Stereoselectivity in the formation of 3-carboxylated-2,5-dihydrothiophenes.

Ivy Elizabeth Ellen. Smith

University of Windsor

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LA THÈSE A ÉTÉ MICROFILMÉE TELLE QUE NOUS L'AVONS RÉCU
STEREOSELECTIVITY IN THE FORMATION OF
3-CARBOXYLATED-2,5-DIHYDROTHIOPHENES

by

Ivy Elizabeth Ellen Smith

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  C

1985
to Medusa's satyr
ABSTRACT

The 3-carboxylated alkyl-substituted 2,5-dihydrothiophenes have been synthesized in a general and effective manner via the combined Michael/Wittig-Horner sequence and efficiently converted to sulfones by oxidation with meta-chloroperbenzoic acid. The sulfones have been thermally decomposed to give 1,3-dienes in a stereoselective fashion in most cases. A transition state model for the observed stereoselectivity has been proposed. A carbomethoxy group in the 3-position of the 2,5-dihydrothiophene ring does not appreciably perturb the stereoselectivity of 1,3-diene formation.
ACKNOWLEDGEMENTS

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"Sulfur-containing compounds have played an increasingly important role in organic synthesis due to ease of incorporation of the element into complex structures, the ability to modify the valency of the atom, the variety of chemical characteristics exhibited by these varied oxidation states, and the ease of removal of sulfur as needed for the synthesis."

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CHAPTER 1

INTRODUCTION

DEFINITIONS

The contemporary organic chemist is preoccupied with the struggle to develop new synthetic pathways in a stereoselective or stereospecific manner. Coupled to these challenges is the justification of a reaction scheme in terms of feasibility and cost.

A stereoselective synthesis\(^1\) produces one diastereoisomer (or diastereoisomeric dL pair) of a given structure in considerable predominance over all the other possible diastereoisomers (or diastereoisomeric dL pairs) of the same structure. The mechanism of stereoselective reactions offers alternative, chemically equivalent pathways so that the reaction may select the most favorable pathway (kinetic control) or the most stable product (thermodynamic control).

Ketone \(^1\) can be reduced to two alcohols, cis-\(^2\) or trans-\(^3\) (Figure 1). Stereoselective reduction\(^2\) with aluminum isopropoxide (Al(OR-i)\(_3\)) forms the more stable product, the dis-equatorial trans alcohol \(^3\) under equilibrating conditions. The line of approach \(^4\) to give the cis alcohol \(^2\) is preferred under conditions of kinetic control - e.g. by reduction with

...
the reactive bulky reagent\(^3\) lithium tri-t-butoxyaluminum hydride (LiHAL[OC(CH\(_3\)]\(_3\))_3\).
In stereospecific reactions, the mechanism demands a specific stereochemical outcome. Each stereoisomer of starting material gives a different stereoisomer of the product, i.e. enantiomers or diastereoisomers. The mechanism in the SN₂ reaction requires "attack from the back" and hence inversion of configuration, so that R-5 gives S-6 and S-5 gives R-6 (Figure 2).

![Diagram showing stereospecific reactions]

Figure 2: Stereospecific Reactions
Chemoselectivity refers to functional group differentiation. In a molecule that contains more than one type of bond, recognition of the different intrinsic reactivity of each bond type becomes the prime consideration. Chemoselective problems arise when it is desirable to react only one of the two reactive groups in a molecule.

Regioselectivity deals with the concept of orientational control at a single reaction centre, i.e. how to react one specific part of a single functional group and no other. When a reagent and/or a substrate is unsymmetrical, their orientation with respect to each other becomes a problem in regioselectivity. Markovnikov or anti-Markovnikov addition to an alkene, the position of substitution in aromatic rings, and the position of unsymmetrical ketones are examples of problems of regiochemistry. For example, phenolate ions react with alkylating agents at oxygen but enolate ions usually react at carbon (Figure 3).

![Figure 3: Regioselectivity Problems: O-alkylation versus C-alkylation](image-url)
THE DIELS-ALDER REACTION

The Diels-Alder reaction\textsuperscript{5-12} represents one of the most important reactions in synthesis. The popularity of this powerful reaction is due to the creation of two new sigma (\(\sigma\)) bonds and one new pi (\(\pi\)) bond in one step with excellent stereocontrol. The combination of stereospecificity, stereoselectivity and regioselectivity allow an unprecedented degree of control of product structure and stereochemistry.

