Tetrahedron Vol. 42, No. 14, pp. 3731 to 3752, 1986
Printed in Great Britain.

0040-4020/86 $5.00+.00
Pergamon Journals Ltd.

TETRAHEDRON REPORT NUMBER 204

ORGANIC SYNTHESIS WITH α-CHLOROSULFIDES

BRID M. DILWORTH and M. ANTHONY MCKERVEY
Department of Chemistry, University College, Cork, Ireland

(*Received in UK* 8 *July* 1985)

CONTENTS

1. INTRODUCTION

Although α-chlorosulfides have been available for many years, it is only relatively recently that their potential as reaction intermediates has been explored systematically, and it is now clear that the juxtaposition of chlorine and sulfur atoms attached to the same carbon atom produces a functionality with several attractive features in chemical synthesis. α-Chlorosulfides are particularly useful as aldehyde or ketone equivalents, as reactive electrophiles for a variety of sulfur-mediated reactions and as precursors of α-chlorosulfones, a distinctive feature of the latter being their ability to produce alkenes via the Ramberg–Bäcklund rearrangement. Our intention in this report is to summarize the more important recent advances with α-chlorosulfides, emphasizing efficient methods of preparation and versatility in synthesis.[1]

2. PREPARATION OF α-CHLOROSULFIDES

2.1. *From alkyl sulfides*

Direct chlorination of an alkyl sulfide possessing at least one hydrogen atom at the α-position (Eq. 1) is by far the most widely used route to α-chlorosulfides. The popularity of this route is hardly surprising, considering the ease with which many alkyl sulfides can be synthesized from readily available compounds.[2] One of the earliest investigations in this area was that of Riche[3] who combined chlorine with dimethyl sulfide and although there followed a period of dispute and uncertainty concerning the constitution of the product, compounded by the difficulty of controlling the extent of reaction, the process is now recognized as α-chlorination.[4] Later, Böhme *et al.*[5] synthesized monochlorodimethyl sulfide by treating dimethyl sulfide with one equivalent of chlorine in carbon tetrachloride at −20°. However, chlorine is no longer the reagent of choice for most substrates, having been largely replaced by more convenient alternatives such as sulfuryl chloride,[6] thionyl chlo-

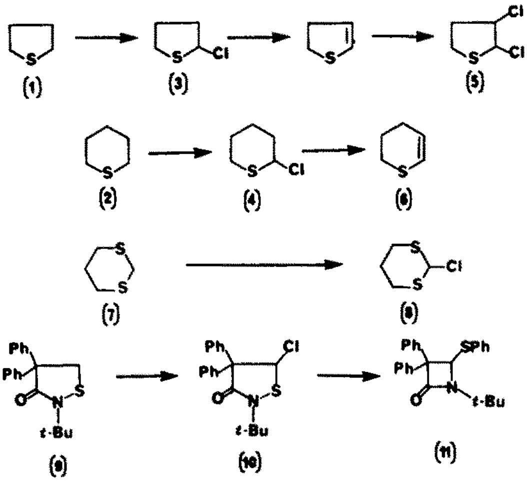
$$\text{R—S—CHR}'\text{R}'' \xrightarrow{\text{chlorination}} \text{R—S—CClR}'\text{R}'' \qquad (1)$$

ride,[6] N-chlorosuccinimide (NCS),[7] N-chlorophthalimide,[8] trichloroisocyanuric acid (Chloreal),[9] iodobenzene dichloride,[10] and benzenesulfenyl chloride.[11] Of these, sulfuryl chloride and NCS are the most widely used today.

The investigations of Truce *et al.*[6] on the chlorination of dimethyl sulfide were greatly facilitated by their introduction of sulfuryl chloride and thionyl chloride.[6] Sulfuryl chloride reacts vigorously with dimethyl sulfide according to Eq. (2); with equimolar quantities of reactants and an initial temperature of −15° it is possible to obtain a 45% yield of monochloride.[6] An increase in the ratio of sulfuryl chloride to sulfide leads to further chlorination following a sequence whereby the methyl

$$CH_3SCH_3+SO_2Cl_2 \rightarrow CH_3SCH_2Cl+SO_2+HCl \qquad (2)$$

group on which the first chlorine atom is introduced is completely chlorinated before there is any attack on the second methyl group; after the tetrachloro stage is reached further chlorination occurs very slowly and is accompanied by sulfur–carbon bond cleavage. Böhme and Gran[12] diluted sulfuryl chloride with carbon tetrachloride for chlorination of dibenzyl sulfide and obtained the monochloride in 79% yield. Similarly, Bordwell and Pitt[13] used this reagent in pentane or dichloromethane to monochlorinate sulfides such as methyl phenyl, methyl *p*-tolyl, methyl *p*-chlorophenyl, methyl *p*-methoxyphenyl, methyl benzyl, methyl t-butyl, phenyl benzyl and bis(carboethoxymethyl). Attempts to obtain monochlorides from diallyl sulfide, phenyl ethyl sulfide, diisopropyl sulfide, methyl isopropyl sulfide, thiacyclopentane, α-methylthiacyclopentane and thiacyclohexane were unsuccessful. In general, alkyl sulfides containing β-hydrogen atoms fail to give monochlorides cleanly with sulfuryl chloride; it seems likely that α-chlorosulfides are indeed produced in these cases but subsequent dehydrochlorination via β-elimination yields α,β-unsaturated sulfides which may undergo further reactions including polymerization. The chlorination of diethyl sulfide is exceptional, though in fact α-chloroethyl ethyl sulfide is a very unstable substance, decomposing with loss of hydrogen chloride at room temperature. Chlorination of thiacyclopentane (**1**) and thiacyclohexane (**2**) with sulfuryl chloride gives only trace amounts of α-chlorosulfides (**3** and **4**), the major products being 2,3-dichlorothiacyclopentane (**5**) and thiacyclohexene (**6**), respectively. Wilson and Albert[14] later found that addition of an *equivalent* amount of triethylamine or pyridine to solutions of sulfuryl chloride suppressed the elimination process to the extent that good yields of α-chlorothiacyclopentane (**3**) could be obtained from **1**. The controlled introduction of two chlorine atoms in phenyl alkyl sulfides has recently been achieved using sulfuryl chloride–pyridine (1:1 molar ratio) in carbon tetrachloride at −5°; under reflux, 1-chloroalk-1-enyl sulfides are produced.[15] Sulfuryl chloride in chloroform at −40° has been used to convert 1,3-dithiane (**7**) into its highly reactive, though synthetically useful 2-chloro derivative (**8**).[16] In carbon tetrachloride, sulfuryl chloride converts isothiozolidine (**9**) into chlorosulfide (**10**) whose ring contraction to β-lactam (**11**) has been proposed as a model for penicillin biosynthesis.[17]



Whereas sulfuryl chloride reacts vigorously with dimethyl sulfide at 0° thionyl chloride requires temperatures in the range 25–95°, a reactivity difference that permits efficient synthesis of the monochloride with the latter reagent.[6] Excellent yields of α,α,α-trichlorodimethyl sulfide can be obtained using thionyl chloride in excess, further chlorination being negligible.

The introduction of NCS for sulfide chlorination in 1966 led to major improvements in the synthesis of α-chlorosulfides.[7] Not only is the reagent particularly easy to handle, but its reactivity is such that the extent of chlorination is easily limited to the monochloride stage. Furthermore, it can be used for chlorination of acid-sensitive molecules. NCS is soluble in carbon tetrachloride at room temperature at normal concentrations whereas its conjugate product, succinimide, is not. Thus solutions of chlorosulfides are frequently prepared in this solvent and filtered for use without further purification; attempted purification by chromatographic procedures often leads to decomposition. Other non-polar solvents that have been used with NCS include dichloromethane, chloroform, and benzene. α-Chlorosulfides cannot be prepared satisfactorily in water or hydroxylic solvents due to their susceptibility to solvolysis which is in itself a useful feature of their reactivity. Some of the very many examples of the use of NCS from the recent literature are summarized in Table 1. The isolation of α-chlorosulfides from substrates of diverse structural type in which β-elimination is possible is particularly noteworthy (entries 2–20). Difunctional sulfides are converted into *bis*-α-chloro derivatives efficiently (entries 4 and 5). It is also evident that functional groups such as alkene,

Table 1. Chlorination of alkyl sulfides with NCS

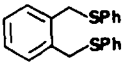
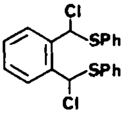
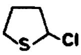
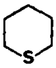
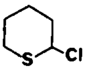
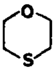
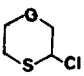
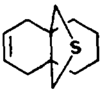
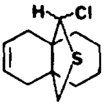
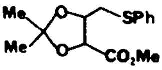
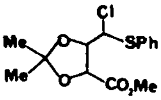
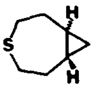
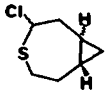
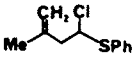
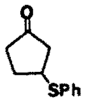
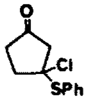
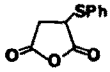
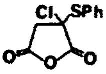
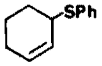
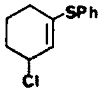
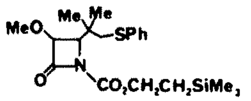
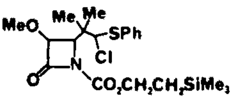
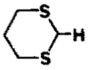
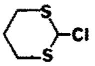
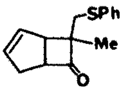
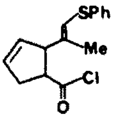
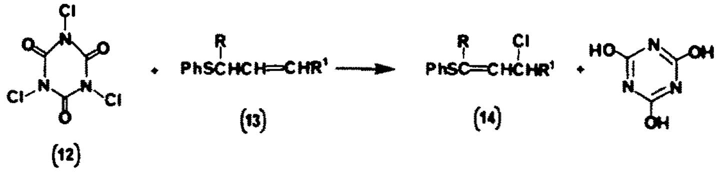
Entry No.	Substrate	Product	Ref.
1	$PhSCH_3$	$PhSCH_2Cl$	7
2	$PhSCH_2CH_3$	$PhSCHClCH_3$	7
3	$PhS(CH_2)_4CH_3$	$PhSCHCl(CH_2)_3CH_3$	18
4	$PhSCH_2(CH_2)_nCH_2SPh$	$PhSCHCl(CH_2)_nCHClSPh$	19
	$n=0$	$n=0$	
	$n=1$	$n=1$	
	$n=2$	$n=2$	
5			19
6			20
7			20
8			20
9			21
10	$PhSCH_2CH_2COMe$	$PhSCHClCH_2COMe$	22
11	$PhSCH_2CH_2CN$	$PhSCHClCH_2CN$	23
12	$Me_3SiOCH_2CH_2SPh$	$Me_3SiOCH_2CHClSPh$	24
13			25
14			26

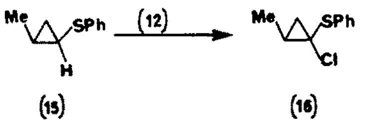
Table 1 (*cont.*)

