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REDUCTION AND ALKYLATION OF 1,3-OXATHIOLAN-5-ONES

AS A ROUTE TO α-MERCAPTOALDEHYDES

by

Maqbool A. Siddiqui

A Thesis
submitted to the Faculty of Graduate Studies through
the Department of Chemistry in Partial Fulfillment
of the requirements for the Degree of
Master of Science at,
The University of Windsor

Windsor, Ontario, Canada
1982

782827

To my father and my dearly departed mother

ABSTRACT

Synthesis of five (5) α-mercaptoaldehydes has been investigated via the reductive hydrolysis of 1,3-oxathiolan-5-ones. The latter compounds were prepared from α-mercaptoacids. α-Mercaptoaldehydes were used for the synthesis of 2,5-dihydrothiophenes.

A method for alkylation and aldol type condensation of 1,3-oxathiolan-5-ones has been investigated.

v

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to my research advisor, Dr. John M. McIntosh, for his help, guidance and efforts in the successful completion of this research project..

I would like to thank Dr. K. E. Taylor for his help and assistance in my coming to Canada.

I further would like to thank my lab mates, who resisted the smell of mercaptans during my work.

I would like to thank Mr. Mike Fuerth for his assistance with the ir, nmr and Bruker CXP-100 instruments.

Finally, the financial support of the University of Windsor in the form of scholarship is gratefully acknowledged.

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LIST OF ABBREVIATIONS

DIBAL-H   diisobutylaluminum hydride

DMSO   dimethyl sulfoxide

HMPA   hexamethylphosphoramide

LAH   lithium aluminum hydride

LDA   lithium diisopropylamide

THF   tetrahydrofuran

TMS   tetramethylsilane

CHAPTER I

INTRODUCTION

Early studies[1,2,3] on α-mercaptoketones have shown that these compounds typically exist in the dimeric dihydroxy-1,4-dithiane form. α-Mercaptoaldehydes (1) would also be expected to exist in the dimeric 2,5-dihydroxy-1,4-dithiane (2a) form. They have been shown to exist in one or both of the two dimeric forms 2a, 2b by Kirrmann and co-workers[4,5] (Figure 1).
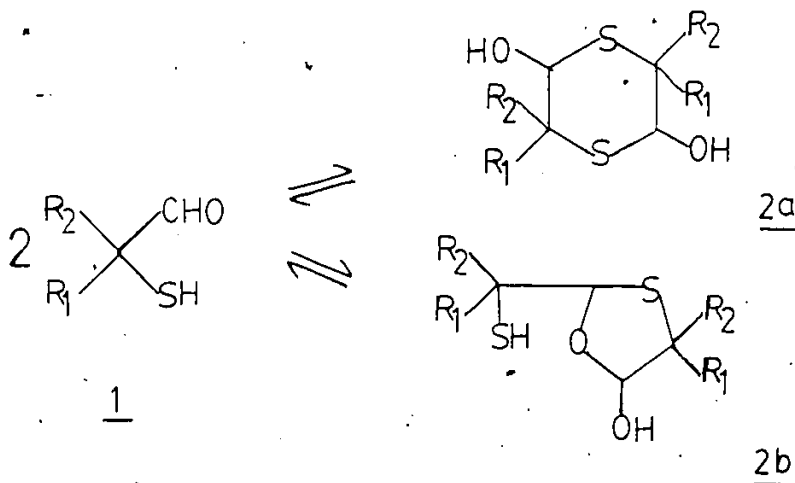
R_{1-2} = Alkyl Groups or Hydrogen

Figure 1.   Dimerization of α-Mercaptoaldehydes.

α-Mercaptoaldehydes are important synthetic reagents. They have been used in a number of organic syntheses. For example, Asinger[6,7] and other workers[8,9] prepared 3-thiazoline derivatives (3) by the condensation of 1 with carbonyl compounds in the presence of gaseous ammonia or an ammonium salt (Figure 2). Compounds 3 containing hydrogen at position 2 and 5 were converted to the corresponding
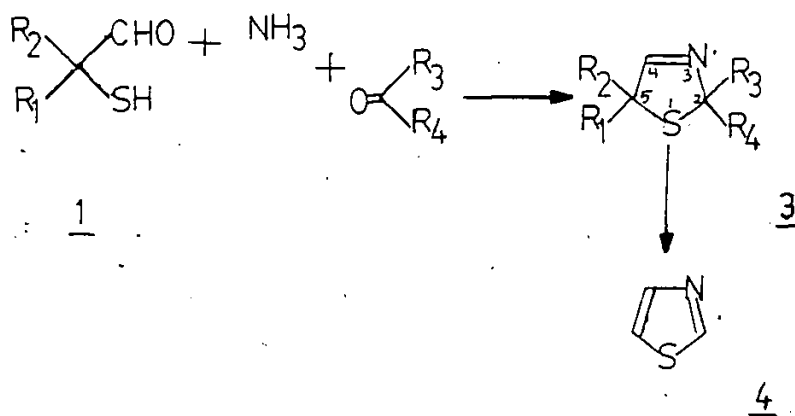
R_{1-4} = Alkyl Groups or Hydrogen

Figure 2. <u>Synthesis of 3-Thiazolines and Thiazoles</u>.

thiazoles (4) by dehydrogenation. Compounds 3 have been used in flavoring food.

DL-cysteine (5) has been synthesized[10] from an α-mercaptoaldehyde (Figure 3).
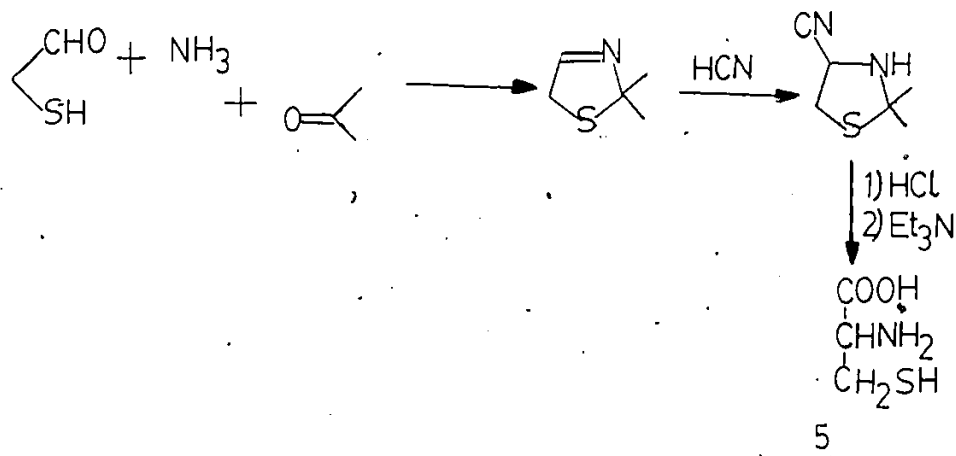
Figure 3. Synthesis of DL-cysteine.

Thiophene derivatives (7) have also been synthesized[11] from 1 by condensation with nitriles (6) (Figure 4).
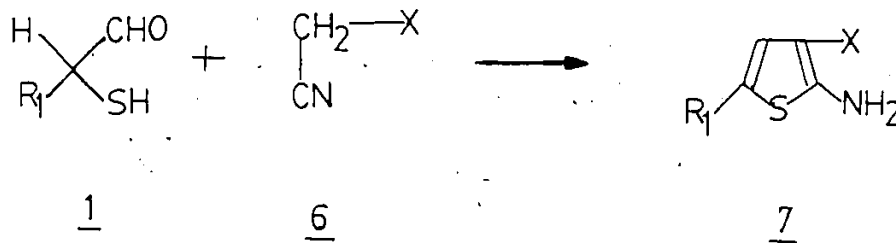
X = COOH, COQEt, CONH$_2$ or COOR$_1$
R$_1$ = Alkyl Groups or Hydrogen

Figure 4. Synthesis of Thiophenes.

Compound 1 has been used in the synthesis of thiopheneamino acids,[12] thienopyridine and thienopyrimidines.[13]

4-Vinylthiophenes (9) have been prepared[14] by the reac-

tion of <u>1</u> with 1,3-butadien-1-yltriphenylphosphonium chloride (<u>8</u>) (Figure 5).

$$\underline{1} \qquad \underline{8} \qquad \underline{9}$$
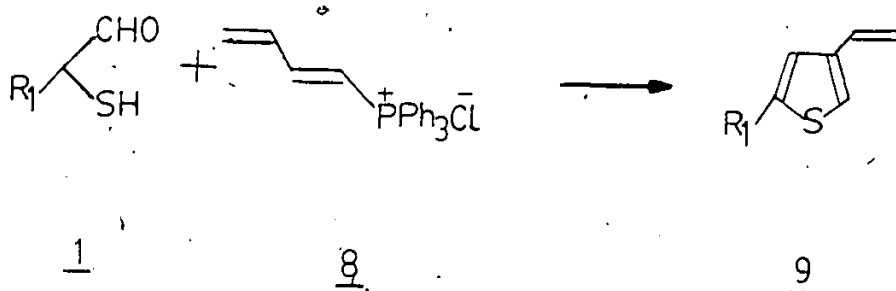
R = Alkyl Group

Figure 5. Preparation of 4-Vinylthiophenes.

One and perhaps the most important use of α-mercapto-aldehydes is in the synthesis of 2,5-dihydrothiophenes. McIntosh and co-workers[15,16,17] have used α-mercaptoaldehydes extensively in the synthesis of various substituted 2,5-dihydrothiophenes (<u>11</u>). Compounds <u>11</u> have been prepared by reacting <u>1</u> with either vinyl or substituted vinyltri-phenylphosphonium bromide (<u>10</u>)[15,16] (Figure 6) or vinyl-phosphonates.[17]

$$\underline{1} \qquad \underline{10} \qquad \underline{11}$$
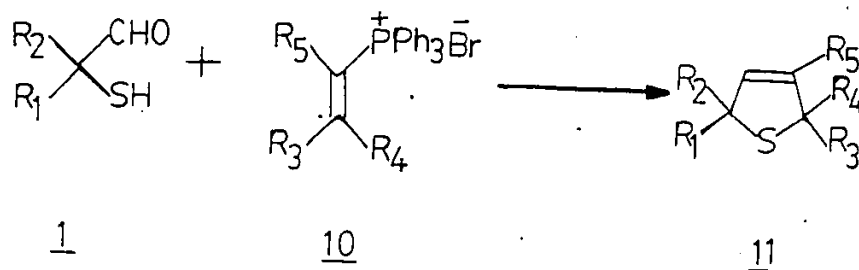
R_{1-5} = Alkyl Groups or Hydrogen

Figure 6. Synthesis of 2,5-Dihydrothiophenes.

Dihydrothiophenes have been used in the synthesis of dienes[16,17,18] (Figure 7), divinylethers,[18] divinyl amines[19] and cyclobutenes.[20] Compounds 11 can be oxidized to sulfones 12 which on thermal decomposition give dienes 13[16,17] (Figure 7). This method of producing dienes is stereospecific.
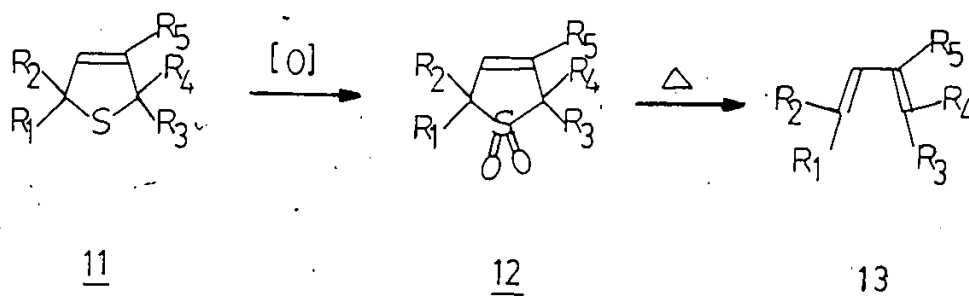
R_{1-4} = Alkyl Groups or Hydrogen

R_5 = $COOCH_3$ or H

Figure 7.   Thermal Decomposition of Sulfones to Dienes.

