonium salts **20** (Scheme **F** and Table 3) which can be isolated[116,117] (as well as their bis-sulfonium analogues[118].) The published hydrolysis procedures employ methyl iodide in water[119], aqueous methanol[120], acetone[121], acetonitrile[122,123], dimethylformamide[123], or treatment with trimethyl- or triethyloxonium tetrafluoroborate (Meerwein's reagent)[116–118,124,125] or methyl fluorosulfonate (magic methyl)[116,121,126] without solvents[116], or in benzene[126] or liquid sulfur dioxide[121], and subsequent hydrolysis or alcoholysis[126b,c]. To avoid the formation of strongly acid conditions, this step is often carried out with addition of base [sodium hydroxide[117,122,124] or carbonates[121,123]]. Work up of many alkylative hydrolysis reactions involves addition of copper(II) sulfate[116,124,125]. Acylative *S,S*-acetal hydrolysis has also been reported (use of acetyl chloride, acetic anhydride/boron trifluoride, or trifluoroacetic anhydride/$H^{\oplus}$)[127].



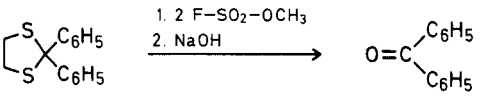
Dethioacetalization using Sulfuryl Chloride and Moist Silica Gel[258c]:
Procedure: see *Synthesis* **1976** (10), 679.



Alkylative Hydrolysis of *S,S*-Acetals with Methyl Iodide; General Procedure[120]:
A solution of the steroidal *S,S*-acetal (1.32 g) and methyl iodide (2.96 ml) in 96% aqueous methanol (32 ml) is refluxed for 2–20 h and then evaporated. The residue is treated with water and extracted with ether. The ether extracts are washed first with sodium hydroxide solution, then with water, dried, evaporated, and ketone isolated, yield: 60–83%.



Alkylative Hydrolysis of *S,S*-Acetals using Triethyloxonium Tetrafluoroborate[116]:
The *S,S*-acetal is allowed to react at room temperature for four days with two equivalents of triethyloxonium tetrafluoroborate in dichloromethane. The resultant sulfonium salt is hydrolyzed with 3% copper(II) sulfate solution, followed by basification with 30% ammonia solution. After work up, the ketone is isolated in 95% yield.

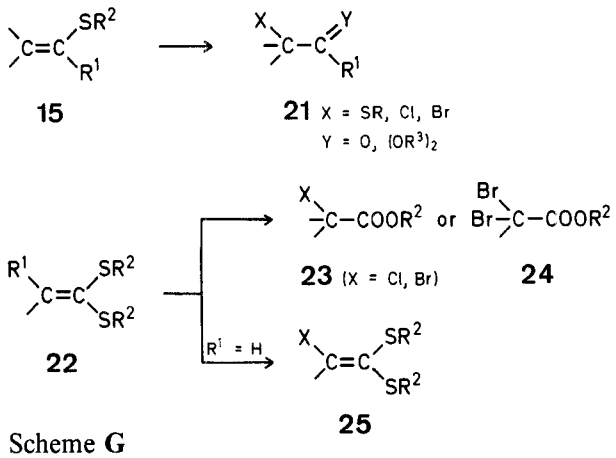


Alkylative Hydrolysis of *S,S*-Acetals using Methyl Fluorosulfonate[126]:
Procedure: see *Synthesis* **1972** (10), 561.

130 C. B. Gauthier, C. Vaniscotte, *Bull. Soc. Chim. Fr.* **1956**, 30.
131 C. B. Gauthier, *Ann. Pharmac. Fr.* **12**, 281 (1954); *C. A.* **48**, 13547 (1954).
132 F. Weygand, H. J. Bestmann, *Chem. Ber.* **90**, 1230 (1957).
133 F. Weygand, H. J. Bestmann, H. Ziemann, *Chem. Ber.* **91**, 1040 (1958).
134 F. Weygand, H. J. Bestmann, H. Ziemann, E. Klieger, *Chem. Ber.* **91**, 1043 (1959).
135 W. E. Truce, F. E. Roberts, *J. Org. Chem.* **28**, 961 (1963).
136 H. Baganz, H. J. May, *Chem. Ber.* **99**, 3771 (1966).
137 T. L. Moore, *J. Org. Chem.* **32**, 2786 (1976).
138 J. B. Chattopadhyaya, A. V. Rama Rao, *Tetrahedron Lett.* **1973**, 3735.
139 J. B. Chattopadhyaya, A. V. Rama Rao, *Synthesis* **1974**, 865.
140 B. M. Trost, T. N. Salzmann, *J. Org. Chem.* **40**, 148 (1975).
141 E. W. Colvin, T. A. Purcell, R. A. Raphael, *J. Chem. Soc. Chem. Commun.* **1972**, 1031.
142 A. Closse, R. Huguenin, *Helv. Chim. Acta* **57**, 533 (1974).
143 R. A. Ellison, E. R. Lukenbach, C. Chiu, *Tetrahedron Lett.* **1975**, 499.
144 P. G. Strange et al., *J. Chem. Soc. Perkin Trans. I* **1972**, 2364.
145 F. Sher, J. L. Isidor, H. R. Taneja, R. M. Carlson, *Tetrahedron Lett.* **1973**, 577.
146 A. M. Sepulchre, G. Vass, S. D. Gero, *Tetrahedron Lett.* **1973**, 3619.

2.4. Oxidative Solvolysis of Vinyl Sulfides and Ketene *S,S*-Acetals

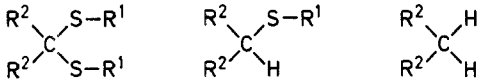
The mechanism and the nature of the products obtained from the few known examples of this reaction are different from those of the corresponding reactions of *S,S*-acetals. Here, carbonyl derivatives heterosubstituted in the α-position are obtained (Scheme **G**) from vinyl ethers **15**, α-thiolated[147] or α-halogenated aldehydes[27b] and ketones or their respective acetals **21**[27b]; from ketene *S,S*-acetals **22** α-halo-[92,148a,b] **23** or α,α-dihalo esters[148a] **24** which probably arise through the intermediate haloketene *S,S*-acetals **25**[149]. To our knowledge, there is only one report of an alkylative vinyl sulfide hydrolysis[150].



Scheme **G**

2.5. Reductive Desulfurizations

As is evident from the following sections, the nucleophilicity of α-thiocarbanions in C—C-bond forming processes is extremely high. Therefore, we find a number of new examples in which their products with electrophiles are reductively desulfurized. This can lead from *S,S*-acetals **13** to sulfides **26** or to CH_2-derivatives **27**. Calcium/liquid ammonia[151] and irridation in *t*-butyl alcohol[152] are recommended for the first conversion. Raney nickel[153] from Al/Ni-alloy[154] or from nickel(II) chloride and sodium borohydride[135] effects total desulfurization for which the use of tetrahydrofuran as solvent is a new modification[155]. New methods of desulfurization use lithium tetrahydroaluminate and copper(II) chloride/zinc(II) chloride[156] or titanium(IV) chloride[157]. Finally, we would like to draw attention to the hydrazine method for this purpose[158,159].



13 **26** **27**

3. Reactions of *S,S*-Acetal Derivatives (E^1-Type)

In this section some theoretical aspects, applications, and new developments of *S,S*-acetal-anion derivatives for nucleophilic acylation reactions are described. The use of these reagents for the preparation of ketene *S,S*-acetals and the chemistry of the latter compounds are covered in Section 5.2; see also natural product synthesis in Section 7.

3.1. Metallated 1,3-Dithianes

The high stability (thermal, towards acids and bases, and during chromatographic purification) of the 1,3-dithiane system renders 2-lithio-1,3-dithianes especially useful if the *S,S*-acetal unit is to be carried through a multistep synthesis (see below and Section 7).

2-Lithio-1,3,5-trithianes have not received much attention since our last report[1], [full paper[4], *Organic Synthesis*-procedure[160], use for the preparation of deuterated aldehydes[161], polymetallation[162], and mechanistic investigations[163]].

A number of papers deal with I.R.[164], U.V.[165], M.S.[166], and P.E. spectra[167] of 1,3-dithianes, and

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147 H. J. Bestmann, J. Angerer, *Justus Liebigs Ann. Chem.* **1974**, 2085.

148 (a) B.-T. Gröbel, R. Bürstinghaus, D. Seebach, *Synthesis* **1976**, 112.
(b) K. Ogura, S. Furukawa, G. Tsuchihashi, *Bull. Chem. Soc. Jpn.* **48**, 2219 (1975); (monosulfoxide).

149 F. A. Carey, J. R. Neergaard, *J. Org. Chem.* **36**, 2731 (1971).

150 M. Iyoda, M. Morigaki, M. Nakagawa, *Tetrahedron Lett.* **1974**, 3677.

151 B. C. Newman, E. L. Eliel, *J. Org. Chem.* **35**, 3641 (1970).

152 K. Matsuura, Y. Araki, Y. Ishido, *Bull. Chem. Soc. Jpn.* **46**, 2261 (1973).

153 (a) G. R. Pettit, E. E. van Tamelen, *Org. React.* **12**, 356 (1962).
(b) H. Hauptmann, W. F. Walter, *Chem. Rev.* **62**, 347 (1962).

154 (a) See for example: M. L. Wolfrom, L. V. Karabinos, *J. Am. Chem. Soc.* **66**, 909 (1944).
(b) H. Hauptmann, *J. Am. Chem. Soc.* **69**, 562 (1947).
(c) M. S. Newman, H. M. Walborsky, *J. Am. Chem. Soc.* **72**, 4296 (1950).

155 B. Kainradl, E. Langer, H. Lehner, K. Schlögl, *Justus Liebigs Ann. Chem.* **766**, 16 (1972).

156 T. Mukaiyama, K. Narasaka, K. Maekawa, M. Furusato, *Bull. Chem. Soc. Jpn.* **44**, 2285 (1971).

157 T. Mukaiyama, M. Hayashi, K. Narasaka, *Chem. Lett.* **1973**, 291.

158 V. Georgian, R. Harrisson, N. Gubisch, *J. Am. Chem. Soc.* **81**, 5834 (1959).

159 W. H. Baarschers, T. L. Loh, *Tetrahedron Lett.* **1971**, 3483.

160 D. Seebach, A. K. Beck, *Org. Synth.* **51**, 39 (1971).

161 J. B. Chattopadhyaya, A. V. Rama Rao, K. Venkataraman, *J. Indian Chem. Soc.* **11**, 987 (1973).

162 M. Schmidt, E. Weissflug, *Z. Anorg. Allg. Chem.* **418**, 208 (1975).

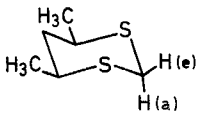
163 M. Fukunaga, T. Sugawara, M. Oki, *Chem. Lett.* **1972**, 55.
M. Fukunaga, M. Oki, *Chem. Lett.* **1972**, 1081.
M. Fukunaga, *Yugi Gosei Kagaku Kyokai Shi* **32**, 153 (1974).

164 M. J. Hitch, S. D. Ross, *Spectrochim. Acta Part A* **25**, 1041 (1969).

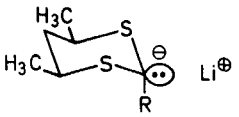
165 D. R. Williams, L. T. Kontnik, *J. Chem. Soc.* [B] **1971**, 312.
L. K. Dyall, S. Winstein, *Spectrochim. Acta Part A* **27**, 1619 (1971).

with conformational N.M.R.-analyses (for a review see[174]) of dithianes[168], dithianesulfonium salts[170], and the monosulfoxides[172,173] as well as of the corresponding trithiane derivatives[169,171,173]; ^{13}C-N.M.R. data have been obtained from dithiane derivatives of carbohydrates[175].

The origin of the acidity of hydrogen atoms adjacent to divalent sulfur is the subject of two recent papers[176a,b] which independently reach the conclusion that d-orbitals are not involved; it is proposed that the great acidity difference between α-oxygen and α-sulfur CH-groups, which is used for many preparative purposes, stems from "the greater polarizability of sulfur and the longer C—S-bond length". The acidities of some dithianes [unsubstituted, 2-methyl, and 2-phenyl derivatives have pK_A's of 31, 38, and 29, respectively; Streitwieser-scale[176a]] and phenylthiomethanes [$(C_6H_5S)_2CH_2$ and $(C_6H_5S)_3CH$ have pK_A's of 30.8 and 22.5, respectively; Bordwell-scale[176c]] have been measured. In a series of papers[177], Eliel et al. described a high kinetic preference for abstraction of H(e) versus H(a) in **28** and concluded, from reactions of the lithio dithianes **29**, a thermodynamic preference for the conformation with equatorial lithium (cf. similar observations in the 1,3,5-trithiane series[163]).



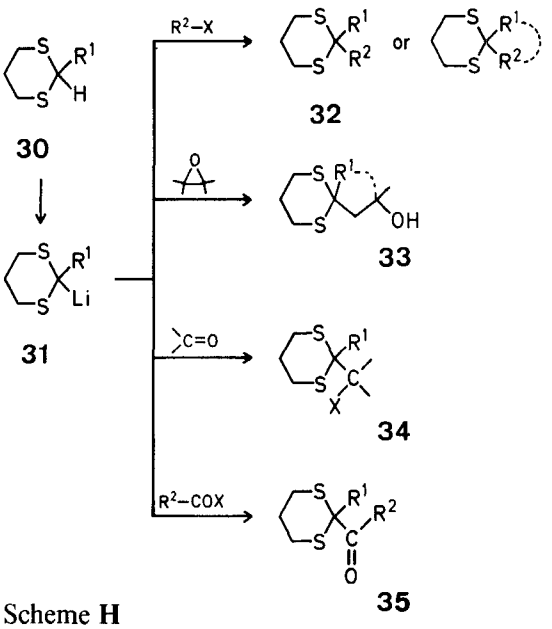
28



29

3.1.1. C—C-Bond Formation in Reactions between Metallated Dithianes and Alkyl Halides, Sulfonates, Epoxides, and Carbonyl Compounds

Dithianes **30** (R^1 = H, alkyl) are, in most cases, converted to the lithio derivatives **31** by treatment with *n*-butyllithium[1,5] at temperatures between −30° and −10°. Lower temperatures can be used if additional acidification by R^1 (for instance aryl, −80°) is present. In these cases, other metallating reagents and metals other than lithium are applicable: thus 2-phenyl-1,3-dithiane was converted to its potassium derivative[178]; glyoxylic acid derivatives **30** (R^1 = COOR, $CONR_2$[113,179]) have been metallated with sodium hydride and with lithium diisopropylamide.



Scheme **H**

Details of the reactions leading to the products **32**, **33**, **34** (X = OH), and **35** with alkyl halides, epoxides, aldehydes or ketones, and acid derivatives, respectively, have been described[1,5], see Scheme **H**. Some selected, recent examples are given in Tables 4 and 5 together with cases in which one of the C—C-bond forming steps is a cyclization. Alkylations, **31**→**32**, have been shown to be possible with tosylates and – preferably – benzenesulfonates[181]. Carbonyl additions have been extended to the analogous immonium salts $R_2C{=}NR_2^{\oplus}$ which furnish α-aminoketone derivatives **34**, X = NR_2[108], (R on carbon without α-hydrogens!). The examples in Table 5 confirm the previous findings[208] that nitriles and amides act as acylating reagents to give products of type **35** only if they have no acidic α-hydrogen atoms.

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166 D. L. Coffen, K. L. Bank, P. E. Garrett, *J. Org. Chem.* **34**, 605 (1969).
J. H. Bowie, P. Y. White, *Org. Mass. Spectrom.* **1969**, 611.

167 D. A. Sweigart, D. W. Turner, *J. Am. Chem. Soc.* **94**, 5599 (1972).
H. Bock, G. Wagner, *Angew. Chem.* **84**, 119 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 150 (1972).

168 E. L. Eliel, R. O. Hutchins, *J. Am. Chem. Soc.* **91**, 2703 (1969).
J. Gelan, M. Anteunis, *Bull. Soc. Chim. Belg.* **78**, 599 (1969).
H. R. Buys, *Recl. Trav. Chim. Pays-Bas* **89**, 1253 (1970).
K. Pihlaja, *J. Chem. Soc. Perkin Trans. 2* **1974**, 890.

169 M. Oki, T. Endo, T. Sugawara, *Bull. Chem. Soc. Jpn.* **48**, 2496 (1975).

170 I. Stahl, J. Gosselck, *Tetrahedron* **30**, 3519 (1974).

171 H. Iwamura, M. Fukunaga, *Chem. Lett.* **1974**, 1211.

172 M. J. Cook, A. P. Tonge, *J. Chem. Soc. Perkin Trans. 2* **1974**, 767.
L. van Acker, M. Anteunis, *Tetrahedron Lett.* **1974**, 225.

173 S. A. Khan, J. B. Lambert, O. Hernandez, F. A. Carey, *J. Am. Chem. Soc.* **97**, 1468 (1975).

174 C. H. Bushweller, *Mech. React. Sulfur Compd.* **5**, 75 (1970).
A. V. Bogatskii, *Vopr. Stereokhim.* **1971** (1), 3; *C. A.* **78**, 1583 (1973).

175 A. M. Sepulchre et al., *Tetrahedron* **30**, 905 (1974), and literature cited therein.

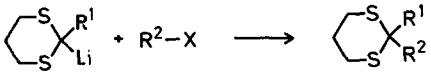
176 (a) A. Streitwieser, Jr., S. P. Ewig, *J. Am. Chem. Soc.* **97**, 190 (1975).
(b) F. Bernardi et al., *J. Am. Chem. Soc.* **97**, 2209 (1975).
(c) F. G. Bordwell, W. S. Matthews, N. R. Vanier, *J. Am. Chem. Soc.* **97**, 442 (1975).

177 E. L. Eliel, *Angew. Chem.* **84**, 779 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 739 (1972).
E. L. Eliel, A. G. Abatjoglou, A. A. Hartmann, *J. Am. Chem. Soc.* **94**, 4786 (1972).
E. L. Eliel, A. A. Hartmann, A. G. Abatjoglou, *J. Am. Chem. Soc.* **96**, 1807 (1974).
E. L. Eliel, *Tetrahedron* **30**, 1503 (1974).

178 R. Weil, N. Collignon, *Bull. Soc. Chim. Fr.* **1974**, 253.

Table 4. Reactions of 2-Lithio-1,3-dithiane Derivatives

(a) Alkylations:



31 **32**

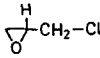
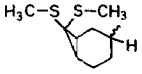
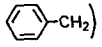
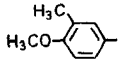
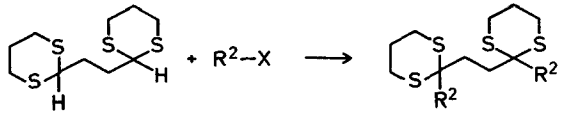
R^1	Electrophile R^2—X	Yield [%]	Reference
H	$(H_3C)_3Si-CH_2-J$	66	180
H	$H_3C-(CH_2)_n-O-S(=O)_2-C_6H_5$ (n = 0, 1, 2, 7)	55–71[a]	181
H	$(H_3CO)_2CH-CH_2-Br$	–	182
H	$C_2H_5-CH(CH_3)-C(=CH_2)-CH_2-Br$	82	183
H_3C		88	65
H_3C	$C_2H_5-O-S(=O)_2-C_6H_4-CH_3$	40	181
i-C_3H_7	$H_3C-O-S(=O)_2-C_6H_5$	82	181
H_3C	$C_6H_5-{}^{14}CH_2-Cl$	-	258 d
	H_3C-J	100	65
	n-C_4H_9-Br	63	178
	$H_3C-(CH_2)_n-O-S(=O)_2-C_6H_5$ (n = 0, 1, 2, 7)	76–81[a]	181
 (X = 4-NC, 3-Br, 4-C_2H_5OOC)	$(H_3C)_2C=CH-(CH_2)_2-C(CH_3)=CH-CH_2-Cl$	–	185
 (R = CH_3, C_2H_5, )	$Br-(CH_2)_n-Br$ (n = 3, 4)	45–78	186

Table 4. (Continued)

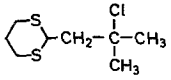
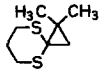
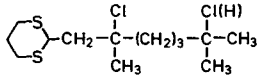
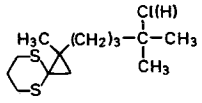
R^1	Electrophile R^2—X	Yield [%]	Reference
	$Br-(CH_2)_4-Br$	77	186
$(H_3C)_3Sn$	H_3C-J	96	187
$(n$-$C_4H_9)_3Sn$	n-$C_7H_{15}-J$	94	187
C_2H_5OOC	i-C_3H_7-Br, n-C_4H_9-Br, s-C_4H_9-Br	75–90	113

(b) Double Alkylations:



—	Electrophile R^2—X	Yield[b] [%]	Reference
	$H_3C-(CH_2)_n-hal$ (n = 1, 2, 3)	54–79	184
	$(H_3C)_2CH-(CH_2)_n-hal$ (n = 0, 1)	43–62	184

(c) Cycloalkylations of β-chloroalkyl derivatives:

1,3-Dithiane derivative	Product	Yield [%]	Reference
		90	188
		80–85	188

(d) Cycloalkylations with bifunctional electrophiles:

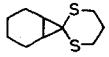
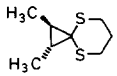
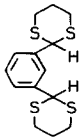
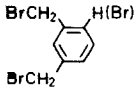
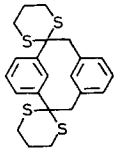
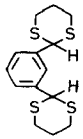
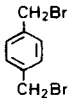
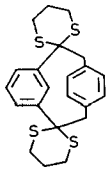
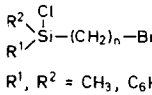
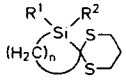
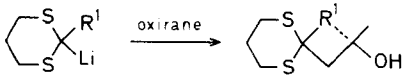
Dithiane	Electrophile	Product	Yield [%]	Reference
			75	65

Table 4. (Continued)

Dithiane	Electrophile	Product	Yield [%]	Reference
			58	189
			28–71	155, 190, 191
			36	190 b, 191
	 $R^1, R^2 = CH_3, C_6H_5$; $n = 3, 4, 5$		36–62	192

(e) β-Hydroxyalkylations:



31 **33**

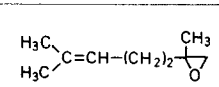
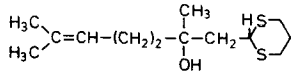
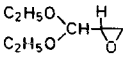
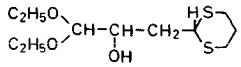
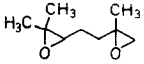
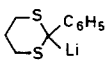
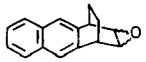
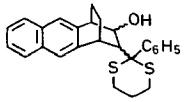
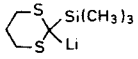
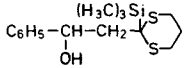
Dithiane	Electrophile (Oxirane)	Product	Yield [%]	Reference
			98	46
			90[c]	45
		product mixture	—	193

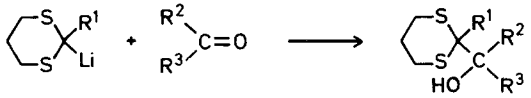
Table 4. (Continued)

Dithiane	Electrophile (Oxirane)	Product	Yield [%]	Reference
			75	194
	*endo* or *exo* 	*endo* or *exo* 	17	180

[a] Reaction also performed with tosylates.
[b] via dimetallation and dialkylation or metallation, alkylation, metallation, and alkylation.
[c] Yield after *O*-acylation.