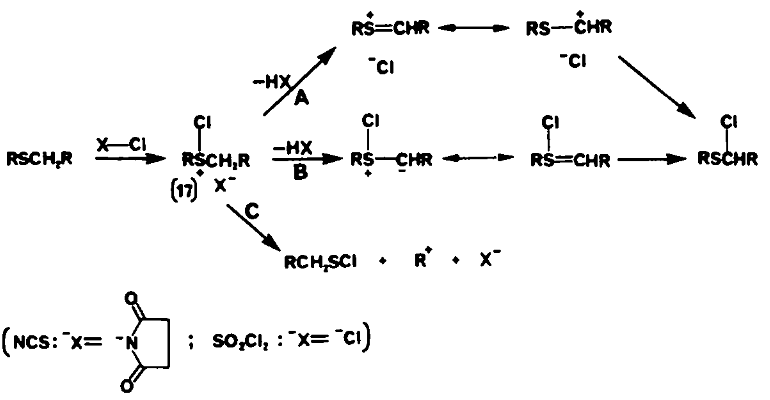
Entry No.	Substrate	Product	Ref.
15			27
16			28
17			29
18	$Me_3Sn(CH_2)_4SPh$	$Me_3Sn(CH_2)_3CHClSPh$	30
19	 $PhS\underset{SiMe_3}{C}HMe$	 $PhS\underset{SiMe_3}{C}ClMe$	31
20			9
21	$MeSCH_2CO_2Et$	$MeSCHClCO_2Et$	32
22			33
23			34
34			35

ester, cyanide, β-lactam, ketal, ketone and trimethylsilyl are unaffected in the course of sulfide chlorination with NCS, though allylic rearrangement is observed with allyl phenyl sulfide, e.g. entry 20. NCS in benzene has been recommended for the preparation of 2-chloro-1,3-dithiane from 1,3-dithiane (entry 23). Small ring carbinyl systems are prone to ring opening rearrangement as exemplified by the [3.2.0] system in entry 24.

Although NCS continues to be the most popular reagent for sulfide chlorination, a less expensive alternative has been available for several years. In 1975 Cohen and his co-workers[9] reported that trichloroisocyanuric acid (**12**) which is an ingredient of some industrial deodorants and household cleaners under the trade name Chloreal®, is capable of sulfide chlorination. In a comparative study limited to allylic sulfides (**13**) Cohen found that NCS was a less effective reagent than Chloreal, affording mainly starting material when R = alkyl; even at room temperature complete conversion





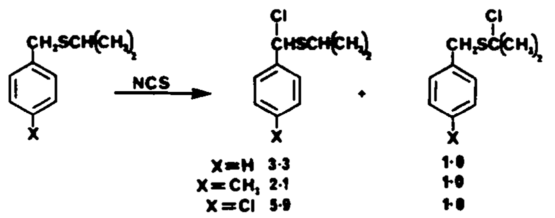


Scheme 1. Mechanism of sulfide chlorination by NCS and SO_2Cl_2.

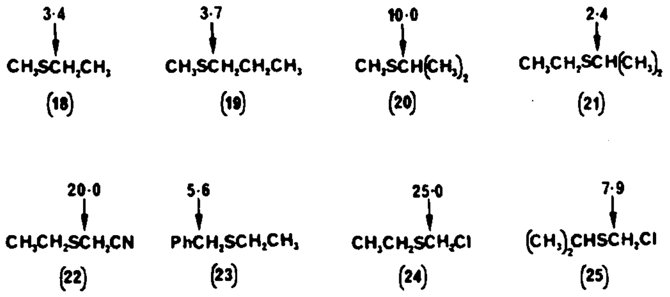
was not observed. Furthermore, chlorination of primary allylic sulfides (**13**; R = H) is significantly faster with Chloreal than with NCS, though the latter can be used successfully. For example, phenyl crotyl sulfide (**13**; R = H, R′ = Me) gives a 36% yield of **14** (R = H, R′ = Me) after 24 h at 5° whereas the yield is quantitative with Chloreal. However, the percentage *E* stereoselectivity in **14** is higher with NCS. Chloreal has also been used to chlorinate cyclopropyl phenyl sulfides, e.g. **15** → **16**.[36] However, in our experience Chloreal is a less efficient reagent than NCS for simple alkyl phenyl sulfides.

There is now general agreement that these various sulfide chlorination reactions follow ionic mechanisms reminiscent of the Pummerer rearrangement of sulfoxides,[37] the net result of which is transfer of functionality from sulfur to carbon. Initial attack on sulfide produces an S-chlorosulfonium ion (**17**; Scheme 1) whose conversion to chlorosulfide has been vividly described by Bordwell and Pitt[13] as "riding downhill from sulfur to carbon on an electron cloud". Two mechanistic extremes of how this may be brought about are illustrated by paths A and B in Scheme 1. Which pathway will be favoured in any particular situation will no doubt be influenced by structural considerations, e.g. the acidity of the α-hydrogen atom(s), and the choice of chlorinating agent since the basicity of the anion X^- is also implicated. The work of Tuleen and Stephens[38] on the chlorination of unsymmetrical sulfides provides valuable information on the directive effects implicit in the mechanisms encompassed by Scheme 1. It was known already that chlorination of benzyl methyl sulfide by sulfuryl chloride[3] or chlorine[12] gives chlorobenzyl methyl sulfide exclusively. Furthermore, chlorination of unsymmetrical benzyl sulfides by NCS (Scheme 2) reveals internal competition between the two available α-positions, yielding mixtures of products.[38] Directive effects in these internal competitions are correlated by the Hammett relationship with a value of $\rho = 1.0$. This observation is consistent with a mechanism involving abstraction of the more acidic proton in the chlorosulfonium ion intermediate.

The results of chlorination of a series of aliphatic sulfides[38] with NCS are summarized in Scheme 3; the site of preferential reaction is denoted by an arrow and the major : minor product ratios are also indicated. While consideration of the relative acidities of the α-hydrogen atoms accounts satisfactorily for the dominant direction of chlorination of ethylthioacetonitrile (**22**), benzyl ethyl sulfide (**23**), and the chlorosulfides (**24** and **25**), it does not explain the directive effects exhibited by the simple dialkyl sulfides (**18**–**21**). These substrates reveal an increasing susceptibility to chlorination

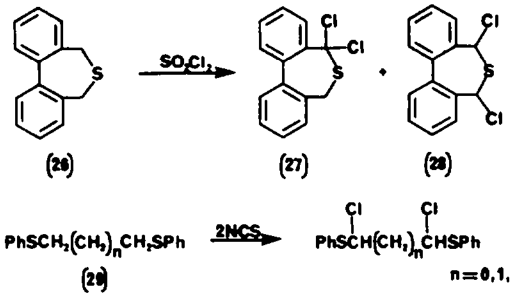


Scheme 2.



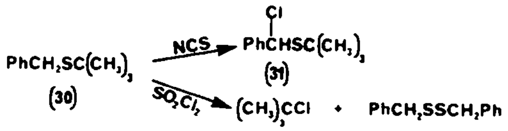
Scheme 3.

of alkyl groups in the order methyl < ethyl–n-propyl < i-propyl which is also that expected if the α-carbon atom assumes some carbonium ion character in the transition state for hydrogen abstraction. This is consistent with path A in Scheme 1 in which concerted removal of hydrogen chloride from the chlorosulfonium ion generates a delocalized carbonium ion. Paths A and B are in fact variations on the well-known E2 and E1cb mechanisms for 1,2-elimination reactions. Path B, by analogy with the E1cb process, should therefore become more significant in sulfonium salts having an α-hydrogen atom of pronounced acidity; undoubtedly there is a continuum of mechanisms between the two extremes.[39] The behaviour of chlorosulfides (**24** and **25**) towards further chlorination and of dimethyl sulfide towards polychlorination demonstrates that a chloro substituent exerts a powerful directive effect in these systems. That this is not invariably so is shown by chlorination of the tricyclic sulfide (**26**) which with two equivalents of sulfuryl chloride furnishes a 4 : 1 mixture of dichlorosulfides (**27** and **28**).[40] NCS chlorination of the symmetrical *bis*-sulfide series (**29**) is similarly exceptional in that symmetrical *bis*-chlorosulfides are produced exclusively.[19]



Tuleen and Stephens noted also a difference in regioselectivity in the chlorination of ethyl methyl sulfide by NCS and sulfuryl chloride, the latter being the more selective towards the internal position (ratio : 4.9 vs 3.4). In chlorination with sulfuryl chloride proton abstraction from the chlorosulfonium ion is brought about by chloride ion whereas with NCS the more basic succinimidyl ion is responsible. This difference suggests that of the two, the sulfuryl chloride reaction is more likely to follow the mechanism of path A. Consequently, carbonium ion relative stabilities should be more important in determining product composition with sulfuryl chloride.

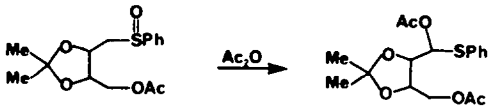
Although path C in Scheme 1 is unproductive vis-à-vis chlorosulfide synthesis, it is included here to highlight further differences between the reactivity of sulfuryl chloride and NCS. Treatment of benzyl t-butyl sulfide (**30**) with NCS gives the expected chlorosulfide (**31**). In contrast, sulfuryl chloride affords predominantly the fragmentation products t-butyl chloride and dibenzyl disulfide. Similarly, benzyl *p*-methoxybenzyl sulfide behaves normally with NCS, but is cleaved to *p*-methoxy-



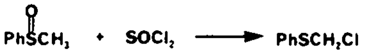
benzyl chloride and disulfide by sulfuryl chloride.[38] The carbon–sulfur bond cleavage observed with sulfuryl chloride may be interpreted in terms of fragmentation of the intermediate chlorosulfonium salt (X = Cl, path C), a process which should be facilitated by the release of a relatively stable carbonium ion. That this does not happen when the reagent is NCS suggests that the competition between path C leading to fragmentation and those leading to chlorosulfide is controlled by the relative basicity of chloride and succinimidyl ion.[38,39] The most effective way of directing chlorination towards one side of the heteroatom in a sulfide is by using an alkyl phenyl sulfide.

2.2. *From sulfoxides*

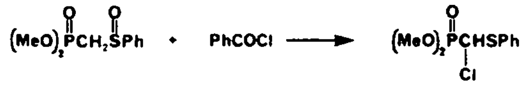
In the foregoing discussion of the mechanism, α-chlorination of sulfides was classified as a Pummerer-type rearrangement[37] involving functional group transfer from sulfur to carbon. In its original form, the Pummerer rearrangement refers to transfer of functionality from sulfoxide to carbon; Eq. (3) provides a recent illustrative example.[41] In practice, it is possible through the appropriate choice of reagent to transform sulfoxides into α-chlorosulfides in a completely analogous manner. This route is of course less important than sulfide chlorination since sulfoxides are normally less accessible than sulfides. Reagents that have been employed include thionyl chloride (Eq. 4);[13]



(3)



$$Ph\overset{O}{\overset{\|}{S}}CH_3 + SOCl_2 \longrightarrow PhSCH_2Cl \qquad (4)$$



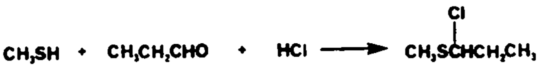
$$(MeO)_2\overset{O}{\overset{\|}{P}}CH_2\overset{O}{\overset{\|}{S}}Ph + PhCOCl \longrightarrow (MeO)_2\overset{O}{\overset{\|}{P}}\underset{Cl}{\underset{|}{C}}HSPh \qquad (5)$$

benzoyl chloride (Eq. 5)[13] and acetyl chloride.[13] Hydrogen chloride[42] can also be used for this purpose provided provision is made to remove the water liberated in the reaction, e.g. by adding molecular sieves.