McIntosh and Khalil[21] have shown that dihydrothio-phenes can be easily oxidized to the corresponding thiophenes by chloranil.   Thiophenes have been used as dienes[22] in the Diels-Alder reaction (Figure 8).
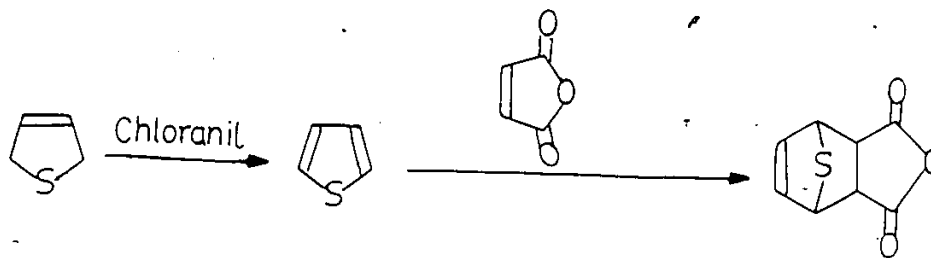
Figure 8.   Preparation of Thiophene and its Diels-Alder Reaction.

The reductive desulfurization of dihydrothiophene could lead to a stereospecific olefin synthesis (Figure 9). This has not yet been achieved.[66]

α-Mercaptoaldehydes have been prepared[15] by
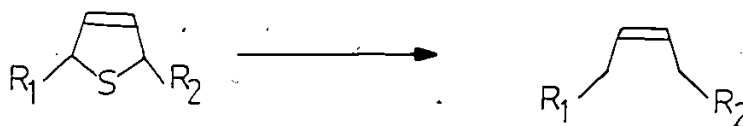
R_{1-2} = Alkyl Groups or Hydrogen

Figure 9.   Proposed Olefin Synthesis.

chlorinating the parent aldehydes[23] followed by reaction with sodium sulfhydrate[4] (Figure 10).   The yields were, in general, only modest at best.   McIntosh and Masse[16] reported that
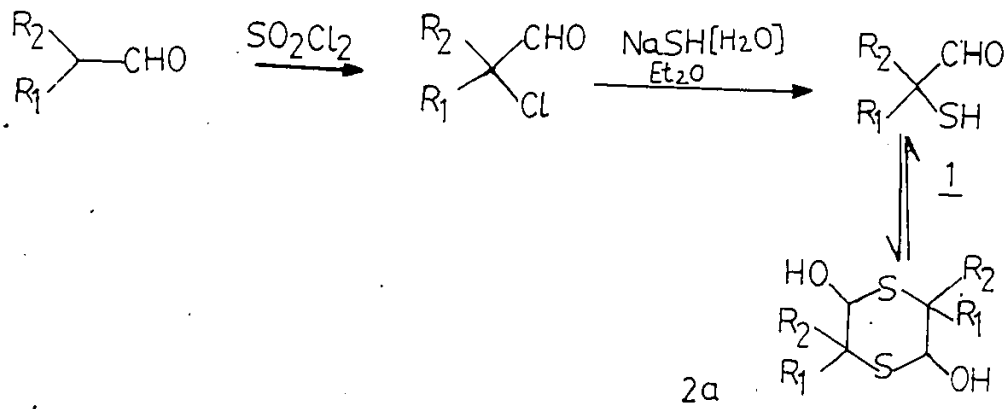
R_{1-2} = Alkyl Groups or Hydrogen

Figure 10.   Preparation of α-Mercaptoaldehydes.

the yield of α-mercaptopropionaldehyde prepared by the above method was very low (6%). This is not surprising considering the reaction conditions. Both aldehyde and thiol groups are quite reactive. Aldehyde groups usually cannot tolerate strongly the basic conditions which are present in the second reaction (NaSH). In addition, thiol groups are known to undergo base-catalyzed oxidative di-merization and degradation. We felt that the use of basic conditions with such reactive functionalities could be the reason for the generally low yields of α-mercapto-aldehydes.

To maximize the use of dihydrothiophene methodology, the incorporation of other functional groups into the . α-mercaptoaldehyde is necessary. For example, generation of diene 16 (Figure 11) would require the construction of
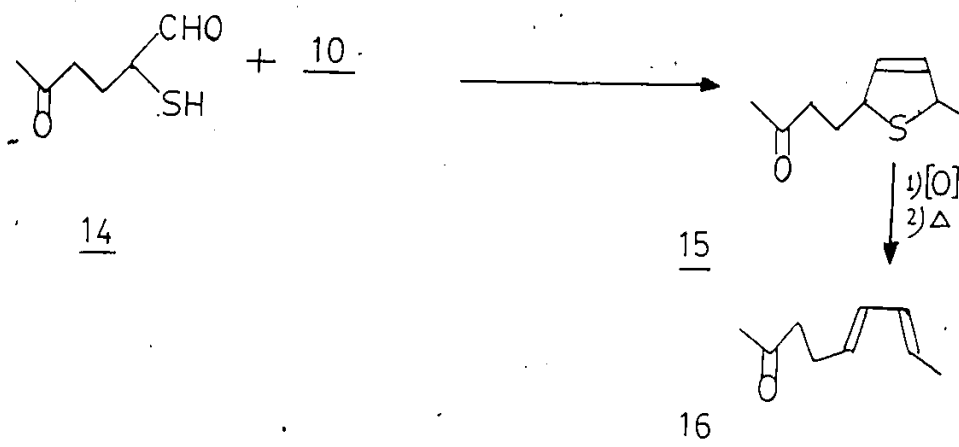
Figure 11. Proposed Synthesis of Diene.

mercaptoaldehyde 14. Useful chemical operations designed
to introduce the extra functionality into a molecule which
contains free aldehyde and thiol groups are severely limited
by the reactivity of the existing groups.

The importance of α-mercaptoaldehydes led us to in-
vestigate a new method for their proparation, in which the
reactive functional groups would be carried in a protected
state, which would be relatively stable to various condi-
tions and would liberate both the aldehyde and the thiol
groups under specific conditions.

The 1,3-oxathiolan-5-one (18) system was chosen to
start our investigation because of the following advantages:

(i) It could be easily prepared from mercaptoacids
and acetone (17)) (Figure 12).
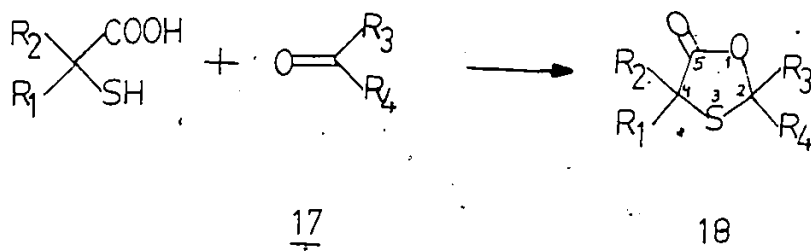
R_{1-2} = Alkyl Groups or Hydrogen
R_{3-4} = Me

Figure 12. Preparation of 1,3-Oxathiolan-5-Ones.

(ii) It should be capable of being alkylated at
position 4 thereby introducing the desired functional
groups into a larger molecule.

(iii) Its reduction with lithium aluminum hydride
(LAH) or diisobutylaluminum hydride (DIBAL-H) would be
expected to give α-mercaptoaldehydes (Figure 13).
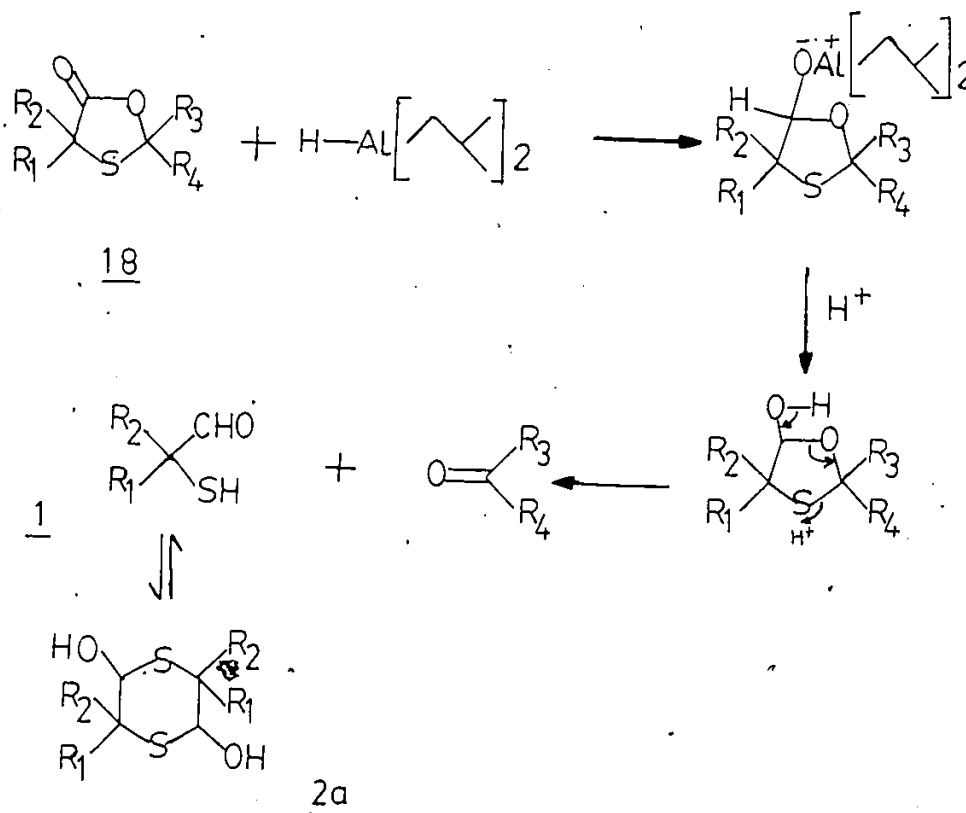
R_{1-4} = Alkyl Groups or Hydrogen

Figure 13. Proposed Mechanism of DIBAL-Reduction.

Before investigating the preparation of oxathiolanes
it was necessary to consider the preparation of the mercapto-
acids.   Levene[24] prepared α-mercaptoacids by treating
α-bromoacids with aqueous potassium hydrosulfide.   Billman[25,26]
and Bonner[27] prepared mercaptoacids from xanthates.
α-Mercaptoacids have also been prepared from pseudothio-
hydantoins.[28,29]

Bistrzycki[30] prepared 4,4-diphenyl-1,3-oxathiolan-5-one
by condensing thiobenzillic acid and formaldehyde.   Since
then many oxathiolanes have been prepared by the reaction
of α-mercaptoacids with either 2-methoxypropene ($\underline{19}$)[31]
(Figure 14) or carbonyl compounds in the presence of an
acid catalyst[32,33,34,35] (Figure 12).
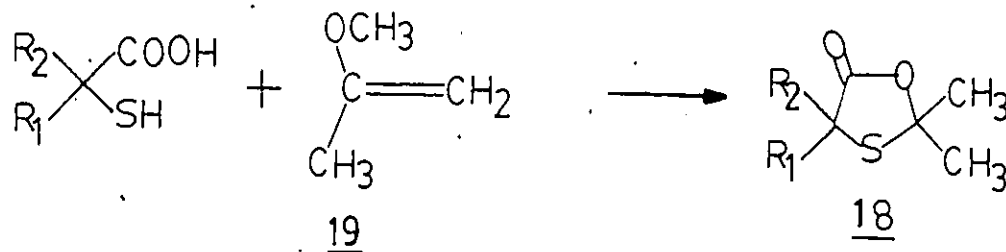
$$\underline{33}, \underline{39} \quad R_1 = R_2 = H$$

$$\underline{34}, \underline{40} \quad R_1 = Me, \ R_2 = H$$

Figure 14.   Reaction of α-Mercaptoacids with 2-Methoxypropene.