Table 5. Reactions of Metallated 1,3-Dithianes with Carbonyl Compounds and Derivatives Thereof

(a) α-Hydroxyalkylations:



31 **34**

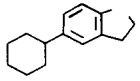
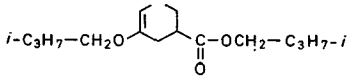
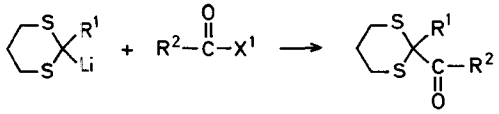
R^1	R^2	R^3	Yield [%]	Reference
H	CH_3	H	65[a]	151
CH_3	n-C_5H_{11}	H	84[b]	36
CH_3	i-C_3H_7	H	17[b]	36
CH_3	t-C_4H_9	H	54[b]	36
$(H_3C)_3Sn$	C_6H_5	H	54	195
H			—	28 b
H	 X = H_3CO, H_3CO-CH_2-O, $(H_3C)_2N-(CH_2)_2-O$		—	196
H_3C	C_6H_5	CH_3	54[b]	36
H_3C			—	197

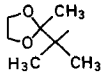
Table 5. (Continued)

R^1	R^2	R^3	Yield [%]	Reference
CH_3			35	258 e
$(H_3C)_3Sn$	CH_3	CH_3	87[a]	195
$(H_3C)_3Sn$		$-(CH_2)_5-$	87[a]	195
$(H_3C)_3Sn$		$-CH=CH-(CH_2)_3-$	69	195

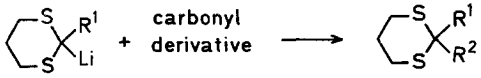
(b) Acylations:

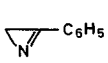
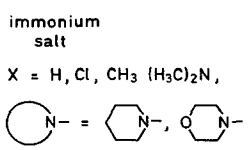
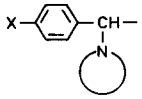
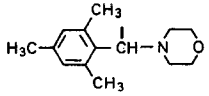
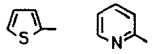
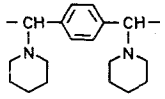
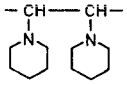
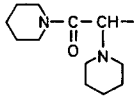
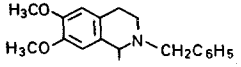


31 **35**

R^1	R^2	X^1	Yield [%]	Reference
H		OR^3	45	199
H		OR^3	29	199
H		OR^3	85	200
$(H_3C)_3Si$	C_6H_5	OR^3	45 (R^1 = H)	201
$(H_3C)_3Sn$	C_6H_5	OR^3	68 (R^1 = H)	195
$(H_3C)_3Si$	C_6H_5	hal	40 (R^1 = H)	202
H	H	NH_2	81	203

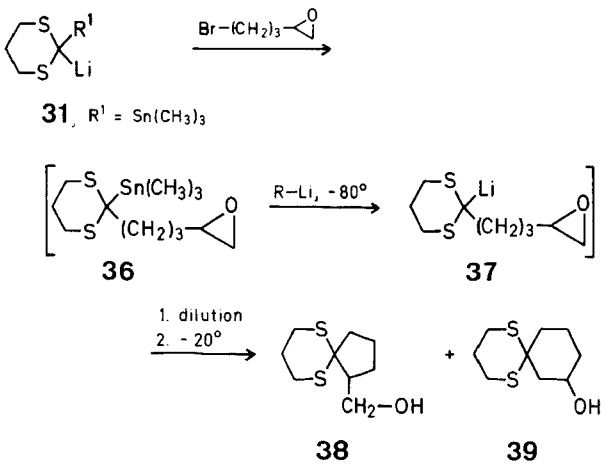
(c) Miscellaneous Reactions:



R^1	Carbonyl Derivative	R^2	Yield [%]	Reference
C_6H_5	CO_2	HOOC–	–	204
$(H_3C)_3Si$	C_6H_5-NCO	$C_6H_5-NH-CO-$	60 (R^1 = H)	202
$(H_3C)_3Si$	$(H_3C)_2N-C(=O)-NH_2$	$(H_3C)_2N-CO-$	69 (R^1 = H)	201
H	R–CN R = H, CH_3, C_2H_5, n-C_5H_{11}	R–CO–	52-78	205
C_6H_5			54	206
H	immonium salt X = H, Cl, CH_3 $(H_3C)_2N$, 		35-90	108, 108 b
H	immonium salt		38	108 b
H	immonium salt heteroaryl = 	heteroaryl-CH– 	45-70	108 b
H	immonium salt		40	108
H	immonium salt		20	108 b
H	immonium salt		65	108 b
H	immonium salt		70	207

[a] Yield of crude products.
[b] Yield after hydrolysis.

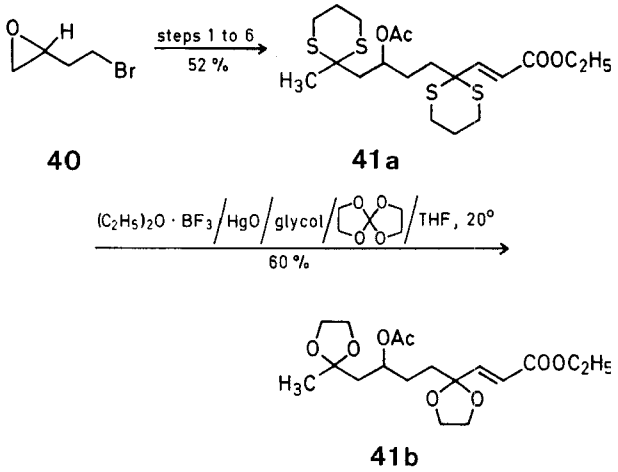
Sn/Li-Transmetallation at the 2-position of the dithiane is a much faster process than the direct metallation and occurs within minutes at $-80°$[195]. This allows generation of the nucleophilic 2-dithiane center (see **36**→**37**, Scheme **I**) in the presence of electrophilic sites which would not survive the metallation process under the usual conditions; e.g. preparation of the two isomers **38** and **39** (~1:1) in 60% total yield from **31**.



Scheme **I**

The lithio dithiane **31**, $R^1 = Sn(CH_3)_3$, readily available from either **30**, $R^1 = Sn(CH_3)_3$, and lithium diisopropylamide or **32**, $R^1 = R^2 = Sn(CH_3)_3$, and methyllithium, is alkylated and cyclized without isolation of intermediates, as shown in Scheme **I**.

The advantage of 1,3-dithianes as masked acyl anions in multistep syntheses is demonstrated by the conversion of 2-bromoethyl-oxirane (**40**) to the precursor (**41a**) of vermiculine[209] in six steps in an overall yield of 50–60%[210].



step 1: +**31** (R = H) at $-80°$ to $-30°$ (substitution of bromide);
step 2: +**31** ($R = CH_3$) at $-15°$ to $+20°$ (opening of oxirane ring);
step 3: + n-C_4H_9Li/tetramethylethylenediamine at $-30°$ for 20 h (dithiane metallation);
step 4: + $HCO-N(CH_3)_2$ (formylation);
step 5: + $(C_6H_5)_3P{=}CH-COOR$ in dioxan (Wittig reaction);
step 6: + acetic anhydride/pyridine (acetylation);

The first 4 steps can be performed *in situ* in tetrahydrofuran (one-pot reaction), steps 5 and 6 are performed on crude precursors, only the product **41a** is purified before conversion to **41b**. This is possible due to the high yields of dithiane-C—C-bond-forming steps, the great stability of the dithiane system, the fact that it introduces no additional asymmetric centers, and that hydrolysis or alcoholysis of the intermediates can be achieved under mild conditions.

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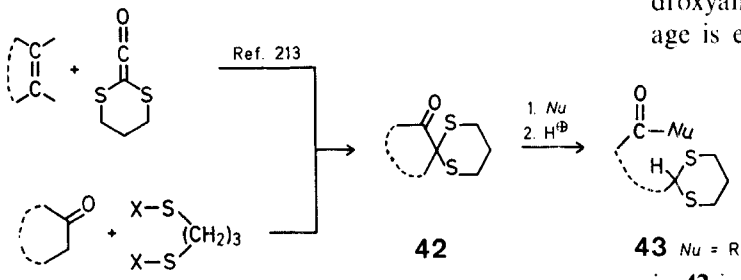
3.1.2. Further Reactions Involving 1,3-Dithiane Anions

3.1.2.1. Cleavage of Acyl Dithianes

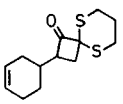
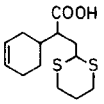
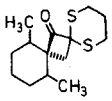
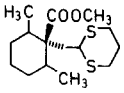
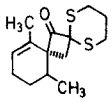
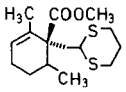
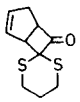
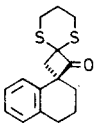
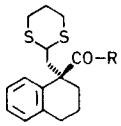
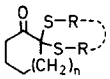
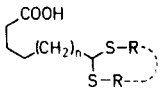
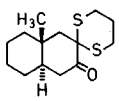
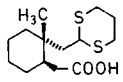
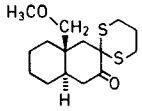
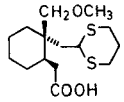
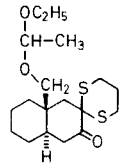
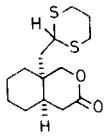
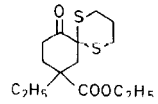
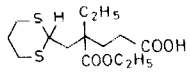
The reaction of dithiane anions with carbonyl compounds mentioned in the previous section can be reversed. This result allows a synthetically useful C—C-bond cleavage reaction. The general scheme[211] and the preparations of the precursors[212–214] are shown in Scheme **J** and examples are listed in Table 6.



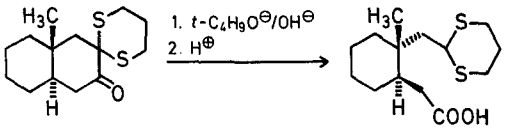
Scheme **J**

The 1,2-diketone derivatives **42** may be open chain, cyclic (4-8-membered ring) or polycyclic. Alkoxides (retro-acylation) or lithium compounds (retro-hydroxyalkylation) are used as nucleophiles. The cleavage is especially facile if the keto-dithiane moiety in **42** is part of a 4-membered ring (strain). Instead of dithiane derivatives, other α-acylated *S,S*-acetals

Table 6. Cleavage of 2-Acyl-1,3-dithianes (**42**) to Products **43** (Scheme J)[258k]

Precursor **42**	Nucleophilic Reagent	Product **43**	Yield [%]	Reference
	$HO^{\ominus}/H_2O$		100	122
	$H_3CO^{\ominus}/H_2O$		57	122
	1. H_3CLi / H_2O 2. $H_3CO^{\ominus}$ / CH_3OH		91	122
	$RO^{\ominus}/ROH$	 (R = H, *cis*) (R = CH_3, *trans*)	98	213
	$H_3CO^{\ominus}$/ CH_3OH or 1. H_3CLi / H_2O 2. $H_3CO^{\ominus}$ / CH_3OH		R = CH_3 : 59 % R = OCH_3 : 60 %	122
 R R = 2 C_6H_5, $-(CH_2)_3-$; n = 1, 2,3	t-C_4H_9OH/$HO^{\ominus}$/$H^{\oplus}$		66–95	215
	$H_3CO^{\ominus}$/DMSO$^{\ominus}$ or t-$C_4H_9O^{\ominus}$/$HO^{\ominus}$/$H^{\oplus}$		74 92	211 216
	t-$C_4H_9O^{\ominus}$/$HO^{\ominus}$/$H^{\oplus}$		92	215, 216
	t-C_4H_9OH/$HO^{\ominus}$/$H^{\oplus}$		87	217
	NaH / H_2O			258 f

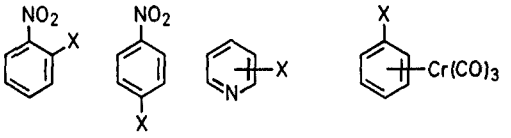
can also be used for this haloform-type cleavage (see Table 6).



Alkaline Cleavage of a 2-Acyl-1,3-dithiane[216]; Typical Procedure: To a stirred suspension of a 57% sodium hydride/oil dispersion (2.11 g, 50 mmol of sodium hydride) in ether (25 ml) is added *t*-butyl alcohol (3.70 g, 50 mmol) and water (0.27 g, 15 mmol). After the hydrogen evolution has ceased, the ketone (1.35 g, 5.0 mmol) in benzene (15 ml) is added with stirring. Stirring is continued for 6 h at room temperature, water is added, the aqueous phase is extracted with ether, and the extract acidified with cold concentrated hydrochloric acid. The acidic product is isolated by ether extraction to give a crystalline solid; yield: 1.46 g; after recrystallization from ether; yield: 1.33 g (92%) m.p. 112–112.5°.

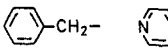
3.1.2.2. *Arylation of Dithianes*

Another development in dithiane anion chemistry is arylation using activated arenes. The classically activated *o*- and *p*-nitroaryl halides **44** and **45** cannot be used with lithio-dithianes **31** as they undergo one electron transfer with subsequent dimerization to give the bis-dithiane derivatives of 1,2-dicarbonyl compounds[159]. Pyridines **46**, however, act as arylating reagents[159,218] under these conditions. Finally, chromium tricarbonyls **47** are sufficiently electrophilic to undergo overall replacement of hydrogen (X = H) by dithiane[219]. The derivatives **48** obtained by these methods are shown below.



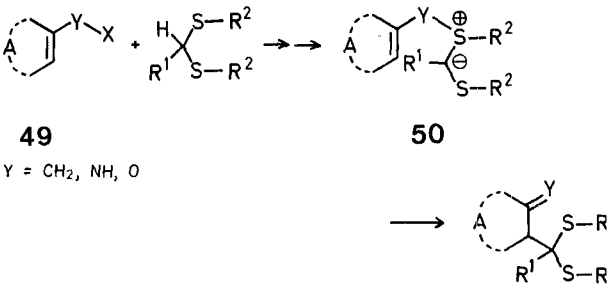
44 **45** **46** **47**

48 a-e

48	R	Ar	Yield [%]	Ref.
a			50	159
b	H		69	218
c	H_3C		69	218
d			47	218
e	H		93	219

3.1.2.3. *Reactions Involving Ylides with Dithiane and Related S,S-Acetal Structures*

The high nucleophilicity of the sulfide sulfur atom lends itself to reactions which can be generalized as shown in Scheme **K**.

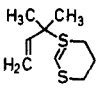
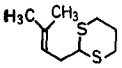
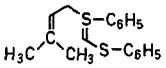
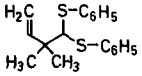
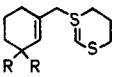
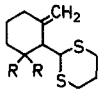
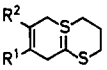
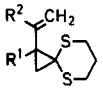
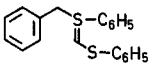
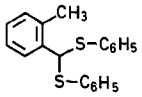
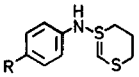
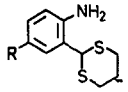
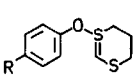
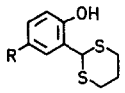


49 **50** **51**

Scheme **K**

The double bond may be part of an aromatic system so that *ortho*-substituted aryl-dithianes can be prepared, examples are listed in Table 7. Similar uses of other sulfur derivatives in the preparation of carbonyl compounds are dealt with in Section 4.

Table 7. Rearrangement of Dithiane and Related Ylides (**50**) to Products **51** (Scheme **K**)

Ylide **50**	Product **51**	Yield [%]	Reference
		–	220
		80	221
 R = H, CH_3		≥80	220
 R^1, R^2 = H, CH_3		87–96	55
		70	221
 R = H, Cl, CH_3		25–54	59
 R = H, CH_3, OCH_3, Cl		30–46	60

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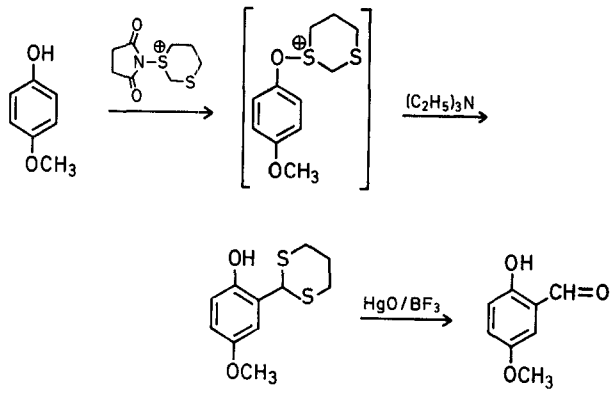
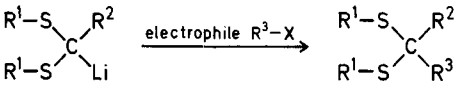


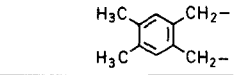
Formylation of Phenols[60]; Typical Procedure:
The phenol (1.7 equiv) is allowed to react with the sulfonium salt (1 equiv) for 15 min at −70° in dichloromethane. Triethylamine (1 equiv) is then added and the reaction mixture is allowed to warm to 25°. Finally water is added, the organic phase is separated, dried, and concentrated. Chromatography of the crude residue gives the arylated dithiane. After hydrolysis with mercury(II) oxide/boron trifluoride (procedure above) the formylated phenol is isolated; overall yield: 30%.

3.2. Use of Metal Derivatives of *S,S*-Acetals other than 1,3-Dithianes

Many *S,S*-acetals have been tested as possible substitutes for the 1,3-dithianes in nucleophilic acylations (E_1-type). Thus, the lithio derivatives **52a–g** were generated from the corresponding *S,S*-acetals and reacted with various electrophiles (Table 8).

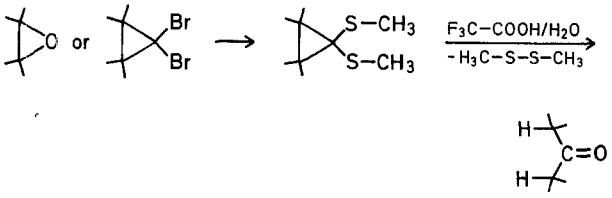


52a-g **53a-g**

	2 R¹	or R¹ R¹
a	2 CH3 (alkyl)	—
b	2 C6H5	—
c	CH3 + (H3C)2N–CS–	—
d	2 (H3C)2N–CS–	—
e	2 	—
f	—	–(CH2)2–
g	—	

Various reasons have been put forward which suggest the use of derivatives **52** instead of dithianes **31**:
(a) the thiols for the preparation of the *S,S*-acetal precursors of **52a, b,** and **f** are less expensive than propanedithiol;
(b) products **52b** and **d**, (R^2 = Li = H) are readily prepared from the thiol and dichloromethane[227,230];
(c) the corresponding sodium derivative **52b** (Na instead of Li) can be employed[223];
(d) compound **52c** (R^2 = Li = H) is accessible from chloromethyl methyl sulfide, carbon disulfide and dimethylamine[226];
(e) hydrolysis of the products **53c, d,** and **e** is facilitated by the presence of a nitrogen in R^1 [226–228];
(f) high tendency to crystallize and lower vapor pressure accompanied by less or no bad odor is claimed advantageous for the derivatives of type **d**, **e**, and **g**;
(g) compound **52f** is only stable if R^2 is an anion-stabilizing group (e.g. COOR)[58], otherwise metallated dithiolanes disproportionate to ethene and dithiocarboxylates[1,2,5].

Some of the derivatives **52** also have the advantage that they undergo specific reactions which are not observed with the dithianes **31** (e.g. Michael-addition, see Section 3.5) or that the products **53** are capable of transformations not possible with the respective dithianes (see also Sections 2 and 5). An example of the latter case is the disproportionative hydrolysis of cyclopropanone *S,S*-acetals to ketones **54**.



54

The preparation of dithiane and C_6H_5S-derivatives of cyclopropanones is equally feasible (see Tables 4 and 8) from alkenes through epoxides and/or dibromocarbene adducts; but only the H_3CS-substituted compounds can be converted to the ketones **54**[65,231].

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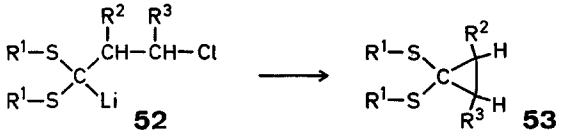
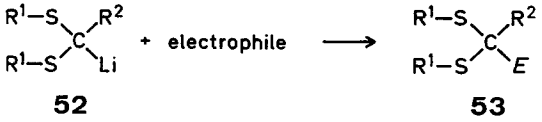
Table 8. Reactions of Miscellaneous Lithiated *S,S*-Acetals **52** with Electrophiles to give Products **53**

(a) Intramolecular Reactions:



Precursor **52** Type	R^1	R^1	R^2	R^3	Yield [%]	Reference
52a	CH_3	CH_3	H	H	73	222
52a	CH_3	CH_3	C_2H_5	H	71	222
52a	CH_3	CH_3	CH_3	CH_3	70	222
52a	CH_3	CH_3	C_2H_5	CH_3	59	222
52a	C_2H_5	C_2H_5	H	H	71	222
52a	C_2H_5	C_2H_5	CH_3	H	68	222
52a	i-C_3H_7	i-C_3H_7	H	H	60	222
52a	n-C_4H_9	n-C_4H_9	H	H	72	222

(b) Intermolecular Reactions:



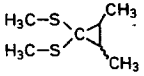
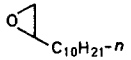
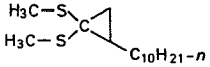
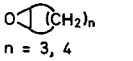
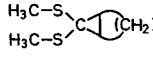
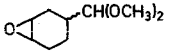
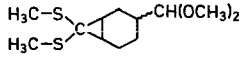
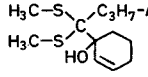
R^2	Electrophile	Product **53**	Yield [%]	Reference
Precursor Type **52a**, $R^1 = CH_3$:				
H	 *cis* or *trans*		66–67	65 b
H			77	65 b
H	 $n = 3, 4$		70–81	65 b
H			97	65 b
n-C_3H_7			68	148

Table 8. (Continued)

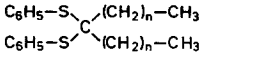
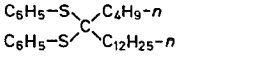
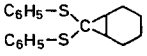
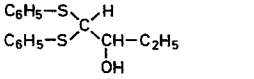
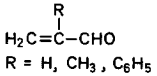
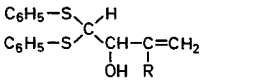
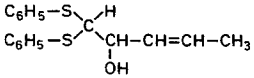
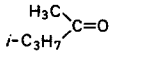
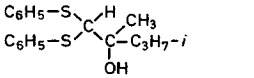
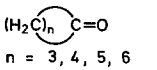
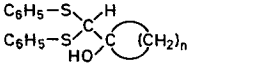
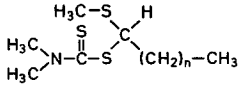
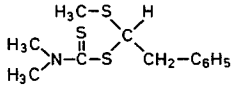
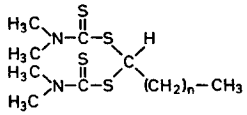
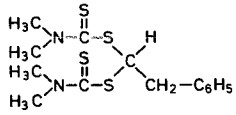
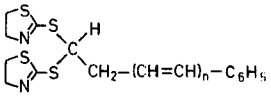
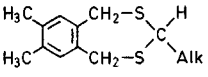
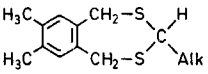
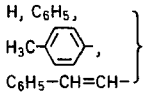
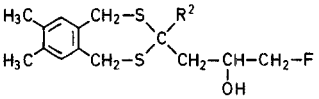
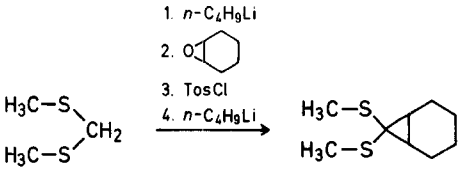
R^2	Electrophile	Product **53**	Yield [%]	Reference
Precursor Type **52b**:				
H	$H_3C-(CH_2)_n-Br$ $n = 3, 7, 11$		68–84	223
n-C_4H_9	n-$C_{12}H_{25}-Br$		76	223
H			51	65
H	C_2H_5-CHO		80	224
H	 $R = H, CH_3, C_6H_5$		—	225
H	$H_3C-CH=CH-CHO$		90	224
H	 i-C_3H_7		85	224
H	 $n = 3, 4, 5, 6$		74–86	224
Precursor Type **52c**:				
H	$H_3C-(CH_2)_n-J$ $n = 4, 5, 7$		66–70	226
H	$C_6H_5-CH_2-Br$		68	226
Precursor Type **52d**:				
H	$H_3C-(CH_2)_n-J$ $n = 0, 1, 3$		65–98	227
H	$C_6H_5-CH_2-J$		93	227

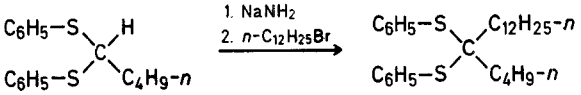
Table 8. (Continued)

R^2	Electrophile	Product 53	Yield [%]	Reference
Precursor Type **52e**:				
H	$C_6H_5-(CH=CH)_n-CH_2-Br$ n = 0, 1		35–58	228
Precursor Type **52g**:				
H	Alk–Br		71–92	229
CH_3	Alk–Br		50–88	229
H, C_6H_5, 			30–55	47



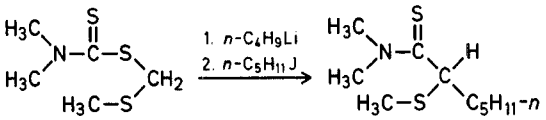
Replacement of an Epoxide Oxygen Atom by the $(CH_3S)_2C$ Moiety[65a]; Typical Procedure:

To a solution of bis[methylthio]methane (10.8 g, 100 mmol) in tetrahydrofuran (120 ml) are added successively under an inert atmosphere with stirring *n*-butyllithium (110 mmol; addition at −50°, reaction time 2.5 h at −25°), cyclohexene oxide (11.0 ml, 108 mmol; −78°, 15 h, 0°), *p*-toluenesulfonyl chloride (19.0 g, 100 mmol in 100 ml of tetrahydrofuran; −78°, 6 h, 0°), and again *n*-butyllithium (110 mmol; −78° to −30° in 2 h, 20 h, 0°). Workup with pentane furnishes the cyclopropanone *S,S*-acetal; yield: 15.2 g (81%).