2.3. *From aldehydes and thiols*

There are other synthetically useful routes to α-chlorosulfides which are related mechanistically to sulfide chlorination even though there is not a formal functional group transfer from sulfur to carbon. One such method devised by Böhme and co-workers[5,43] is based on the condensation of an aldehyde with a thiol in the presence of hydrogen chloride. This synthesis is quite versatile and product homologation is possible through the appropriate choice of the aldehyde component. Use of formaldehyde results in a one-carbon homologation as in Eq. (6). Higher aldehydes lead to secondary chlorides, e.g. Eq. (7). Furthermore, the process can be used to prepare regiochemically pure α-chlorosulfides without danger of isomer contamination in situations where use of NCS and the corresponding alkyl sulfide could reasonably be expected to be nonregioselective. For example,

$$PhSH + HCHO + HCl \longrightarrow PhSCH_2Cl \qquad (6)$$

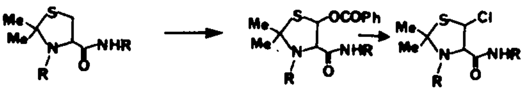


$$CH_3SH + CH_3CH_2CHO + HCl \longrightarrow CH_3S\overset{Cl}{\overset{|}{C}}HCH_2CH_3 \qquad (7)$$

$$PhCH_2SCH_2C_6H_4CH_3 + NCS \longrightarrow PhCHClSCH_2C_6H_4CH_3 + PhCH_2SCHClC_6H_4CH_3 \qquad (8)$$

$$PhCH_2SH + CH_3C_6H_4CHO + HCl \longrightarrow PhCH_2SCHClC_6H_4CH_3 \qquad (9)$$

$$CH_3C_6H_4CH_2SH + PhCHO + HCl \longrightarrow PhCHClSCH_2C_6H_4CH_3 \qquad (10)$$



Scheme 4.

NCS chlorination of benzyl *p*-methylbenzyl sulfide gives both possible monochlorosulfides (Eq. 8) whereas the condensation alternatives of aldehyde, thiol and hydrogen chloride in Eqs (9) and (10) gives one or other of the monochlorides exclusively.[44] A closely related process in which the halogen substituent is introduced via hydrogen chloride cleavage of a benzoate has been used in synthesis of *β*-lactams (Scheme 4), the initial functionalization to the sulfur atom having been achieved by a free radical process.[45,46]

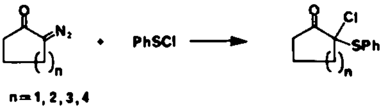
2.4. *From α-diazocarbonyl compounds*

Although chlorination of sulfides remains the most popular route to α-chlorosulfides, there are other useful methods of synthesis not based on sulfides. One such method, which has the commendable feature of simultaneous introduction of both chlorine and sulfur atoms, is particularly useful when one wishes to place the chlorosulfide unit adjacent to the carbonyl group of a ketone in a regiospecific manner. It is based on the propensity of diazoalkanes to undergo α,α-addition reactions with various sulfenyl chlorides.[47] Weygand and Bestmann[48] found that α-diazoketones and benzenesulfenyl chloride react smoothly together with loss of nitrogen at room temperature to furnish α-chloro-α-(phenylthio)ketones, e.g. Eq. (11), in excellent yield. These workers later extended the reaction to include diazo esters (Eq. 12) and 2-diazo-1,3-dicarbonyl compounds (Eq. 13).[49] More

$$\mathrm{PhCOCHN_2 + PhSCl \longrightarrow PhCOCH(SPh)Cl} \qquad (11)$$

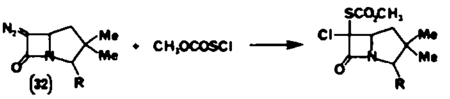
$$\mathrm{CH_3CH_2OCOCHN_2 + PhSCl \longrightarrow CH_3CH_2OCOCH(SPh)Cl} \qquad (12)$$

$$\mathrm{CH_3COCN_2COCH_3 + PhSCl \longrightarrow CH_3COC(SPh)ClCOCH_3} \qquad (13)$$

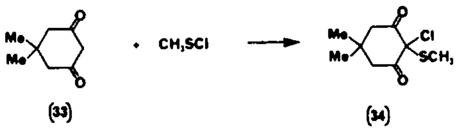


(14)

recently, cyclic α-diazoketones and benzenesulfenyl chloride have been found to yield α-chloro-α-(phenylthio)cycloalkanones (Eq. 14).[50,51] Since terminal α-diazoketones can be obtained in excellent yield from acyl chlorides and diazomethane, this route to α-chloro-α-(phenylthio)ketones is particularly useful in that it depends neither on the availability of the parent ketone nor on prior regiospecific introduction of the phenylthio group. Displacement of nitrogen from diazoketones in the *β*-lactam series has been used extensively to introduce functional groups at the 6-position. The simultaneous introduction of chlorine and sulfur substituents at this position was achieved by Sheehan and Commons[52] through the reaction of diazo ester (**32**) with carbomethoxysulfenyl chloride as shown in Eq. (15). Some enolizable *β*-diketones react directly with sulfenyl halides, dimedone (**33**) furnishing chlorosulfide (**34**) when treated with methanesulfenyl chloride.[53]

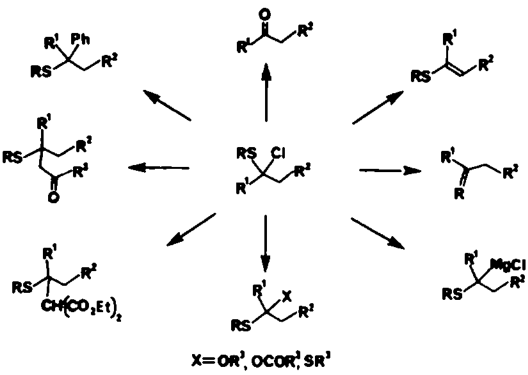


(15)



3. REACTIONS OF α-CHLOROSULFIDES

α-Chlorosulfides exhibit a range of reactivity which renders them useful as intermediates in organic synthesis (Scheme 5). Their ready oxidation to α-chlorosulfones with peracids has been



Scheme 5.

exploited extensively in the Ramberg–Bäcklund olefin synthesis. α-Chlorosulfides are prone to solvolysis: in aqueous media they thus serve as a source of aldehydes and ketones; exposure to alcohols or thiols leads to hemithioacetals or dithioacetals. They form and couple with Grignard reagents. Elimination of hydrogen chloride provides access to vinyl sulfides and thiocarbenoids. α-Chlorosulfides are also important sources of reactive electrophiles not only in S_N2 reactions, but also in alkylation reactions of arenes, alkenes, alkynes and enol ether derivatives.

3.1. *Ramberg–Bäcklund reaction*

Under anhydrous conditions α-chlorosulfides can be oxidized to α-chlorosulfones in excellent yield. Where structural considerations permit, α-chlorosulfones are capable of intramolecular 1,3-elimination in base, leading to replacement of the sulfonyl group by a carbon–carbon double bond with loss of hydrogen chloride and sulfite ion. This extrusion process, often called the Ramberg–Bäcklund reaction, constitutes an efficient alkene synthesis. Conversion of the optically active sulfide in Eq. (16) into (*R*)-(−)-3-methylcyclopentene[55] and of the bicyclic sulfide in Eq. (17) into *trans*-bicyclo[4.1.0]hept-3-ene[26] are recent applications. The reaction has been reviewed in detail elsewhere and will not be discussed further here.[54]

(16)

(17)

3.2. *Hydrolysis*

The use of α-chlorosulfides as aldehyde or ketone equivalents is widespread. α-Chloromethyl methyl sulfide (**35**; R = Me) and α-chloromethyl phenyl sulfide (**35**; R = Ph) decompose in water according to Eq. (18), producing hydrochloric acid, formaldehyde, and the appropriate dithioacetal.[5]

$$\underset{(35)}{RSCH_2Cl} \xrightarrow{H_2O} HCHO + HCl + (RS)_2CH_2 \qquad (18)$$

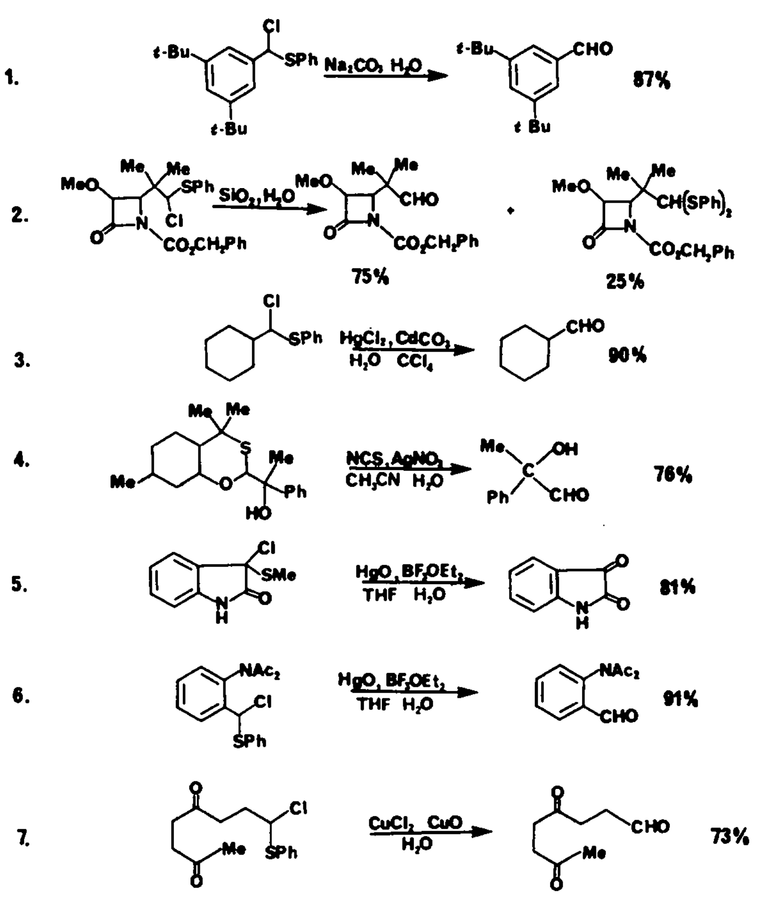
$$RS-\overset{+}{C}H_2 \longleftrightarrow R\overset{+}{S}{=}CH_2$$

(36)