A literature survey designed to find a suitable reducing agent for oxathiolane system showed that the reduction of lactones at room temperature using LAH normally gives diols.[36] This reaction proceeds through the aldehyde which cannot be isolated in the usual case, but suffers further reduction.[37]

Diisobutylaluminum hydride (DIBAL-H) has been known for a long time to reduce a number of functional groups.[38,39] For example, nitriles have been reduced to aldehydes with DIBAL-H.[38,40,41] Zakharkin[42,43] and Teisseire[41] reduced a large number of aliphatic and aromatic esters to aldehydes (Figure 15).
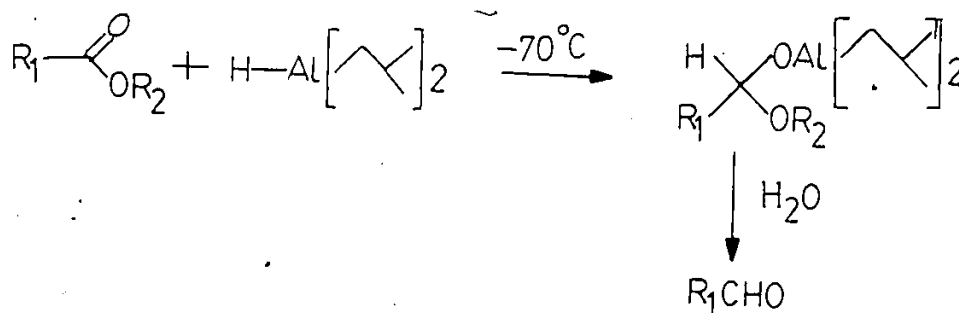
R_{1-2} = Alkyl Groups or Hydrogen

Figure 15.   Reduction of Esters to Aldehydes.

DIBAL-H has also been used in the reduction of lactones to lactols.[44] Schmidlin and Wettstein[45] reported an application of DIBAL-H in the steroid field. A lactone was re-

duced to a lactol in a stereospecific manner. Baran[46]

reduced lactone 20 to lactol 21 with DIBAL-H (Figure 16).

20 , 21
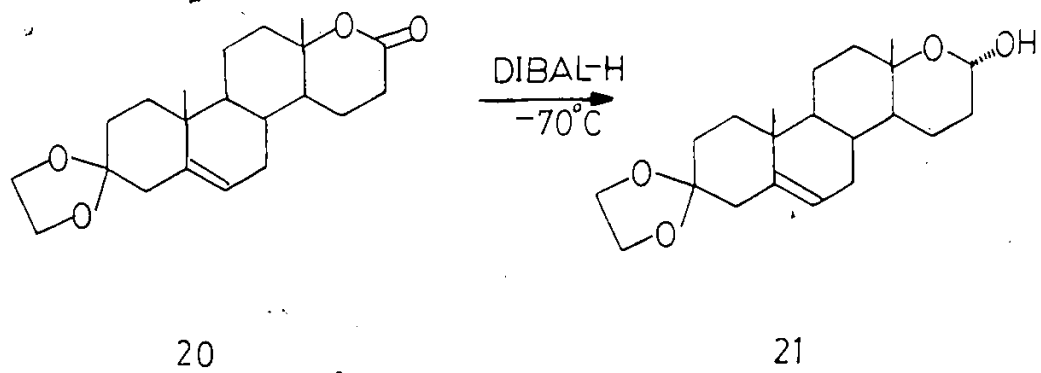
Figure 16. Reduction of Lactone to Lactol.

Corey and co-workers[47] used DIBAL-H in the total synthesis

of prostaglandins $F_{2\alpha}$ and E_2.

We first tried to reduce 1,3-oxathiolan-5-ones with

LAH at -78°C. The results obtained were not encouraging

and therefore DIBAL-H was applied. The results of these

experiments are the subject of Chapter II of this thesis.

In addition to the use of 1,3-oxathiolan-5-ones in

the synthesis of α-mercaptoaldehydes (which is discussed

in Chapter II), they have been used in the preparation of

thiiranes 22[35,48] (Figure 17). Thermal extrusion of carbon

dioxide from 18 gave thiirane 22. Conversion of 18 to 22,

has been found to be stereospecific and it proceeded by

the inversion of configuration at position 2 of 18.[35]

18   22
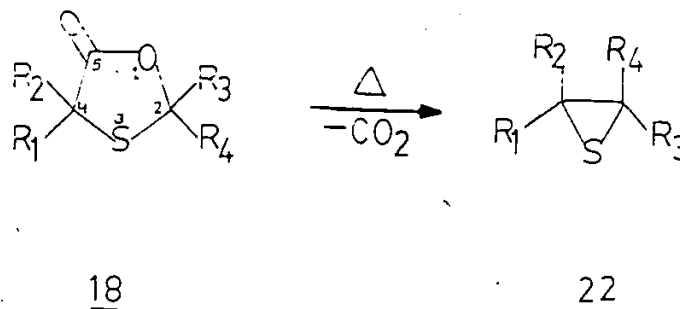
R_{1-4} = Alkyl, Aryl, Arylvinyl Groups or Hydrogen.

Figure 17.   Thermal Decomposition of 1,3-Oxathiolan-5-ones.

Thiiranes are useful precursors for the synthesis of
olefins[49] by phosphite[50] or phosphine[51] initiated desul-
furization. Many thiiranes, especially those with vinyl
or aryl substituents are thermally unstable. They extrude
sulfur on heating or standing. 2,2,3-Triphenylthiirane,
obtained from 2,4,4-triphenyl-1,3-oxathiolan-5-one, loses
sulfur when refluxed to give triphenylethylene (23)[48]
(Figure 18).
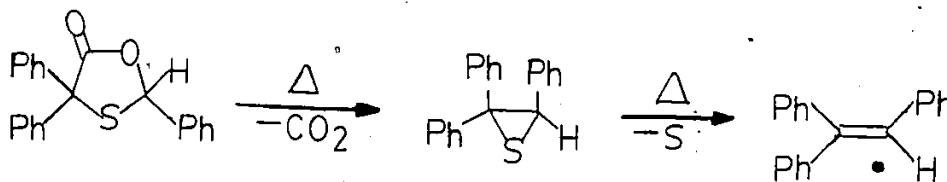
23

Figure 18.   Formation of Triphenylethylene.

There are two factors which must be taken into account when the use of the described reduction of oxathiolanes as a preparation of α-mercaptoaldehydes containing other functional groups is considered. These are the expected sensitivity of the lactone grouping and the divalent sulfur atom to hydrolytic or oxidative conditions and the known sensitivity of α-mercaptoaldehydes to a wide variety of reactions.

These factors make chemical transformation of functional groups in either intact oxathiolanes or their derived α-mercaptoaldehydes a problematic process. These problems could, in principle, be overcome by incorporation of the oxathiolane molecule, as an intact unit, into a molecule which already contains the other required functionality. Hydrogen atoms adjacent to sulfur and or carbonyl groups are well known to be susceptible to abstraction by strong bases (Figure 19).
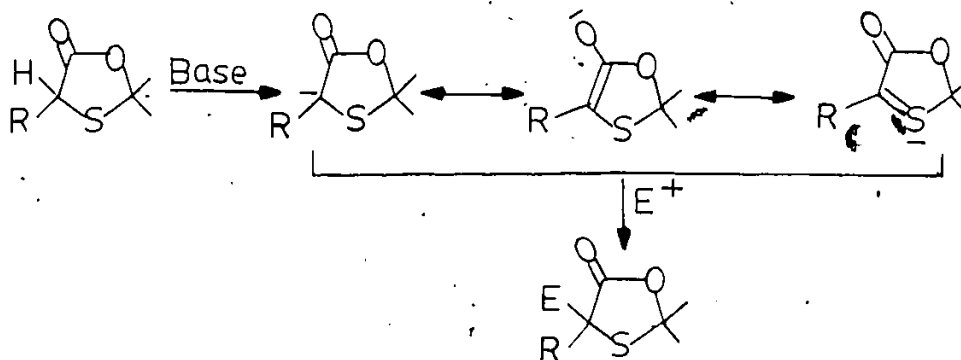
R = Alkyl Group or Hydrogen
E = Alkyl or Carbonyl Groups

Figure 19. Proposed Alkylation of Oxathiolanes.

It therefore appeared that a solution to the problem
mentioned above might be found in an alkylation of such
carbanions. The electrophilic species E^+ might consist
of alkyl, benzyl or allyl halides or of carbonyl groups,
in which case the reaction would be of the aldol type.
The only report of such a reaction prior to this report
was the report by Schultz and co-worker[52] of the addition
of carbanion 24 to cyclohexenone to give the conjugate
addition product 25 (Figure 20).

24   25
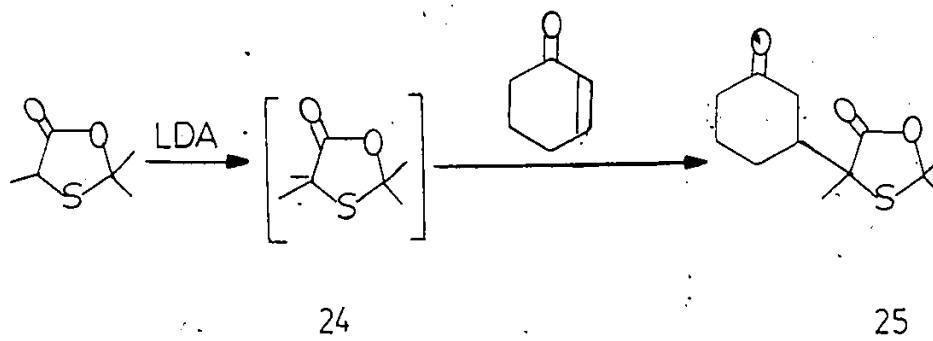
Figure 20. Conjugate Addition of Cyclohexenone.

Considering the importance of 1,3-oxathiolan-5-ones
to our work we have investigated their alkylation and
aldol type condensation. The results of these experiments
are discussed in Chapter III.

CHAPTER II

THE PREPARATION AND REDUCTION OF

.1,3-OXATHIOLAN-5-ONES

Results and Discussion

In order to synthesize 1,3-oxathiolan-5-ones it was necessary to prepare the related α-mercaptoacids. α-Bromoacids were made by two methods. (A) Carboxylic acids were converted to α-bromoacids directly by treatment with bromine in the presence of a catalytic amount of phosphorus trichloride;[53] (B) an acid chloride was first made which on bromination followed by hydrolysis gave the α-bromoacid.[54] α-Bromoacids 26 and 27 were obtained in acceptable yield and short reaction time by method A. The physical constants and spectral data for compounds 26-27 are given in Tables 1 and 2. α-Bromophenylacetic acid (28) was purchased.

The method of preparing α-mercaptoacids by treatment of α-bromoacids with potassium hydrosulfide[24] was unsuccessful. The xanthate method[25,26,27] was successful. Potassium O-ethyldithiocarbonate (29) was prepared according to literature procedure.[27] Employing the procedure of Bonner,[27] (using α-bromoacids 26-28 and xanthate 29) S-(thioncarboethoxy)-

Figure 22. Preparation of α-Mercaptobutyric Acid from 5-Ethylpseudothiohydantoin.

The 1,3-oxathiolan-5-ones were prepared by two procedures: (A) condensation of mercaptoacids 33 and 34 with 2-methoxypropene (19)[31] gave oxathiolanes 39 and 40 (Figure 14); (B) employing the procedure of Pihlaja and co-workers[34] (using mercaptoacids 33-37 and acetone (17)) the oxathiolanes 39-43 were obtained (Figure 12). The physical constants and spectral data for the 1,3-oxathiolan-5-ones prepared from both methods are given in Tables 7 and 8. The carbon-13 spectra and analytical data on new compounds are given in Tables 9 and 10. The yield of 39 was larger (42%) when procedure A was applied. Compound 40 was obtained in higher yield (63%) by procedure B.