Alkylation of Pentanal *S,S*-Diphenyl Acetal with Sodium Amide and Alkyl Halide[223];

Procedure: *Synthesis* **1975** (6), 387–388.

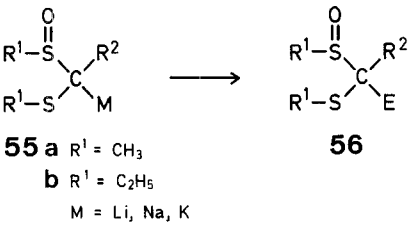


Pentylation of Methylthiomethyl *N,N*-Dimethyldithiocarbamate[226];

Procedure: *Synthesis* **1974** (10), 705–707.

3.3. *S,S*-Acetal *S*-Oxides; Alkylation, Cycloalkylation, Arylation, Hydroxyalkylation, and Acylation Reactions

In this section the transformations of *S,S*-acetal *S*-oxide anions mentioned above are discussed, for Michael additions and formation in N^2-addition reactions see Sections 3.5 and 5. It turns out that *S*-methyl[232] and *S*-ethyl[233] substituted derivatives have been used exclusively in this major field of development of carbonyl reactivity umpolung with sulfur compounds since our last report[1].



55a $R^1 = CH_3$
b $R^1 = C_2H_5$
M = Li, Na, K

56

57 **58**

1,3-Dithiane *S*-oxides are not useful for this modification[234]. Lithiodiethyl *S,S*-acetal *S*-oxides (**55b**, M = Li) are superior to the methyl analogues **55a**, especially when R^2 = alkyl[233] (perhaps because of competing metallation at the α-sulfoxide-CH_3-group).

In addition to the dithiane method, the *S*-oxide route is the most widely employed method for reactivity umpolung of carbonyl compounds. The following points are important for a comparison of the two alternatives:

(a) the *S*-oxides are quoted to be less expensive reagents;

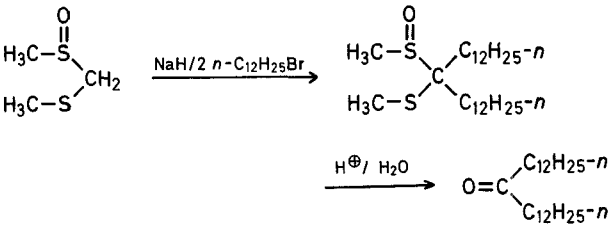
(b) they are more acidic and therefore the anions are easier to generate, i.e. instead of butyllithium, lithium diisopropylamide[233], sodium hydride[232], potassium hydride[235], or Triton B[236] may be used. Butyllithium is recommended for the alkylated species **55**, $R^1 = C_2H_5$, R^2 = alkyl[233];

(c) in some instances, the more stable anions of **55** are more nucleophilic than the corresponding dithianes; e.g. in reactions with nitriles, the former reagents add to the cyano group[237] and the latter abstract α-hydrogen atoms[208];

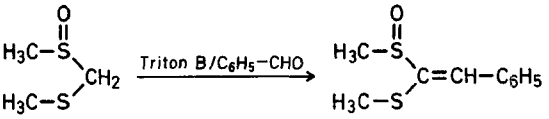
(d) lower temperatures are normally required for the more reactive lithio-dithianes;

(e) the difference most often referred to is the ready acidic hydrolysis of the product *S*-oxides **56** to carbonyl compounds; this is an advantage if and only if the carbonyl group is to be set free right after the step **55**→**56** during a synthesis;
(f) in cases where protection of the carbonyl function must be carried through many steps of a complex synthesis, the instability towards hydrolysis (see Section 2.3) and the additional center of chirality at the *S*-oxide sulfur atom (diastereomers!) are severe disadvantages as compared to the dithiane-method (see e.g. synthesis of **41a**);
(g) with α,β-unsaturated carbonyl compounds, the preferred addition of lithio-dithianes is in the 1,2-position, that of metallated thioacetal *S*-oxides **55** is in the 1,4-position (see Section 3.5).

Apart from the comments (a)–(g), it is not necessary at this point to go into details about the reactions of the *S*-oxides **55** since the types of transformations are very much the same as described above for dithiane anions. Tables 9 and 10 contain a summary of the published examples of the reactions covered in this section and leading to compounds **56**. In the case of addition to aromatic aldehydes, with Triton B as base, and to nitriles, the isolated products are of type **57** because dehydration reactions (to **57**, R^3 = H, R^2 = aryl) and tautomerization reactions (to **57**, $R^3 = NH_2$), respectively, occur; these enaminoketene *S*,*S*-acetal *S*-oxides **57** are transformed to amino acid esters **58**, $R^3 = NH_2$, by a sequence of steps involving a Pummerer-type rearrangement and reductive desulfurization. A brief survey of the chemistry of methyl methylthiomethyl sulfoxide is available[238].

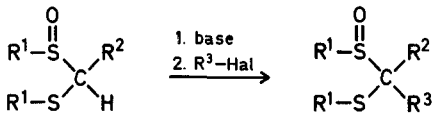


Preparation of Didodecyl Ketone from Dodecyl Bromide[240]:
Procedure: see *Synthesis* **1974** (2), 117–118.



Olefination of Benzaldehyde with Methyl Methylthiomethyl Sulfoxide[236]:
To a solution containing methyl methylthiomethyl sulfoxide (2.57 g, 20.7 mmol) and benzaldehyde (3 ml) in tetrahydrofuran (5 ml) is added 40% Triton B solution in methanol (2 ml) and the resultant mixture is refluxed for 4 h. Separation by column chromatography on silica gel gives the ketene *S*,*S*-acetal monosulfoxide, yield 3.99 g (91%); b.p. 149–150°/0.08 torr.

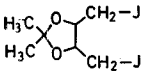
Table 9. Alkylation of *S*,*S*-Acetal *S*-Oxides with Organic Halides and Tosylates



56

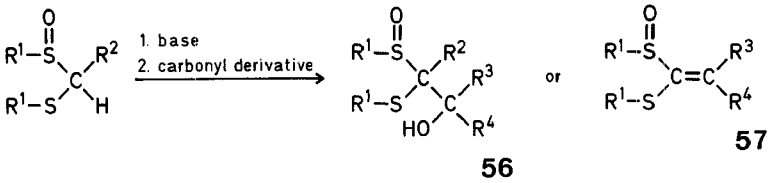
R^1	R^1	R^2	Base	Electrophile R^3-Hal	Yield [%]	Reference
Simple alkylation:						
CH_3	CH_3	H	NaH	alkyl iodide, (subst.)-benzyl bromide	37–92[a]	232
C_2H_5	C_2H_5	H	n-C_4H_9Li or $LiN(C_3H_7\text{-}i)_2$	n- or isoalkyl bromide or iodide or allyl bromide	95	233
—$(CH_2)_3$—		H	n-C_4H_9Li	methyl iodide or benzyl bromide	14–24	234
CH_3	CH_3	H	NaH	 X = 2- or 4-Cl or -Br, 2,6-Cl_2 or -Br_2	10–74[b]	239
C_2H_5	C_2H_5	C_2H_5	n-C_4H_9Li or $LiN(C_3H_7\text{-}i)_2$	n-alkyl or allyl bromide	90[c]	233
double alkylation:						
CH_3	CH_3	H	2 NaH	2 n-alkyl bromide	54–81[c]	240
CH_3	CH_3	H	2 NaH	2 ThpO—$(CH_2)_{11}$—Br	75[c]	240

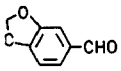
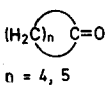
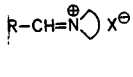
Table 9. (Continued)

R^1	R^1	R^2	Base	Electrophile R^3-Hal	Yield [%]	Reference
cyclization:						
CH_3	CH_3	H	2 KH	X—$(CH_2)_3$—X X = Br, OTos	87–91[d]	235
CH_3	CH_3	H	2 KH	branched chain dibromides	76–80[d]	235
CH_3	CH_3	H	2 KH	$(Cl—CH_2—CH_2—)_2O$	66[c]	241
CH_3	CH_3	H	2 KH	$(Cl—CH_2—CH=)_2$	75	241
CH_3	CH_3	H	2 n-C_4H_9Li	TosO—$(CH_2)_n$—OTos n = 2, 3, 4, 5, 6	78–91	241
CH_3	CH_3	H	2 KH	Br—$(CH_2)_n$—Br n = 2, 3, 4, 5, 6	trace–88	241
CH_3	CH_3	H	2 n-C_4H_9Li	Br—$(CH_2)_n$—Br n = 2, 3, 4, 5, 6	33–80	241
CH_3	CH_3	H	2 n-C_4H_9Li		53[c]	242

[a] Yields based on reacted *S*-oxide except for 4-methoxybenzyl bromide (79%) and 3,4-methylenedioxybenzyl bromide (62% based on reacted electrophile).
[b] Yield for 2-bromopyridine: 74% after conversion to carbonyl compound, similarly for 2,6-dibromopyridine (61%), 2,6-dichloropyridine (42%), and 4-chloropyridine (43%).
[c] Yields after conversion to ketone.
[d] Yields based on unrecovered *S,S*-acetal *S*-oxide.

Table 10. Reactions of Carbonyl Compounds with *S,S*-Acetal *S*-Oxide Derivatives **55**

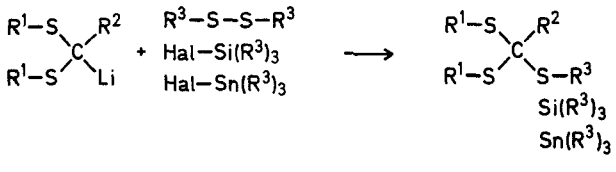


R^1	R^1	R^2	Base	Carbonyl Compound	Product Type	R^3	R^4	Yield [%]	Reference
C_2H_5	C_2H_5	H	n-C_4H_9Li	C_3H_7—CHO	**56**	C_3H_7	H	95–97	243
CH_3	CH_3	H	n-C_4H_9Li	C_6H_5—CHO	**56**	C_6H_5	H	—	189c
CH_3	CH_3	H	n-C_4H_9Li		**56**		H	—	189c
—$(CH_2)_3$—		H	n-C_4H_9Li	C_6H_5—CHO	**56**	C_6H_5	H	54	234
CH_3	CH_3	H	triton B	C_6H_5—CHO	**57**	C_6H_5	H	91[a]	236
CH_3	CH_3	H	triton B	subst.-benzaldehyde	**57**	subst.-phenyl	H	73–99[a]	236
C_2H_5	C_2H_5	C_2H_5	n-C_4H_9Li	C_3H_7—CHO	**56**	C_3H_7	H	70–89	243
C_2H_5	C_2H_5	H	n-C_4H_9Li		**56**	—	—	96–97	243
CH_3	CH_3	H	n-C_4H_9Li	n = 4, 5	**56**	—	—	—	189c
CH_3	CH_3	H	n-C_4H_9Li	$(C_6H_5)_2CO$	**56**	C_6H_5	C_6H_5	67	189e
—$(CH_2)_3$—		H	n-C_4H_9Li	$(C_6H_5)_2CO$	**56**	C_6H_5	C_6H_5	79	234
CH_3	CH_3	H	NaH	C_6H_5—$(CH_2)_2$—COOR	**56**	C_6H_5—$(CH_2)_2$—CO	H	50	224
C_2H_5	C_2H_5	H	n-C_4H_9Li	n-C_3H_7—COOR	**56**	n-C_3H_7—CO	H	90	243
CH_3	CH_3	H	NaH	(subst.) benzoate	**56**	subst.-phenyl-CO	H	66–83	244
—$(CH_2)_3$—		H	n-C_4H_9Li	C_6H_5—COOR	**56**	C_6H_5—CO	H	52	234
C_2H_5	C_2H_5	H (C_2H_5)	n-C_4H_9Li	H_3C—CO—Hal	**56**	H_3C—CO	H	90–92	243
C_2H_5	C_2H_5	H (C_2H_5)	n-C_4H_9Li	C_6H_5—CO—Hal	**56**	C_6H_5—CO	H	90	243
CH_3	CH_3	H	NaH	alkyl or aryl nitrile	**57**	alkyl or aryl	NH_2	72–77	237
CH_3	CH_3	H	n-C_4H_9Li		**56**		H	29–60	108b

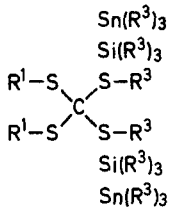
[a] Yield based on reacted *S*-oxide.

3.4. Reactions of Metallated *S,S*-Acetals with Heteroelectrophiles

As the most simple heteroelectrophiles one may consider $D^{\oplus}$ and $T^{\oplus}$; their reactions with lithiated 1,3-dithianes were used for the preparation of aldehydes 1-D and 1-T[245]. Lithiated *S,S*-acetals have been thiolated with disulfides[85,246] and attached to silicon[166,201,247], germanium[166,247a], and tin[1,195,247]. The derivatives **59** thus obtained are useful precursors of silyl and germanyl ketones (see also Table 4). More recently, the R^3S-, $(R^3)_3Si$-, and $(R^3)_3Sn$-substituted derivatives **59** and **60** have proved to be useful starting materials for other purposes as well. These are mainly described in other sections of this review, see Peterson-olefinations with **59b**, $R^2=Li$ (Section 5), Sn/Li-exchange with **59c** (Sections 1.1 and 5), and hydrolysis of orthotrithiocarboxylates **59a** (Section 2). We, therefore mention here only their preparation.



59 a-c

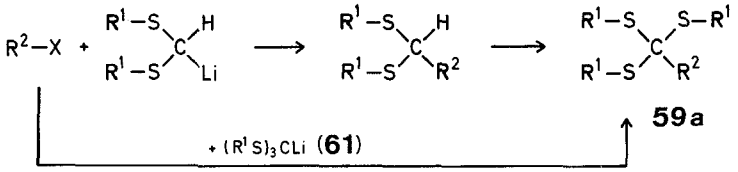


60 a-c

Scheme **L**

In all three cases it is necessary to use inverse addition and/or excess of heteroelectrophile if R^2 in **59** is hydrogen because otherwise the acidifying effect of the X-groups in **59** causes H/Li-exchange with the precursor, and consequently dihetero-derivatives **60** are formed[201,246].

Thiolation of a lithio-*S,S*-acetal is in effect, an oxidation of an aldehyde to an acid (R—CHO→ R—COOR[85,246]), since the alkylation of metallated orthotrithioformates **61** is a process inferior to the alkylation of the more reactive lithiated *S,S*-acetals, this "oxidation" is also part of a method to do the overall transformation RX→ R—COOR[83,84,248] (see Scheme **M**).



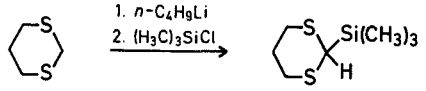
Scheme **M**

For examples of the preparation of orthotrithiocarboxylates **59a** by this route see Table 11. Open chain and cyclic silicon- and tin-substituted *S,S*-acetals **59** and **60** are also listed in Table 11.

Table 11. Thiolation, Silylation, and Stannylation of Lithio-*S,S*-acetals to give Products **59** and **60** (see Scheme **L**)

Acetal R^1	R^1	R^2	Hetero-electrophile	Product Type	Reference
—$(CH_2)_3$—		H	H_3C—S—S—CH_3	**59**	85
—$(CH_2)_3$—		*n*-C_4H_9	H_3C—S—S—CH_3	**59**	85
—$(CH_2)_3$—		cinnamyl	H_3C—S—S—CH_3	**59**	85
—$(CH_2)_3$—		C_6H_5	H_3C—S—S—CH_3	**59**	85
C_6H_5	C_6H_5	H	H_3C—S—S—CH_3	**59**	246
—$(CH_2)_3$—		H/CH_3	H_3C—S—S—CH_3	**59**	246
1,2-phenylene		H/CH_3	H_3C—S—S—CH_3	**59**	246
CH_3	CH_3	H	$(H_3C)_3SiCl$	**59**	201
—$(CH_2)_3$—		H	$(H_3C)_3SiCl$	**59**	201, 247
—$(CH_2)_3$—		ferrocenyl	$(H_3C)_3SiCl$	**59**	67
—CH_2—S—CH_2—		H	$(H_3C)_3SiCl$	**59**	201
C_6H_5	C_6H_5	H	$(H_3C)_3SiCl$	**59**	201
CH_3	CH_3	H	$(H_3C)_3SnCl$	**59**	68
—$(CH_2)_3$—		H	$(H_3C)_3SnCl$	**59**	187
—$(CH_2)_3$—		H	$(n\text{-}C_4H_9)_3SnCl$	**59**	187
CH_3	CH_3	$(H_3C)_3Sn$	$(H_3C)_3SnCl$	**60**	195
—$(CH_2)_3$—		$(H_3C)_3Sn$	$(H_3C)_3SnCl$	**60**	195

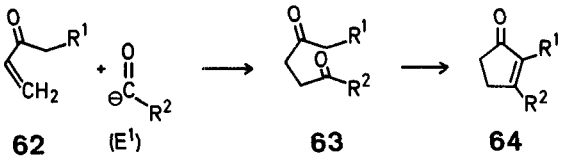
236 K. Ogura, G. Tsuchihashi, *Tetrahedron Lett.* **1972**, 1383.
237 K. Ogura, G. Tsuchihashi, *J. Am. Chem. Soc.* **96**, 1960 (1974).
238 Aldrich No. 806 Reader Service Card; available from Aldrich at request.
239 G. R. Newkome, J. M. Robinson, J. D. Sauer, *J. Chem. Soc. Chem. Commun.* **1974**, 410.
240 G. Schill, P. R. Jones, *Synthesis* **1974**, 117.
241 K. Ogura et al., *Tetrahedron Lett.* **1975**, 2767.
242 K. Ogura, M. Yamashita, G. Tsuchihashi, *Tetrahedron Lett.* **1976**, 759.
243 J. L. Herrmann, J. E. Richman, P. J. Wepplo, R. H. Schlessinger, *Tetrahedron Lett.* **1973**, 4707.
244 K. Ogura, S. Furukawa, G. Tsuchihashi, *Chem. Lett.* **1974**, 659.



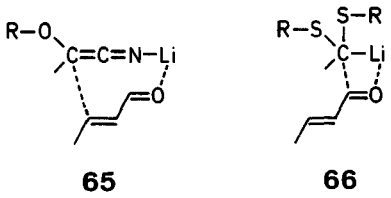
2-Trimethylsilyl-1,3-dithiane from 1,3-Dithiane[201b]:
1,3-Dithiane (24 g, 200 mmol) in tetrahydrofuran (200 ml) is combined at −30° with a solution of *n*-butyllithium (200 mmol) in tetrahydrofuran. After 3 h, the resultant solution of 2-lithio-1,3-dithiane is added to freshly distilled chlorotrimethylsilane (40 g, 370 mmol) with stirring at −60°. The mixture is held for 20 min at this temperature and then at +20° for 5 h. Work-up with pentane/water gives 2-trimethylsilyl-1,3-dithiane; yield: 36 g (94%); b.p. 75–77°/2 torr.

3.5. Michael-Addition of *S,S*-Acetal Metal Derivatives

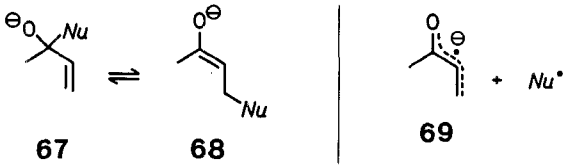
This reaction is of special importance because it allows one to synthesize 1,4-dicarbonyl compounds **63** from α,β-unsaturated carbonyl systems **62**. The products **63** are much sought after as precursors of jasmonoids, rethrolonoids, and prostanoids **64**[16,17]. All C—C-bond-forming syntheses of these diketones with an even number of carbon atoms between the carbonyl functions (see Section 1) must, at some stage, involve an umpolung of reactivity. Thus almost all methods of carbonyl umpolung have been tested for their applicability to this problem (see also Section 7).



Metallated thioacetals show a high preference for non-conjugate 1,2-addition to α,β-unsaturated carbonyl compounds. We originally stated[1] that 2-lithio-1,3-dithianes do not undergo Michael-type 1,4-additions. A possible explanation was offered[249] to account for the difference in this respect between thioacetal-derived and cyanohydrin-based nucleophilic acylating reagents: since coordination of the metal with the oxygen atom of the Michael-acceptor may be important, it was argued that the α-cyano-carbon atom can reach the β-carbon of the unsaturated system as shown in **65** while the nucleophilic center of a lithiated thioacetal in the complex **66** cannot.



We believe that this is too simple a picture because of some observations which we will describe below. One must also consider the possibility that the equilibrium **67**⇌**68** is established by which a kinetically formed 1,2-adduct may equilibrate with the thermodynamically more stable Michael-product[258j]; steric bulk of the attacking nucleophile could influence the course of the reaction. Furthermore, a correlation between the redox potentials of the components and the occurrence of Michael-additions was found recently[250]. Finally, radical pair formation, **69**, by one-electron-transfer from the nucleophile to the acceptor may initiate a conjugate addition[251,252].



Many more mechanistic studies will be necessary for a full understanding of the factors responsible for 1,2- or 1,4-addition.

3.5.1. Lithium and Copper *S,S*-Acetals which form Michael-Adducts with Unsaturated Carbonyl Compounds

It is found that additionally anion-stabilizing groups enhance the tendency of metallated *S,S*-acetals **70** toward conjugate addition. Thus, the only published example of a smooth 1,4-addition of a lithio-dithiane **70a** to an unsaturated carbonyl compound (2-butenolide) is that leading to **71**[253]. On the other hand, neither the trimethylsilyl nor the trimethylstannyl derivatives **70a**[187,201] nor the cuprates **72a**[254] added in a 1,4-fashion to simple α,β-unsaturated ketones. Open chain cuprates **72b**[89b] and methyl- or phenyl *S,S*-acetals **70b**[68,255] react in many cases exclusively with formation of 1,4-dicarbonyl mono-*S,S*-acetals **73**.