Hydrolysis rates follow first-order kinetics and the process is best represented mechanistically by ionization to form a sulfur-stabilized carbonium ion (**36**) prior to combination with water.[56] The contribution of sulfur participation in promoting hydrolysis is indicated by the fact that **35** (R = Me) reacts 2000 times faster than t-butyl chloride under the same conditions. The nature of the R group is also significant, **35** (R = Me) hydrolyzing 200 times faster than **35** (R = Ph). Sulfur participation is, however, much less than that of oxygen in comparable α-chloroethers.[57]

Dithioacetal formation in addition to carbonyl product (as indicated in Eq. 18) is usually a feature of hydrolysis unless one deliberately adds a reagent capable of preventing the thiol released from combining with the carbocation intermediate. A number of hydrolysis procedures, examples of which are collected in Table 2, have been employed, some specifically designed to sequester thiol and thereby optimize yields of carbonyl products. Simple procedures are quite effective in some instances, aqueous sodium carbonate furnishing a high yield of the aromatic aldehyde in entry 1;[58] aqueous sodium hydroxide, however, is generally much less satisfactory. Chu[59] has recently introduced water-deactivated silica gel as a hydrolysis medium, illustrating its success with production of the β-lactam aldehyde in entry 2; 25% of the dithioacetal was also isolated. Other procedures are related to systems developed for 1,3-dithiane hydrolysis for which mercury(II) chloride in aqueous methanol, ethanol, tetrahydrofuran, dimethyl sulfoxide, acetone, acetonitrile or benzene is generally successful.[60] An insoluble base such as mercuric oxide, cadmium carbonate or calcium carbonate is often added to neutralize the HCl formed during hydrolysis. Paquette *et al.* used the mercury(II) chloride–cadmium carbonate combination in water–carbon tetrachloride to synthesize cyclohexanecarboxaldehyde from the chlorosulfide in entry 3.[58] Other reagents that also act as Lewis acids to promote hydrolysis of dithiane derivatives include acidic mercuric acetate,[61] mercuric oxide–boron trifluoride etherate,[62] NBS, NBS with silver ion and NCS with silver ion.[63] Lynch and Eliel[64] recently accomplished the conversion of the optically active oxathiane in entry 4 into the α-hydroxyaldehyde shown without loss of optical activity by treatment with NCS and silver nitrate in aqueous acetonitrile. In their work on isatin synthesis, Gassman *et al.*[65] found that although treatment of 3-chloro-3-methylthiooxindole (entry 5) with aqueous tetrahydrofuran did cause hydrolysis, appreciable quantities of bisthioacetal were also produced; use of mercuric oxide–boron trifluoride etherate in aqueous tetrahydrofuran eliminated the by-product. This same com-

Table 2. Hydrolysis of α-chlorosulfides



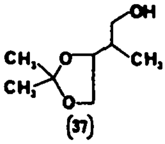
bination of reagents was also effective in formylation of aromatic amines, e.g. entry 6, via the chlorosulfide route.[66] The ability of Cu(II) ion to oxidize thiophenol forms the basis of yet another procedure for α-chlorosulfide hydrolysis, an example of which is the Cu(II)Cl_2–CuO catalyzed hydrolysis of the dihydrojasmone intermediate in entry 7.[67]

3.3. *Reactions of α-chlorosulfides with alcohols, carboxylic acids, thiols and amines*

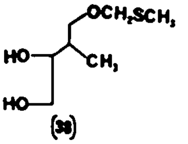
The manner in which α-chlorosulfides react with alcohols, carboxylic acids, thiols, and amines is of more than passing interest for the process can lead to derivatives that constitute a convenient form of functional group protection. Corey and Bock,[68] addressing the on-going need for new selective protecting groups for alcohols, introduced the methylthiomethyl (MTM) hemithioacetal group via the commercially available chloromethyl methyl sulfide. The alcohol, as its alkoxide, is treated with iodomethyl methyl sulfide generated *in situ* from the chlorosulfide and sodium iodide

$$CH_3SCH_2Cl \xrightarrow{NaI,\ R\bar{O}} CH_3SCH_2OR \qquad (19)$$

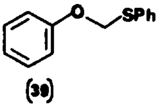
(Eq. 19). The halogen exchange step is necessary for efficient conversion to the hemithioacetal since reaction of the alkoxide with the chlorosulfide is sluggish and eventually leads to mixtures of products. Hemithioacetal formation is very efficient with primary alcohols, but much less so with secondary and tertiary alcohols. The MTM ether group is stable to basic and nucleophilic reagents and is moderately resistant to cleavage in aqueous acid. Treatment with either Hg(II) chloride in aqueous acetonitrile or $AgNO_3$ in aqueous tetrahydrofuran regenerates the alcohol. The conversion of **37** into the maytansine intermediate (**38**) provides an illustration of the introduction and manipulation of the MTM ether group in an acid-sensitive molecule. Holton and Nelson[69] extended this



(37)



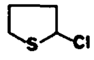
(38)



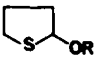
(39)

type of chemistry to the protection of phenols, using the phenoxide and chloromethyl phenyl sulfide to produce PTM ethers (**39**); halogen exchange with sodium iodide was necessary in this series also.

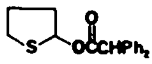
Kruse *et al.*[70] introduced the 2-tetrahydrothienyl (THT) group for alcohol protection and found that while reaction of 2-chlorotetrahydrothiophene (**40**) with primary and secondary alcohols in base was too sluggish to be practicable, THT ethers (**41**) were formed very efficiently by an alternative acid-catalyzed exchange reaction between the alcohol and 2-tetrahydrothienyl diphenyl acetate (**42**).



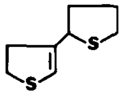
(40)



(41)



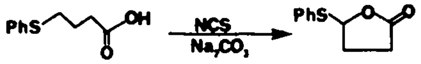
(42)



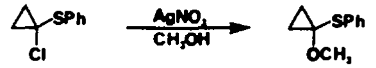
(43)

By contrast, reaction of THT ester (**42**) with tertiary alcohols or phenols produced mixtures of THT ethers and the dimer (**43**). THT ether protection of a primary alcohol in the presence of a tertiary alcohol can be achieved with better than 90% selectivity, and deprotection occurs very rapidly in aqueous acetonitrile containing Hg(II) chloride. The THT ester used in this study was obtained by treating diphenylacetic acid with 2-chlorotetrahydrothiophene (**40**) in the presence of triethylamine, following an earlier observation that carboxylic acids furnish MTM protected esters when treated with chloromethyl methyl sulfide.[71] However, Kruse *et al.*[70] found that acid-catalyzed exchange with primary alcohols to form ethers was much more successful with THT diphenyl acetate (**42**) than with MTM diphenyl acetate. Intramolecular reaction between the chlorosulfide function and a carboxylic acid has also been observed, e.g. formation of the sulfenylated lactone in Eq. (20).[72]

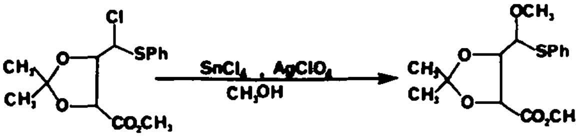
Another example of the reaction of α-chlorosulfides with alcohols that has found use in synthesis is Cohen's preparation of 1-methoxycyclopropyllithium from 1-phenylthio-1-methoxycyclopropane, the latter having been obtained from 1-phenylthio-1-chlorocyclopropane in methanol containing silver nitrate–calcium carbonate (Eq. 21).[36] Lewis acid-catalyzed reaction with methanol was also employed by Mukaiyama *et al.*[25] to prepare the hemithioacetal in Eq. (22) as part of a general synthesis of α-L-threofuranosides. Additional aspects of the versatility of α-chlorosulfides in methanol are summarized in Eqs (23) and (24): in Eq. (23) an α-chlorodithioacetal S,S-dioxide collapses in methanol furnishing a methyl ester;[73] and in Eq. (24), where the leaving group is adjacent to a carbonyl group, attack by methoxide ion results in a 1,2-carbonyl transposition.[74]



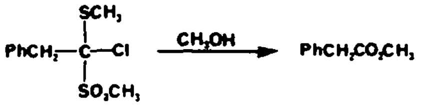
(20)



(21)

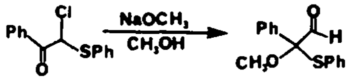


(22)



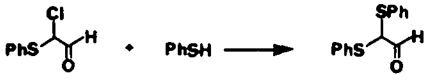
$$PhCH_2-\underset{SO_2CH_3}{\overset{SCH_3}{\underset{|}{\overset{|}{C}}}}-Cl \xrightarrow{CH_3OH} PhCH_2CO_2CH_3$$

(23)

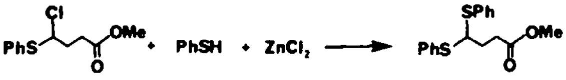


(24)

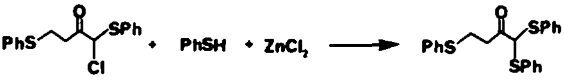
In discussing aspects of the hydrolysis of α-chlorosulfides we drew attention to the fact that dithioacetal formation is frequently a concomitant feature of the process unless thiol is removed as it is released. Conversely, by adding thiols α-chlorosulfides can be transformed into dithioacetals. In fact, this route to dithioacetals has been little employed. Duhamel *et al.*[74] found that α-chloro-α-(phenylthio)acetaldehyde and thiophenol gave α-bis(phenylthio)acetaldehyde (Eq. 25). Recent work in this laboratory has established that reaction of thiophenol with α-chlorosulfides in the presence of zinc chloride constitutes an efficient general route to a variety of dithioacetals; some representative examples are summarized in Eqs (26)–(30).[75]



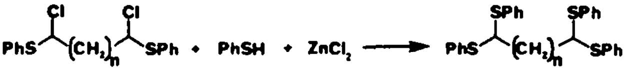
(25)



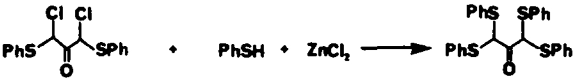
(26)



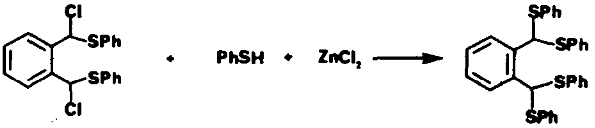
(27)



(28)

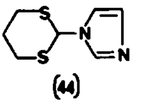


(29)

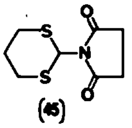


(30)

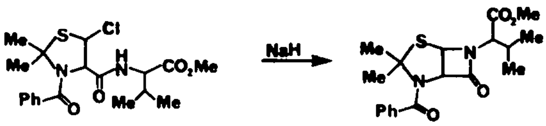
Nitrogen nucleophiles whose ability to displace chloride ion from α-chlorosulfides has been studied include imidazole and succinimide,[34] 2-chloro-1,3-dithiane furnishing adducts **44** and **45**, respectively. In the β-lactam area, ring closure of a nitrogen nucleophile onto an α-chlorosulfide derived from L-cysteine has been used to demonstrate the stereospecific *in vitro* conversion of peptides into β-lactam antibiotics (Eq. 31).[45] A very similar type of ring closure was employed subsequently by Koppell *et al.* in their synthesis of the β-lactam, nocardicin A.[46]



(44)



(45)



(31)

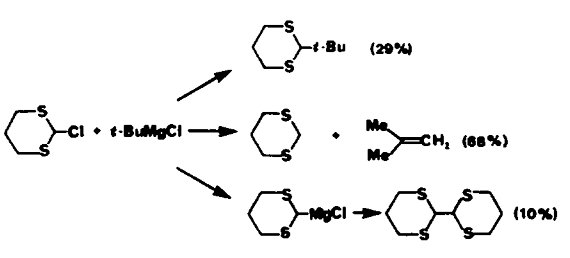
3.4. *Reactions of α-chlorosulfides with carbon nucleophiles*

Reactions of α-chlorosulfides with carbon nucleophiles in the form of Grignard reagents date back to the early work of Böhme[76] who found that phenylmagnesium bromide and chloromethyl methyl sulfide form the coupled product in Eq. (32). The reaction has been extended considerably in the intervening years and it is now a general method for introducing α-alkyl or aryl substituents.