It is interesting to note that a by-product, [propane-

$$Me_2C(SCH_2COOH)_2 \quad \underline{44}$$
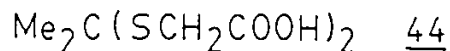
2,2-bis(mercaptoacetic acid) (44)], was obtained in 30% yield in the preparation of 39 by method B. The physical constant and spectral data for compound 44 is given in the experimental section. Compound 44 is formed[56] by the condensation of one mol of acetone with two mol of 33 in the presence of an acid catalyst. In our cases, acetone was used in excess but 44 was still formed in significant amounts. The absence of products analogous to 44 in other reactions is probably due to the higher degree of substitution at the α-carbon in those cases which would retard the formation of the thioacetal by a steric effect.

Baran's method[46] of reducing lactones to lactols (Figure 16) was successful in reducing 1,3-oxathiolan-5-ones. 1,3-Oxathiolan-5-ones 39-43 were reduced by DIBAL-H at -78°C to give corresponding α-mercaptoaldehydes. The yields, spectral data and analytical data are shown in Tables 11, 12 and 13. The proposed mechanism of reduction is shown in Figure 13.

In all the reductions carried out a mixture of liquid and solid products was obtained. Spectral data of the solid compounds 46, 48, 53 and 55 showed them to be the dimers of the corresponding α-mercaptoaldehydes. The reduction of 41 also gave a mixture of liquid and solid product. The nmr spectrum of the solid indicated it to be a mixture of dimers 50 and 51. Kirrmann and co-workers[5] have shown previously that α-mercaptoisobutyraldehyde (49) exists in two dimeric forms 50 and 51 in the ratio of 1:10 (Figure 23). The
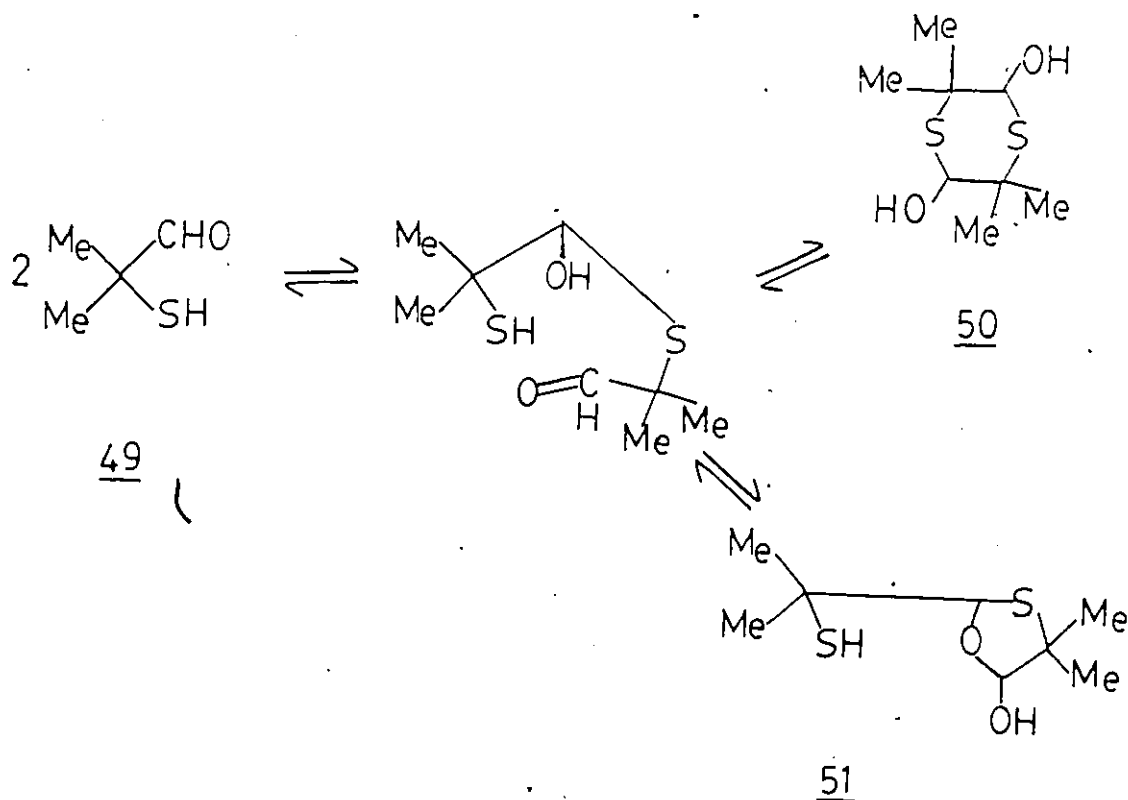
Figure 23. Dimerization of α-Mercaptoisobutyraldehyde.

melting points of 50 and 51 were reported to be 225-30°C and 65°C. The ir spectra of liquids obtained in the reduction of 41 and 42 showed the presence of aldehyde as well as hydroxy groups. The preparation of dihydrothiophenes from these liquids in the same yields as from the solid product confirmed that they were mixtures of monomers, dimers and perhaps the higher oligomers. Therefore, it is concluded that α-mercaptoaldehydes exist in different degrees of association and the combined yield of liquid and solid products was calculated to show the total yield of α-mercapto-aldehydes. This is reported in Table 11 and the experimental section.

Many of the α-mercaptoaldehydes are highly insoluble in the usual organic solvents and they can exist in several diastereomeric forms when substituents are found on the α-position. It has been shown[4] that, under basic conditions, an equilibrium between the dimer 2a and monomer 56 is readily established. However, in the presence of trace amounts of acid, the dimeric dihydroxydithianes 2a are easily dehydrated to transannular ethers 57[1] which are highly stable and unreactive (Figure 24).
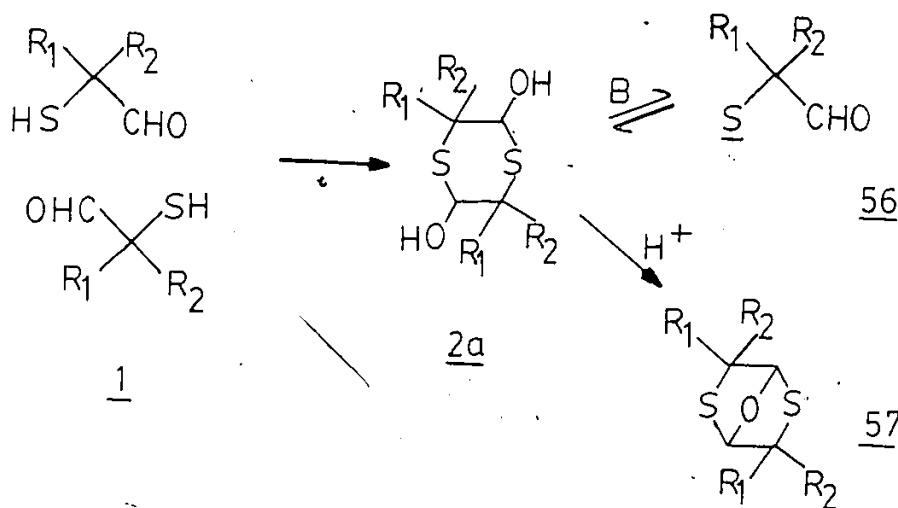
R_{1-2} = Alkyl Groups or Hydrogen

Figure 24. Acid-Base Reactions of Dimeric α-Mercaptoaldehydes.

α-Mercaptoaldehydes cannot be distilled.[4] Attempted distillation leads to a variety of reactions including polymerization, oxidation or dehydration to 1,4-dithiadiene 58.[14] Compound 58 can undergo thermal extrusion of sulfur

to give the corresponding thiophene $\underline{59}$[14,57] (Figure 25).
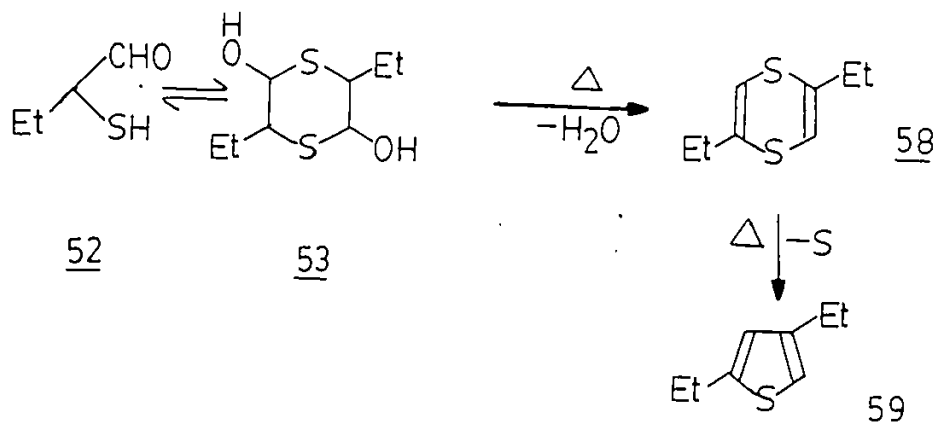
Figure 25. Formation of Thiophene via 1,4-Diathiadiene.

Some comments about the DIBAL reduction are required. We have found that the reduction proceeds best at -78°C and superior results are obtained when the DIBAL-H solution is used in four fold excess. The reaction should be worked up after stirring for 2-3 hours at -78°C. Allowing it to stir at room temperature for 3-4 hours before work up afforded a mixture of several compounds.

Although the yields of α-mercaptoaldehydes shown in Table 11 are generally modest, comparison of the results of this method with those previously obtained[5,16] suggests that, with the exception of $\underline{46}$, the reduction method is superior. Not only are the yields greater, but the sample

handling and product isolation are easier.

Employing the literature procedure[15] 2,5-dihydro-
thiophenes 61-65 were obtained from α-mercaptoaldehydes
and vinyltriphenylphosphonium bromide (60) (Figure 26).
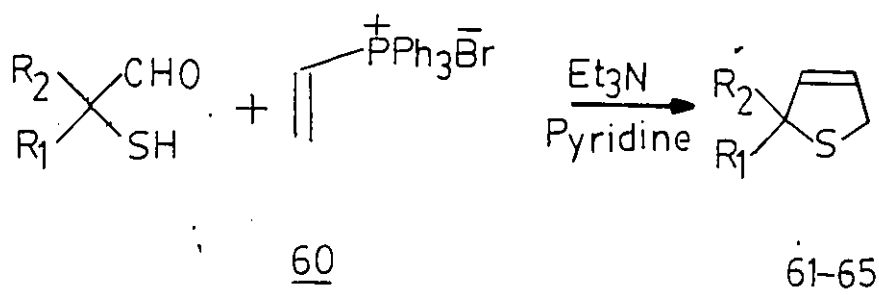
R_{1-2} = Alkyl, Phenyl Groups or Hydrogen

Figure 26.   Reaction of α-Mercaptoaldehydes with
             Vinyltriphenylphosphonium bromide.

The yield, proton nmr spectra and carbon-13 nmr spectra for
the dihydrothiophenes 61-65 are given in Tables, 14, 15
and 16.