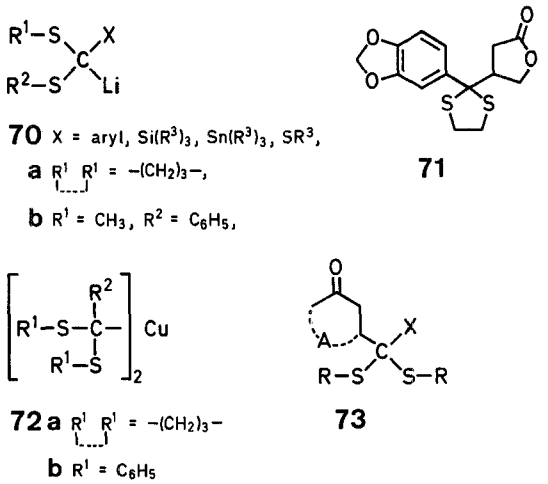
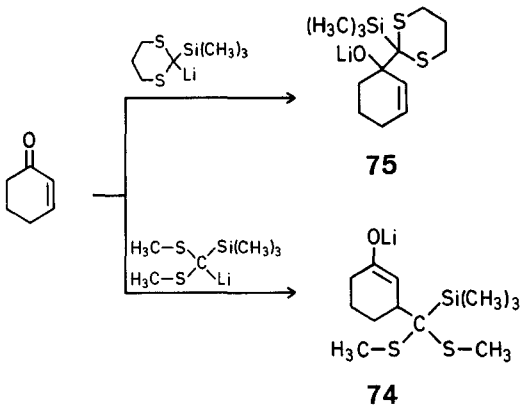


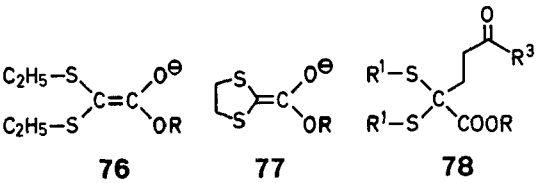
Table 12 lists examples of the various products of type **73**. No straightforward explanation can be offered for the pronounced differences in reactivity between such closely related systems as **70a** and

[245] (a) W. Meister et al., *J. Am. Chem. Soc.* **91**, 4452 (1969).
(b) P. B. Woller, N. H. Cromwell, *J. Org. Chem.* **35**, 888 (1970).
(c) A. Hessing, H. W. Schneeberger, *Chem. Ber.* **105**, 2447 (1972).
(d) A. R. Battersby, J. E. Kelsey, J. Staunton, K. E. Snekling, *J. Chem. Soc. Perkin Trans. 1* **1973**, 1609.
(e) F. Mutterer, J. P. Fleury, *J. Org. Chem.* **39**, 640 (1974).

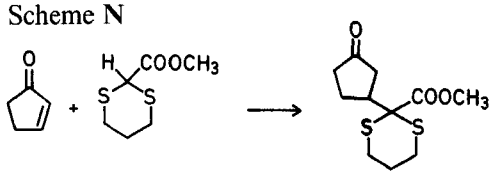
70b, $R^1 = CH_3$. We have confirmed that we are dealing with inherently different reactivity in this case: quenching of the reaction leading to **74** after 15 min at −100° gave no indication of kinetic 1,2-addition while only **75** was formed with the cyclic analogue[195]; the same is true for the addition of **70b**, $R^1 = CH_3$ or C_6H_5, X = SCH_3 or SC_6H_5, respectively.



If the *S,S*-acetal anion stability is further increased, Michael-addition becomes the preferred process. Table 12 contains many examples of useful 1,4-additions of enolate type anions **76** and **77** to unsaturated ketones, esters, lactones, and amides[58, 69] furnishing 1,2,5-tricarbonyl derivatives **78** (Scheme N).

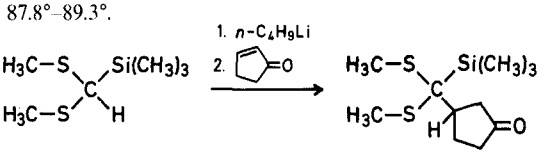


Scheme N



Preparation of 3-(2-Methoxycarbonyl-1,3-dithian-2-yl)-1-cyclopentanone[258a]:

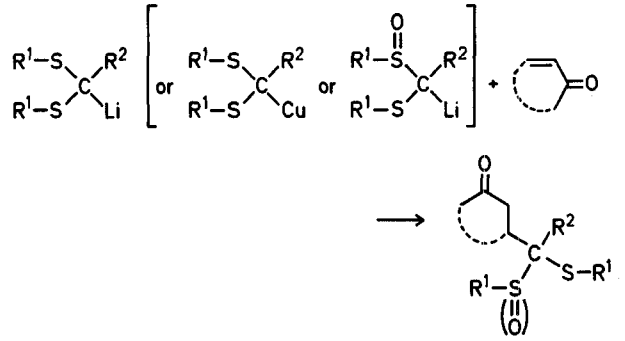
To a solution of lithium diisopropylamide (5.0 mmol) stirred in tetrahydrofuran (15 ml) under argon is added at −78° a solution of 2-methoxycarbonyl-1,3-dithiane (0.89 g, 5.0 mmol) in tetrahydrofuran (5 ml). After 20 min, neat 1-oxo-2-cyclopentene (0.42 ml, 0.41 g, 5.0 mmol) is added. Stirring at −78° is continued for an additional hour, after which anhydrous methanol (0.4 ml) is added to quench the adduct-enolate. The mixture is allowed to warm to ambient temperature, is then poured into saturated aqueous ammonium chloride solution (15 ml) and extracted with dichloromethane. The organic layers are dried (Na_2SO_4) and the solvent removed to afford the ketoester as an oil which slowly crystallized; yield: 1.25 g (96%). An analytical sample was prepared by recrystallizing from ether/dichloromethane/pentane; m.p. 87.8°–89.3°.



Michael-Addition of Bis[methylthio]-trimethylsilylmethyllithium to Cyclopentenone[68]:

A solution of bis[methylthio]trimethylsilylmethane (2.71 g, 15 mmol) in tetrahydrofuran (30 ml) is combined with *n*-butyllithium (15 mmol) solution at −60° to −70°. The temperature is allowed to rise to 0° within 3–5 h. The reaction mixture is cooled to −78° and cyclopentenone (1.23 g, 15 mmol) is added. After 2 h, the temperature is allowed to rise to +20° within 5 h. The reaction mixture is poured into water and extracted with pentane. After washing with water and brine, drying over sodium sulfate and removing the solvent, the Michael-adduct is obtained by distillation; yield: 2.86 g (73%).

Table 12. Michael-Type Addition Reactions of Metallated *S,S*-Acetals

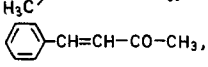
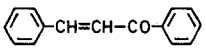
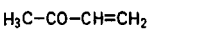
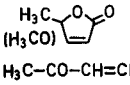


R^1	R^1	R^2	Carbonyl compound	Yield [%]	Reference
Lithio-*S,S*-acetal:					
CH_3	CH_3	$(H_3C)_3Si$	$(H_2C)_n$=O, n = 1, 2, 3	60–78 71–75[a]	68 68
CH_3	CH_3	$(H_3C)_3Sn$[b]	$(H_2C)_n$=O, n = 1, 2	65[a]–75	68
C_2H_5	C_2H_5	$COOCH_3$	H_3C–CO–CH=CH_2	93	69
C_2H_5	C_2H_5	$COOCH_3$	$(H_2C)_n$=O, n = 1, 2	96–97	69
C_2H_5	C_2H_5	$COOCH_3$	H_2C=CH–$COOCH_3$ (t-C_4H_9)	92–95	69
C_2H_5	C_2H_5	$COOCH_3$	H_3CO, O, =O	92	69
–$(CH_2)_2$–		$COOC_2H_5$	Cl, H_3C, CH_3, =O	94	58
–$(CH_2)_2$–		$COOC_2H_5$	H_3C–CH=CH–$COOC_2H_5$	90	58
–$(CH_2)_2$–		$COOC_2H_5$	O, =O, H_3COOC	70	58
–$(CH_2)_2$–		$COOC_2H_5$	α,β-unsaturated keto sugars	–	258 g
–$(CH_2)_3$–		H_3C–S	=O	–	258 h
CH_3	CH_3	H_3C–S	α,β-unsaturated lactone	–	258 i
C_6H_5	C_6H_5	C_6H_5–S	R–CH=CH–CO–R′	60–95	255
C_6H_5	C_6H_5	C_6H_5–S	=O, R	65–95	255

246 D. Seebach et al., *Chem. Ber.* **105**, 3280 (1972).

247 (a) A. G. Brook, J. M. Duff, P. F. Jones, *J. Am. Chem. Soc.* **89**, 431 (1967).
(b) E. J. Corey, D. Seebach, R. Freedman, *J. Am. Chem. Soc.* **89**, 434 (1967).

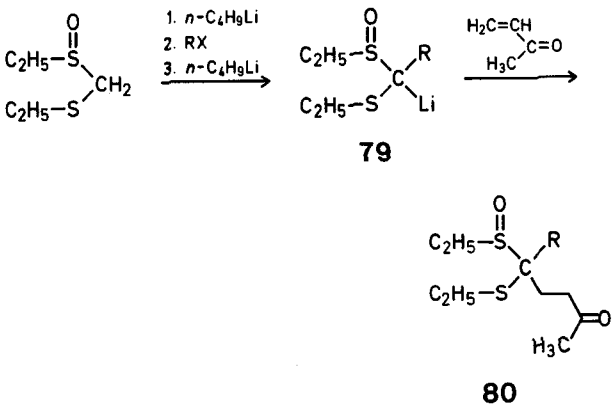
Table 12. (Continued)

R^1	R^1	R^2	Carbonyl compound	Yield [%]	Reference
Cuprate:					
C_6H_5	C_6H_5	H, CH_3, n-C_5H_{11}, C_6H_5	H_3C–CO–CH=CH_2	73–94	89 b, 256
C_6H_5	C_6H_5	C_6H_5	$(H_3C)_2C$=CH–CO–CH_3,  –CH=CH–CO–CH_3,  –CH=CH–CO– 	82–94	89 b
C_6H_5	C_6H_5	C_6H_5–S	H_3C–CO–CH=CH_2	70	89 b
C_6H_5	C_6H_5	CH_3	α,β-unsaturated keto sugars	–	258 g
Lithio-*S,S*-Acetal *S*-Oxide:					
C_2H_5	C_2H_5	H	H_3C–CH=CH–$COOCH_3$	90	257
C_2H_5	C_2H_5	H(C_2H_5)	H_2C=C(S–CH_3)(COOCH_3)	93–94	257
C_2H_5	C_2H_5	C_2H_5	α,β-unsat. carbonyl	70–96	257
C_2H_5	C_2H_5	C_2H_5		82–85	257
C_2H_5	C_2H_5	n-C_6H_{13}	H_3C–CO–CH=CH_2	90[c]	258
C_2H_5	C_2H_5	C_2H_5–C≡C–$(CH_2)_2$	H_3C–CO–CH=CH_2	96[c]	258

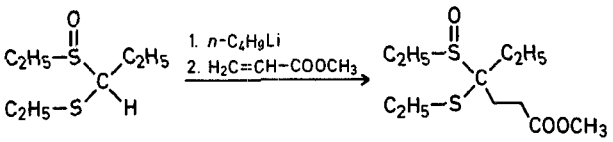
[a] Yield includes subsequent alkylation of the enolate.
[b] Also examples with $R^2=(n\text{-}C_4H_9)_3Sn$ and $(C_6H_5)_3Sn$ are reported.
[c] Yield includes subsequent hydrolysis.

3.5.2. Michael-Additions of Lithiated *S,S*-Acetal *S*-Oxides to α,β-Unsaturated Carbonyl Derivatives

In contrast to the simple thioacetals and very much like the ester-stabilized representatives, **76** and **77**, the ethyl *S,S*-acetal *S*-oxides, **79**, have been shown to add smoothly at the β-carbon atom of α,β-unsaturated ketones, esters, and lactones[257,258].



This is an important field of application of the *S*-oxide anions and a great extension of the usefulness of metallated *S,S*-acetals as nucleophilic acylating reagents. Actual examples may be found in Table 12 (see also Section 7).



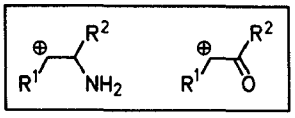
Michael-Addition of Propanal Ethyl-*S,S*-acetal *S*-Oxide to Methyl Acrylate[257]:
A solution of the sulfoxide (1 equivalent, 1 molar in tetrahydrofuran) is treated at 0° with *n*-butyllithium (1 equivalent) to afford quantitatively the corresponding lithium derivative in 20 min. After cooling the solution to −78°, a 1.8 molar tetrahydrofuran solution of the α,β-unsaturated ester (1.1 equivalents) is added and the resultant mixture is stirred at this temperature for 2 h. The mixture is then poured into saturated aqueous ammonium chloride solution and extracted several times with dichloromethane. The combined extracts are washed 3 times with water, dried, and the solvent evaporated to give the product; crude yield: 95%.

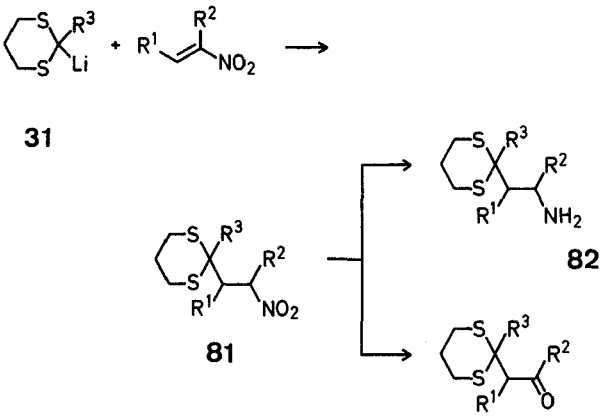
3.5.3. Conjugate Addition of Thioacetal-Masked Acyl Anions to Nitroalkenes

The earliest cases of Michael-type additions of lithiodithianes reported[1] were those to nitroalkenes. The product **81** can be reduced to β-amino-carbonyl derivatives **82** or converted by the Nef-reaction to monoprotected 1,3-diketones or β-ketoacids **83**[179,207] (Scheme **O**). In these reactions the nitroalkene plays the role of a β-aminocation and of an enolate cation, respectively, as indicated in the box above the nitroalkene formula. Since both components of the C—C-bond-forming process leading to **82** and **83** thus have a reactivity umpolung, we obtain products with

[248] G. A. Wildschut, H. J. T. Bos, L. Brandsma, J. F. Arens, *Monatsh. Chem.* **98**, 1043 (1967).

an odd number of carbon atoms between the two functional groups. Compound **82**, for instance, has the same functionality pattern as a Mannich-base. Again, the yields of the adducts **81** clearly depend upon the stability of the dithiane anions employed; it is important to work at low temperatures to avoid side reactions; examples are collected in Table 13.





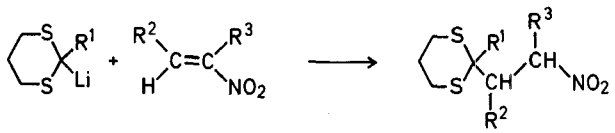
Scheme O

Addition of 2-(3,4-Methylenedioxyphenyl)-1,3-dithiane to 3,4-Methylenedioxy-ω-nitrostyrene[179]**:**

The dithiane (6.0 g, 25 mmol) in tetrahydrofuran (60 ml) is added at −78° to *n*-butyllithium (25.5 mmol). The mixture is stirred for 1 h at −30° and then a solution of the nitroalkene (4.6 g, 24 mmol) in tetrahydrofuran (90 ml) is added dropwise at −78°. After 2 h, acetic acid (2 ml) is added and the temperature is allowed to rise to −20° within 30 min. The reaction mixture is poured into dichloromethane/water. After removing the solvent, an oil is obtained, which crystallizes occasionally; yield: 7.3 g (70%).

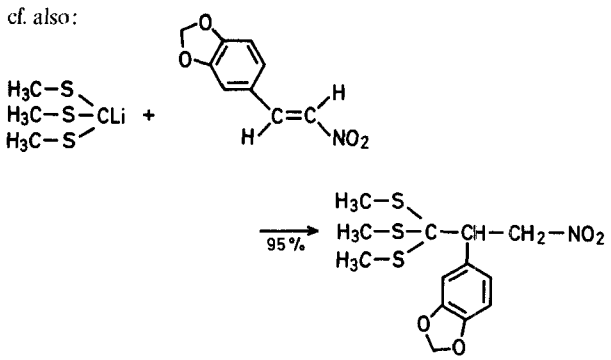
Table 13. Addition Reactions of Metallated 1,3-Dithianes **31** to Nitroalkenes[179] and Vinylphosponium Salts[205]

(a) Additions to Nitroalkenes:



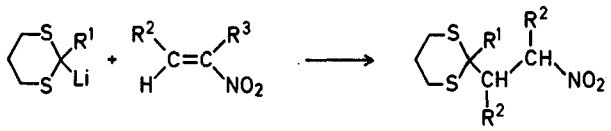
R^1	R^2	R^3	Yield [%]
H	CH_3	H	65
H	X-C6H4-	H	25–75
H	X-C6H4-	CH_3	50–70
H_3C	H_3CO-C6H4-	H	25
C6H5-	3,4-methylenedioxyphenyl-	H	36
X^1-C6H4-	X^2-C6H4-	H	70–90
H-CO-	3,4-methylenedioxyphenyl-	H	68
H_3CO-CO-	3,4-methylenedioxyphenyl-	CH_3	70
$(H_3C)_2N$-CO	3-OCH_3-4-H_3CO-C6H3-	H	88
N-CO-	X-C6H4-	H	83–87

cf. also:



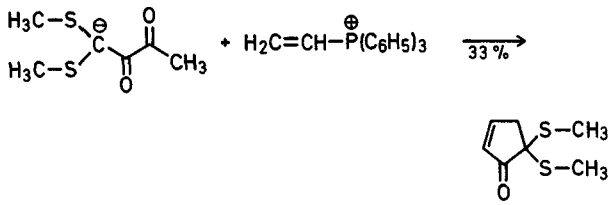
249 G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **96**, 5272 (1974).
250 H. O. House, M. J. Umen, *J. Am. Chem. Soc.* **94**, 5495 (1972).
251 H. O. House, P. D. Weeks, *J. Am. Chem. Soc.* **97**, 2770, 2778, 2785 (1975).
252 See also radical type Michael-additions of boranes: H. C. Brown, M. M. Midland, *Angew. Chem.* **84**, 702 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 692 (1972).
253 F. E. Ziegler, J. A. Schwartz, *Tetrahedron Lett.* **1975**, 4643.
254 D. Seebach unpublished results, Karlsruhe 1969–1971.
255 A. R. B. Manas, R. A. J. Smith, *J. Chem. Soc. Chem. Commun.* **1975**, 216.
256 T. Cohen, G. Herman, J. R. Falck, A. J. Mura Jr., *J. Org. Chem.* **40**, 812 (1975).
257 J. L. Herrmann, J. E. Richman, R. H. Schlessinger, *Tetrahedron Lett.* **1973**, 3271.
258 J. L. Herrmann, J. E. Richman, R. H. Schlessinger, *Tetrahedron Lett.* **1973**, 3275.
(a) D. Seebach, M. Hoekstra, unpublished results, Gießen, 1975.
(b) H. Muxfeldt, W.-D. Unterweger, G. Helmchen, *Synthesis*, **1976**, 694.
(c) M. Hojo, R. Masuda, *Synthesis* **1976**, 678.
(d) L. Pichat, J. P. Beaucourt, *J. Labelled Compds. Radiopharm.* **12**, 31 (1976); *C. A.* **85**, 93976 (1976).
(e) R. S. Grasserode, P. S. Tobin, M. S. Wheeler, *Synth. Commun.* **6**, 377 (1976).
(f) S. Takano, S. Hatakeyama, K. Ogasawara, *J. Am. Chem. Soc.* **98**, 3022 (1976).
(g) H. Paulsen, W. Koebernick, H. Koebernick, *Tetrahedron Lett.* **1976**, 2297.
(h) W. D. Woessner, *Chem. Lett.* **1976**, 43.
(i) R. E. Damon, R. H. Schlessinger, *Tetrahedron Lett.* **1976**, 1561.
Note added in Proof:
(j) This has just been observed: E. Juaristi, E. L. Eliel, *Tetrahedron Lett.* **1977**, 543.
(k) cf. A new variant of this process: B. M. Trost, K. Hiroi, *J. Am. Chem. Soc.* **98**, 4313 (1976).

(b) Additions to Vinylphosphonium Salts:

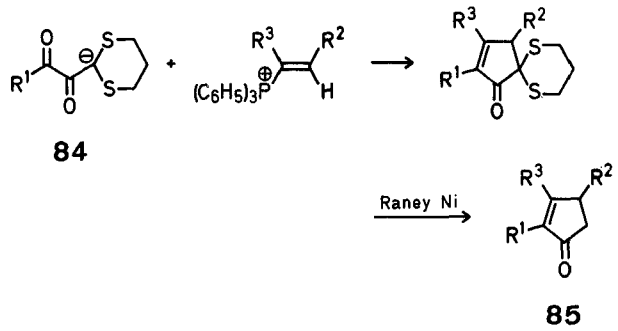


R^1	R^2	R^3	Yield [%]
CH_3	H	H	55
CH_3	H	CH_3	52
CH_3	CH_3	H	7
C_2H_5	H	H	63
C_2H_5	H	CH_3	35
C_2H_5	CH_3	H	9
n-C_5H_{11}	H	H	31
n-C_5H_{11}	H	CH_3	51

cf. also:



A reaction related to the nitroalkene addition has been reported for the tricarbonyl derivatives **84** (preparation, see Table 5) which combine with vinylphosphonium salts to give cyclopentenones **85** as final products[205]. See also Table 14 (second part).



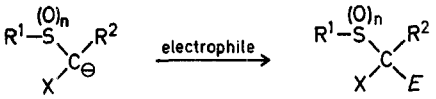
84

85

4. Miscellaneous Sulfur-Containing Reagents

4.1. Nucleophilic Acylations with Diheterosubstituted Anionic Reagents ($XYRC^{\ominus}$)

It is obvious that in principle one or both[259] sulfur atoms of *S,S*-acetals can be replaced by another group X for the purpose of a nucleophilic acylation process. Depending on the nature of the group X in the anion **86**, the conditions of anion generation, the reactivities, and the modes of setting free of the desired final carbonyl compound product may vary within a wide range. This range may even be extended if the sulfur atom is oxidized to the sulfoxide or sulfone state. Some recent applications are listed below in Table 14.



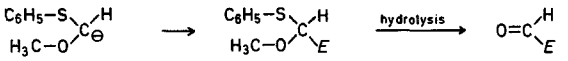
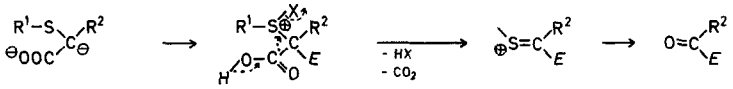
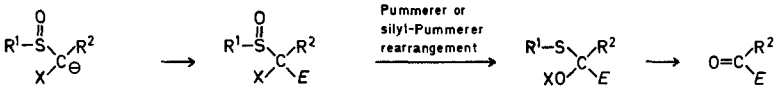
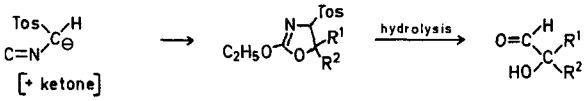
86 n = 0, 1, 2

Entry 1 represents the first use of a metallated *O,S*-acetal[260], entry 2 employs a doubly metallated[261,262], α-thiolated carboxylic acid[263] as nucleophile and an oxidative decarboxylation to furnish the carbonyl compound[264], entry 3 shows that α-sulfoxide anions may be considered as acyl anion equivalents by virtue of the Pummerer rearrangement[265] – a silyl-modification of which was recently proposed[266,267] [generally and, in many cases advantageously, the rôle of the proton in organic reactions can be taken over by a silyl group[268]], in entry 4 a sulfonyl- and isonitrile-stabilized[269] anion – generated with thallium(I) ethoxide in ethanol/dimethoxyethane – serves as a masked formyl anion[270,271].