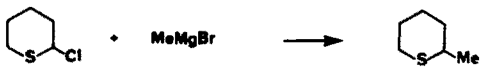
$$\mathrm{PhSCH_2Cl} + \mathrm{PhMgBr} \longrightarrow \mathrm{PhSCH_2Ph} \qquad (32)$$

However, Grignard reagent structure can impose limitations, Bordwell and Pitt[13] having found several examples where competing reactions diminish or suppress the coupling process: chloromethyl phenyl sulfide and t-butyl Grignard do not yield coupled products, rather the Grignard acts as a reducing agent to furnish methyl phenyl sulfide and isobutene. A somewhat similar situation is obtained in the reaction of 2-chloro-1,3-dithiane with t-butyl Grignard (Scheme 6) where coupling of the reactants is less significant than reduction and Grignard exchange.[77] Primary and secondary alkyl, aryl, vinyl, and acetylenic Grignards generally present less difficulties and good yields of dithiane-coupled products can generally be obtained by adding 2-chloro-1,3-dithiane to the Grignard reagent at −10°. This approach nicely complements the alternative of dithiane lithiation followed by treatment with an electrophile, a process that is less effective with secondary and tertiary halides and quite ineffective with vinyl and aryl systems. Examples of coupling reactions between α-chlorosulfides and representative Grignard reagents are summarized in Eqs (33),[20] (34),[78] (35),[79] and (36).[77] Vinologous chlorosulfides, e.g. **44**, also couple with Grignard and organolithium reagents, conjugate and direct attack by PhMgBr giving equal amounts of **45** and **46** unlike the reaction with the lithium salt of 2,6-dimethyllutidine where the unrearranged sulfide (**47**) is formed exclusively.[9]

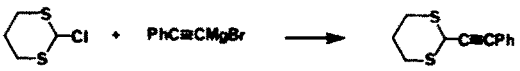
It is appropriate to mention here that in addition to their ability to couple with Grignard reagents α-chlorosulfides can also be used to prepare α-sulfenylated Grignards by reaction with magnesium. Optimum conditions for the preparation of methylthiomethylmagnesium chloride (**48**) involve treatment of chloromethyl methyl sulfide with magnesium in tetrahydrofuran containing dibro-



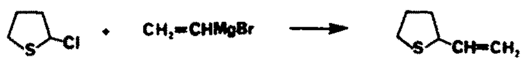
Scheme 6.



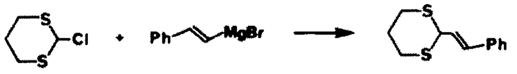
(33)



(34)



(35)



(36)

moethane at 10–20°.[80] Reagent **48** reacts very efficiently with alkyl halides, aldehydes and sulfinic esters, confirming its usefulness in organic synthesis.[80]

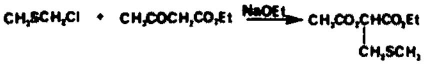
$$\underset{(44)}{PhSCH{=}CHCH_2Cl} + PhMgBr \longrightarrow \underset{(45)}{PhSCH{=}CHCH_2Ph} + \underset{(46)}{PhSCHPhCH{=}CH_2}$$

(47)

$MeSCH_2MgBr$

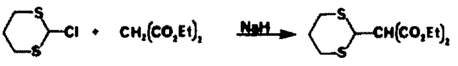
(48)

Preparative use has also been made of the reaction of α-chlorosulfides with enolates and related reactive intermediates, early typical examples being alkylation of ethyl acetoacetate and of diethyl malonate with CH_3SCH_2Cl and $PhSCH_2Cl$, respectively (Eqs 37 and 38).[81] The use of 2-chloro-1,3-dithiane has received particular attention due to its ability to serve as a formyl cation equivalent (Eq. 39).[16,82] The dianion of ethyl acetoacetate (**49**) can also be alkylated under kinetic control, though the iodosulfide is a much more successful electrophile than the chlorosulfide.[83] The product (**50**) of such alkylation reactions can be oxidized to sulfoxide and pyrolyzed to introduce unsaturation (Eq. 40). The efficacy of sulfoxide elimination as a route to α,β-unsaturated carbonyl system has led to the use of α-halomethyl sulfides as formaldehyde equivalents, best results being obtained with bromomethylbenzyl sulfide, e.g. Eq. (41).[84]



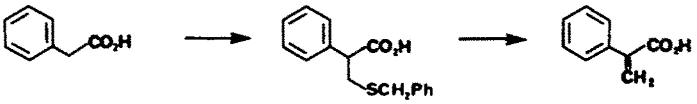
$$CH_3SCH_2Cl + CH_3COCH_2CO_2Et \xrightarrow{NaOEt} CH_3CO\underset{\substack{|\\ CH_3SCH_2}}{CH}CO_2Et \qquad (37)$$

$$PhSCH_2Cl + CH_2(CO_2Et)_2 \xrightarrow{NaOEt} PhSCH_2CH(CO_2Et)_2 \qquad (38)$$



(39)

$$\underset{(49)}{CH_2{=}\overset{^-O}{\overset{|}{C}}CH{=}\overset{^-O}{\overset{|}{C}}OEt} \longrightarrow \underset{(50)}{CH_3SCH_2CH_2\overset{O}{\overset{\|}{C}}CH_2CO_2Et} \longrightarrow CH_2{=}CH\overset{O}{\overset{\|}{C}}CH_2CO_2Et \qquad (40)$$

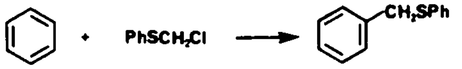


(41)

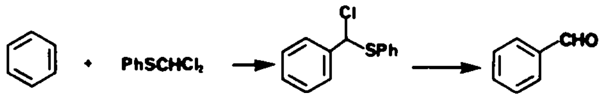
3.5. *α-Chlorosulfides as reactive electrophiles in aromatic alkylation*

The activating effect of the geminal sulfur atom towards ionization of the C—Cl bond during hydrolysis is also reflected in the ease with which α-chlorosulfides engage in aromatic alkylation.

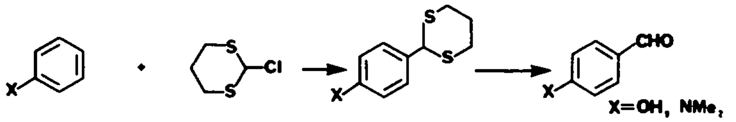
Although much of the earlier work employed aluminium chloride as the catalyst, it is now clear that milder Lewis acids such as stannic or zinc halides are just as effective. Alkylation of benzene with chloromethyl methyl sulfide gives benzyl methyl sulfide in excellent yield (Eq. 42). Gross and Matthey[85] elaborated this reaction into an aromatic aldehyde synthesis by combining alkylation with hydrolysis using dichloromethyl methyl sulfide as the electrophile (Eq. 43). An alternative route to similar products was demonstrated independently by Kruse *et al.*[77] and Arai and Oki[34] who found that phenol and N,N-dimethylaniline could be alkylated with 2-chloro-1,3-dithiane largely at the *para*-position, following which the aldehyde function was released by hydrolysis (Eq. 44).[86] Fleming and Iqbal[87] used thioalkylation with chloromethyl phenyl sulfide followed by Raney nickel hydrogenolysis to synthesize various alkyl phenols (Eq. 45).



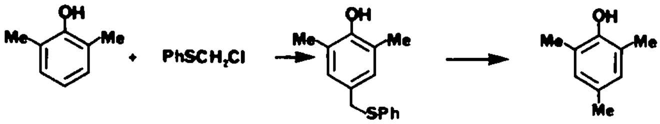
(42)



(43)

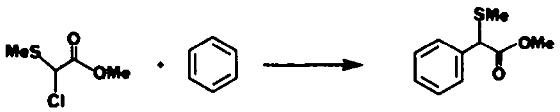


(44)

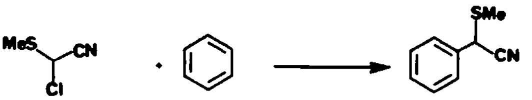


(45)

The beneficial effects of placing a phenylthio or alkylthio group at the ionizing electrophilic centre in Friedel–Crafts alkylation are also very apparent when the electrophile bears a contiguous carbonyl or cyano group. Whereas α-chlorocarbonyl compounds are generally rather inert in aromatic alkylation, this is not the case with their α-chloro-α-(alkyl or arylthio) carbonyl counterparts. A number of workers have exploited the enhanced reactivity of the latter, in some instances combining alkylation with desulfurization to produce benzyl derivatives from benzene. Tamura *et al.*[32] found that NCS chlorination of the α-(methylthio)carbonyl and cyano series in Eqs (46) and

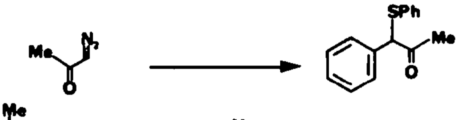


(46)

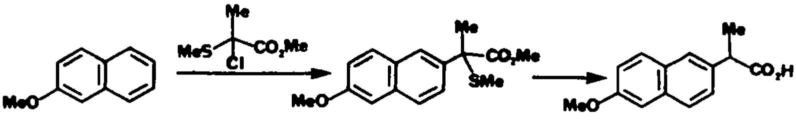


(47)

(47) followed by stannic chloride-catalyzed reaction with benzene gave α-phenyl-α-(methylthio) adducts in excellent yield. A recent alternative approach which broadens the scope of the reaction in the ketone series is based on the ready formation of α-chloro-α-(phenylthio)ketones from α-diazoketones and benzenesulfenyl chloride. It is thus possible in a one-pot reaction to convert diazoacetone into 1-phenyl-1-(phenylthio)acetone in 85% yield (Eq. 48).[50,51] Naproxen, the Syntex

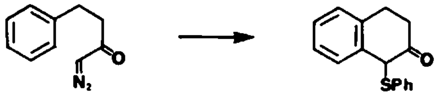


(48)