The Diels-Alder reaction is a pericyclic [4 + 2] cycloaddition between a conjugated diene 9 and a conjugated alkene 10 (the dienophile or monoene - usually conjugated with an electron-withdrawing group(\(\mathcal{Z}\))) which forms a cyclohexene derivative 11 (Figure 4). The term pericyclic describes concerted reactions that involve \(\pi\)-electron systems and proceed via a cyclic transition state.

\[ \begin{array}{c}
\text{9} \\
\text{10} \\
\rightarrow \\
\text{11}
\end{array} \]

\textbf{Figure 4:} The Diels-Alder reaction
The Woodward - Hoffmann rules for pericyclic reactions such as the Diels-Alder reaction are explained by frontier orbital theory. Molecular orbital (MO) interactions are responsible for the four well-known rules which were originally empirically derived. These are:

1. Electron-withdrawing substituents (Z) on dienophiles and electron-donating ones (X) on dienes increase the rate of the reaction (Diels-Alder with direct electron demand). The reverse substituent effects (Diels-Alder with inverse electron demand) likewise increase the rate. This is rationalized in terms of the effect of substituents on MO energy levels. The dominant interactions are between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile in Diels-Alder reactions with normal electron demand and LUMO_{dienophile}/HOMO_{dienophile} for inverse electron demand. The lower the LUMO of the dienophile (lowered by Z) and the higher the HOMO of the diene (raised by X), the closer are the interacting levels (stronger orbital interactions) and this results in an increased rate of reaction.

2. The diene and dienophile configurations are retained in the adduct. The reaction occurs in one step and the stereochemistry of each must be faithfully reproduced in the product. This stereospecific "cis principle" reflects the fact that product stereochemistry is determined by the stereochemistry
of the starting materials and not at all by how favorable one reaction pathway may be. Because the Diels-Alder reaction occurs in a $[4\pi s + 2\pi s]$ way under thermal conditions, there is no reason to lose or invert the configuration.

3. The stereoselective "endo rule"$^{16}$ states that the endo transition state is favored over the exo transition state. This is rationalized in terms of secondary, nonbonding interactions if the dienophile has additional orbitals that can be involved. Using cyclic dienes, two addition products can be formed; viz. exo and endo (Figure 5). These terms refer to the relationship between the Z groups of the dienophile (here CO) and the double bond in the new cyclohexene ring. The endo adduct is formed faster than the exo adduct even though the latter is thermodynamically more stable. The Z groups in the dienophile attract the diene through space in the endo transition state$^{13}$ (Figure 6). This secondary orbital interaction does not lead to new bonds but lowers the energy of the endo transition state relative to that of the exo transition state.

4. Intermolecular Diels-Alder reactions between unsymmetrically substituted dienes and dienophiles usually produce mixtures of both regioisomers, although one often predominates.$^7$ The "ortho effect" dictates that 2-substituted dienophiles react with 1-substituted butadienes in Diels-Alder with normal electron demand to give 3,4-disubstituted cyclohexenes$^{14}$ as major products, independent of the nature of the diene. 2-substitut-
ed butadienes give "para" products particularly under Lewis acid catalysis\textsuperscript{17-20} (Figure 7). Although this regio-
specificity was first successfully explained in terms of "hard and soft" centres in diene and dienophiles\textsuperscript{21,22}, various theories exist\textsuperscript{23-28}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Diels-Alder reaction between Cyclopentadiene and Maleic Anhydride}
\end{figure}
Figure 6: Secondary overlap of the frontier orbitals of Diels-Alder reactions. The dotted lines show the bonding overlap which stabilizes the endo transition state. The dashed lines are the primary interactions representing the sites of the new bonds.
Some of the most elegant syntheses of the twentieth century have involved approaches based on the Diels-Alder reaction. The simple and efficient total synthesis of cantharidin, the active principle of Cantharis vesicatoria, obtained in two steps from furan and 2,5-dihydrothiophene-3,4-dicarboxylic anhydride in 85% yield amply demonstrates this statement (Figure 8). The exo adduct of this putative aphrodisiac is preferred in the high-pressure Diels-Alder reaction.