These methods complement those covered in previous sections: for entry 1 the acid hydrolysis is facile; 2 is useful because an α-carbon atom of a carboxylic acid can be readily thiolated[263,272], reacted with electrophiles by the above sequence, and, in effect, converted to a carbonyl group; for entry 3, X = H, rather drastic conditions are required for the Pummerer rearrangement, whereas, with $X = SiR_3$, the conditions are much milder; finally, the usefulness of entry 4 is based on the mild basic conditions needed for the C—C bond-forming step and the fact that the rather sensitive α-hydroxy-aldehydes are accesible in 40–80% overall yields from ketones (the reaction can also be carried out so that carboxylic acids $R^1R^2CH—COOH$[273] or nitriles $R^1R^2CH—CN$[274] are the products).

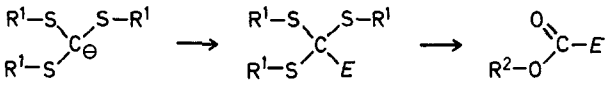
[259] This is not subject of the present review, see Lit.[7,8].
[260] B. M. Trost, C. H. Miller, *J. Am. Chem. Soc.* **97**, 7182 (1975).
[261] P. A. Grieco, C. L. J. Wang, *J. Chem. Soc. Chem. Commun.* **1975**, 714.
[262] B. M. Trost, Y. Tamaru, *Tetrahedron Lett.* **1975**, 3797.
[263] B. M. Trost, T. N. Salzmann, *J. Am. Chem. Soc.* **95**, 6840 (1973).
[264] B. M. Trost, Y. Tamaru, *J. Am. Chem. Soc.* **97**, 3528 (1975).
[265] S. Iriuchijima, K. Maniwa, G. Tsuchihashi, *J. Am. Chem. Soc.* **96**, 4280 (1974); **97**, 596 (1975).
[266] A. G. Brook, D. G. Anderson, *Can. J. Chem.* **46**, 2115 (1968). E. Vedejs, M. Mullins, *Tetrahedron Lett.* **1975**, 2017.
[267] F. A. Carey, O. Hernandez, *J. Org. Chem.* **38**, 2670 (1973).
[268] I. Fleming, *Chem. Ind. (London)* **1975**, 449.
[269] D. Hoppe, *Angew. Chem.* **87**, 879 (1974); *Angew. Chem. Int. Ed. Engl.* **13**, 789 (1974).
[270] O. H. Oldenziel, A. M. van Leusen, *Tetrahedron Lett.* **1974**, 163, 167.
[271] See also: U. Schöllkopf, E. Blume, *Tetrahedron Lett.* **1973**, 629.
[272] D. Seebach, M. Teschner, *Tetrahedron Lett.* **1973**, 5113; see also: Lit.[214].

Table 14. Nucleophilic Acylations with Substituted Anionic Reagents

Entry	Nucleophile of type **86**	Process leading to carbonyl compound
1		
2	 $R^1 = CH_3, C_6H_5$; $R^2 = H$, alkyl	
3	 X = H, $Si(CH_3)_3$	
4	 [+ ketone]	

4.2. Reactions of $(RS)_3C^{\ominus}$-Reagents and of Thioformyl Anions with Electrophiles

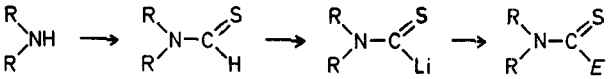
As mentioned before (Sections 2 and 3.4) orthotrithiocarboxylates **88** can be hydrolyzed to acid derivatives **89**.



87 **88** **89**

Therefore, the reaction sequence **87**→**88**→**89**, constitutes a nucleophilic carboxylation (**89**, R^2=H) or alkoxycarbonylation (**89**, R^2=alkyl). The various methods of generating derivatives of **87** [H/Li- and SR^1/Li-exchange, and R^1Li-addition to $(R^1S)_2C{=}S$[84,275]] and reactions with electrophiles are collected in Table 15. For the use of reagents of type **87**, with $Si(R^3)_3$ or $Sn(R^3)_3$ in place of one R^1—S *group, see Sections 3.5.1 and 5.*

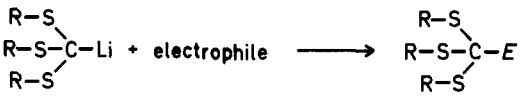
Among the rare cases in which unprotected alkali acyls are directly available[8], are the lithiated aminothiocarbonyl derivatives **90**[276].



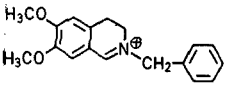
90 **91**

These compounds are formed from their thioformamide precursors by treatment with lithium diisopropylamide in tetrahydrofuran at −100° and react especially well with carbonyl compounds as electrophiles to give the corresponding products **91**. This method has a broad scope with respect to the secondary amines which are originally thiocarbonylated; a full account has been published[276b]; Table 16 contains some examples.

Table 15. Reactions[a] of Metallated Orthotrithiocarboxylates (**87**) with Electrophiles



87

R (or 3R)	Electrophile	Yield [%]	Reference
H_3C		90	207
C_2H_5	$H_2C{=}CH{-}CH_2{-}Br$	76	248
$H_3C{-}C(CH_2{-})_3$	i-C_3H_7–J, C_6H_5–CHO,  , $(C_6H_5)_2C{=}O$, C_2H_5OCOCl	52-79	83
C_6H_5	H_3C–Hal, C_2H_5–Hal, n-C_3H_7–Hal, i-C_3H_7–J, n-C_4H_9–Hal, $H_2C{=}CH{-}CH_2$–Hal	>22->80	83, 84, 248
C_6H_5		>25	84
C_6H_5	n-C_3H_7–CHO, C_6H_5–CHO	>75->78	83, 84
C_6H_5	C_2H_5OCOCl	15	83, 84
C_6H_5	CO_2	82	248

[a] See also Michael additions to α,β-unsaturated carbonyl compounds[255].

[273] U. Schöllkopf, R. Schröder, E. Blume, *Justus Liebigs Ann. Chem.* **766**, 130 (1972).
U. Schöllkopf, R. Schröder, *Angew. Chem.* **84**, 289 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 311 (1972).

[274] O. H. Oldenziel, A. M. van Leusen, *Synth. Commun.* **2**, 281 (1971); *Tetrahedron Lett.* **1973**, 1357.

[275] P. Beak, J. W. Worley, *J. Am. Chem. Soc.* **94**, 597 (1972).

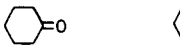
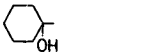
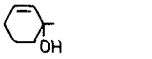
[276] (a) D. Enders, D. Seebach, *Angew. Chem.* **85**, 1104 (1973); *Angew. Chem. Int. Ed. Engl.* **12**, 1014 (1973).
(b) D. Seebach, W. Lubosch, D. Enders, *Chem. Ber.* **109**, 1309 (1976).

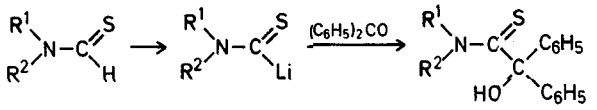
[277] G. Büchi, H. Wüest, *J. Org. Chem.* **34**, 1122 (1969).
H. J. J. Loozen, *J. Org. Chem.* **40**, 520 (1975).

[278] (a) K. Kondo, D. Tunemoto, *Tetrahedron Lett.* **1975**, 1007.
(b) K. Kondo, D. Tunemoto, *Tetrahedron Lett.* **1975**, 1397.
(c) K. Kondo, D. Tunemoto, *Tetrahedron Lett.* **1975**, 2275.

Table 16. Reactions of Aminothiocarbonyl Derivatives **90** with Electrophiles[276b]

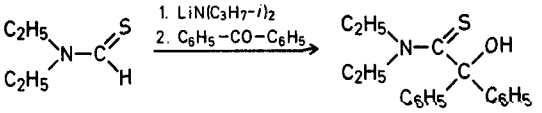
90 **91**

Electrophile	*E*	Yield [%]
H_3C-J	H_3C-	45
C_2H_5-CHO	$C_2H_5-CH(OH)-$	65
C_6H_5-CHO	$C_6H_5-CH(OH)-$	65
$(H_3C)_2C=O$	$(H_3C)_2C(OH)-$	75
		50
		50[a]
$(C_6H_5)(H_3C)C=O$	$(C_6H_5)(H_3C)C(OH)-$	50
$(C_6H_5)_2C=O$	$(C_6H_5)_2C(OH)-$	80
$(C_6H_5)(H_3CO)C=O$	$(C_6H_5)(H_3CO)C(OH)-$	75



R^1	R^2	Yield [%]
H_3C	t-C_4H_9	42
H_3C	$C_6H_5-CH_2$	79
H_3C	C_6H_5	29
C_2H_5	C_2H_5	83
n-C_4H_9	n-C_4H_9	64
t-C_4H_9	$H_2C=CH-CH_2$	54
$C_6H_5CH_2$	$C_6H_5CH_2$	70
$-(CH_2)_4-$		77
$-(CH_2)_5-$		79
$-(CH_2)_2-O-(CH_2)_2-$		68
$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		60

[a] Yield determined spectroscopically.



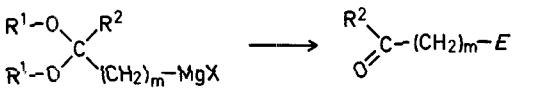
Addition of Diethylaminothiocarbonyllithium to Benzophenone[276b]: A solution of the thioformamide (10 mmol) in tetrahydrofuran (2 ml) is added at −100° within 1 min to a stirred solution of lithium diisopropylamide (10 mmol). After 3 min, the resultant yellow reaction mixture is combined with a solution of benzophenone (10 mmol) in tetrahydrofuran (10 ml). After stirring for 1 h at −70°, acetic acid (0.6 g, 10 mmol) is added and the reaction mixture is allowed to warm to room temperature. The solution is poured into water (70 ml), the aqueous mixture is extracted 3 times with dichloromethane/chloroform (1:1, 50 ml), the extract is washed with water, and dried (Na_2SO_4). The solvent is evaporated and the residue recrystallized from chloroform/ether/pentane to give the desired product; yield: 2.47 g (83%); m.p. 163°.

4.3. Umpolung of Carbonyl Reactivity with α-Phenylsulfonyl Nucleophiles and with Sulfur-Substituted Cyclopropanes

There is a classical method of carbonyl reactivity umpolung which uses *O*-acetal protected α-haloaldehydes and -ketones[13,27,87]. With the halides **92**, the attack by nucleophiles, with the Grignard reagents **93** that by electrophiles, can be directed to carbon atoms which have the opposite reactivity in normal carbonyl- and vinylogous carbonyl chemistry.

92

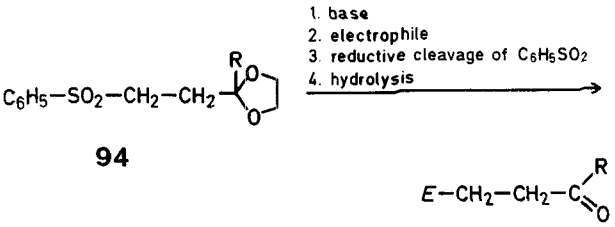
$N^{2,4,\cdots}$-umpolung with n = 1, 3, ... (odd)



93

$E^{3,5,\cdots}$-umpolung with m = 2, 4, ... (even)

The disadvantage with Grignard compounds is that they do not cleanly undergo coupling with halides (E = alkyl) and that they cannot be easily acylated with acid derivatives (E = acyl). These problems are absent in the corresponding, highly nucleophilic sulfonyl-substituted derivatives. For the E^3-case, **94** is applied as shown in the formula below[278,279]. The simple and smooth reductive removal of phenylsulfonyl groups with Na/Hg[279], Al/Hg[278], Raney nickel, or lithium/methylamine and its elimination to form alkenes[278] make α-phenylsulfonyl carbanions useful intermediates for C—C-coupling reactions[280].



94

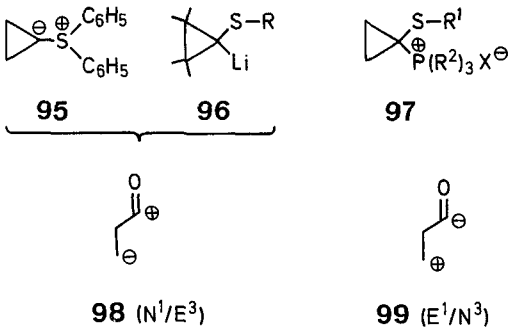
Sulfur-substituted cyclopropanes are also applicable to carbonyl reactivity umpolung: the ylide **95**[281] and the lithiocyclopropanes **96** with $R = C_6H_5$[281] and

[279] M. Julia, B. Badet, *Bull. Soc. Chim. Fr.* **1975**, 1363.

[280] The use of the cyano group for this purpose is also possible: M. Larchêveque, T. Cuvigny, *Tetrahedron Lett.* **1975**, 3851, and literature cited therein.

[281] B. M. Trost, *Acc. Chem. Res.* **1974**, 85; *Topics in Current Chemistry* **41**, 1 (1973).

CH_3[65,231] are synthons with reactivity pattern **98** (E^3-umpolung), while the phosphonium salt **97**[282] represents the synthon **99** with E^1-umpolung.



The use of unsubstituted cyclopropanes **95** and **96** has been reviewed extensively[281], a full paper on substituted H_3C—S-derivatives **96** has appeared[65], and a special review on cyclopropanes in reactivity umpolung is being prepared[283].

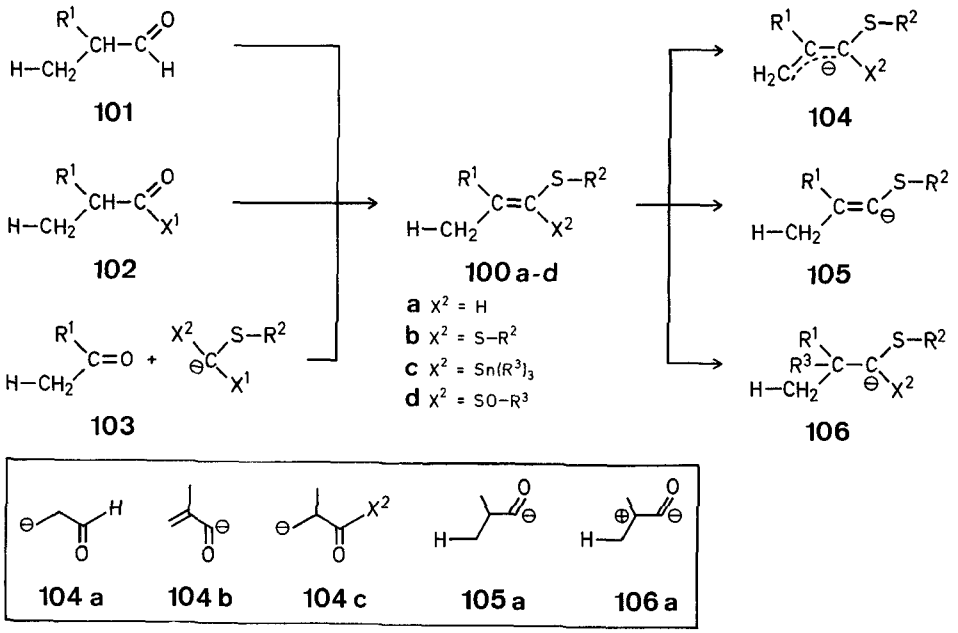
5. The Use of Vinyl Sulfides and Ketene *S,S*-Acetal Derivatives (E^1-, N^2-, N^4-Type Reactions)

The nucleophilic acylating reagents (E^1-reactions) treated previously (Sections 3. and 4.) were all of the acetal type ($XY\overset{\ominus}{C}R$). It is obvious that one should also be able to metallate[284] the thio-enol ethers **100a** of aldehydes **101** to give the nucleophiles **105** which are synthetically equivalent to **105a**. The thio-enol ethers **100a** are also available using the combination **103** ($X^2 = H$) by Peterson[285,286] or Wittig type olefinations[287]. The deprotonation sequence **100a**→**105** is not as clear cut as the corresponding metallation of acetal precursors because allylic protons, if present in **100a**, can be abstracted instead; this leads to the allylic anions **104**, ($X^2 = H$) which can react in the α- or γ-position (synthetic equivalent **104a**) of the heterosubstituents. Furthermore, addition of the proton-abstracting reagent to the thio-enol ether double bond may give **106** ($X^2 = H$).

Ketene *S,S*-acetals, **100b** prepared from acid derivatives **102**[82,288] or by the combination **103** ($X^2 = S—R^2$)[289] can similarly be converted to the allylic nucleophiles **104** which, depending upon the site of reaction with electrophiles, are equivalent to **104b** or **104c**. If **100b** reacts by way of addition of a nucleophile, **106** ($X^2 = S—R^2$) is formed. This means that the ketene *S,S*-acetal derivative may be considered as a synthon **106a** with reactivity umpolung at both the carbonyl carbon (nucleophilic acyl) and at the α-carbon atom (electrophilic enolate), i.e. as a ketene with reversed reactivities. The different modes of reaction of **100** can be controlled to a large extent by varying the conditions and the substituent X^2. Thus, reaction with *sec.*-butyllithium leads to abstraction of an α-proton from thio-enol ethers **100a** (→**105**) whereas treatment with lithium diisopropylamide tends to deprotonate an allylic carbon (→**104**). From the reaction of **100c** and an alkyllithium only **105** is obtained, while the addition to the double bond readily takes place with the ketene *S,S*-acetal *S*-oxides **100d** (→**106**, $X^2 = SO—R^2$). Similarly, the α- and ω-reactivities of **104** can be controlled to some extent. It is evident from these general remarks that compounds **100** have great synthetic potential. The different types of reactions are described in the following sections.

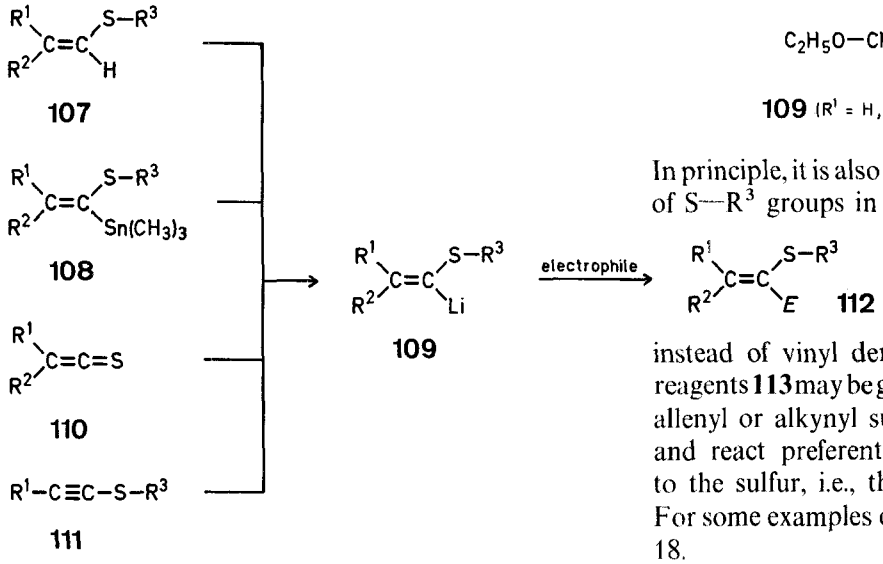
5.1. Generation and E^1-Reactions of α-Lithiovinyl Sulfides

As mentioned above, the precursors **107** and **108** of the reagents **109** are readily prepared by connective[285–287] or non-connective[294] methods. Compound **107** is best converted to **109** by treatment

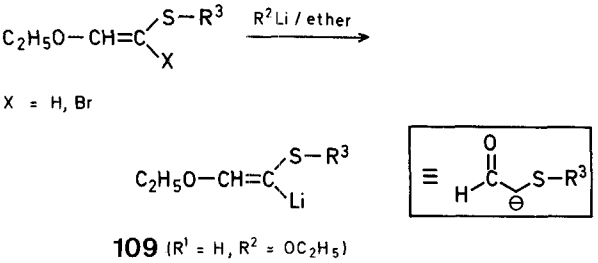


Scheme **P**

with *sec.*-butyllithium[40], **108** undergoes transmetallation on treatment with methyllithium or *n*-butyllithium[92,295]. Other modes of formation of **109** are thiophilic addition[84,275] to thioketenes **110**[296] and $(R^2)^{\ominus}$-addition to acetylenic sulfides **111**[297]. Some reactions with electrophiles furnishing products of type **112** are listed in Table 17.



The reagent **109** (R^1 = H, R^2 = C_2H_5O) is a useful synthetic equivalent of the enolate of α-thiolated acetaldehyde[360].



In principle, it is also possible to have SO—R^3 instead of S—R^3 groups in **109**[299] and to use allenyl (**113**) instead of vinyl derivatives[53,300–303]. The allenyl reagents **113** may be generated from the corresponding allenyl or alkynyl sulfides, **114** or **115**, respectively, and react preferentially at the carbon atom next to the sulfur, i.e., they are synthons of type **104b**. For some examples of the reactions of **113**, see Table 18.

Table 17. Reaction of α-Lithiovinyl Sulfides (**109**) with Electrophiles

R^3	R^1	R^2	Electrophile	Yield [%] of **112**	References
H_3C	n-C_8H_{17}	H	C_6H_5–CHO or n-C_8H_{17}–Br	51-82[a]	40
H_3C	C_6H_5	H	C_6H_5–CHO, n-C_8H_{17}–Br, or 	54-65[a]	40
H_3C	$-C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$		H_2O	28	296
C_2H_5	H	H	n-C_8H_{17}–Br	90[a]	40
C_2H_5	H	H	Br–$(CH_2)_n$–Br (n = 3, 4)	52-60[a]	40
C_2H_5	H	H		68[a]	40
C_2H_5	H	H	n-C_8H_{17}–CHO or C_6H_5–CHO	58-64[a]	40
C_6H_5	H	H	H_3C–J or $(C_6H_5)_2CO$	57-78	295, 298
C_6H_5	n-C_3H_7 or n-C_5H_{11}	H	H_3C–J	52[b]-59[c]	295
C_6H_5	i-C_3H_7 or t-C_4H_9	t-C_4H_9	$H^{\oplus}$	81-85	296
C_6H_5	$-C(CH_3)_2-(CH_2)_3-C(CH_3)_2-$		$H^{\oplus}$, H_3C–J, or CO_2	74-88	296
C_6H_5	$-CH(C_4H_9\text{-}t)-(CH_2)_3-CH(C_4H_9\text{-}t)-$		$H^{\oplus}$	81	296
C_6H_5	C_6H_5	C_6H_5	$H^{\oplus}$, $D^{\oplus}$, or H_3C–J	63-92	284, 295

[a] Yield includes hydrolysis with mercury(II) chloride.
[b] Yield includes hydrolysis with titanium(IV) chloride.
[c] Yield includes preparation of precursor **108** and hydrolysis with titanium(IV) chloride.

282 J. P. Marino, R. C. Landick, *Tetrahedron Lett.* **1975**, 4531.
283 R. Dammann, M. Liesner, H. Neumann, D. Seebach, in preparation.
284 E. J. Corey, D. Seebach, *J. Org. Chem.* **31**, 4097 (1966).
285 D. J. Peterson, *J. Org. Chem.* **33**, 780 (1968).
286 F. A. Carey, A. S. Court, *J. Org. Chem.* **37**, 939 (1972).
287 e.g. G. Wittig, M. Schlosser, *Chem. Ber.* **94**, 1373 (1961). M. Green, *J. Chem. Soc.* **1963**, 1324. T. Mukaiyama, S. Fukuyama, T. Kumamoto, *Tetrahedron Lett.* **1968**, 3787.