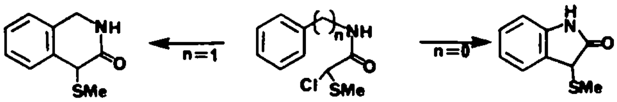


(49)

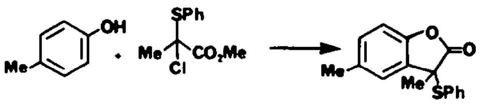
anti-inflammatory agent, has been synthesized via Friedel–Crafts alkylation with an α-chlorosulfide (Eq. 49).[88] Regioselective alkylation of 2-methoxynaphthalene with ethyl 2-chloro-2-methylthiopropionate in the presence of stannic chloride gave an adduct which was transformed into Naproxen by successive treatment with Raney nickel and alkali. Intramolecular versions of these various aromatic alkylations provide convenient synthetic routes to bi- and tricyclic systems. For example, diazoketones derived from dihydrocinnamic acids have been converted into 1-substituted 2-tetralones by successive exposure to benzenesulfenyl chloride and zinc(II) chloride (Eq. 50).[50,51] In a similar fashion, N-alkylanilines and benzyl amines combine with α-chloro-α-(methylthio)acetyl chloride in the presence of stannic chloride to yield cyclized products which on Raney nickel treatment furnish oxindoles and oxatetrahydroisoquinolines, respectively (Eq. 51). Work in progress in this Department demonstrates the extension of this type of chemistry to the synthesis of aromatic γ-lactones, an example being the conversion of *p*-cresol and of 2-naphthol into the lactones shown in Eqs (52) and (53).[89]



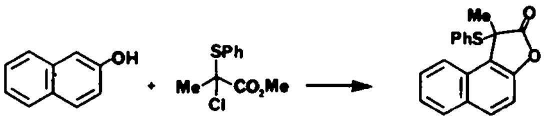
(50)



(51)



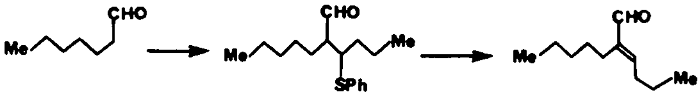
(52)



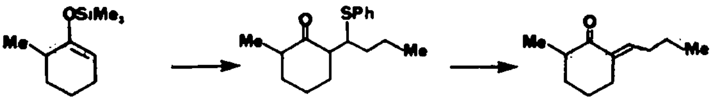
(53)

3.6. *Alkylation of carbonyl compounds via silyl enol ethers*

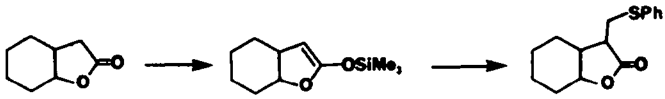
The use of α-chlorosulfides for alkylation of silyl enol ethers has been developed, mainly by Fleming and Paterson,[18,90] to the point where it now represents an important regiospecific method for the introduction of thioalkyl substituents α to the carbonyl group of enolizable aldehydes, ketones, carboxylic acids, esters and lactones.[18] The carbonyl group is first activated by conversion to the silyl enol ether (usually the trimethylsilyl derivative) prior to reaction with an α-chloroalkyl phenyl sulfide, choice of the phenylthio group ensuring that the overall process is restricted to one side of the sulfur atom. A mild Lewis acid is required, usually zinc chloride or bromide, and dichloromethane is the preferred solvent. The presence of the phenylthio group facilitates the alkylation step; it can be removed subsequently by Raney nickel hydrogenolysis. Yet another advantage of the presence of the phenylthio group is that it can be used to place additional functionality in the alkyl group, oxidation to sulfoxide followed by thermal β-elimination representing a particularly effective way of inserting a carbon–carbon double bond. Some representative examples of this approach to α,β-unsaturated aldehydes (Eq. 54), ketones (Eq. 55) and lactones (Eq. 56) are shown below. Phenylthioalkylation has also been used to introduce primary alkyl or



(54)

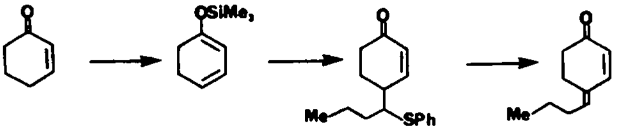


(55)

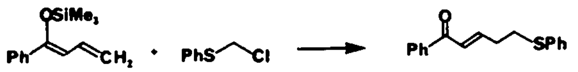


(56)

alkylidene groups in the γ-position of silyl dienyl ethers as shown in Eqs (57) and (58). The extent of γ-relative to α-alkylation is not always complete, though the regiochemistry is strikingly different from that of the corresponding reaction of alkyl halides with dienolates where there is a strong preference for α-alkylation.[91]

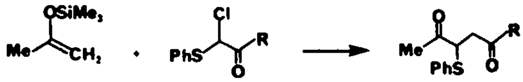


(57)



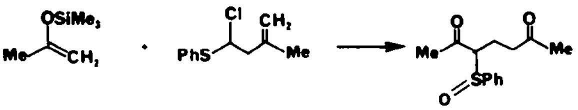
(58)

Several workers have recognized the scope for extension of the basic phenylthioalkylation reaction through the use of α-chlorosulfides bearing additional functional groups. Zinc bromide-catalyzed addition of silyl enol ethers to α-chloro-α-(phenylthio)ketones and esters leads directly to 1,4-diketones[92] and 1,4-keto-esters (Eq. 59).[93] Less directly, 1,5-diketones have been synthesized



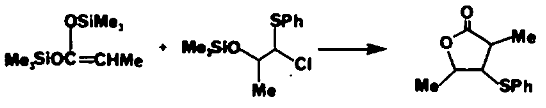
(59)

using the homoallylic α-chlorosulfide in Eq. (60) as the electrophile, ozonolysis after the alkylation stage introducing the second carbonyl group with concomitant oxidation of sulfide to sulfoxide.[94]



(60)

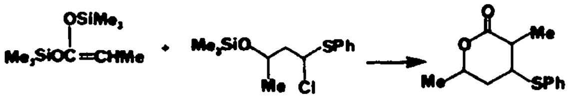
Related methods have been applied to lactone production (Eq. 61). Thus α-chlorosulfide (**51**) bearing a protected hydroxyl group can be used to alkylate ketene (bis-trimethylsilyl)acetals; in the course of the reaction the electrophile sheds its protecting group and intramolecular condensation furnishes



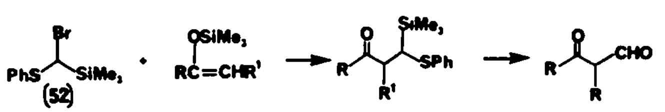
(51)

(61)

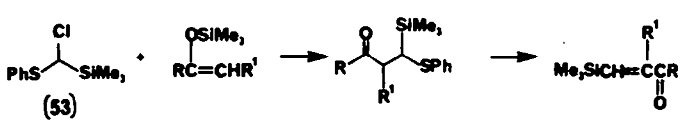
the γ-lactone.[95] By moving the protected hydroxy group one carbon atom further away from the site of alkylation, as illustrated in Eq. (62), the above sequence can be adapted to the synthesis of δ-lactones.[95] In both the γ- and δ-lactone series the phenylthio group is nicely located for introduction of a double bond by pyrolytic elimination after sulfoxide formation. Ager's β-ketoaldehyde synthesis represents yet another application of phenylthioalkylation of silyl enol ethers in which the electrophile in an α-bromosulfide rather than the α-chloro derivative geminally substituted with a trimethylsilyl group (**52**).[96] Oxidation of the adduct at sulfur initiates a sila-Pummerer rearrangement, terminating after hydrolysis in a β-ketoaldehyde (Eq. 63). Chloro(phenylthio)methyltrimethylsilane (**53**) also reacts with silyl enol ethers in the presence of zinc bromide to give β-silyl ketones which are capable of being converted into β-functionalized vinyl silanes (Eq. 64).



(62)



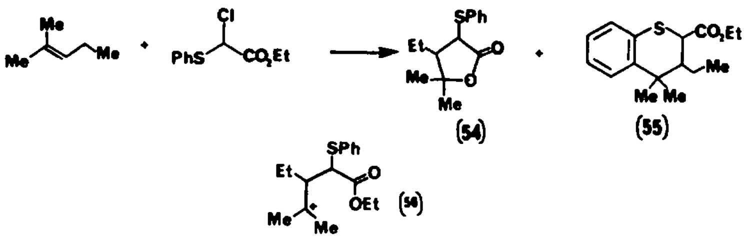
(63)



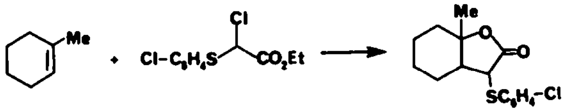
(64)

3.7. *Reactions of α-chlorosulfides with alkenes and alkynes*

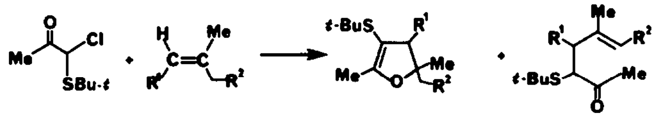
Alkenes and alkynes can be alkylated with α-chlorosulfides in much the same way as arenes, reaction usually requiring mild Lewis acid catalysis. 2-Methyl-2-pentene combines with ethyl α-chloro-α-(phenylthio)acetate in the presence of stannic chloride to give equal amounts of γ-butyrolactone (54) and thiachromane (55) (Eq. 65). Both products are the result of alkene alkylation, but the latter represents that of additional involvement of the phenylthio group through aromatic alkylation. It seems likely that attack of the alkene on the ionizing electrophile produces the tertiary cationic intermediate (56) which, in addition to closing to the lactone, undergoes aromatic substitution with the electron-rich phenylthio group. The latter feature is eliminated when the phenylthio group bears a *p*-chloro substituent. Thus 1-methylcyclohexene and ethyl α-chloro-α-(*p*-chlorophenylthio)acetate give the bicyclic lactone in Eq. (66) in good yield. Under catalytic conditions α-chloro-α-(phenylthio)acetone and alkenes combine to give mixtures of 4,5-dihydrofurans and ene reaction products (Eq. 67).[97] This type of alkylation chemistry has been extended to include reactions of allylsilanes with α-chlorosulfides containing an ester or ketonic carbonyl group at the α-, β-, or γ-position (Eq. 68). The major products are α-allylsulfides, e.g. 57, the location of the trimethylsilyl group ensuring ready β-elimination after the initial alkylation step.[98] Ishibashi *et al.*[99] have examined [3⁺+2] polar cycloaddition of α-chloro-α-(methylthio)acetone and methyl α-chloro-α-(methylthio)acetate with alkynes in the presence of Lewis acids. The former reagent affords furan derivatives (Eq. 69) whereas the latter affords 2-furanone derivatives (Eq. 70); vinyl cations are likely reaction intermediates. A quite different mode of reaction is observed when α-chlorosulfides are subjected to strong bases in the presence of alkenes. α-Elimination to thiocarbenes or thiocarbenoids is then possible leading to characteristic cyclopropanation reac-