Dihydrothiophenes are formed by a combined Michael-
Wittig reaction. It is proposed that nucleophilic attack
of the mercaptan on the vinyl salt produces a phosphorus
ylid which, by intramolecular Wittig reaction, loses
triphenylphosphine oxide and gives dihydrothiophene
(Figure 27). Low yields of dihydrothiophenes were obtained

when the reaction was carried out at 35°C. The yields
were improved when the temperature was raised to 100°C.
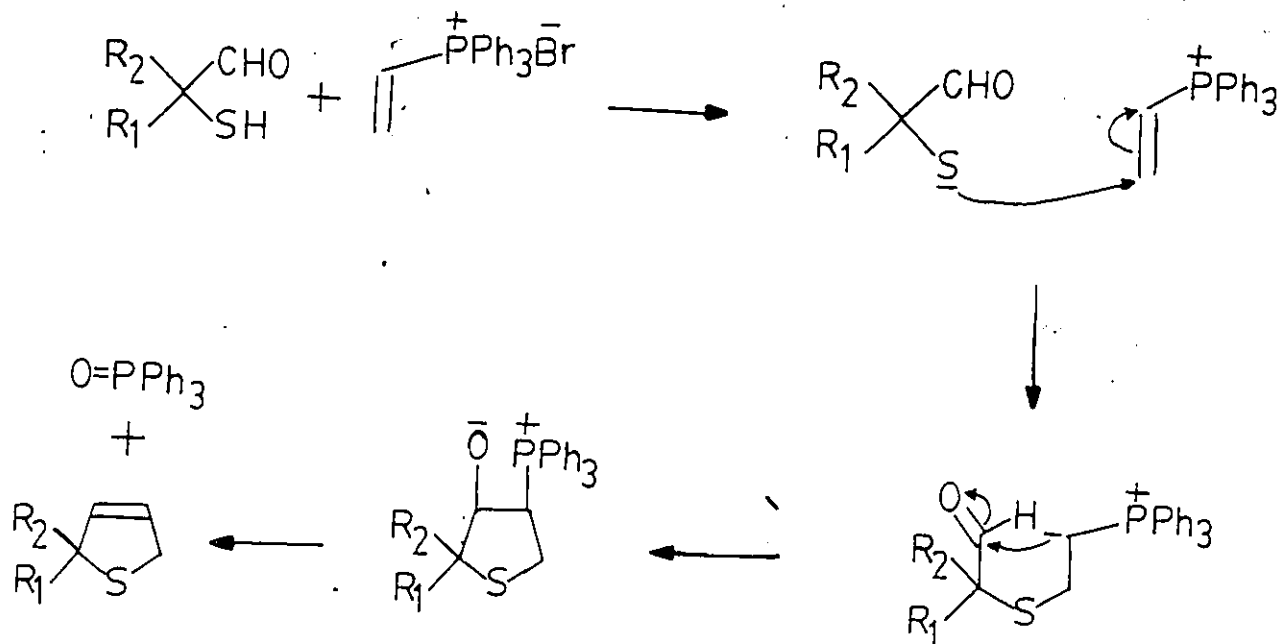
R_{1-2} = Alkyl, Phenyl Groups or Hydrogen

Figure 27. Proposed Mechanism for 2,5-Dihydrothiophene Synthesis.

TABLE 1

α-Bromoacids

Compound	R_1	R_2	MP(°C)[a]	BP(°C/Torr)[a]	Yield (%)	Ref.
26	Me	Me	41-43 (45-48)	114-115/23 (110-116/20)	63	55
27	Et	H	-	134-137/49 (122-126/25)	81	55

[a]Values in parentheses are literature values.
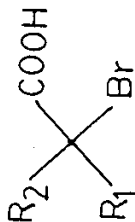
TABLE 2

Spectral Data for α-Bromoacids

Compound	IR[a] (cm^{-1})	PMR[b] (ppm)
26	3500-2400, 1717, 1295, 1180.	12.02 (s,1), 1.98 (s,6).
27	3500-2400, 1720, 1275, 1170.	12.28 (s,1), 4.22 (t,1,J=7 Hz), 2.38-1.82 (m,2), 1.08 (t,3, J=7 Hz).

[a]Four most intense peaks.

[b]See experimental for coding.

TABLE 3

Products and Yields of S-(Thioncarboethoxy)-α-Mercaptoacids

Bromoacid	Xanthate	Product	R_1	R_2	MP(°C)[a]	Yield (%)	Ref.
26	29	30	Me	Me	101-103[b] (102-103)	62	26
27	29	31	Et	H	54-57	85	25
28	29	32	Ph	H	85-87 (90.5-91.5)	84	27

[a] Values in parentheses are literature values.

[b] Recrystallized from petroleum ether.

TABLE 4

Spectral Data

Compound	IR[a] (cm^{-1})	PMR[b] (ppm)
30	3500-2400, 1718, 1260, 1060.	11.52 (s,1), 4.64 (q,2, J=7 Hz), 1.70 (s,6), 1.40 (t,3, J=7 Hz).
31	3500-2400, 1710, 1230, 1050.	11.66 (s,1), 4.66 (q,2, J=7Hz) 4.35 (t,1, J=7 Hz), 2.32-1.72 (m,2), 1.42 (t,3, J=7 Hz), 1.10 (t,3, J=7 Hz).
32	3420-2400, 1715, 1250, 1055.	11.60 (s,1), 7.49 (s,5), 5.53 (s,1), 4.68 (q,2, J=7 Hz), 1.35 (t,3, J=7 Hz).

[a] Four most intense peaks.

[b] See experimental for coding.

TABLE 5

α-Mercaptoacids Prepared

Compound	Product	R_1	R_2	MP(°C)[a]	BP(°C/Torr)[a]	Yield (%)	Ref.
30	35	Me	Me	—	105-110/16 (101-102/15)	76	26
31	36	Et	H	—	105-110/9.3 (118-122/19)	88	25
32	37	Ph	H	57-60 (83.5-86.5)		79	27

[a] Values in parentheses are literature values.

TABLE 6

Spectral Data For α-Mercaptoacids

Compound	IR^a (cm^{-1})	PMR^b (ppm)
35	3400-2400, 1710, 1280, 1170.	12.22 (s,1), 2.58 (s,1), 1.60 (s,6).
36	3400-2400, 1710, 1280, 1080.	11.82 (s,1), 3.38 (td,1, J$_t$=7 Hz, J$_d$=9 Hz), 2.16 (d,1, J=9 Hz), 2.10-1.60 (m,2), 1.06 (t,3, J=7 Hz).
37	3400-2400, 1720, 1310, 705^c.	11.72 (s,1), 7.40 (m,5), 4.70 (d,1, J=7.5 Hz), 2.60 (d,1, J=7.5 Hz).

^{a}Four most intense peaks.

^{b}See experimental for coding.

^{c}KBr pellet.

31

TABLE 7

Products and Yields of 1,3-Oxathiolan-5-ones

Mercaptoacid	2-Methoxypropene (19)/ Acetone (17)	Product	R_1	R_2	MP(°C)[a]	BP(°C/Torr)[a]	Yield (%)[a]	Ref.
33	19	39	H	H	–	90-93/20 (76-86/8)	42	
33	17	39 + 44	H	H	– 137-138 (129-130)	– –	26 30	34 56
34	19	40	Me	H	–	98-103/20 (82/14)	44	34
34	17	40	Me	H	–	–	63	
35	17	41	Me	Me	52-54	86-90/24	53	
36	17	42	Et	H	–	79-82/9	85	
37	17	43	Ph	H	85-88[b]	–	85	

$$R_2 \overset{COOH}{\underset{R_1}{\bigtimes}} SH \quad + \quad O = \overset{R_3}{\underset{R_4}{<}}$$

33-37   17

$\longrightarrow$

(structure 39-43, with $R_3 = R_4 = Me$)
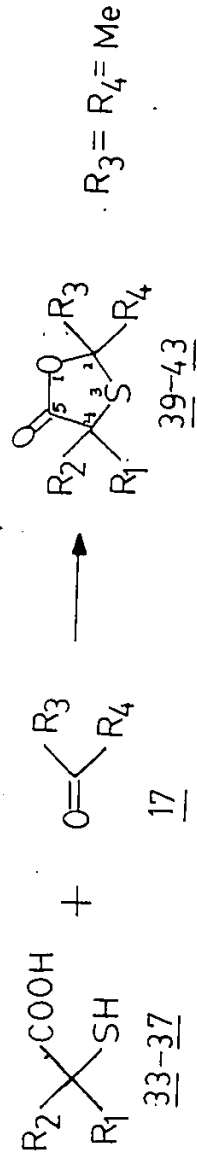
[a]Values in parentheses are literature values.

[b]Recrystallized from absolute ethanol.

TABLE 8

Spectral Data of Oxathiolanes

Compound	IR^a (cm^{-1})	PMR^b (ppm)
39	1775, 1230, 1095, 982^c.	3.84 (s,2), 1.78 (s,6).
40	1770, 1228, 1175, 1050c.	4.16 (q,1, J=7 Hz), 1.75 (s,6), 1.60 (d,3, J=7 Hz).
41	1765, 1745, 1175, 1078.	1.78 (s,6), 1.68 (s,6).
42	1760, 1230, 1178, 980.	4.14 (dd, 1, J=8, 5 Hz), 2.38-1.60 (m,2), 1.64 (s,6), 1.0 (t,3, J=7 Hz).
43	1768, 1250, 1108, 990.	7.51 (s,5), 5.31 (s,1), 1.85 (s,6).

^{a}Four most intense peaks.

^{b}See experimental for coding.

^{c}In CCl$_4$ solution.

TABLE 9

Carbon-13 NMR Spectra of 1,3-Oxathiolan-5-ones

Compound	C-2	C-4	C-5	R_1	R_2	R_3	R_4
39	88.9	33.3	172.0	–	–	30.7	30.7
40	86.0	42.4	174.6	17.9	–	30.9	31.3
41	84.5	52.8	177.8	30.2	30.2	32.6	32.6
42	86.3	50.2	174.0	26.3 (CH_2) 11.9 (CH_3)	–	31.2	31.8
43	86.0	52.7	172.7	128.8) 128.6) Ph	–	31.0	31.7
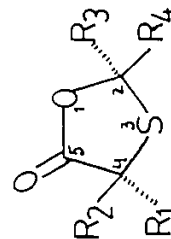
$R_3 = R_4 = Me$

TABLE 10

Analytical Data

Compound	Calculated			Found			
	C(%)	H(%)	S(%)	C(%)	H(%)	S(%)	m/e
41	52.47	7.54	20.01	52.55	7.42	19.86	–
42	52.47	7.54	20.01	52.43	7.57	19.67	–
43	63.46	5.80	15.39	63.53	5.67	15.39	208

TABLE 11

Products and Yields of α-Mercaptoaldehydes

Compound	Product		R_1	R_2	Yield (%)		
	Monomer	Dimer			Solid	Liquid	Combined
39	45	46	H	H	9	5	14
40	47	48	Me	H	31	8	39
41	49	50, 51	Me	Me	21	26	47
42	52	53	Et	H	8	62	70
43	54	55	Ph	H	27	39	66

39-43
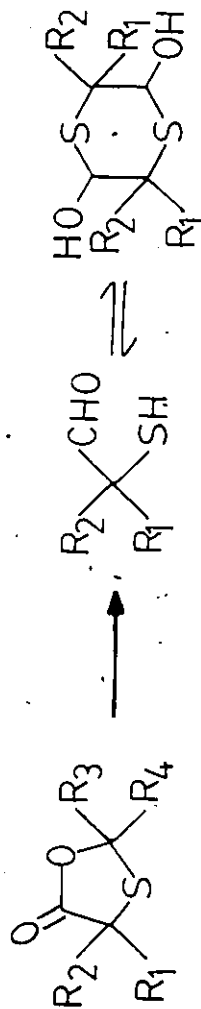
TABLE 12

Spectral Data for α-Mercaptoaldehydes

Compound	IR[a] (cm^{-1})	PMR[b] (ppm)
46	3400, 1385, 1055, 960[c].	[d] 688 (br s,2), 5.40 (X Part of ABX,2, $J_{BX(ax-ax)}$=7 Hz, $J_{AX(eq-ax)}$=3 Hz) 3.58 (AB Part of ABX, 4, J_{AB}(gem) = 14 Hz, J_{BX}=7 Hz, J_{AX}= 3 Hz).
48	3340, 1128, 1025, 975[c].	[e] 5.79 (d,2, J=6 Hz), 4.67 (br d, 2, J=6 Hz), 3.73 (br q,2, J=7.5 Hz), 1.11 (d,6, J=7.5 Hz).
Mixture of 50 and 51 (solid)	3450, 2995, 1120, 1035[c].	[e] 6.41 (d, J=5 Hz), 5.52 (s), 5.19 (d, J=5 Hz), 3.05 (s), 2.13 (s), 1.40(br s).
Liquid	3440, 2995, 1710, 1035.	
53	3400, 2997, 1135, 1028[c].	[d] 6.90 (br s,2), 5.18(d,2, J=2 Hz), 3.92 (td,2, J_t=7 Hz, J_d=2 Hz); 1.95-1.50 (m,4), 0.92 (t,6, J=7 Hz).
Liquid	3440, 2995, 1720, 1108.	
55	3400, 1092, 952, 708[c].	[e] 7.40 (m,10), 6.40 (br d, 2), 5.06 (br s,2) 4.96 (br s,2).