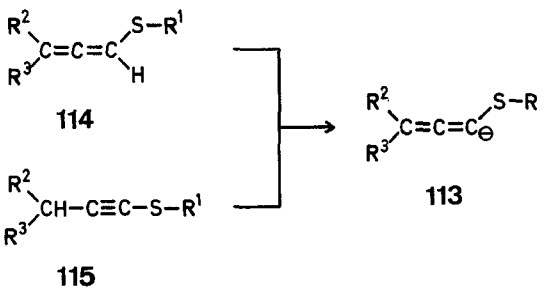
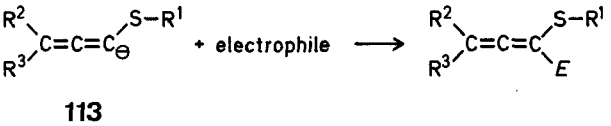
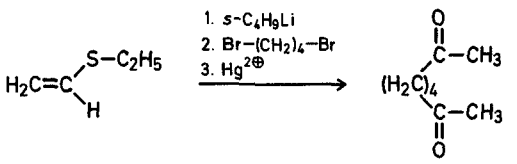


Table 18. Reactions of α-Lithioallenyl Sulfides (**113**) with Electrophiles



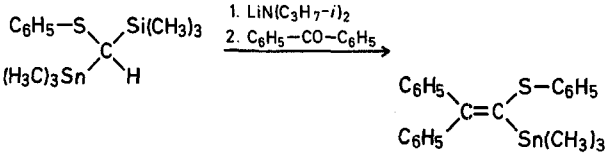
R^1	R^2	R^3	Electrophile	Yield [%]	Reference
H_3C	H	H	$(H_3C)_2CO$	62-66	301
H_3C	H_3CO	H	H_3C-J, C_2H_5-Br, $n-C_4H_9-J$, $i-C_3H_7-Br$	73-94	302
H_3C	H_3CO	H	Thp-O-CH_2-CH_2-Br (or Cl)	54-82	302
H_3C	C_2H_5O	C_2H_5O	H_3C-Hal, C_2H_5-Hal, $i-C_4H_9-Hal$	80-90[a]	53
H_3C	C_2H_5O	C_2H_5O	H_3C-CHO, C_2H_5-CHO, $n-C_7H_{15}-CHO$, C_6H_5-CHO, $(H_3C)_2CO$	63-92[b]	53
C_2H_5	H	H	C_2H_5-Br, $i-C_3H_7-Br$	70-75	300
C_2H_5	CH_3	H	C_2H_5-Br, $(H_3C)_2CO$, $(C_2H_5)_2CO$	70-78	300, 301
C_2H_5	CH_3	H	$(H_2C)_n C=O$ n = 4, 5	71-75	301

[a] The ketene acetal group is hydrolyzed during work-up.
[b] The isolated products are lactones.



Preparation of Octane-2,7-dione from Ethyl Vinyl Sulfide and 1,4-Dibromobutane[40]:

To a solution of the vinyl sulfide (0.422 g, 4.8 mmol) in tetrahydrofuran/hexamethylphosphoric triamide (9:1, 20 ml) is added *sec.*-butyllithium (4.4 mmol) at −78°. The solution is maintained at this temperature for 30 min. The resultant orange solution is treated with the dibromide (0.432 g, 2 mmol) and the mixture is stirred at −78° for 30 min and at 25° for 30 min. Water is then added, the mixture extracted with ether, and the extract concentrated to give the crude sulfide; yield: 0.51 g. The crude product is dissolved in acetonitrile/water (3:1, 20 ml). The solution is treated with mercury(II) chloride (2.17 g) and the mixture heated under reflux for 12 h. Extractive work-up (dichloromethane) followed by T.L.C. purification affords the pure diketone as a colorless semi-solid; yield: 60%.



Olefination of Benzophenone with Phenylthio-trimethylsilyl-trimethylstannyl-methyllithium[292]:

A solution of the heterosubstituted methane (7.1 g, 19.5 mmol) in tetrahydrofuran/hexamethylphosphoric triamide (3:1, 30 ml) is combined at −78° with lithium diisopropylamide (20.5 mmol). The temperature is allowed to rise to −20° within 1.5 h. After 3 h, the reaction mixture is cooled to −78° and benzophenone

I. Shahak, J. Almog, *Synthesis* **1969**, 170; **1970**, 145.
E. J. Corey, J. I. Shulman, *J. Org. Chem.* **35**, 777 (1970); *J. Am. Chem. Soc.* **92**, 5522 (1970).
M. Mikołajczyk, S. Grzejszczak, W. Midura, A. Zatorski, *Synthesis* **1975**, 278.

288 E. J. Corey, A. P. Kozikowski, *Tetrahedron Lett.* **1975**, 925.

289 Through Peterson Olefination: Lit.[182,201,290,291,292]; through Wittig-type reaction: Lit.[293].
Through Horner-Emmons-type olefination:
H. Yoshida, T. Ogata, S. Inokawa, *Synthesis* **1976**, 552.
M. Mikołajczyk, S. Grezejszczak, A. Zatorski, *Tetrahedron Lett.* **1976**, 2731.
C. C. Kruse, N. L. J. M. Broekhof, A. Wejsman, A. van der Gen, *Tetrahedron Lett.* **1977**, 885.

290 P. F. Jones, M. F. Lappert, *J. Chem. Soc. Chem. Commun.* **1972**, 526.

291 F. A. Carey, A. S. Court, *J. Org. Chem.* **37**, 1926 (1972).

292 B.-T. Gröbel, D. Seebach, *Chem. Ber.* **110**, 852 (1977).

293 D. M. Lemal, E. H. Banitt, *Tetrahedron Lett.* **1964**, 245.
E. J. Corey, G. Märkl, *Tetrahedron Lett.* **1967**, 3201.

294 Direct conversion of carbonyl compound to vinyl sulfide: e.g. Lit.[228].
T. Mukaiyama, K. Saigo, *Chem. Lett.* **1973**, 479.
Addition of mercaptan to acetylene; W. E. Truce, J. A. Simms, M. M. Boudakian, *J. Am. Chem. Soc.* **78**, 695 (1956).
A. A. Oswald, K. Griesbaum, B. E. Hudson Jr., J. M. Bregman, *J. Am. Chem. Soc.* **86**, 2877 (1964).
Substitution of vinyl halide with mercaptide: J. Loevenich, J. Losen, A. Dietrichs, *Ber. Dtsch. Chem. Ges.* **60**, 950 (1927).
Through elimination from mercaptals: e.g. Lit.[26a,266].
A. Deljac, Z. Stefanac, K. Balenovic, *Tetrahedron Suppl.* No. 8, 33 (1966).

295 B.-T. Gröbel, D. Seebach, *Chem. Ber.* **110**, 867 (1977).

296 E. Schaumann, W. Walter, *Chem. Ber.* **107**, 3562 (1974).

297 H. Westmijze, J. Meijer, P. Vermeer, *Tetrahedron Lett.* **1975**, 2923.

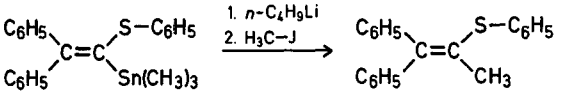
298 B. W. Erickson, Report, Harvard, Cambridge Mass., July 1966.

299 P. Vermeer, J. Meijer, C. Eylander, *Recl. Trav. Chim. Pays-Bas* **93**, 240 (1974).

300 L. Brandsma, H. E. Wijers, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **82**, 1040 (1963).

301 L. Brandsma, C. Jonker, M. H. Berg, *Recl. Trav. Chim. Pays-Bas* **84**, 560 (1965).

(3.7 g, 20.2 mmol) in tetrahydrofuran (8 ml) is added. The temperature is raised to 20° over 14 h and the solution is then poured into pentane/water. The organic layer is washed with water, dried (Na_2SO_4), and the solvent removed to give the olefin; yield: 5.27 g (60%); m.p. 73°.



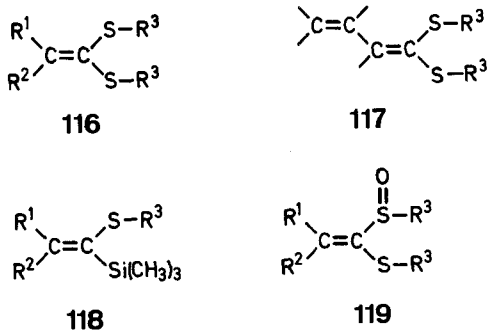
Generation of an α-Phenylthio-vinyllithium Reagent by Sn/Li-Exchange and Methylation with Methyl Iodide[295]:
The alkene (3.26 g, 7.2 mmol) in tetrahydrofuran (10 ml) is combined at −78° with *n*-butyllithium (7.5 mmol). After 10–15 min, methyl iodide (1.06 g, 7.5 mmol) is added and the reaction mixture is allowed to warm to 20° within 30 min. Work up as described above gives the vinyl sulfide; yield: 2.01 g (92%); b.p. 160°/10^{-2} torr.

5.2. Derivatives of Ketene *S,S*-Acetals

5.2.1. Preparation and Reactivity

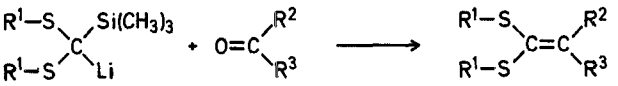
These 1,1-diheterosubstituted 1-alkenes (**116**) are most conveniently – and with greatest structural variety, cf. **117** – accessible by Peterson olefination[182,201,289–292] (see above, reaction **103**, $X^1=S—R^2$, $X^2=Si(CH_3)_3$, Scheme **P** and Table 19) while olefination with phosphorus ylides (Wittig olefination) is only of limited applicability[293]; phosphonates have only recently become available for this purpose[289]. Without alteration of the carbon skeleton **116** can, of course, be made from acid derivatives[245,305], for which purpose a greatly improved method was communicated recently[82,288].

The "*S,Si*-acetal" derivatives **118** may be used for similar purposes[292] instead of the *S,S*-acetals **116**. Finally, the synthetically especially useful monosulfoxides **119**, except for those which are aryl-substituted[236,237], have either been made from α-haloaldehydes by rather elaborate routes[306] or by metaperiodate oxidation of the ketene *S,S*-acetals **116** from the Peterson process[307].



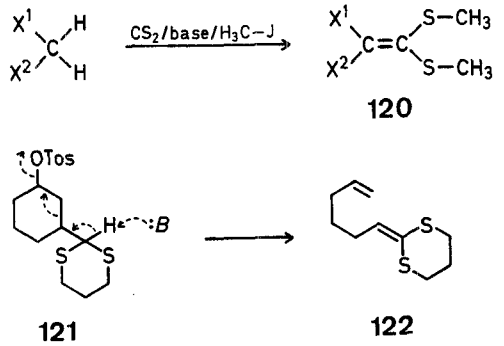
Scheme **Q**

Table 19. Ketene *S,S*-Acetals from Peterson Olefination Reactions (Scheme **P**)



R^1	R^1	Carbonyl Compound	Yield [%]	Reference
H_3C	H_3C	Alk–CHO	80–86	201, 292
H_3C	H_3C	Ar–CHO	85–88	292
H_3C	H_3C	$(H_2C)_n$C=O	54–80	292
H_3C	H_3C	$(C_6H_5)_2CO$	85	201
$-(CH_2)_3-$		Alk–CHO	69–75	201
			45–69	182, 290
			44	291
			72–78	304
$-(CH_2)_3-$		Ar–CHO	95	201
			68	182, 290
$-(CH_2)_3-$		$(Alk)_2CO$	75–85	261
			45	182, 290
			62–64	291
			72	304
$-(CH_2)_3-$		$(H_2C)_n$C=O	43–95	201, 292
			70	182, 290
			62–64	291
			72	304
$-(CH_2)_3-$		tropone	40–85	361
$-(CH_2)_3-$		$(C_6H_5)_2CO$	87	201
			75	182, 290
			78	291
$-(CH_2)_3-$		>C=C(H)–CHO	90	201
			66	182, 290
			70–80	291
$-(CH_2)_3-$		>C=C(H)–CO–	63–78	201
			40	291
$-CH_2-S-CH_2-$		$(C_6H_5)_2CO$	42	201
C_6H_5	C_6H_5	H_3C, C_6H_5 >CH–CHO	85	201

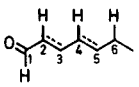
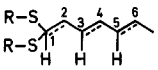
The preparation of representatives **120**[308] from *CH*-acidic precursors, carbon disulfide, and methyl iodide and the elimination **121**→**122**[29b] are further possible ways of access to this class of compounds.

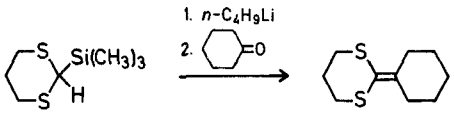


[302] R. M. Carlson, R. W. Jones, A. S. Hatcher, *Tetrahedron Lett.* **1975**, 1741.
[303] See also metallated cumulenyl sulfide: Lit.[300].
J. H. van Boom, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **85**, 580 (1966).
R. Mantione et al., *Tetrahedron Lett.* **1969**, 2483.
R. Mantione et al., *Recl. Trav. Chim. Pays-Bas* **89**, 97 (1970).
[304] G. H. Posner, D. J. Brunelle, *J. Org. Chem.* **38**, 2747 (1973).
[305] A. Fröling, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **81**, 1009 (1962).
L. C. Rinzema, J. Stoffelsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **78**, 354 (1959).
[306] J. L. Herrmann et al., *Tetrahedron Lett.* **1973**, 4711.

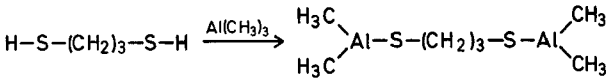
Ketene *S,S*-acetals **116** or conjugated ketene *S,S*-acetals such as **117** (Scheme **Q**) are the counterparts of unsaturated carbonyl compounds in the field of nucleophilic acylation. This is shown schematically in the accompanying Table 20. There are examples of all of the processes outlined in the Table for ketene *S,S*-acetals (see Section 5.2.2).

Table 20. Reactivity Umpolung with Ketene *S,S*-Acetals and with their Deprotonated Derivatives in Reactions with Nucleophiles ($N^{2,4\cdots}$), and Electrophiles ($E^{1,3\cdots}$), respectively; Comparison with Carbonyl Compounds ($E^{2,4\cdots}$- and $N^{1,3\cdots}$-Reactivity).

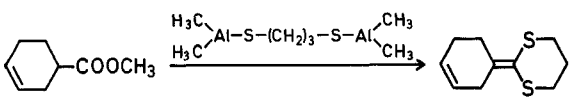
System	Carbon atom no. Abstraction of $H^{\oplus}$ from	Attack by electrophile at	Attack by nucleophile at
	2, 4, 6···	2, 4, 6···	1, 3, 5···
	1, 3, 5···	1, 3, 5···	2, 4, 6···



2-Cyclohexylidene-1,3-dithiane from Cyclohexanone and 2-Trimethylsilyl-1,3-dithiane[201]:
2-Trimethylsilyl-1,3-dithiane (3.8 g, 20 mmol) in tetrahydrofuran (40 ml) is combined at −55 to −70° with *n*-butyllithium (21 mmol). The temperature is allowed to rise to 0° within 4 h. The resultant yellow solution is cooled to −78° and combined with cyclohexanone (2.0 g, 20.4 mmol). The temperature is allowed to raise to 20° over 14 h and the reaction mixture is poured into dichloromethane/water. The crude product is recrystallized from methanol; yield: 3.4 g (80%); m.p. 93°.



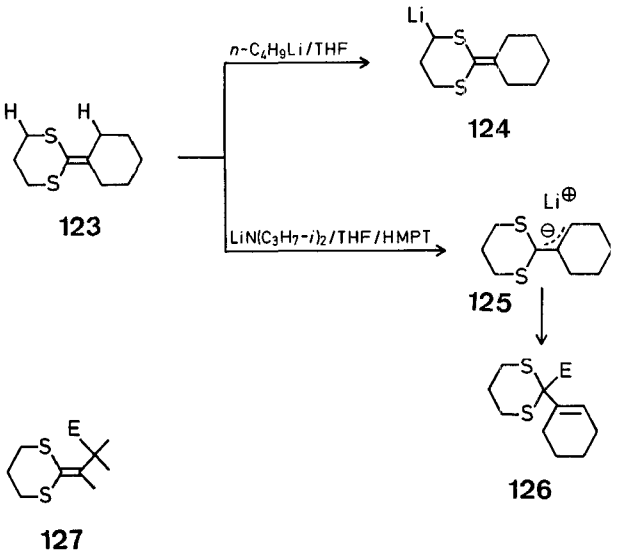
Bis-dimethylaluminium Derivative of 1,3-Propanedithiol[288]:
A solution of trimethylaluminium (61.2 ml of 1.63 molar solution in toluene, from Texas Alkyls, Inc.) is diluted with degassed dichloromethane (110 ml), cooled to 0°, and treated with dry 1,3-propanedithiol (5.04 ml). After the addition is complete (~40 min), the cooling bath is removed and the reaction mixture is stirred at 25° for 1 h to give the reagent in solution.



2-(3-Cyclohexene-1-ylidene)-1,3-dithiane from Methyl 3-Cyclohexene-1-carboxylate[288]:
To the toluene/dichloromethane solution of the aluminium reagent (88 ml, prepared as described above) is added a solution of methyl 3-cyclohexene-1-carboxylate (3.5 g) in dichloromethane (50 ml) in one portion. The mixture is allowed to stand at room temperature for two days and then concentrated on a rotary evaporator. The residue is diluted with ether and a few grams of moist sodium sulfate are added. Filtration through dry sodium sulfate and concentration of the ethereal filtrate yields the partially crystalline ketene *S,S*-acetal which can be further purified by chromatography on silica gel with benzene/hexane (1:1) as eluent to give the pure product; yield: 3.58 g; m.p. 42–44°.

5.2.2. Metallation and E^1-Reactions of Ketene *S,S*-Acetals

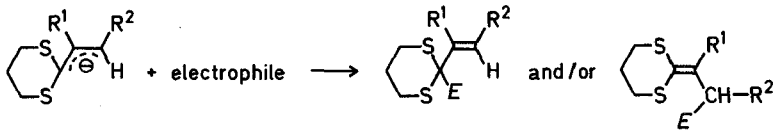
As has been found with other vinyl/allyl-heterosubstituted systems, proton abstraction is more facile from the α-position to the hetero-atom in the allyl compound than from the γ-position of the vinyl derivative[107]. This effect may be strong enough to kinetically favor proton abstraction with formation of a much less stable carbanionoid species, see the conditions for the conversions of **123** to **124** and **125**, as shown in the following scheme.



As stated in our earlier report[1], allylic lithiodithianes of type **125** show a pronounced preference to react with alkyl halides and aliphatic aldehydes and ketones at the position next to the sulfur atoms. Only aromatic carbonyl compounds have occasionally been observed to furnish products of type **127**[1,309]. Table 21 gives the examples of reactions leading from dithiane-derived ketene *S,S*-acetals to *S,S*-acetals of α,β-unsaturated aldehydes and ketones. Abstraction of a proton from C-5 of a conjugated ketene *S,S*-acetal as indicated in Table 20 above is also observed (with lithium diisopropylamide as base[49], see Table 21).

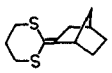
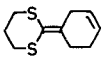
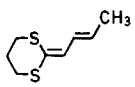
307 D. Seebach, R. Bürstinghaus, B.-T. Gröbel, M. Kolb, *Justus Liebigs Ann. Chem.* **1977**, in press.
308 E. J. Corey, R. H. K. Chen, *Tetrahedron Lett.* **1973**, 3817. I. Shahak, Y. Sasson, *Tetrahedron Lett.* **1973**, 4207, and literature cited therein.
309 (a) D. Seebach, M. Kolb, unpublished results. Gießen 1973. (b) M. Kolb, *Dissertation*, Gießen, 1976, and *Justus Liebigs Ann. Chem.* **1977**, in press.
310 D. L. Coffen, T. E. McEntee, Jr., D. R. Williams, *J. Chem. Soc. Chem. Commun.* **1970**, 913.
311 A. I. Meyers et al., *J. Org. Chem.* **38**, 1974 (1973).
312 J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, R. H. Schlessinger, *Tetrahedron Lett.* **1973**, 4715.
313 K. Ogura, M. Yamashita, G. Tsuchihashi, *Synthesis* **1975**, 385.

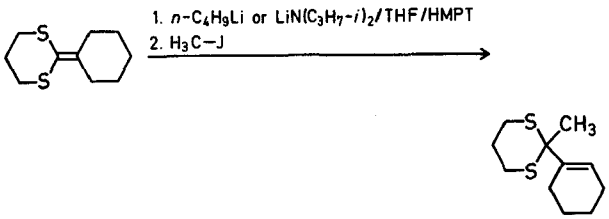
Table 21. Reactions of Metallated Ketene *S,S*-Acetals **125** with Electrophiles



125 **126** **127**

R^1	R^2	Electrophile	Yield [%] of **126**	of **127**	References
H	n-C_3H_7	H_3C–J	90	–	50
H	C_6H_5	H_3C–J	– (1:1)	–	310
H	C_6H_5	$(H_3C–S)_2$	90	–	85
H	CN	C_2H_5–J, i-C_3H_7–Br	–	31-75	203, 311
H	H_3CS	n-C_6H_{13}–J, $C_6H_5CH_2$–Br	93-94	–	288
H_3C	H	i-C_3H_7–Cl	92	–	50
n-C_3H_7	H	$H^{\oplus}$	86	–	288
n-C_3H_7	H	H_3C–J, n-C_6H_{13}–J	81-88	–	288
n-C_3H_7	H	$(H_3C–S)_2$	33 (1:1)	33	288
C_2H_5	H_3C	H_3C–J, i-C_3H_7–Cl, c-C_6H_{11}–J	80-87	–	50
$-(CH_2)_2-$		$C_6H_5CH_2$–Br	80	–	50
$-(CH_2)_3-$		n-C_7H_{15}–J	75	–	50
$-(CH_2)_4-$		$H^{\oplus}$, H_3C–J	74-93	–	50, 288
$-(CH_2)_4-$		$H_2C=CH–CH_2$–Br	86	–	288
$-(CH_2)_4-$		$(C_6H_5)_2CO$	–	50	309
$-CH_2-CH(C_4H_9\text{-}t)-(CH_2)_2-$		H_3C–J	77	–	50

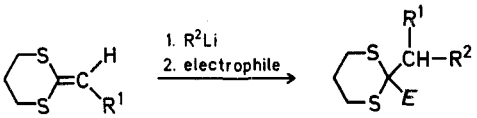
S,S-Acetal	Electrophile	Yield [%] of **126**	of **127**	References
	H_3C–J	81	–	288
	$H_2C=CH–CH_2$–Br	(1.7:1)	total: 82	288
kètene *S, S*-acetal from cholestanone	H_3C–J	75		50
	$H^{\oplus}$	73		288
	H_3C–J	(5:1)	total: 78	288
	H_3C–J	90	–	49



Conversion of 2-Cyclohexylidene-1,3-dithiane to 2-Cyclohexenyl-2-methyl-1,3-dithiane[50]:
The ketene-*S,S*-acetal (2.0 g, 10 mmol) in tetrahydrofuran/hexamethylphosphoric triamide (20 ml/4–8 ml) is combined at −78° with *n*-butyllithium or lithium diisopropylamide (11 mmol). The temperature is allowed to rise to +20° over 2–3 h, the resultant dark red solution is then cooled again to −78° and combined with methyl iodide (1.56 g, 11 mmol). The temperature is allowed to rise to −20° over 24 h and the reaction mixture is poured into pentane/water. Distillation affords the pure product; yield: 87%; b.p. 110°/1 torr.