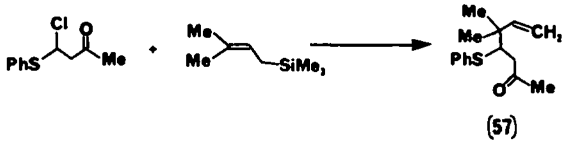
(65)



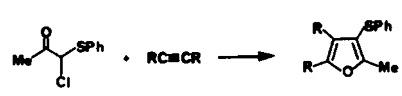
(66)

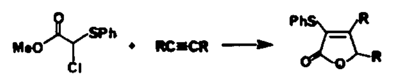


(67)

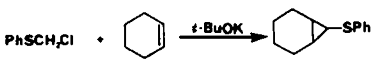


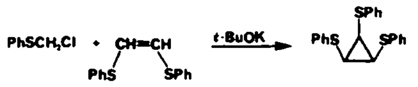
(68)


(69)

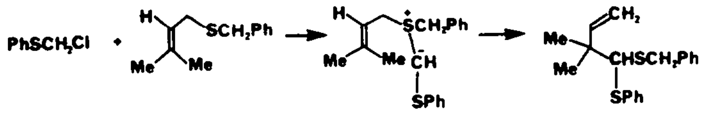

(70)

tions. For example, treatment of chloromethyl phenyl sulfide with potassium t-butoxide in the presence of styrene, cyclohexene, 2-butene, and stilbene gives excellent yields of the appropriate phenylthiocyclopropane, e.g. Eq. (71).[100] With *cis*-2-butene and phenylthiocarbene, both *cis*- and *trans*-


(71)

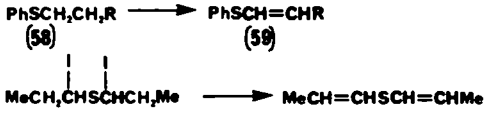

(72)

cyclopropane adducts are produced, but with *cis*-di(phenylthio)ethylene only the all *cis* adduct was obtained (Eq. 72). Julia and his co-workers have used the reaction of chloromethyl phenyl sulfide with allylic sulfides in the presence of strong base to generate β,γ-unsaturated sulfonium ylides for [2,3]sigmatropic rearrangement into β,γ-unsaturated dithioacetals (Eq. 73).[101]


(73)

3.8. *Vinyl sulfides from α-chlorosulfides*

Vinyl sulfides (enolthioethers) are beginning to show considerable synthetic promise in a variety of organic reactions. Their preparation from ketones and thioketals and their efficacy as enolate substitutes have been examined in detail by Trost and Lavoie.[102] β-Elimination of hydrogen chloride from appropriately substituted α-chlorosulfides offers yet another synthetic route to these systems, and while examples are available the reaction appears under utilized and is limited largely to systems in which the chlorosulfide function is α or β to a carbonyl group. Bakuzis has briefly examined the preparation of vinyl sulfides not activated by electron-withdrawing groups.[28] Thus (phenylthio)ethane (**58**; R = H) and (phenylthio)octane (**58**; R = C_6H_{13}) on successive treatment with NCS and refluxing pyridine are converted into phenyl vinyl sulfide (**59**; R = H) and 1-(phenylthio)-1-octene (**59**; R = C_6H_{13}) in 57 and 84% isolated yields, respectively. (Phenylthio)-1-cyclohexene can also be obtained in this way, though yields are variable and the product mixture is difficult to purify.[28] In other cases, the elimination step is particularly easy, a case in point being the isolation of thiacyclohexene (**6**) from reaction of thiacyclohexane and sulfuryl chloride.[13] Chan and his co-workers[103] have described a useful synthesis of divinyl sulfides by HI elimination from α,α′-diiodosulfides (Eq. 74) the latter having been obtained quantitatively from α,α′-*bis*-trimethylsiloxysulfides and iodotrimethylsilane.



$$\underset{(\mathbf{58})}{PhSCH_2CH_2R} \longrightarrow \underset{(\mathbf{59})}{PhSCH{=}CHR}$$

$$MeCH_2\overset{I}{C}HS\overset{I}{C}HCH_2Me \longrightarrow MeCH{=}CHSCH{=}CHMe \qquad (74)$$

The presence of electron-withdrawing groups α or β to the chlorosulfide function contributes significantly to the ease of HCl elimination. This is particularly so in the β-series where in some instances the chlorosulfides are very unstable. Bakuzis has taken advantage of this ready elimination to develop a useful general method for oxidative functionalization of the β-carbon atom of α,β-unsaturated ketones, esters, lactones, and nitriles.[28] The β-phenylthio derivative is first prepared by triethylamine-catalyzed addition of thiophenol to the corresponding α,β-unsaturated compound. NCS is then used to prepare the α-chlorosulfide the stability of which depends on the nature of the group R (Eq. 75). In the ketone and lactone series, e.g. Eqs (76) and (77), base is not required in the final step, elimination occurring spontaneously during reaction work-up. The less acidic ester and nitrile chlorosulfides give fairly stable chlorosulfides which require treatment with triethylamine to complete the transformation to vinyl sulfide, e.g. Eqs (78) and (79). This route has recently been used to convert maleic anhydride into dimethyl 2-(phenylthio)maleate (Eq. 80).[29]

$$\mathrm{CH_2{=}CHR} + \mathrm{PhSH} \longrightarrow \mathrm{PhSCH_2CH_2R} \longrightarrow \mathrm{PhSCH{=}CHR} \qquad (75)$$

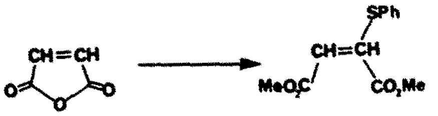

(76)


(77)


(78)

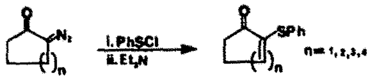
$$\mathrm{CH_2{=}CH}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{OMe} \xrightarrow[\text{ii. NCS} \;\; \text{iii. Et}_3\text{N}]{\text{i. PhSH Et}_3\text{N}} \mathrm{PhSCH{=}CH}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{OMe} \qquad (78)$$

$$\mathrm{CH_2{=}CHCN} \longrightarrow \mathrm{PhSCH{=}CHCN} \qquad (79)$$


(80)

α-(Phenylthio)-α,β-unsaturated ketones have been obtained from α-chloro-α-(phenylthio)ketones using similar methods, e.g. Eqs (81) and (82).[104] The examples in the cyclic series were obtained via the α-diazoketone route discussed earlier.[50,51] Thus the diazocycloalkanone is treated successively with benzenesulfenyl chloride and triethylamine. α- and β-(Phenylthio)-α,β-unsaturated ketones and esters are highly functionalized and several have been used in important synthetic transformations. In the α-(phenylthio) series they have been used in Diels–Alder reactions,[105] Michael additions[106] and as a source of regiodefined enolates.[107] In the β-(phenylthio) series uses include lactone and cyclopentenone synthesis,[108] Danishefsky *et al.*'s cyclohexadienone synthesis,[109] and the synthesis of α,β- and α,β,γ,δ-unsaturated aldehydes.[110]

A final interesting example of elimination reactions of α-chlorosulfides is the formation of the alkene in Eq. (83) through loss of the trimethylstannyl group.[111]


(81)


(82)


(83)

REFERENCES

[1] As far as we are aware the only previous review of α-chlorosulfides is that by K. Arai, *Yuki Gosei Kagaku Kyokaishi* (*J. Syn. Org. Chem. Jap.*) **39**, 374 (1981).

[2] G. C. Barrett, *Comprehensive Organic Chemistry* (Edited by D. H. R. Barton and W. D. Ollis), Vol. 3, p. 33. Pergamon Press, Oxford (1979).

[3] M. A. Riche, *Annls Chim. Phys.* **43**, 283 (1855).

[4] T. Zinke and W. Frohenberg, *Ber.* **42**, 2721 (1909); F. G. Mann and W. J. Pope, *J. Chem. Soc.* **121**, 594 (1922).

[5] H. Böhme, H. Fisher and R. Frank, *Annln Chem.* **563**, 54 (1949).

[6] W. E. Truce, G. H. Birum and E. T. McBee, *J. Am. Chem. Soc.* **74**, 3594 (1952).

[7] D. L. Tuleen and T. B. Stephens, *Chem. Ind. London* 1555 (1966).

[8] B. M. Dilworth and M. A. McKervey, unpublished results.

[9] A. J. Mura, Jr., D. A. Bennett and T. Cohen, *Tetrahedron Lett.* 4433 (1975).

[10] K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.* **26**, 2478 (1961).

[11] M. Oki and K. Kobayashi, *Bull. Chem. Soc. Japan* **43**, 1223 (1970).

[12] H. Böhme and H. J. Gran, *Annln Chem.* **581**, 133 (1953).

[13] F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.* **77**, 572 (1955).

[14] G. E. Wilson, Jr. and R. Albert, *J. Org. Chem.* **38**, 2156, 2160 (1973).

[15] C. C. Fortes, H. C. Fortes and D. C. R. G. Goncalves, *J. Chem. Soc. Chem. Commun.* 857 (1982).

[16] C. G. Kruse, N. L. J. M. Broekhof, A. Wijsman and A. van der Gen, *Tetrahedron Lett.* 885 (1977).

[17] C. J. Easton, *J. Chem. Soc. Chem. Commun.* 1349 (1983).

[18] I. Paterson and I. Fleming, *Tetrahedron Lett.* 993, 995, 2179 (1979).

[19] B. M. Dilworth and M. A. McKervey, unpublished results.

[20] D. J. Tuleen and R. H. Benett, *J. Heterocycl. Chem.* **6**, 115 (1969).

[21] L. A. Paquette, R. E. Wingard, Jr., J. C. Philips, G. L. Thompson, L. K. Read and J. Clardy, *J. Am. Chem. Soc.* **93**, 4508 (1971).

[22] M. Wada, T. Shigehisa and K. Akiba, *Tetrahedron Lett.* **24**, 1711 (1983).

[23] J. P. Cronin and M. A. McKervey, unpublished results.

[24] H. A. Khan and I. Paterson, *Tetrahedron Lett.* **23**, 5083 (1982).

[25] T. Mukaiyama, T. Sugaya, S. Marui and T. Nakatsuka, *Chem. Lett.* **10**, 1555 (1982).

[26] P. Gassman and S. Bonser, *J. Am. Chem. Soc.* **105**, 667 (1983).

[27] H. A. Khan and I. Paterson, *Tetrahedron Lett.* **23**, 2399 (1982).

[28] P. Bakuzis and M. L. F. Bakuzis, *J. Org. Chem.* **46**, 235 (1981).

[29] J. A. Kaydos and D. L. Smith, *J. Org. Chem.* **48**, 1096 (1983).

[30] E. Murayama, M. Uematsu, H. Nishio and T. Sato, *Tetrahedron Lett.* **25**, 313 (1984).

[31] I. Yamamoto, K. Okuda, S. Nagai, J. Motoyoshiya, H. Gotoh and K. Matsuzaki, *J. Chem. Soc. Perkin Trans. 1* 435 (1984).