Figure 7: Regiospecificity in the Diels-Alder reaction. Ortho versus Para effects

Figure 8: Synthesis of Cantharidin

\[ i \] 15kbar, 6hr

\[ ii \] Raney Ni, EtOH
The synthesis of the Aspidosperma alkaloid, aspidospermine\textsuperscript{30, 22} (Figure 9) and the steroid estra-1,3,5(10)-triene-17-one\textsuperscript{31-33} 26 (Figure 10) both utilize a cheletropic approach, via sulfur dioxide (SO\textsubscript{2}) extrusions for in situ generation of 1,3-dienes\textsuperscript{34, 35}. Thermolysis at 600°C of the enamide\textsuperscript{19} causes SO\textsubscript{2} extrusion, giving 20, which cyclizes to the tricyclic synthon hydrolubolidine 21. The all-cis configuration of 21 suggests an endo transition state for the intramolecular Diels-Alder reaction (IDA), i.e., less energy strain in the cis ring junction than in the trans one.

\textbf{Figure 9: Synthesis of Aspidospermine}
A SO$_2$ extrusion from alkenoyl 23 gave o-quinodimethane 24 and produced steroids 25 and 26 via exo transition states. In the in situ generation of dienes for IDA's, the exo transition state is preferred in the absence of favorable MO interactions or significant development of conjugation.$^{36}$

![Chemical structures]

Figure 10: Stereoselective Synthesis of Estra-1,3,5(10)-trien-17-one
Cycloaddition of tetrachlorothiophene-S,S-dioxide 27, a Diels-Alder diene with inverse electron demand, to azulene 28 forms the benzazulene 29 via loss of SO₂ and subsequent aromatization³⁷ (Figure 11).

![Chemical Structures](image1)

**Figure 11:** Diels-Alder cycloaddition of Tetrachlorothiophene-S,S-dioxide to Azulene

Danishefsky's diene 30, a siloxysubstituted diene of high electron density, reacts with electron-poor dienophiles. This diene was utilized in the synthesis of the tumor inhibitor (+)-vernolepin³⁸ ³¹ (Figure 12).

![Chemical Structures](image2)

**Figure 12:** Use of Danishefsky's diene in synthesis of Vernolepin
SYNTHESIS OF 1,3-DIENES

In the Diels-Alder reaction, the stereochemistry of the diene and dienophile are directly reflected in the product formed. Therefore use of the reaction in total synthesis requires starting materials whose stereochemistry is known. This is relatively straightforward for dienophiles but in the case of dienes many problems remain. A stereoselective synthesis of 1,3-dienes of high isomeric purity is thus an important and continuing goal.

1,3-dienes are important as synthons in natural product synthesis and as elastomers in the synthetic rubber industry. The formation of 1,3-dienes can be effected in a number of ways.

1. Partial Reduction of 1,3-diynes and conjugated enynes

Both catalytic hydrogenation of 1,3-diynes over Lindlar's catalyst \(^{39}\) or dihydroboration of 1,3-diynes with dicyclohexylborane followed by protonolysis \(^{40}\) afford \((Z,Z)\)-1,3-dienes. \((Z,Z)\)-1,3-Dienes are also formed from monohydroboration – protonolysis of conjugated \((Z)\)-enynes using disiamylborane \(^{40}\) or by partial catalytic hydrogenation. Similarly, catalytic hydrogenation of conjugated \((E)\)-enynes give \((E,Z)\)-dienes. \(^{41,42}\)
2. From Alkynes via Hydroalumination, Hydroboration, Mer-
vation and Hydrosilylation

High yields of isomerically pure (E,E)-1,3-dienes are
prepared from alkynes by addition of cuprous chloride to
vinylalanes. The latter are produced by reaction of the al-
kyne with di-isobutylaluminum hydride.\textsuperscript{43,44} Reaction between
dialkenylchloroboranes \textsuperscript{32} and methylcopper at 0 °C also leads
to the same (E,E)-1,3-dienes\textsuperscript{45} (Figure 13).

\[ \text{R}_1 \equiv \text{R}_2 \xrightarrow{\text{i-Bu}_2\text{AlH}} \text{R}_1 \equiv \text{Al-i-Bu} \]

\[ \downarrow \text{Cu}_2\text{Cl}_2 \]

\[ \left( \text{R}_1 \equiv \text{R}_2 \right)_{\text{BCl}} \xrightarrow{3 \text{ MeCu}} \text{R}_1 \equiv \text{R}_2 \equiv \text{R}_1 \]

Figure 13: Stereoselective Synthesis of (E,E)-1,3-dienes
via hydroalumination and hydroboration of alkynes
Symmetrically substituted (Z,E)-1,3-dienes are produced from disubstituted acetylenes by hydroboration – iodination. Unsymmetrically substituted (E,E)-1,3-dienes are formed by stepwise addition of two acetylenic units to thexylborane, via chloro-organoborane 33 47 (Figure 14).