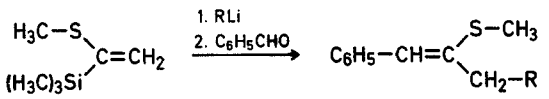
5.2.3. N^2- and N^4-Additions to Ketene *S,S*-Acetals and Similar Compounds

The enolate cation reactivity **106a** (Scheme **P**) of simple ketene *S,S*-acetals is only found in the absence of allylic protons[1,309] (see the preparation of **128a** and **128b**[309b]). The reaction can be combined with a Peterson olefination if α-silyl-thio-enol ethers are employed as shown by the preparation of **129**[307]. Organocuprates, which are ideal reagents for Michael



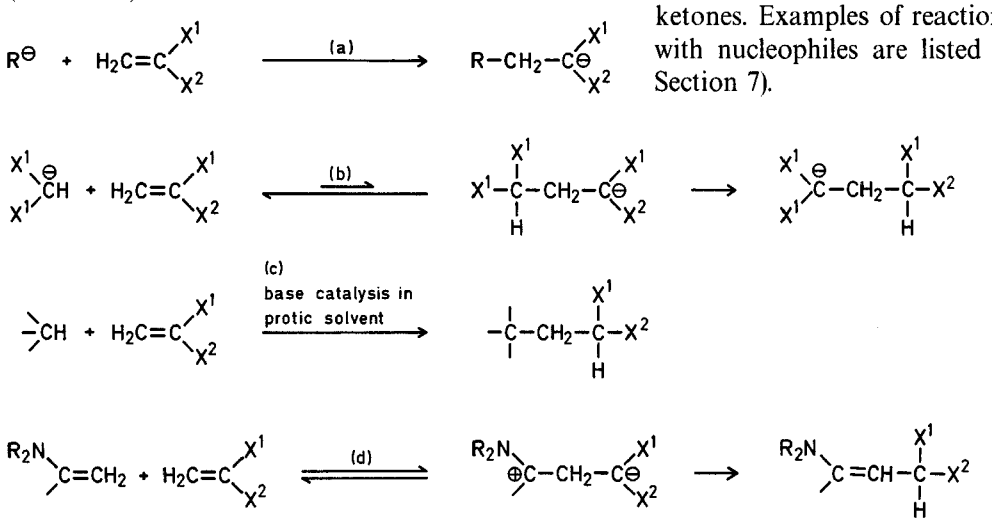
128 a R^1 = H, R^2 = t-C_4H_9, E = CH_3
b R^1 = C_6H_5, R^2 = t-C_4H_9, E = CH_3

addition (N^3-reaction), do not facilitate the N^2-addition to ketene *S,S*-acetals[304]; they do not even add to mono-sulfonium salts of ketene *S,S*-acetals[304].



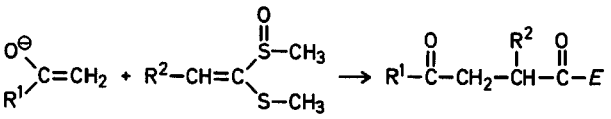
129

From what we know about Michael additions, we can expect that additions of the type leading to **128** and **129** may occur under four different sets of conditions as indicated in the accompanying flow diagram (Scheme **R**).



Scheme **R**

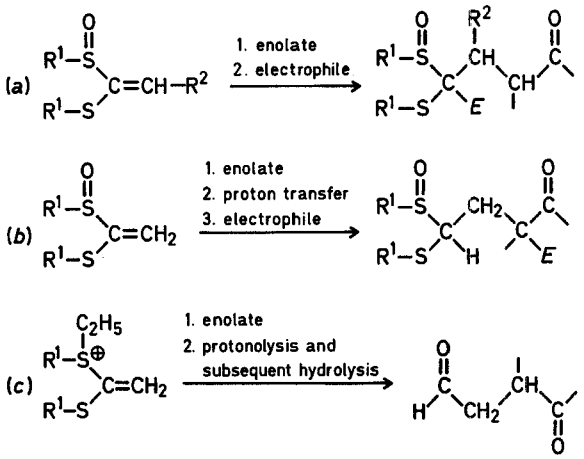
(a) If the attacking anion is much less stable than the one formed by addition, the reaction is at least thermodynamically favorable; the product anion may be formed quantitatively and can be directly used for further reactions. This is obviously the case in the transformations giving **128** and **129**, above.
(b) If the nucleophile is derived from a strongly *CH*-acidic precursor such as malonic or acetoacetic ester or a 1,3-diketone, the thermodynamically unfavorable addition step is followed by a proton shift which draws the equilibrium towards the desired product; this type of reaction requires that the difference in anion stability of the nucleophile and the adduct is not too large.
(c) Base catalysis in a protic solvent may also lead to adducts in cases where the anion produced is less stable than the one added: rapid protonation of the adduct anion provided in small equilibrium concentration "saves" the product.
(d) Enamines can be used instead of anionic nucleophiles.



130 **131**

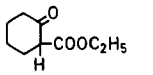
All of these conditions have been employed in additions to vinyl sulfoxides. Synthetically the most useful are the ketene *S,S*-acetal *S*-oxides **130** as enolate cations **106a**. They have been coupled with enolate anions from ketones[307], esters[306,312], β-ketoesters[306], β-diketones[306], malonates[306,312], α,β-unsaturated esters[306,312], and amides[307] as well as with enamines[306]. By virtue of the facile acid-catalyzed hydrolysis of *S,S*-acetal *S*-oxides to carbonyl compounds this is a versatile method for preparing 1,4-dicarbonyl derivatives **131**, which are important precursors in natural product synthesis (see also Sections 5.3 and 7). It is an alternative to the production of the same 1,4-bifunctional compounds by Michael addition of masked acyl anions to α,β-unsaturated ketones. Examples of reactions of the *S*-oxides **130** with nucleophiles are listed in Table 22 (see also Section 7).

Table 22. N^2-Additions to Ketene *S,S*-Acetal *S*-Oxides and Ketene *S,S*-Acetal Monosulfonium Salts



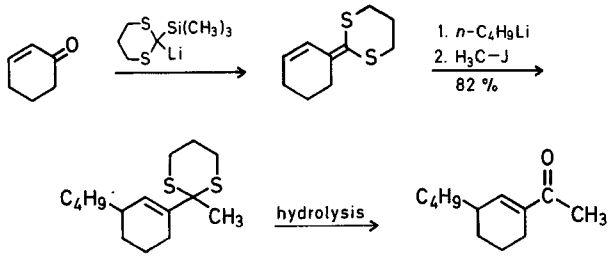
Enolate from	Electrophile	Yield [%]	Reference
equation (*a*): $R^1 = CH_3$, $R^2 = H$:			
$H_3C-COOC_4H_9-t$	$H^\oplus$	94	306
$n-C_3H_7-COOCH_3$	$H^\oplus$	93	306
$H_3C-CH=CH-COOCH_3$	$H^\oplus$	88	306
$(C_2H_5)(H_3C-S)CH-COOCH_3$	$H^\oplus$	90	306
$H_2C(COCH_3)_2$	$H^\oplus$	91	306

Table 22. (Continued)

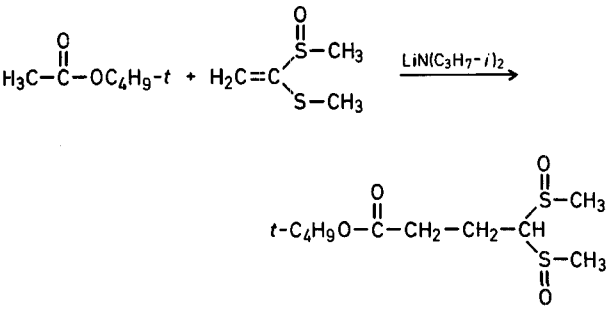
Enolate from	Electrophile	Yield [%]	Reference
$H_3C-CO-CH_2-COOCH_3$	$H^{\oplus}$	92	306
$H_2C(COOCH_3)_2$	$H^{\oplus}$	98	306
$H_3C-COOC_4H_9-t$	H_3C-J	91	312
$H_3C-COOC_4H_9-t$	$H_2C=CH-CH_2-Br$	88	312
$C_2H_5-COOC_2H_5$	H_3C-J	90	312
	$H^{\oplus}$	92	306
equation (*a*): $R^1=R^2=CH_3$:			
$n-C_3H_7-COOC_4H_9-t$	$H^{\oplus}$	90	306
$H_2C(COOCH_3)_2$	$H^{\oplus}$	75	306
equation (*b*): $R^1=CH_3$:			
$H_2C=CH-CH_2-COOC_2H_5$	H_3C-J, $n-C_3H_7-J$, $i-C_3H_7-J$, $H_2C=CH-CH_2-Br$, $H-C\equiv C-CH_2-Br$	74-96	312
$H_2C(COOCH_3)_2$	H_3C-J, C_2H_5-J, $n-C_3H_7-J$, $H_2C=CH-CH_2-Br$, $H-C\equiv C-CH_2-Br$	75-98	312
equation (*c*): $R^1-R^1=-(CH_2)_3-$:			
$H_3C-CH(COOC_2H_5)_2$	$H^{\oplus}$	70[a]	125
$C_2H_5-CH(COOC_2H_5)_2$	$H^{\oplus}$	46[a]	125
	$H^{\oplus}$	82[a]	125
$H_3C-CH(COOCH_3)COC_6H_5$	$H^{\oplus}$	62[a]	125

[a] Yield includes base-catalyzed formation of ketene *S,S*-acetal monosulfonium salt.

Ketene *S,S*-acetals derived from unsaturated carboxylic acids are easily made by Peterson olefination (cf. **117**, Scheme **Q**). Alkylithium reagents add to them exclusively in the 4-position even when allylic hydrogens are present[49]. The application of this homo-Michael addition in the functional modification of cyclohexenone is demonstrated by the preparation of the ketone **132**.



132



Addition of *t*-Butyl Acetate Enolate to Ketene Dimethyl *S,S*-Acetal *S*-Oxide[306]:

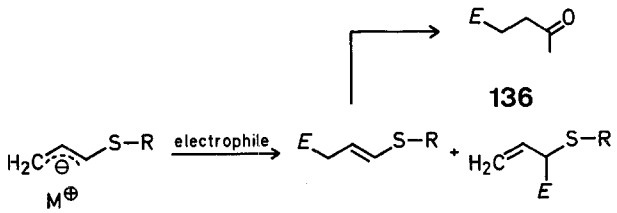
The ketene *S,S*-acetal *S*-oxide (1 equiv of a 2 molar solution in tetrahydrofuran) is added at −78° to a solution of the lithium enolate of *t*-butyl acetate (1 equiv, prepared in 0.5 molar tetrahydrofuran solution by reaction of the ester with lithium diisopropylamide). Work up after 30 min affords the Michael adduct; yield: 94%.

5.3. Survey of Useful Transformations through Vinyl Sulfides and Ketene *S,S*-Acetals

As evident from Table 23, the aforementioned chemistry and preparation of vinyl sulfides and ketene *S,S*-acetals allows one to carry out a number of useful synthetic transformations: carbonyl homologation (entries A, B, and C); nucleophilic acylation (entry B); conversion of ketones and aldehydes to the homologous acids, thiolesters, and α-haloesters (entries D and E); reductive or C—C connective transformation of aldehydes, ketones, and esters to α,β-unsaturated aldehydes and ketones (entries F, G, H, K, L; also with additional introduction of a nucleophile); directed enolate coupling to 1,4-dicarbonyl derivatives (entries I and J).

6. Applications of Sulfur-Substituted Allylic Anions (E^3-, E^5-Type)

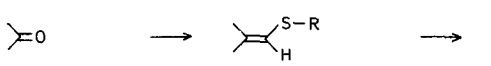
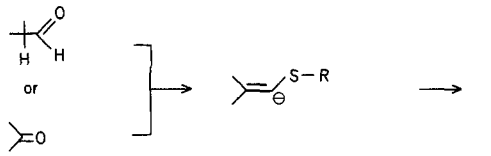
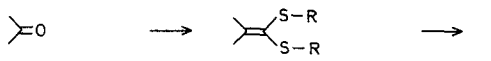
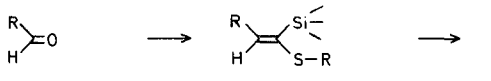
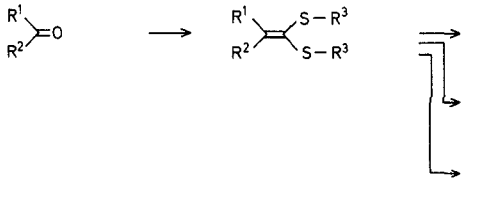
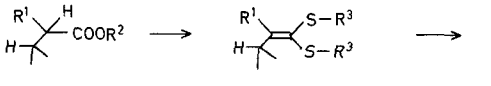
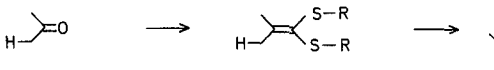
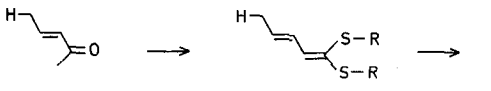
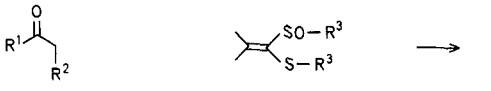
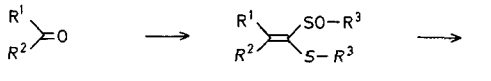
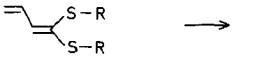
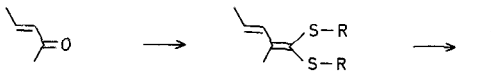
R—S-Substituted allylic anions **133**, which react with electrophiles in the γ(3)-position, are potentially useful reagents because the products **134** of this coupling are derivatives of aldehydes or ketones **136** (cf. **104a**, **104c**, Scheme **P**).



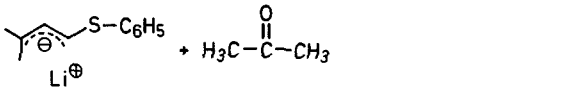
133 **134** **135**

The crucial point is the question how to direct reactivity to the γ-postion: as was known from the corresponding allylic ketene *S,S*-acetal-derived lithium compounds (see Section 5.) for some time[1], there is a great preference for reaction of these systems at the α(1)-position to give **135**. Unfortunately, in spite of a large number of investigations in this field,

Table 23. Possible Transformations through Vinyl Sulfides or Ketene *S,S*-Acetals

Entry	Precursor	Intermediate or Reagent	Product	References
A				285, 28b, 287
B				40, 295
C				149, 313
D				148 a
E				28 b, 81, 82 26 i, 29 c 148
F				288
G				50
H				49
I				306, 312
J				307
K	Alk-Li			49
L				49

there are no foolproof rules about how to control this α/γ-ambiguity completely. Influencing factors[12,314] are: steric hindrance of attack at the two allylic positions by substituents, the counterion, the group R on sulfur, the nature of the attacking electrophile, the solvent, additives, and the reaction temperature. In the case of an individual system of type **133** reacting with a certain kind of electrophile all of these factors have to be checked for optimization.

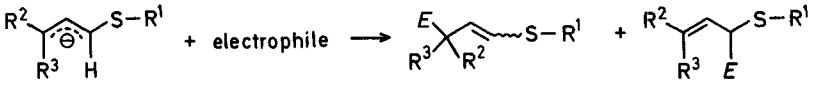


Conditions	$\alpha:\gamma$ ratio
THF alone	*25:75*
HMPT added	40:60
[2.2.2.] cryptate added	100:0
DABCO added	0:100

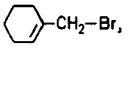
Scheme S

[314] P. M. Atlani, J. F. Biellmann, S. Dube, J. J. Vicens, *Tetrahedron Lett.* **1974**, 2665.

Table 24. Reactions of Metallated Allyl Sulfides (**133**) with Electrophiles



133 **134** **135**

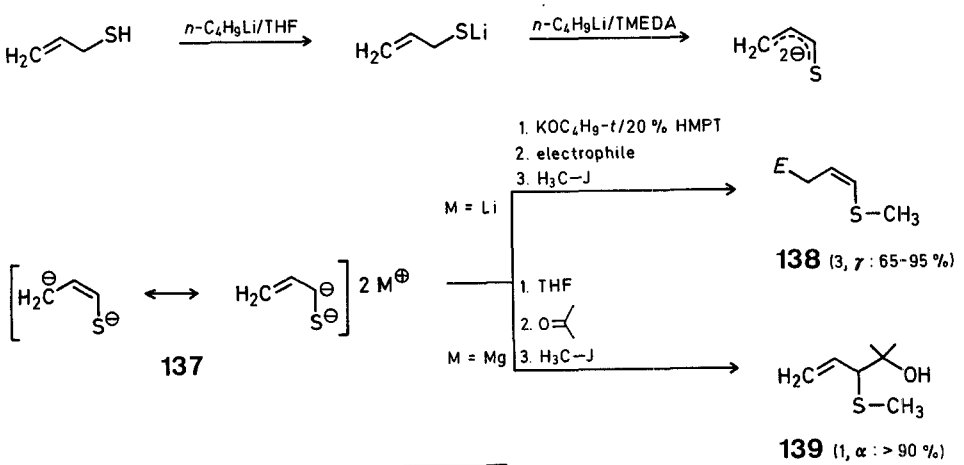
R^1	R^2	R^3	Electrophile	Yield [%]	Distribution **134**	**135**	Reference
H_3C	$H_3C-O-\underset{\underset{O}{\parallel}}{C}-$	H	H_3C-J, $H_2C=CH-CH_2-Br$, $H-C\equiv C-CH_2-Br$	63-92	100	–	316
H_3C	$H_3C-O-\underset{\underset{O}{\parallel}}{C}-$	H_3C	H_3C-J, $H_2C=CH-CH_2-Br$, $H-C\equiv C-CH_2-Br$	49-95	100	–	316
H_3C	$H_3C-O-\underset{\underset{O}{\parallel}}{C}-$	H_3C	$H_3C-\underset{\underset{O}{\parallel}}{C}-CH=CH_2$	55[a]	100	–	316
i-C_3H_7	H	H	$H_2C=CH-CH_2-Br$, 	87-92[b]	100	–	317
$-(CH_2)_2-$		H	n-$C_6H_{13}-CHO$, n-$C_6H_{13}-\underset{\underset{O}{\parallel}}{C}-CH_3$	79-94	100	–	318
C_6H_5	H	H	H_3C-J	–	55[c]	45[c]	319
C_6H_5	H_3C	H_3C	$H_2C=CH-CH_2-Br$	60	50	50	314
C_6H_5	H_3C	H_3C	C_2H_5-CHO, C_6H_5-CHO	85-92	100	–	320
C_6H_5	H_3C	H_3C	$(H_3C)_2CO$, 	70-85	91-95	9-5	320

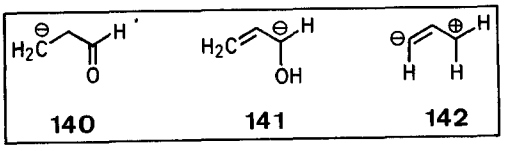
[a] Yield after hydrolysis and cyclization.
[b] Reaction with cuprate.
[c] Determined by G.L.C.

Thus, as shown in Scheme **S**, the addition of 1-phenylthio-3,3-dimethylallyllithium to acetone gives the two possible products in strongly varying ratios depending upon the different additives[314]. A collection of examples for this type of reaction may be found in Table 24[375].

Three possibilities have emerged by which the inherent α-reactivity of metallated allyl sulfides and sulfoxides can be converted to selective γ-reactivity: (a) a thioallylic dianion is used, (b) the α- and γ-positions are made equivalent, (c) a 1,3-shift is carried out after the α-reaction.

Thus, treatment of allylmercaptan with two equivalents of butyllithium gives a dianion **137**, the lithio-derivative of which reacts with all electrophiles studied in the γ-position (→**138**, γ:α preference 65:36 to 95:5, Table 25[27b,72,321]), while the magnesium derivative combines with carbonyl compounds exclusively at the carbon atom next to sulfur (→**139**, Table 26[72,322]). Transformations of the primary products to sulfur-free compounds shows that the dianion can be synthetically applied as one of the building blocks **140**, **141**, **142**; see Tables 25 and 26.



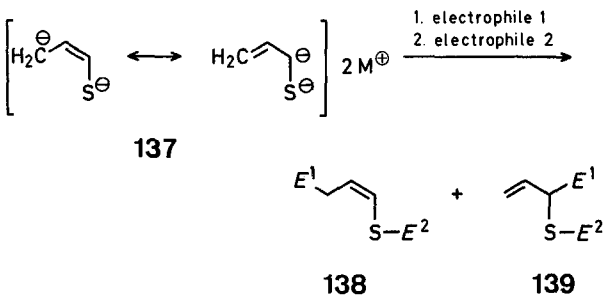


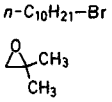
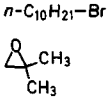
140 **141** **142**

Scheme **T**

[315] For Michael-addition of metallated allyl sulfides, see: J. P Marino, B. Mesbergen, *J. Am. Chem. Soc.* **96**, 4050 (1974)
[316] A. S. Kende, D. Constantinides, S. J. Lee, L. Liebeskind *Tetrahedron Lett.* **1975**, 405.

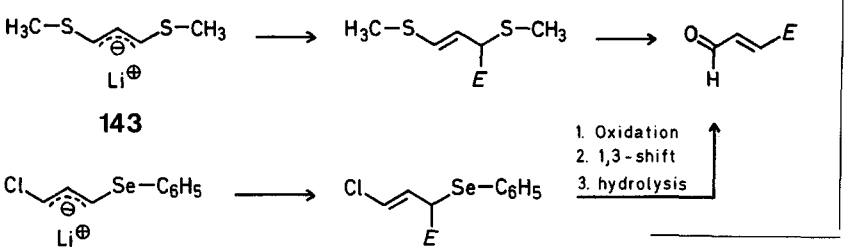
Table 25. Reaction of Doubly Lithiated Allylthiol (**137**) with Electrophiles (Scheme T)



Electrophile 1	Electrophile 2	Yield[a] [%]	Distribution 138[b]	139
C_2H_5-Br	C_2H_5-Br	71	67	33
i-C_3H_7-Cl	$C_6H_5-CH_2-Br$	85	58	42
n-C_4H_9-Cl	n-C_4H_9-Cl	80	86	14
n-$C_5H_{11}-Cl$	H_3C-J	75[b]	65	35
n-$C_6H_{17}-Cl$	H_3C-J	81	74	26
n-$C_{10}H_{21}-Br$	n-$C_{10}H_{21}-Br$	93	68	32
		60	86	14
C_2H_5-CHO	H_3C-J	73	74	26
C_6H_5-CHO	H_3C-J	90	85	15
	H_3C-J	73	73	27
$C_6H_5-CO-CH_3$	H_3C-J	90	72	28
$(H_3C-S)_2$	H_3C-J	40	80	20
$(H_3C)_3Si-Cl$	$C_6H_5-CH_2-Br$	89	82	18

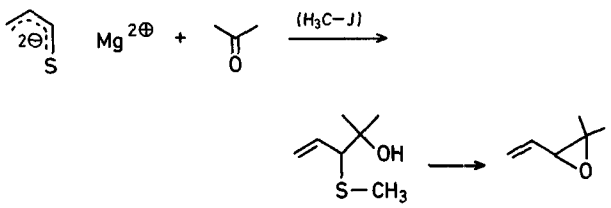
[a] Determined by N.M.R. spectroscopy of the crude product.
[b] The vinyl sulfides can be transformed to *S,S*-acetals (hydrochloric acid/methanethiol, > 90% yield), acetals (mercury(II) ions/methanol, > 85% yield), α-bromoaldehydes (*N*-bromosuccinimide/acetonitrile/water, > 70% yield), and α-bromoacetals (*N*-bromosuccinimide/acetonitrile/methanol, > 80% yield).

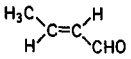
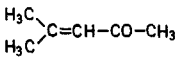
If the two ends of the allylic anion are both heterosubstituted, it does not make any difference which end reacts.



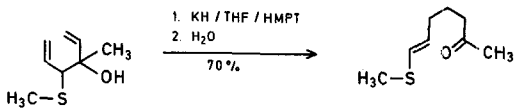
The products of the reactions of **143**[26k] and **144**[323] with electrophiles are both derivatives of β-heterosubstituted carbonyl compounds, so that hydrolysis is accompanied by elimination to give the α,β-unsaturated aldehyde, see Table 27 (last entry gives a ketone).