[32] Y. Tamura, H. Shindo, J. Uenishi and H. Ishibashi, *Tetrahedron Lett.* **21**, 2547 (1980).

[33] D. T. W. Chu, J. E. Hengeveld and D. Lister, *Tetrahedron Lett.* **24**, 139 (1983).

[34] K. Arai and M. Oki, *Bull. Soc. Chem. Japan* **49**, 553 (1976).

[35] Y. Ohshiro, H. Isihida, J. Shibata, T. Minami and T. Agawa, *Chem. Lett.* 587 (1982).

[36] T. Cohen and J. R. Matz, *Tetrahedron Lett.* **22**, 2455 (1981).

[37] Reviews: R. Pummerer, *Ber.* **43**, 1401 (1910); G. A. Russell and J. G. Mikol, *Mech. Mol. Migr.* **1**, 157 (1958); T. Durst, *Adv. Org. Chem.* **6**, 285 (1969); C. R. Johnson and W. G. Phillips, *J. Am. Chem. Soc.* **91**, 682 (1969); S. Wolfe and P. M. Kazmair, *Can. J. Chem.* **57**, 2388 (1979).

[38] D. L. Tuleen and T. B. Stephens, *J. Org. Chem.* **34**, 31 (1969).

[39] For a more detailed outline of the mechanisms of sulfide chlorination including a reassessment of product controlling factors see T. P. Ahern, D. G. Kay and R. F. Langler, *Can. J. Chem.* **56**, 2422 (1978).

[40] L. A. Paquette, *J. Am. Chem. Soc.* **86**, 4089 (1964).

[41] T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham and J. F. Walker, *J. Org. Chem.* **47**, 1373 (1982).

[42] R. H. Rynbrandt, *Tetrahedron Lett.* 3553 (1971).

[43] H. Böhme and H. J. Gran, *Annln Chem.* **577**, 68 (1952).

[44] L. A. Paquette and L. S. Wittenbrook, *J. Am. Chem. Soc.* **89**, 4483 (1967).

[45] J. E. Baldwin, A. Au, M. Christie, S. B. Haber and D. Hesson, *J. Am. Chem. Soc.* **97**, 5957 (1975).

[46] G. A. Koppell, L. McShane, F. Jose and R. D. G. Cooper, *J. Am. Chem. Soc.* **100**, 3933 (1978).

[47] K. A. Petrov, G. A. Sokolovsky and A. A. Neimysheva, *J. Ger. Chem. U.S.S.R.* **27**, 855 (1957).

[48] F. Weygand and H. J. Bestmann, *Z. Naturf.* **106**, 296 (1955).

[49] F. Weygand, H. J. Bestmann and H. Fritzsche, *Chem. Ber.* **93**, 2340 (1960).

[50] M. A. McKervey and P. Ratananukul, *Tetrahedron Lett.* **24**, 117 (1983).

[51] J. P. Cronin, M. A. McKervey and P. Ratananukul, *J. Chem. Soc. Perkin Trans.* submitted.

[52] J. C. Sheehan and T. J. Commons, *J. Org. Chem.* **43**, 2203 (1978).

[53] I. W. J. Still and G. W. Kutney, *J. Org. Chem.* **46**, 4911 (1981).

[54] L. A. Paquette, *Org. React.* **25**, 1 (1977).

[55] H. R. Sliwka and H. J. Hansen, *Helv. Chim. Acta* **67**, 434 (1984).

[56] F. G. Bordwell, G. D. Cooper and H. Morita, *J. Am. Chem. Soc.* **79**, 376 (1957).

[57] F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.* **78**, 854 (1956).

[58] L. A. Paquette, W. D. Klobucar and R. A. Snow, *Synth. Commun.* **6**, 575 (1976).

[59] D. T. W. Chu, *J. Org. Chem.* **48**, 3571 (1983).

[60] D. Seebach, *Synthesis* **1**, 17 (1969), and refs therein.

[61] R. B. Woodward, *Harvey Lect.* **59**, 31 (1965).

[62] E. Vedejs and P. L. Fuchs, *J. Org. Chem.* **36**, 366 (1971).

[63] E. J. Corey and B. W. Erickson, *J. Org. Chem.* **36**, 3553 (1971).

[64] J. E. Lynch and E. L. Eliel, *J. Am. Chem. Soc.* **106**, 2943 (1984).

[65] P. G. Gassman, B. W. Cue, Jr. and T. Y. Luh, *J. Org. Chem.* **42**, 1344 (1977).

[66] P. G. Gassman and H. R. Drewes, *J. Am. Chem. Soc.* **96**, 3002 (1974).

[67] P. Bakuzis, M. L. F. Bakuzis, C. C. Fortes and R. Santos, *J. Org. Chem.* **41**, 2769 (1976); P. Bakuzis, O. Campos and M. L. F. Bakuzis, *Ibid.* **41**, 3261 (1976).

[68] E. J. Corey and M. G. Bock, *Tetrahedron Lett.* 2643, 3269 (1975); see also E. J. Corey and T. Hase, *Ibid.* 3267 (1975).

[69] R. A. Holton and R. V. Nelson, *Synth. Commun.* **10**, 911 (1980).

[70] C. G. Kruse, E. K. Poels, F. L. Jonkers and A. van der Gen, *J. Org. Chem.* **43**, 3548 (1978).
[71] T. L. Ho and C. M. Wong, *J. Chem. Soc. Chem. Commun.* 224 (1973).
[72] J. P. Cronin and M. A. McKervey, unpublished results.
[73] K. Ogura, J. Watanabe and H. Iida, *Tetrahedron Lett.* **22**, 4499 (1981).
[74] L. Duhamel, J. Chauvin and A. Messier, *Tetrahedron Lett.* **21**, 4171 (1980); L. Duhamel and J. Chauvin, *Ibid.* **23**, 1665 (1982).
[75] J. P. Cronin, B. M. Dilworth and M. A. McKervey, *Tetrahedron Lett.* **27**, 757 (1986).
[76] H. Böhme, *Ber.* **69**, 1610 (1936).
[77] C. G. Kruse, A. Wijsman and A. van der Gen, *J. Org. Chem.* **44**, 1847 (1979).
[78] K. Arai, H. Iwamura and M. Oki, *Bull. Chem. Soc. Japan* **48**, 3319 (1975).
[79] E. Vedejs, M. J. Mullins, J. M. Renga and S. P. Singer, *Tetrahedron Lett.* 519 (1978).
[80] K. Ogura, M. Fujita, K. Takahashi and H. Iida, *Chem. Lett.* **11**, 1697 (1982).
[81] H. Gross and E. Höft, *Angew. Chem.* **79**, 358 (1969).
[82] E. C. Taylor and J. L. LaMattina, *Tetrahedron Lett.* **24**, 2077 (1977).
[83] B. M. Trost, *J. Org. Chem.* **39**, 2648 (1974).
[84] H. J. Reich and J. M. Renga, *J. Chem. Soc. Chem. Commun.* 135 (1974).
[85] H. Gross and G. Matthey, *Ber.* **97**, 2606 (1964).
[86] For a modification of this process leading to *ortho* substitution see P. Gassman and D. R. Amick, *Tetrahedron Lett.* 3463 (1974).
[87] I. Fleming and J. Iqbal, *Synthesis* 937 (1982).
[88] K. Arai, Y. Ohara, T. Iizumi and Y. Takakuwa, *Tetrahedron Lett.* 1531 (1983).
[89] M. Kennedy, M. A. McKervey and A. R. Maguire, *Tetrahedron Lett.* **27**, 761 (1986).
[90] For general reviews see I. Fleming, *Chem. Soc. Rev.* **10**, 83 (1981); P. Brownbridge, *Synthesis* 1, 85 (1983).
[91] I. Fleming, J. Goldhill and I. Paterson, *Tetrahedron Lett.* 3205, 3209 (1979).
[92] L. Duhamel, J. Chauvin and C. Goument, *Tetrahedron Lett.* **24**, 2095 (1983).
[93] T. V. Lee and J. O. Okonkwo, *Tetrahedron Lett.* **24**, 323 (1983).
[94] H. A. Khan and I. Paterson, *Tetrahedron Lett.* **23**, 2399 (1982).
[95] H. A. Khan and I. Paterson, *Tetrahedron Lett.* **23**, 5083 (1982).
[96] D. J. Ager, *Tetrahedron Lett.* **24**, 419 (1983).
[97] M. Wada, T. Shigehisa, H. Kitani and K. Akiba, *Tetrahedron Lett.* **24**, 1715 (1983).
[98] M. Wada, T. Shigehisa and K. Akiba, *Tetrahedron Lett.* **24**, 1711 (1983).
[99] H. Ishibashi, S. Akai, H. D. Choi, H. Nakagawa and Y. Tamura, *Tetrahedron Lett.* **24**, 3877 (1983).
[100] U. Schöllkopf and G. J. Lehmann, *Tetrahedron Lett.* 165 (1962); U. Schöllkopf, A. Lerch and J. Paust, *Ber.* **96**, 2206 (1963); U. Schöllkopf, G. H. Lehmann, J. Paust and H. D. Haertl, *Ibid.* **97**, 1527 (1964); U. Schöllkopf, E. P. Woerner and E. Wiskott, *Ibid.* **99**, 806 (1966).
[101] S. Julia, C. Huynh and D. Michelot, *Tetrahedron Lett.* 3587 (1972); C. Huynh, V. Ratovelomanana and S. Julia, *Bull. Soc. Chim. Fr.* 710 (1977).
[102] B. M. Trost and A. C. Lavoie, *J. Am. Chem. Soc.* **105**, 5075 (1983).
[103] T. Aida, T. H. Chan and D. N. Harpp, *Tetrahedron Lett.* **22**, 1089 (1981).
[104] F. Leyendecker and M. T. Comte, *Tetrahedron Lett.* **23**, 5031 (1982).
[105] S. Knapp, R. Lis and P. Michna, *J. Org. Chem.* **46**, 624 (1981).
[106] H. J. Monteiro, *J. Org. Chem.* **42**, 2324 (1977); S. Kurozumu, T. Toru, T. Tanaka, M. Kobayashi, S. Miura and S. Ishimoto, *Tetrahedron Lett.* **17**, 4091 (1976); J. M. Fang, *J. Org. Chem.* **47**, 3464 (1982).
[107] T. V. Lee and J. Toczek, *J. Chem. Soc. Chem. Commun.* 968 (1982).
[108] K. Isobe, M. Fuse, H. Kosugi, M. Hagiwara and H. Uda, *Chem. Lett.* 785 (1979).
[109] S. Danishefsky, T. Harayama and R. K. Singh, *J. Am. Chem. Soc.* **101**, 7008 (1979).
[110] S. Akiyama, S. Nakatsuji, T. Hamamura, M. Kataoka and M. Nakagawa, *Tetrahedron Lett.* 2809 (1979).
[111] E. Murayama, M. Uematsu, H. Nishio and T. Sato, *Tetrahedron Lett.* **25**, 313 (1984).