[a] Four most intense peaks; [b] See experimental for coding; [c] KBr pellet; [d] In Pyridine-d$_5$ solution; [e] In DMSO-d$_6$ solution.

TABLE 13

Analytical Data for α-Mercaptoaldehydes

Compound	Calculated			Found			m/e
	C(%)	H(%)	S(%)	C(%)	H(%)	S(%)	
46	31.57	5.29	42.12	31.52	5.29	41.85	152
48	39.97	6.70	35.57	40.09	6.80	35.97	180
50,51[a]	46.12	7.74	30.78	-	-	-	-
53	46.12	7.74	30.78	46.22	7.52	30.42	-
55	63.12	5.29	21.06	63.21	5.19	20.84	304

[a]Insufficient sample for analysis.

TABLE 14

Products and Yields of 2,5-Dihydrothiophenes

Mercaptan	Salt	Product	R_1	R_2	Time(hr)	Yield (%)	Ref.
46	60	61	H	H	5	44	59
48	60	62	Me	H	6	42	
50,51	60	63	Me	Me	24	59	
53	60	64	Et	H	14	75	15
55	60	65	Ph	H	12	48	
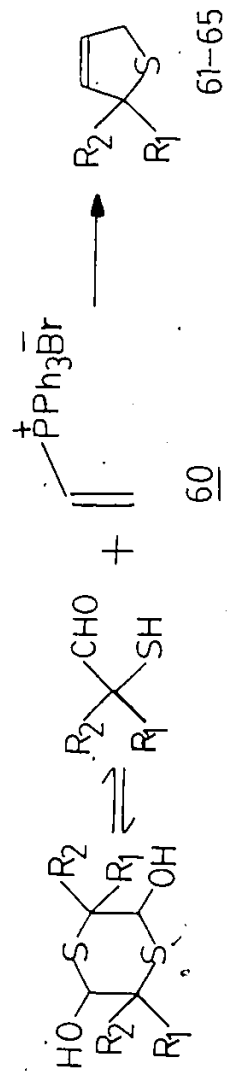
TABLE 15

NMR Spectral Data of Dihydrothiophenes

Compound	PMR^a (ppm).
61	5.88 (s,2), 3.76 (s,4).
62	5.78 (s,2), 4.30 (m,1), 3.77 (m,2), 1.39 (d,3, J=6 Hz).
63	5.60 (s,2), 3.75 (s,2), 1.45 (s,6).
64	5.75 (s,2), 4.20 (m,1), 3.68 (m,2), 1.95-1.41 (m,2) 0.93 (t,3, J=7 Hz).
65	7.34 (s,5), 5.87 (m,2), 5.36 (m,1), 3.89 (m,2).

^{a}See experimental for coding.

TABLE 16

Carbon-13 NMR Spectra of Dihydrothiophenes

Compound	C-2	C-3	C-4	C-5	R_1	R_2
61	38.9	128.6	128.6	38.9	–	–
62	49.7	135.1	127.0	39.1	24.2	–
63	59.8	140.5	124.9	39.1	32.4	32.4
64	57.4	133.2	128.5	38.5	31.1(CH_2) 11.6(CH_3)	–
65	58.8	133.2	128.8	39.6	129.5 128.5 Ph 127.6 127.2	
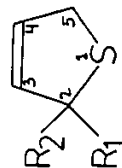
CHAPTER III

ALKYLATION AND CONDENSATION REACTIONS OF

1,3-OXATHIOLAN-5-ONES

Results and Discussion

In order to establish a suitable procedure for alkylating
oxathiolanes, it was necessary to review the alkylation reac-
tions of simple lactones.

Posner[60] reported the first direct conversion of
γ-butyrolactone (66) into α-methyl-γ-butyrolactone (67).
Posner's method of alkylation was modified by Schlessinger
and Herrmann.[61] Lactone 66 was alkylated to give 67 using
lithium diisopropylamide (LDA) as base and hexamethylphos-
phoramide (HMPA) in THF. A second alkylation on 67 gave
α,α-dialkylated lactone 68 (Figure 28).

66   67   68
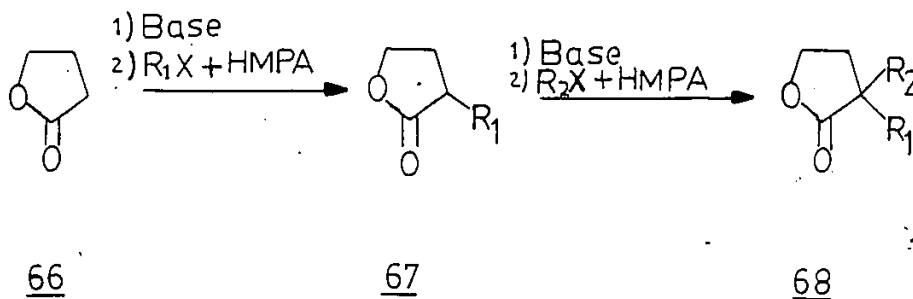
R_{1-2} - Alkyl or Allyl Groups

Figure 28. Alkylation of γ-Butyrolactone.

41

This method gave high yields of alkylated products with several alkylating agents.[61] Grieco and co-workers[62] alkylated γ-lactones in the total synthesis of 2,3,4- substituted furans using LDA and HMPA. Butyrolactone has also been alkylated indirectly.[63,64,65] In this method butyrolactone 66 was condensed with aldehydes and the pro- ducts, α-alkylidine-γ-lactones 69, were hydrogenated to give corresponding α-alkyl-γ-butyrolactones 70 (Figure 29).

1) Base
2) RCHO
=CHR
H₂
—CH₂R

66   69   70
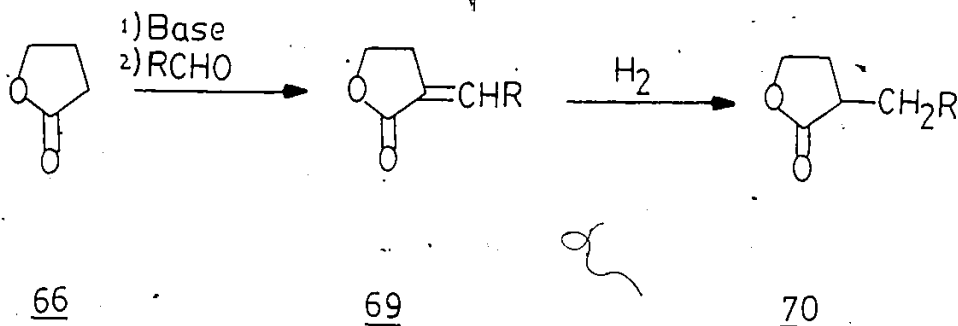
R = Alkyl, Aryl or Substituted Aryl Groups

Figure 29. Condensation and Hydrogenation of γ-Butyrolactone.

1,3-Oxathiolan-5-ones were expected to be more acidic than butyrolactone because of the acidifying influence of the sulfur atom. Therefore we tried Schlessinger's method[61] for the alkylation of 1,3-oxathiolan-5-ones. Compounds 39 and 40 were alkylated with alkyl halides (Figure 30) and condensed with aldehydes. The physical constants, spectral data, carbon-13 spectra and analytical data of the alkylation and condensation products are given in Tables 17-22.

1) LDA/THF
2) RX+HMPA
−78°C
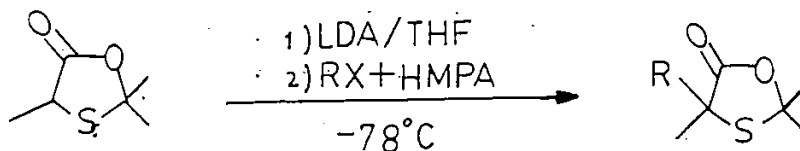
40

R = Alkyl, Allyl or Benzyl halides

Figure 30. Alkylation of 2,2,4-Trimethyl-1,3-Oxathiolan-5-one.

It is postulated that the reaction of the oxathiolane with LDA produces a carbanion which is stablized by the adjacent carbonyl group and sulfur atom (Figure 19). Nucleophilic attack of this lithium enolate on an alkyl halide eliminates lithium halide and gives the α-alkyl oxathiolane. If the oxathiolane contains one more ionizable hydrogen it could also react again in the same way to give the α,α-dialkyl-oxathiolane (Figure 31). Polvalkylation is a common problem when anions derived from only moderately acidic compounds are used. Attack of the lithium enolate on an aldehyde followed by hydrolysis leads to a condensation product. Compound 40 was alkylated and condensed successfully with the halides/aldehydes mentioned in Tables 17 and 19.

However when ethyl bromide and butyl bromide were used for alkylation a very complex mixture containing very little
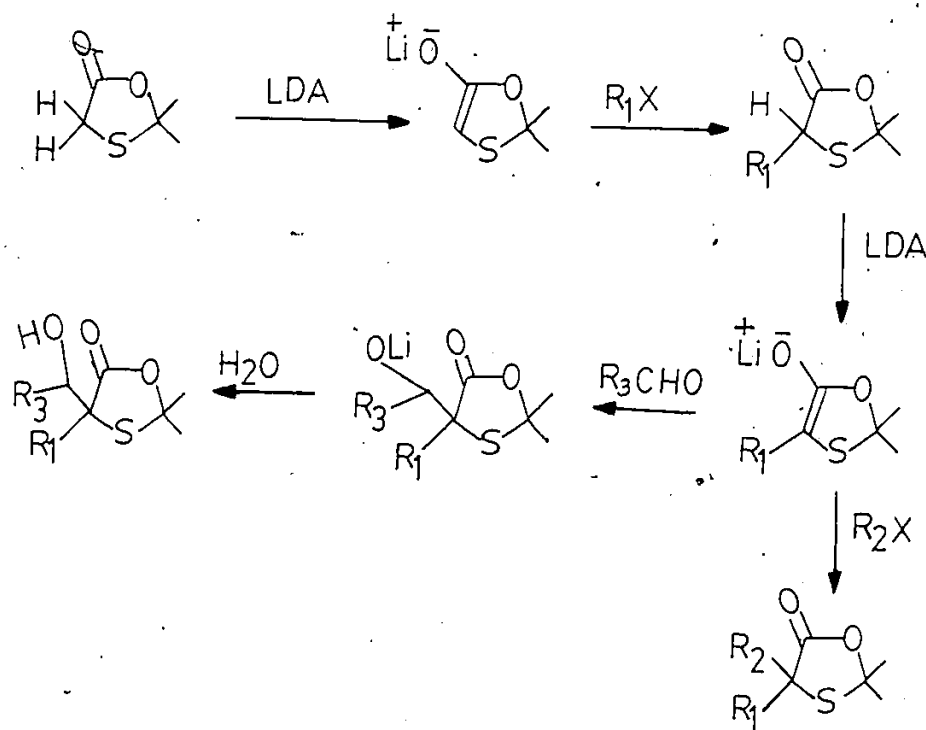
R_1 = Alkyl or Benzyl Group

R_2 = Alkyl, Allyl or Benzyl Group

R_3 = Alkyl or Phenyl Group

Figure 31. <u>Proposed Mechanism of Alkylation and Condensation of Oxathiolanes</u>.

product was formed. This could be due to two reasons. The reactivity of alkyl halides in SN2 reactions decreases in the following order: MeX>EtX>BuX. Benzyl and allyl halides are considerably more reactive than ethyl halides in SN2

reactions; their activity is comparable to a methyl halide, which is more reactive than ethyl halides. Secondly, the reactivity of the halogen in alkyl halides decreases in the following order I>Br>Cl; that is, the order of reactivity for a given alkyl group would decrease in the order: RI>RBr>RCl. Ethyl and butyl iodides would be expected to be more reactive than ethyl and butyl bromides.