Table 26. α-Reaction of the Magnesium Salt of Thioacrolein with Carbonyl Compounds: Formation of Vinyloxiranes (Scheme T)

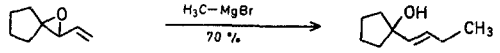


Carbonyl Compound	Yield [%] of **139**[a]	Yield [%] of oxirane[b]
C_2H_5-CHO	75	48
i-C_3H_7-CHO	88	63
C_6H_5-CHO	45	–
	76	78
$C_6H_5-CO-CH_3$	71	70
	80	47
$H_3C-CO-CH=CH_2$	76	52
	81	–
	37	75

[a] Adducts with α,β-unsaturated carbonyl compounds can undergo a Claisen-Cope rearrangement, e.g.:

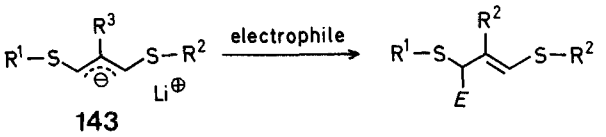


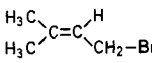
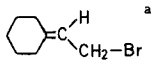
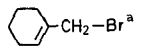
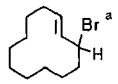
[b] Oxiranes give allyl alcohols on reaction with Grignard reagents, e.g.:



[317] K. Oshima, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **95**, 7926 (1973).
[318] S. Torii, H. Tanaka, Y. Tomotaki, *Chem. Lett.* **1974**, 1541.
[319] J. Hartmann, R. Muthukrishnan, M. Schlosser, *Helv. Chim. Acta* **57**, 2261 (1974), and references cited therein.
[320] K. Kondo, K. Matsui, A. Negishi, *Chem. Lett.* **1974**, 1371.
[321] M. Schlosser et al. have also published one example: Lit.[319].
[322] D. Seebach, K.-H. Geiß, M. Pohmakotr, *Angew. Chem.* **88**, 449 (1976); *Angew. Chem. Int. Ed. Engl.* **15**, 437 (1976).
[323] H. J. Reich, *J. Org. Chem.* **40**, 2570 (1975).
[324] K. Oshima, H. Yamamoto, H. Nozaki, *Bull. Chem. Soc. Jpn.* **48**, 1567 (1975).
[325] R. G. Carlson, W. S. Mardis, *J. Org. Chem.* **40**, 817 (1975).
[326] T. Taguchi, H. Okamura, H. Takei, *Chem. Lett.* **1975**, 853.
[327] R. Tancg, K. Mislow, *J. Am. Chem. Soc.* **92**, 2100 (1970).

Table 27. Reactions of 1,3-Bis-Sulfur-Substituted Allylic Anions (**143**) with Electrophiles

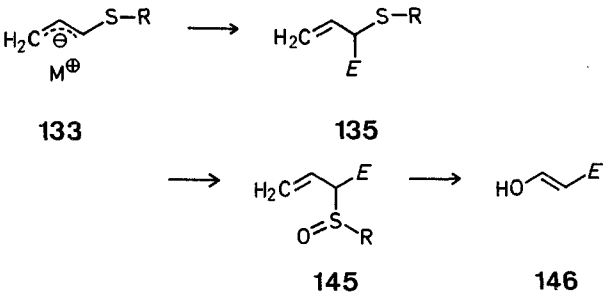


R^1	R^2	R^3	electrophile	Yield [%]	Reference
CH_3	CH_3	H	n-C_5H_{11}–Br	90	26 k
CH_3	CH_3	H		75[b]	324
CH_3	CH_3	H		92[b]	324
CH_3	CH_3	H		90[b]	324
CH_3	CH_3	H		50[b]	324
CH_3	CH_3	H		97	26 k
CH_3	CH_3	H		99	26 k
CH_3	CH_3	H		96	26 k, 325
CH_3	CH_3	H		–	325
CH_3	CH_3	H		–	73
CH_3	CH_3	H	C_2H_5–CHO	89	26 k
CH_3	CH_3	H	H_3C–CO–CH_3	97	26 k
CH_3	CH_3	H	C_6H_5–CO–C_6H_5	95	26 k
C_2H_5	C_6H_5	CH_3	C_6H_5–CHO	100	326
C_2H_5	C_6H_5	CH_3	C_6H_5–CH_2–CH_2–CHO	89	326
C_2H_5	C_6H_5	C_6H_5–CH_2–CH_2	HCHO	84	326
C_6H_5–S		–S–C_6H_5	H_3C–J	70[b]	362

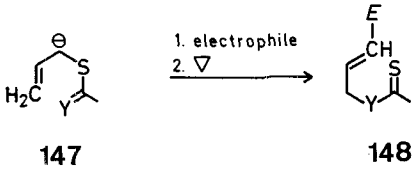
[a] Reaction with cuprate (S_N2' substitution).
[b] Yield includes subsequent hydrolysis.

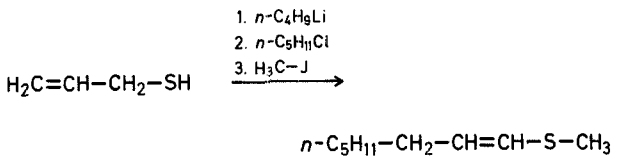
Finally, as in one example of Table 26 (footnote a) and as with the products from reactions of **144**, appropriate α-adducts can be rearranged to the γ-adducts by sigmatropic shifts. Thus, allyl sulfides **135** are oxidized to the sulfoxides **145** (which are of course also available by starting from the parent allylic sulfoxide anion); these are in equilibrium with allyl sulfenylates[327] by a [2,3]-sigmatropic shift, so that the alcohols **146** can be obtained, i.e., the anion of **133** can be used as a R^1–$\overset{\ominus}{C}$=$C(R^2)$–$C(R^3)_2$–OR^4 synthon[12].

[328] A similar route (metallation, alkylation, rearrangement, metallation, alkylation, and elimination) can be used for stereoselective olefin synthesis: T. Hayashi, *Tetrahedron Lett.* **1974**, 339; *Synthesis* **1975**, 100.



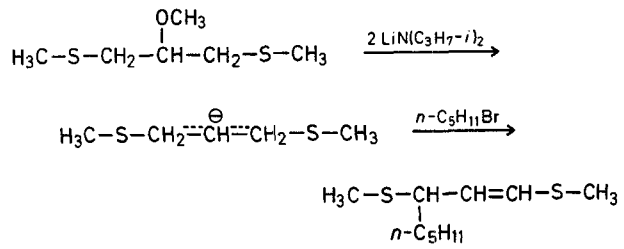
Similarly E^3- or E^5-synthons are provided by allylic anions of the type **147**, which are derived from systems capable of undergoing a Claisen-Cope rearrangement ([3,3]-sigmatropic shift); examples see Table 28.





Methyl Thio-enol Ether of Octanal from Allyl Thiol, Chloropentane, and Methyl Iodide[27b,72]:

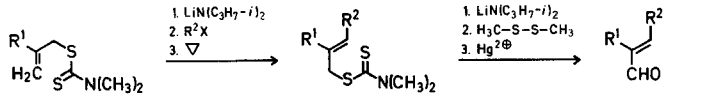
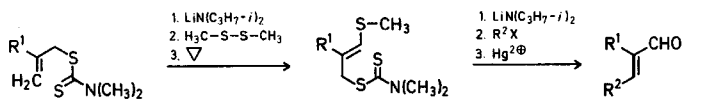
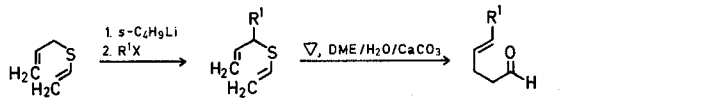
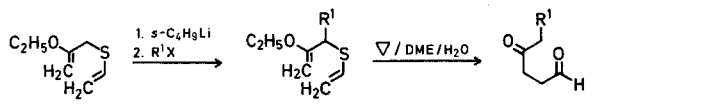
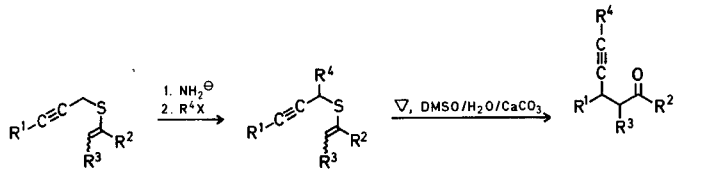
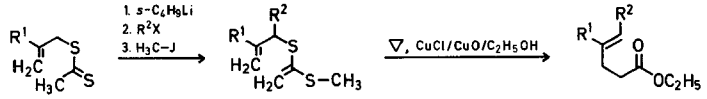
A solution of 2-propenethiol (8 ml, 100 mmol) in tetrahydrofuran (280 ml) and tetramethylethylenediamine (32 ml, 200 mmol) is combined at 0° with n-butyllithium (210 mmol). After 4 h the resultant solution is cooled to −78° and n-pentyl chloride (12.5 ml, 103 mmol) is added. The solution is warmed to +20° and methyl iodide (6.8 ml, 103 mmol) is added. After being stirred for 2 h, the reaction mixture is poured into pentane/water and washed with dilute hydrochloric acid, dilute sodium hydroxide, and finally with saturated sodium chloride solution. The organic layer is dried (K_2CO_3) and the solvent evaporated to give the crude product; yield: 13.3 g, 84% (78% of the desired vinyl sulfide). A sample of the crude product (3.0 g) is purified by filtration through silica/3% silver nitrate with pentane as eluent to give the pure vinyl sulfide; yield: 1.92 g; b.p. 41°/5 torr.



1,3-Bis[methylthio]-1-octene from 1,3-Bis[methylthio]allyllithium and 1-Bromopentane[26k]:

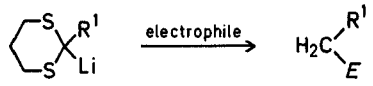
n-Butyllithium (22.3 mmol) is added to a stirred solution of diisopropylamine (2.35 g, 23.2 mmol) and 1,3-bis[methylthio]-2-methoxypropane (1.826 g, 11 mmol) in dry tetrahydrofuran (33 ml) under argon at −75°. The mixture is then kept at −15° for 70 h, treated at −75° with 1-bromopentane (2.155 g, 14.25 mmol) and kept at −75° for 2 h. The alkylation is complete after 1 h at −75°. The solution is treated at −75° with methanol (1 ml), diluted with ether, washed with 5 molar aqueous ammonium sulfate, water, 1 molar aqueous sodium hydrogen carbonate, and sodium chloride solution. The organic phase and the ether extracts of the aqueous washings are dried and freed of solvent. The residual liquid is distilled to afford the vinyl sulfide; yield: 1.94 g (90%); *trans*:*cis* ratio: 80:20; b.p. 130°/0.25 torr.

Table 28. Reactions of S-Containing Allylic Carbanions followed by Claisen-Cope Rearrangements

Reaction Sequence	Synthon	Reference
	E^3	51, 328
	E^3	51, 328, 329
	E^5	330
	E^2, E^5	331
	E^5	332
	E^5	333

7. Natural Product Synthesis

Any new development in synthetic organic methodology should also be applied to natural product synthesis. A survey of the recent literature indicates that the sulfur-substituted carbanionoids have had a strong impact in this field. In addition, their *supernucleophilicity* is taken advantage of very generally for C—C-bond forming processes and for controlling the regiochemistry of reactions[214]. For example, dithianes are used for introducing R^1CH_2-groups (directed Wurtz-type coupling[62,175,185,205,334–336]).



31 **149**

More pertinent to the subject covered here is the fact that the sulfur-containing anions are masked forms of carbonyl derivatives with reactivity umpolung. As elaborated in the introduction (Section 1.), they allow one to construct target molecules with even relationships between the functional groups, which are normally oxygen or nitrogen-containing in natural products. It is therefore probable that applications of the chemistry treated in the present review are to be found where this situation obtains. The following sections contain selected examples.

329 The same reaction with an other disulfide and without alkylation is also described: J. Hori, T. Hayashi, H. Midorikawa, *Synthesis* **1975**, 727.

330 K. Oshima, H. Takahashi, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **95**, 2693 (1973).

331 K. Oshima, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **95**, 4446 (1973).

332 L. Brandsma, H. D. Verkruijsse, *Recl. Trav. Chim. Pays-Bas* **93**, 319 (1974).

333 H. Takahashi, K. Oshima, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **95**, 5803 (1973).

334 J. A. Marshall, D. E. Seitz, *J. Org. Chem.* **40**, 534 (1975).

335 (a) J. B. Jones, R. Grayshan, *J. Chem. Soc. Chem. Commun.* **1970**, 141.
(b) J. B. Jones, R. Grayshan, *J. Chem. Soc. Chem. Commun.* **1970**, 741.
(c) J. B. Jones, R. Grayshan, *Can. J. Chem.* **50**, 810 (1972).
(d) J. B. Jones, R. Grayshan, *Can. J. Chem.* **50**, 1407 (1972).

336 (a) H. Paulsen, V. Sinnwell, P. Stadler, *Chem. Ber.* **105**, 1978 (1972).
(b) A. M. Sepulchre et al., *Tetrahedron Lett.* **1972**, 3945.
(c) A. M. Sepulchre, G. Vass, S. D. Gero, *C. R. Acad. Sci. Ser. C* **274**, 1077 (1972).
(d) A. M. Sepulchre, G. Lukacs, G. Vass, S. D. Gero, *Bull. Soc. Chim. Fr.* **1972**, 4000.

337 Compounds **150–152** can also be synthesized by other routes employing S-containing carbanions, e.g. Lit.[73].

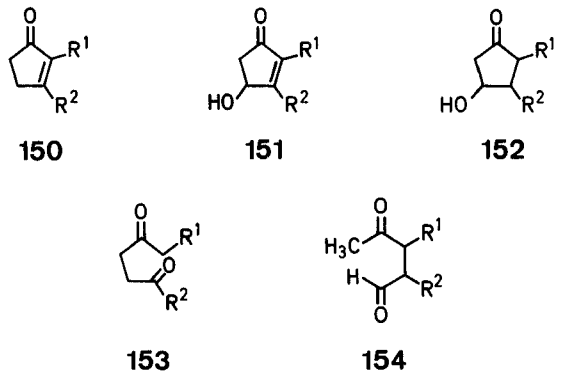
338 P. H. Bentley, *Chem. Soc. Rev.* **2**, 29 (1973).
P. Welzel, *Chem. in Unserer Zeit* **7**, 43 (1973).
W. Bartmann, *Angew. Chem.* **87**, 143 (1975); *Angew. Chem. Int. Ed. Engl.* **14**, 337 (1975), and literature cited therein.

339 R. A. Ellison, W. D. Woessner, *J. Chem. Soc. Chem. Commun.* **1972**, 529.

340 J. Kawamoto, S. Muramatsu, Y. Yura, *Synth. Commun.* **5**, 185 (1975).

7.1. 1,4-Diketone Synthesis: Access to Jasmonoids, Retrolonoids, and Prostanoids

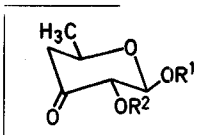
These classes of natural products contain the five-membered ring systems **150**, **151**, and **152** which can be made by aldol-type reactions from the 1,4-dicarbonyl compounds **153**, **154**[337].



150 **151** **152**

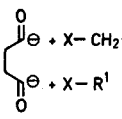
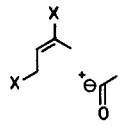
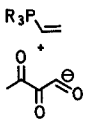
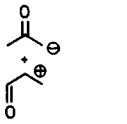
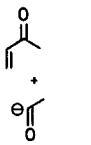
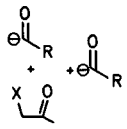
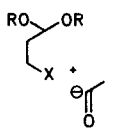
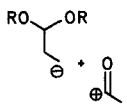
153 **154**

The syntheses of **150–152** have been extensively reviewed in recent years[16,17,338]. In these surveys, the different methods of connective 1,4-diketone syntheses can be nicely compared with respect to their generality and efficiency. The general schemes used for the syntheses of the 1,4- and/or 1,3-unsymmetrically substituted 1,4-dicarbonyl compounds **153** and **154** are given in Table 29.



156

Table 29. General Connective Principles in the Syntheses of **153** and **154** using Sulfur-Substituted Organolithium Compounds for Reactivity Umpolung

Synthons	Reference	Synthons	Reference
	184, 339		112
	205, 340		125, 306, 307, 312, 341, 342
	58, 68, 69, 89 b 256, 257, 258		35
	143		278 b

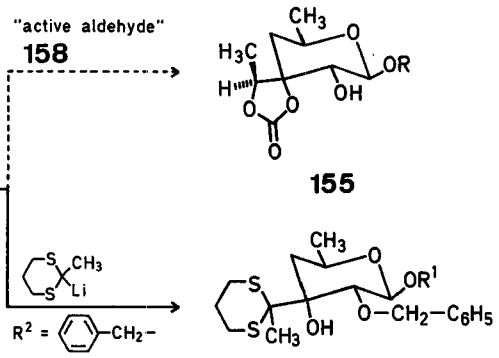
[341] R. F. Romanet, R. H. Schlessinger, *J. Am. Chem. Soc.* **96**, 3701 (1974).

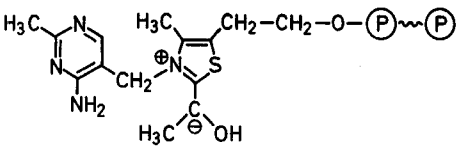
[342] Y. Ban, T. Ohnuma, K. Seki, T. Oishi, *Tetrahedron Lett.* **1975**, 727.

7.2. Use 2-Lithio-1,3-dithianes in Carbohydrate Synthesis[363]

The chemistry of monosaccharides appears to many organic chemists as a somewhat special subject that was all settled long ago. Still, there is obviously room for improving the old methods of chain elongation. Furthermore, many exotic monosaccharide moieties with branched carbon skeletons have been found in nature (for example in antibiotics[343]) and their total synthesis had to be achieved. For these purposes, metallated dithianes have been extensively used since our earlier report[1].

It is interesting to note the similarity of some of these processes with nature's ways. This can be demonstrated by the synthesis of methyl aldgaroside B (**155**) which is probably formed in nature by branching of **156** with the so-called active acetaldehyde **158**[344]. The first laboratory synthesis, and at the same time the final structure determination, was achieved utilizing methyldithiane in the branching step **156**→**157**[37,345].

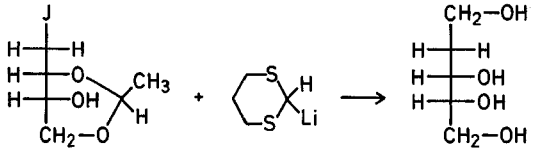




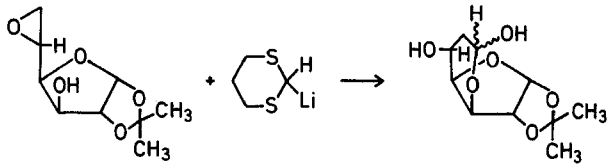
158

The thiamine derivative **158** and the similar active glyoxal are two of nature's nucleophilic acylating reagents for two carbon chain elongations; her reagents are, as usual, much more complex, but work at physiological pH values and do not require protection to direct reaction within the substrate and to prevent undesired conversion[346]. Besides addition to carbonyl groups[37,38,175,336a–c,344,347–352], the processes alkylation[146] and oxirane ring opening[336d,353,354] involving lithiodithianes were used in carbohydrate synthesis. An example of each of the latter two reactions is given in the following two equations, the syntheses of **159**[146] and **160**[351].

[343] H. Grisebach, R. Schmid, *Angew. Chem.* **84**, 192 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 159 (1972).



159



160

7.3. Other Natural Product Syntheses

As a further demonstration of the usefulness of sulfur-substituted compounds as reagents with reactivity umpolung, we have arranged some selected examples in Table 30. There are many more applications which might have been quoted. We think that the cases included in the Table 30 and in Sections 7.1 and 7.2 suffice to prove that natural product synthesis has profited from the methodology described in the present review article, and that it is worthwhile and beneficial to continue the search for ways of reversing the reactivity of common functional groups[15].

Table 30. Selected Examples of the Use of Sulfur-Containing Reagents Providing Reactivity Umpolung in Natural Product Synthesis

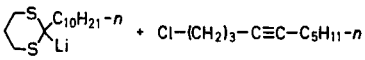
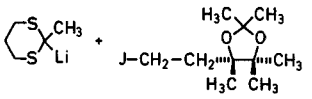
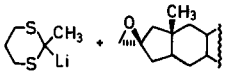
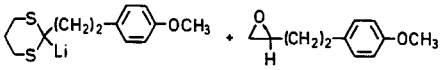
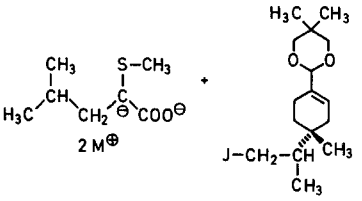
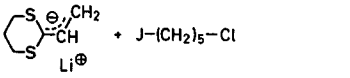
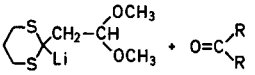
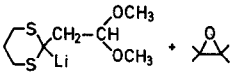
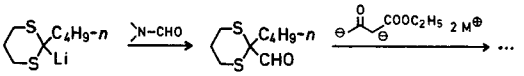
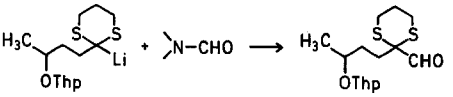
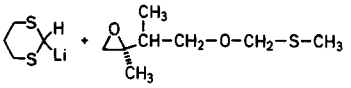
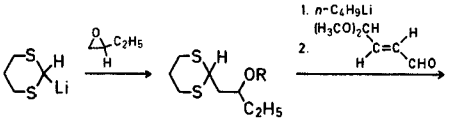
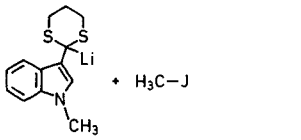
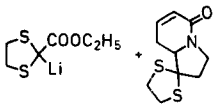
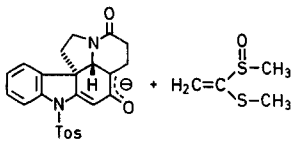
Synthesis target	Key steps involving reactivity umpolung with sulfur derivatives	References
pheromone		355[a]
squalene		105
steroid		44, 335 b
alnusone		356
iuvabione		262
peptide		142
furanones		145
γ-pyrones		145
pestalotin (α-pyrones)		61, 62
pyrenophorin		141
vermiculin	see Section 3.1.1	210
maytansin		357
		358

Table 30. (Continued)

Synthesis target	Key steps involving reactivity umpolung with sulfur derivatives	References
lysergic acid		359
camptothecin		58
aspidoalbidine		342

[a] See also e.g., Lit.[140].
[b] See also e.g., Lit.[335d].

Received: May 12, 1976
(Last additions: April 1977)

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R. Schmid, H. Grisebach, *Z. Naturforsch.* **25b**, 1259 (1970).
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[351] A. Gateau-Olesker et al., *J. Chem. Soc. Chem. Commun.* **1974**, 811.
[352] S. D. Gero, D. Horton, A. M. Sepulchre, J. D. Wander, *J. Org. Chem.* **40**, 1061 (1975).
[353] A. M. Sepulchre, G. Lukacs, G. Vass, S. D. Gero, *C. R. Acad. Sci. Ser. C* **273**, 1180 (1971).
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[355] R. G. Smitz, G. E. Daterman, G. D. Daves Jr., *Science* **188**, 63 (1975).
[356] M. F. Semmelhack, L. S. Ryono, *J. Am. Chem. Soc.* **97**, 3873 (1975).
[357] E. J. Corey, M. G. Bock, *Tetrahedron Lett.* **1975**, 2643.
[358] A. I. Meyers, R. S. Bringmeyer, *Tetrahedron Lett.* **1975**, 1749.
[359] P. Stütz, P. A. Stadler, *Helv. Chim. Acta* **55**, 75 (1972).
[360] I. Vlattas, L. D. Vecchia, A. O. Lee, *J. Am. Chem. Soc.* **98**, 2008 (1976).
[361] R. Gompper, W. Reiser, *Tetrahedron Lett.* **1976**, 1263.
[362] T. Cohen, D. A. Bennett, A. J. Mura, Jr., *J. Org. Chem.* **41**, 2506 (1976).
[363] H. Paulsen, *Pure Appl. Chem.* in press.
See also: H. Paulsen et al., *Chem. Ber.* **107**, 2992 (1974); **108**, 1229 (1975); **109**, 1362 (1976).
H. Paulsen et al., *Angew. Chem.* **88**, 476, 477, 478 (1976); *Angew. Chem. Int. Ed. Engl.* **15**, 438, 439, 440 (1976).
A. Yamashita, A. Rosowsky, *J. Org. Chem.* **41**, 3422 (1976).