![Chemical Structure](image)

Figure 14: Stereoselective Synthesis of (E,E)-1,3-dienes using the novel chloro-organoborane 33.

Vinylmercuric chlorides from mercuration of acetylenes, undergo reaction with palladium-chloride (PdCl₂) and lithium...
chloride (LiCl) in hexamethylphosphoramide (HMPA) at 0°C to produce symmetrical (E,E)-1,3-dienes in near quantitative yields \(^{48}\) (Figure 15). This method has the advantage of tolerating functionality but requires stoichiometric amounts of LiCl and expensive PdCl\(_2\) in HMPA, a severe poison and suspected carcinogen. High selectivity was achieved near the freezing point of HMPA. These disadvantages were overcome by using catalytic amounts of a rhodium complex, [ClRh(CO)]\(_2\) to effect the dimerization. \(^{49}\)

\[
\begin{align*}
2\text{RC}=&\text{CH}(R_1) &\rightarrow &2\text{R}_1\text{C}=&\text{C}H(R_1) &\leftarrow &\text{Li}_2\text{PdCl}_4 \\
&\quad \text{H} & &\quad \text{HgCl} & &\rightarrow &\text{HMPA, 0°C} \\
\text{R} &\text{C}=&\text{C}H(R_1) & &+ &\text{HgCl}_2 &+ 2\text{LiCl} &+ \text{Pd} \\
&\quad \text{H} &\quad \text{H} &\quad \text{R}_1\text{H} &\quad \text{C}=&\text{C}H &\quad \text{R} \\
\end{align*}
\]

Figure 15: Symmetrical 1,3-dienes by dimerization of vinylmercurials

"Head to tail" dimerization of alkynes using vinylmercurials with PdCl\(_2\) and triethylamine (Et\(_3\)N) in benzene at room
temperature produce unsymmetrical 1,3-dienes stereoselectively in excellent yields (Figure 16).

\[
2 \text{RC}≡\text{CH}({R_1}) \rightarrow \begin{array}{c}
\text{H} \\
\text{H}
\end{array} \begin{array}{c}
\text{C} = \text{C} \\
\text{H}({R_1})
\end{array} + \text{HgCl}_2 + \text{Hg}^{2+}
\]

\[
\begin{array}{c}
\text{PdCl}_2 \\
\text{2 Et}_3\text{N} \\
\text{C}_6\text{H}_6
\end{array} \rightarrow \begin{array}{c}
\text{H} \\
\text{H}
\end{array} \begin{array}{c}
\text{C} = \text{C} \\
\text{H}({R_1})
\end{array} \begin{array}{c}
\text{H} \\
\text{H}
\end{array} \begin{array}{c}
\text{C} = \text{C} \\
\text{H}({R_1})
\end{array} + \text{HgCl}_2 + \text{Hg}^{2+}
\]

Figure 16: Unsymmetrical 1,3-dienes by dimerization of alkynes

Symmetrical (E,E)-1,3-dienes can be stereoselectively synthesized in high yields from (E)-alkenylpentafluorosilicates readily obtained by hydrosilylation of alkynes and silicate formation (Figure 17). These coupling reactions occur by treatment with silver fluoride in acetonitrile or by stirring with silver nitrate in water/ether. Air stable reagents with a wide functional group tolerance and mild reaction conditions are utilized to form (E,E)-1,3-dienes with high isomeric purity (99%). The reactions could be monitored by colour changes based on Mueller's colour test for organopenta-
fluorosilicates.

\[ R_1 \overset{\varnothing}{\underset{\varnothing}{\equiv}} C - R_2 + HSiCl_3 \xrightarrow{H_2PtCl_6} R_1 \overset{\varnothing}{\underset{\varnothing}{\equiv}} C \equiv C \overset{\varnothing}{\underset{\varnothing}{\equiv}} SiCl_3 \]