When oxathiolane 39 was alkylated with 1.1 equivalents of benzyl bromide a dibenzylated product, 73, was isolated in 9% yield along with a mixture of 73 and an unknown product. The identity of this unknown product is still being investigated.

In the alkylation of 40 with benzyl bromide, if base was used in excess, trans-stilbene was formed and was iden- tified by its melting point and spectral data.

Condensation of 40 with acetaldehyde and benzaldehyde gave 74 and 75. The nmr spectra of these compounds (Table 20) indicated them to be a mixture of two diastere- omers which were not separated. The ratio of two diastere- omers in 74 was about 70:30 according to the integration on the gas chromatogram.

We have found that alkylation and condensation reactions of 1,3-oxathiolan-5-ones proceed best at low temperature (-78°C). The use of higher temperature leads to complex

product mixtures.

Further work on the alkylation and condensation reactions of 1,3-oxathiolan-5-ones are underway in our laboratory.

TABLE 17

Products and Yields of Alkylation Reactions

Compound	Alkyl halide	(Product	R_1	R_2	MP(°C)	BP(°C/Torr)	Yield (%)
40	CH_3I	41	Me	Me	52-54	86-90/24	90
40	$PhCh_2Br$	71	Me	$PhCH_2$	54-55[a]	--	65
40	$CH_2=CH \cdot CH_2Br$	72	Me	$CH_2=CH \cdot CH_2$	--	113-115/26	63
39	$PhCH_2Br$	73	$PhCH_2$	$PhCH_2$	158-160	--	9

39 $R_1=R_2=H$

40 $R_1=Me, R_2=H$

41, 71-73

$R_3=R_4=Me$
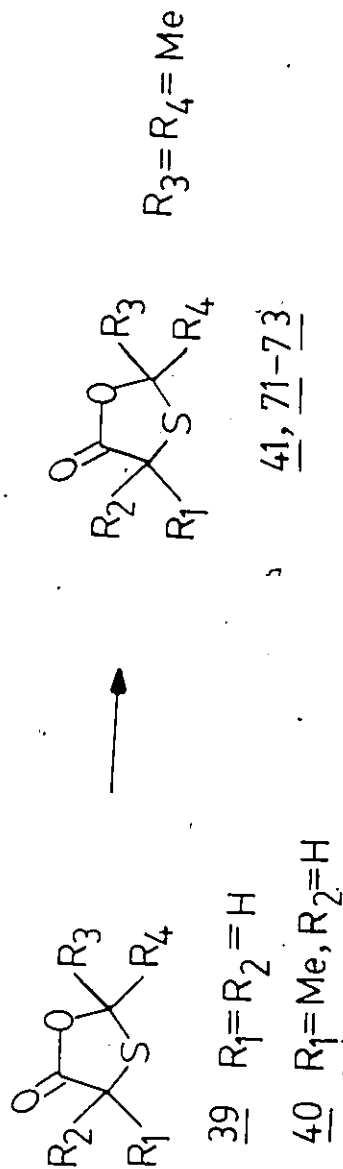
[a] Recrystallized from hexane.

TABLE 18

Spectral Data of Alkylation Products

Compound	IR[a] (cm^{-1})	PMR[b] (ppm)
41[c]		
71	1745, 1215, 1112, 1080.	7.32 (s,5), 3.10 (ABq,2, J=14 Hz), 1.70 (s,3), 1.68 (s,3), 1.20 (s,3).
72	1750, 1225, 1175, 1070.	6.25-4.98 (ABX.m,3), 2.60 (d,2, J=7 Hz), 1.75 (s,6), 1.63 (s,3).
73	1742, 1265, 1215, 695.	7.32 (s,10), 3.21 (ABq, 4, J=14 Hz), 0.84 (s,6).

[a]Four most intense peaks.

[b]See experimental for coding.

[c]See Table 8.

48

TABLE 19

Products and Yields of Condensation Reactions

Compound	Aldehyde	Product	R_1	R_2	BP(°C/Torr)	yield (%)
40	CH_3CHO	74	Me	$CHOH \cdot CH_3$	122-125/53	54
40	PhCHO	75	Me	$CHOH \cdot Ph$	—	70

40 R_1=Me, R_2=H

74-75 R_3=R_4=Me
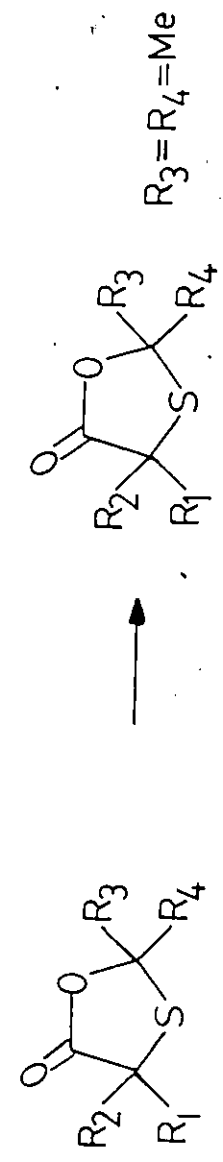
TABLE 20

Spectral Data of Condensation Products

Compound	IR^a (cm^{-1})	PMR^b (ppm)
74	1740, 1260, 1218, 1092.	4.01 (q,1, J=6 Hz), 3.52 (br s,1). 1.78 (s,3), 1.74 (s,3), 1.70 (s,3), 1.25 (d,3, J=6Hz).
Mixture of two diastere-omers		4.05 (q,1, J=Hz), 3.52 (br s,1), 1.56 (s,9), 1.19 (d,3, J=6Hz).
75	1740, 1260, 1175, 1075.	7.40 (m,5), 5.07 (s,1), 4.70 (br s,1), 1.79 (s,3), 1.66 (s,3), 1.19 (s,3).
Mixture of two diastere-omers		7.40 (m,5), 4.93 (s,1), 4.70 (br s,1), 1.65 (s,3), 1.43 (s,3), 1.19 (s,3).

^{a}Four most intense peaks.

^{b}See Experimental for coding.

TABLE 21

Carbon-13 NMR Spectra of Alkylation and Condensation Products

Compound	C-2	C-4	C-5	R_1	R_2	R_3	R_4
41[a]							
71	84.4	59.4	176.5	29.8	136.3 131.0 Ph 128.0 127.1 47.0 (CH_2)	31.8	33.5
72	84.5	57.2	176.3	28.5	132.7 (=CH) 119.8 (=CH_2) 45.7 (CH_2)	32.6	33.4
73	85.1	67.3	176.0	136.0 131.5 Ph 128.0 127.2 47.0 (CH_2)	136.0 131.5 Ph 128.0 127.2 47.0 (CH_2)	32.1	32.1
74	85.2	62.8	176.8	24.7	72.4 (CHOH) 18.5 (CH_3)	32.0	33.8

Table 21 (continued)

Compound	C-2	C-4	C-5	R$_1$	R$_2$	R$_3$	R$_4$
75	85.8	63.5	176.8	25.7	130.1 128.4 128.1 · Ph 127.7 77.9 (CHOH)	31.6	33.7

R$_3$ = R$_4$ = Me

[a] See Table 9.

TABLE 22

Analytical Data of Alkylation and Condensation Products

Compound	Calculated			Found		
	C(%)	H(%)	S(%)	C(%)	H(%)	S(%)
41[a]						
71	66.06	6.82	13.56	66.11	6.86	13.49
72	58.03	7.57	17.17	57.94	7.62	16.97
73	73.04	6.45	10.26	73.17	6.30	10.53
74	50.50	7.41	16.85	50.58	7.73	16.79
75[b]	61.88	6.39	12.70	-	-	-

[a] See Table 10.

[b] Insufficient sample for analysis.

SUMMARY AND CONCLUSION

The synthesis of α-mercaptoaldehydes from 1, 3-oxathiolan-5-one has been accomplished using diisobutyl-aluminum hydride (DIBAL-H) as a reducing agent at -78°C. 1,3-Oxathiolan-5-ones were prepared by the condensation of α-mercaptoacids and acetone. The synthesis of 2,5-dihydrothiopenes using α-mercaptoaldehydes and vinyltri-phenylphosphonium bromide was successful when pyridine was employed as solvent and triethylamine as base.

1,3-Oxathiolan-5-ones were conveniently alkylated using alkyl, benzyl and allyl halides and condensed with aldehydes. Alkylation and condensation were achieved at -78°C using lithium diisopropylamide as base and hexa-methylphosphoramide in THF. Alkylation of 1,3-oxathiolan-5-ones appears to be limited to those electrophiles which readily undergo SN2 displacement reactions.

CHAPTER IV

EXPERIMENTAL

General Information

Reagent grade chemicals were used without further
purification unless otherwise specified. Pyridine and
diisopropylamine were dried over potassium hydroxide pel-
lets and were decanted prior to use. Melting points were
taken on a Fischer-Johns apparatus and are uncorrected.

Infrared (ir) spectra were recorded on a Beckman
IR-12 or Perkin Elmer Model-180 spectrophotometer and are
reported in wavenumbers (cm^{-1}). The solvent was chloroform
unless otherwise stated.

Nuclear magnetic resonance (nmr) spectra were obtained
on a Varian EM-360 or Bruker WP80CW spectrometer in deutero-
chloroform solution unless otherwise stated. Chemical
shifts are expressed in parts per million (δ) downfield from
the internal standard, tetramethylsilane (TMS). The split-
ting pattern of each resonance is reported using the follow-
ing designations: s = singlet, d = doublet, t = triplet,
q = quartet, qt - quintet, dd = doublet of doublets, td =
triplet of doublets, m = multiplet, br = broad. The follow-
ing code was used in the interpretation of nmr spectra;

chemical shifts (δ) (multiplicity, number of protons, coupling constant in Hertz).

Carbon-13 nmr spectra were recorded on a Bruker CXP-100 instrument in deuterochloroform solution. Chemical shifts are reported in parts per million downfield from TMS as internal standard.

Field Ionization (FI) and Field Desorption (FD) mass spectra were recorded on a Varian MAT CH_5-DF instrument.

Gas liquid chromatography (glc) analyses were carried out on a Hewlett Packard 5700 or F and M model 720 or Varian 3700 gas chromatograph using helium carrier gas at a flow rate of 1cc sec^{-1}. The following columns were used: A) 10' x 0.25" 15% SE-30 on chromosorb W; B) 8' x 0.25" 20% SE-30 on chromosorb W; (C) 6' x 0.25" 5% SE-30 on chromosorb W.

Anhydrous sodium sulfate was used as drying agent in all cases. Solvents were removed on a rotatory evaporator at reduced pressure. Fisher acidic alumina, 80 - 200 mesh Brockman activity grade 1 was used for column chromatography. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

α-Bromoisobutyric acid (26) and α-bromobutyric acid (27)

These compounds were prepared by two methods:

Method A:

A variation of the literature procedure[53] was followed. To the appropriate acid (0.1 █████ was added 0.5 mL phosphorus

trichloride. The solution was stirred and bromine (0.12 mol) was added slowly. After complete addition the mixture was refluxed for 20 hrs and then distilled to give <u>26</u> or <u>27</u> in 57% and 81% yield.

Method B:

A variation of the literature procedure[54] was followed. To the isobutyric acid (1 mol) was added thionyl chloride (1.2 mol) slowly. When the addition was complete, the mixture was refluxed for 10 hrs. The evolution of hydrogen chloride gas had ceased by this time. Distillation gave isobutyryl chloride. To the isobutyryl chloride (0.2 mol) was added bromine (0.22 mol) slowly. When the addition was complete the mixture was refluxed for 28 hrs. The cooled solution was poured into water, stirred for 15 min and extracted with ether (2 x 100 mL). After drying, removal of solvent and distillation gave <u>26</u> in overall yield of 63%. The physical constants and spectral data for bromoacids are given in Tables 1 and 2.

<u>α-Bromophenylacetic acid</u> (<u>28</u>), <u>Mercaptoacetic acid</u> (<u>33</u>), <u>Thiolactic acid</u> (<u>34</u>) and <u>2-Methoxypropene</u> (<u>19</u>).
These compounds were purchased from the Aldrich Chemical Company.

<u>Potassium O-ethyldithiocarbonate</u> (<u>29</u>).

This compound was prepared according to a known procedure[27] in 72% yield, nmr (D_2O): 4.50 (q,2, J=7 Hz), 1.42 (t,3, J=7 Hz).

S-(Thioncarboethoxy)-α-Mercaptoacids 30-32

These compounds were prepared according to published procedures.[25,26,27] Melting points, yields and spectral data are given in Tables 3 and 4.

α-Mercaptoacids 35-37

The literature procedure[27] was followed in preparing these acids. The physical constants and spectral data are given in Tables 5 and 6.

5-Ethylpseudothiohydantoins (38)

This pseudothiohydantoin was prepared by a variation of the literature procedures.[28,29] Thiourea (30 g, 0.3941 mol) was dissolved in 95% warm ethanol (200 mL). The solution was cooled slightly and bromoacid 27 (60 g, 0.3592 mol) was added slowly. When the addition was complete the mixture was heated to reflux for 4 hrs. To the cooled solution ether (100 mL) was added and the solid was filtered. After washing with ether (3 x 25 mL) 49 g (95%) of 38 was obtained as a white solid; mp 193-194°C (lit[29] mp 196-198°C); ir (KBr): 3400-2600, 1710, 1670, 1435 cm^{-1}; nmr (D_2O): 4.51 (t,1, partially obscured by water, J = 6 Hz) 1.90 (m,2), 1.80 (t,3, J=7 Hz).

Hydrolysis of 38

A mixture of 38 (10 g, 0.694 mol) and 13.8 g of sodium hydroxide in 120 mL of water was heated to reflux for 20 hrs and then cooled in ice bath. The solution was acidified with dilute sulfuric acid and extracted with ether (2 x 100 mL). The organic layer was washed with water and dried. Removal

of solvent and distillation gave 3.433 g (41%) of 36, iden-
tical to the product obtained from the hydrolysis of 31.
The physical constants and spectral data for this compound
are given in Tables 5 and 6.

Preparation of 1,3-Oxathiolan-5-Ones

Oxathiolanes were prepared by two methods.

Method A

The literature procedure[31] for preparing compound 40
was used for preparing 39 also. To the appropriate mercapto-
acid (0.2 mol) at 0°C was added 2-methoxypropene (0.8 mol)
slowly. Stirring was maintained during the addition. When
the addition was complete the mixture was heated to reflux
for 24 hrs and then cooled. Ether (200 mL) was added and
the mixture was washed with 1N sodium carbonate (3x50 mL),
water (3x50 mL) and dried. The solvent was removed and the
residue distilled to give 39 or 40 in 42% and 44% yield.
Boiling points and spectral data are given in Tables 7, 8
and 9.

Method B

The literature procedure[34] for preparing 39 and 40
was applied to the synthesis of oxathiolanes 39-43. To a
250 mL round bottom flask fitted with a Dean-Stark water
separator and containing the appropriate mercaptoacid
(0.4 mol) was added 100 mL of benzene, a catlytic amount

of p-toluenesulfonic acid and acetone (1.2 mol). The mixture was heated to reflux for 24 hrs and then cooled. Ether (200 mL) was added and the mixture was washed with saturated sodium bicarbonate solution (3x100 mL), water (3x100 mL) and dried. Removal of solvent gave product, which in the case of 39, 40 and 42 were liquids. Distillation gave pure products. The products 41 and 43 were solids which were recrystallized. The physical constants and spectral data are given in Tables 7 and 8. The carbon-13 nmr spectra and analytical data are given in Tables 9 and 10.

In the preparation of 39 by method B a by-product 44 was obtained (30%) as a white solid, mp 137-138°C (lit[56] mp 129-130°C); ir (KBr): 3400-2400, 1720, 1220, 675 cm^{-1}; nmr (CDCl$_3$): 10.96 (s,2), 3.40 (s,4), 1.60 (s,6); m/e: 224.

Diisobutylaluminum hydride (25% and 1M solutions in Toluene), Vinyltriphenylphosphonium bromide (60) were purchased from the Aldrich Chemical Company.

Mercaptoacetaldehyde (45) [as dimer 2,5-dihydroxy-1,4-dithiane (46)]

To a solution of 39 (2.83 g, 0.0214 mol) in 5 mL of dry toluene at -78°C, under a nitrogen atmosphere, was added 48 g (4 equivalents) of DIBAL-H solution (25% in

-toluene) dropwise. When the addition was complete, the mixture was stirred at -78°C for 2 hrs and then poured slowly into 100 mL of water containing 100 mL of acetic acid and 100 g of ice. The mixture was stirred vigorously for 15 min and extracted with chloroform (3x100 mL). The organic layer was washed with saturated sodium bicarbonate solution until washing was basic, water (3x50 mL) and then dried. The solvent was removed and the residue crystallized from ether. The solid was filtered and the mother liquor was treated in the same way three times, to give 46 (0.225 g, 14%); mp 122-125°C (lit[58] mp 138-143°C). Spectral and analytical data for this compound are given in Tables 12 and 13.

α-Mercaptopropionaldehyde (47) [as dimer 2,5-dihydroxy-3, 6-dimethyl-1,4-dithiane (48)]

To a solution of 40 (10 g, 0.0684 mol) in 10 mL of dry toluene at -78°C, under a nitrogen atmosphere, was added 155 g (4 equiv.) of DIBAL-H solution (25% in toluene) slowly. When the addition was complete the mixture was stirred at -78°C for 3 hrs and worked up as for 46 to give 48 (2.40 g, 39%); mp 139-143°C. Spectral and analytical data for 48 are given in Tables 12 and 13.

Reduction of 2,2,4,4-tetramethyl-1,3-oxathiolan-5-one (41)

A solution of 41 (3 g, 0.0187 mol) in 10 mL of dry

toluene was cooled to -78°C under a nitrogen atmosphere.
To this was added 75 mL (4 equiv.) of DIBAL-H solution
(1 M in toluene) dropwise. When the addition was complete
the mixture was stirred at -78°C for 2.5 hrs. The work up
as for 46 gave a mixture of monomer and dimers 50, 51
(0.9042 g, 47%). Spectral data for this compound is given
in Table 12.

α-Mercaptobutyraldehyde (52) [as dimer 2,5-dihydroxy-3,
6-diethyl-1,4-dithiane (53)]

A solution of 42 (5 g, 0.0312 mol) in 10 mL of dry
toluene was cooled to -78°C under a nitrogen atmosphere.
To this was added 125 mL (4 equiv.) of DIBAL-H solution
(1 M in toluene) dropwise. When the addition was complete
the mixture was stirred at -78°C for 2.5 hrs. The reaction
was worked up as for 46 to give 53 (2.28 g, 70%); mp 143-
149°C (lit[4] mp 170°C). Spectral and analytical data for
53 are given in Tables 12 and 13.

α-Mercaptophenylacetaldehyde (54) [as dimer 2,5-dihydroxy-
3,6-diphenyl-1,4-dithiane (55)].

A solution of 43 (2 g, 0.0096 mol) in 10 mL of dry
toluene was cooled to -78°C under a nitrogen atmosphere.
To this was added 22 g (4 equiv.) of DIBAL-H solution
(25% in toluene) dropwise. When the addition was complete
the mixture was stirred at -78°C for 2 hrs. The reaction

was worked up as for 46 to give 55 (0.9584 g, 66%);

mp 175-178°C. This compound was not very soluble even in

DMSO-d$_6$. This produced difficulty in obtaining a good

nmr spectrum on 55. Spectral and analytical data for 55

are given in Tables 12 and 13.

Preparation of 2,5-Dihydrothiophenes

All the dihydrothiophenes listed in Table 14 were pre-
pared according to a published procedure[15]. The following
general procedure was followed.

To a solution of the vinylphosphonium bromide (0.11
mol) in 50 mL of dry pyridine and triethylamine (0.015 mol)
was added a pyridine solution of the dimer aldehyde (0.005
mol) dropwise with stirring under a nitrogen atmosphere.
When the addition was complete the mixture was heated to
reflux at 100°C for the time indicated in Table 14. The
cooled solution was poured into 500 mL of water and extracted
with ether (2x100 mL) and then with pentane (2x100 mL).
The combined organic layers were washed with 10% hydrochloric
acid until the washing was acidic and then with water. The
dried solution was reduced in volume to approximately 10 mL.
The solid crystallized was filtered and the filtrate was
chromatographed on alumina using pentane as eluant. This
removed all phosphorus containing and colored impurities.
Removal of solvent gave dihydrothiophene. Yields, proton
nmr and carbon-13 spectral data of dihydrothiophenes are
given in Tables 14, 15 and 16.

General Procedure for the Alkylation of 1,3-Oxathiolan-5-Ones

All the alkylated products listed in Table 17 were prepared by the following general procedure.

To a solution of diisopropylamine (0.02 mol) in 5 mL of dry THF at 0°C was added 1.55 M n-butyllithium (0.02 mol). The mixture was stirred at 0°C for 1 hr and then cooled to -78°C for 30 min. A solution of oxathiolane (0.0181 mol) in 5 mL of THF was added over 10 min. The mixture was stirred for 45 min and a solution of alkyl halide (0.0181 mol) in 5 mL of THF containing HMPA (0.0217 mol) was added dropwise. The reaction mixture was stirred at -78°C for 3 hrs. The reaction was quenched at -78°C with saturated ammonium-chloride solution and extracted with ether (2x100 mL). The extract was washed with 10% hydrochloric acid (3x25 mL) and then with water (2x50mL) and dried. Evaporation of solvent gave either solid or liquid product, which was distilled. The physical constants, spectral data and analytical data are given in Tables 17, 18, 21 and 22.

General Procedure for the Condensation of 40

All the condensation products listed in Table 19 were prepared by the following general procedure.

To a solution of diisopropylamine (5.13 mL, 0.0365 mol) in 5 mL of dry THF at 0°C was added 1.55 M n-butyllithium

(23 mL, 0.0365 mol). The mixture was stirred at 0°C for 30 min and then cooled to -78°C for 20 min. A solution of oxathiolane 40 (5 g, 0.0342 mol) in 5 mL of THF was added dropwise. The mixture was stirred for 30 min ,and a solution an aldehyde (0.0385 mol) in 10 mL of THF containing 7.3 g (0.0407 mol) of HMPA was added dropwise. The reaction mixture was stirred at -78°C for 2 hrs. Work up as in alkylation reaction gave liquid product, which was distilled. The nmr spectrum of product indicated it to be a mixture of two diastereomers. The physical constants, spectral data and analytical data of condensation products are given in Tables 19, 20, 21 and 22.

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