KF
\[ \rightarrow \]
H_2O or EtOH

\[ K_2 \overset{\varnothing}{\underset{\varnothing}{\equiv}} C \equiv C \overset{\varnothing}{\underset{\varnothing}{\equiv}} SiF_5 \xrightarrow{Ag(I)} \]

\[ \overset{\varnothing}{\underset{\varnothing}{\equiv}} C \equiv C \overset{\varnothing}{\underset{\varnothing}{\equiv}} SiF_5 + Ag(0) \]

Figure 17: Stereoselective Synthesis of (E,E)-1,3-dienes via hydrosilylation of alkynes

3. From Vinyl Halides

Under various catalytic conditions, vinyl halides undergo self-coupling, leading to 1,3-dienes with preservation of the (Z) or (E) configuration in the vinyl halide. Reaction of vinyl halides with bis(cyclo-octa-1,5-diene)nickel(0) produces dienes directly\(^{53}\), whereas vinyl copper reagents couple
thermally\textsuperscript{54,55} or oxidatively\textsuperscript{56-59}. The coupling reactions between vinyl halides and vinylalanes or olefins with palladium catalysts stereoselectively synthesize isomeric dienes\textsuperscript{60-62} (Figure 18).

The palladium-catalyzed olefination of organic halides with alkenes is called the "Heck reaction."\textsuperscript{63,64} Alkene insertion is largely regiospecific with the organic halide adding to the least hindered position of the alkene.

![Chemical reaction diagram]

*Figure 18: 1,3-Dienes from vinyl halides*
Recently, Scott and co-workers\textsuperscript{65} found vinyl trifluoromethanesulfonates (triflates) to be excellent substrates for the Heck olefination. The regioselective conversion of ketones into 1,3-dienes was demonstrated by the two-step conversion of 2-methylcyclohexanone into either $\beta$-(2-methylcyclohexenyl)acrylate \textsuperscript{37} or $\beta$-(6-methylcyclohexenyl)acrylate \textsuperscript{38} via the corresponding vinyl triflates (Figure 19).

\begin{align*}
\text{i)} & \quad (i\text{-Pr})_2\text{NMgBr} \\
\text{ii)} & \quad \text{Tf}_2\text{NPh} \\
\text{63\%} \\
\frac{35:36}{35:36} & \quad 97:3
\end{align*}

\begin{align*}
\text{i)} & \quad \text{LDA} \\
\text{ii)} & \quad \text{Tf}_2\text{NPh} \\
\text{91\%} \\
\frac{36:35}{36:35} & \quad 95:5
\end{align*}

**Figure 19:** Olefination of vinyl triflates to 1,3-dienes
Conjugate addition of vinyl copper reagents to acetylenic esters is a facile route to (Z)-diene esters \(^{39,66,67}\) (Figure 20).

\[
\begin{align*}
\text{R} & \quad \text{C} \quad \text{Cu} + \quad \text{C} \equiv \text{C} \equiv \text{C} \quad \text{CO}_2\text{Me} & \rightarrow & \quad \text{R} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{CO}_2\text{Me}
\end{align*}
\]

Figure 20: Synthesis of (Z)-diene esters

Conjugated dienes of very high stereoisomeric purity are obtained in high yields by coupling of vinyl copper derivatives (alkenyl cuprates and alkenyl halides) in the presence of zinc bromide (ZnBr\(_2\)) and a catalytic amount of Pd\(\cdot\)L\(_4\) \(^{68}\) (Figure 21).

\[
\begin{align*}
\text{R}_1 \quad \text{C} \quad \text{C} \quad \text{X} \quad \text{R}_2 & \quad \text{CuLi} + \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{R}_3 & \quad 2\text{nX}_2 \rightarrow & \quad \text{R}_1 \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{R}_4 & \quad 5\% \text{Pd} \cdot \text{L}_4 & \rightarrow & \quad \text{R}_1 \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{R}_4 & \quad \text{R}_2 \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{R}_3
\end{align*}
\]

Figure 21: Synthesis of 1,3-dienes via coupling of organo-copper derivatives
4. From allylic halides and $\alpha,\beta$-unsaturated carbonyl compounds using the Wittig reaction and its variants

The Wittig olefin synthesis and its variants provide a general and flexible route to diastereoisomers of substituted 1,3-dienes. Dienes of type 40 can be produced by reaction of formaldehyde with ylides from allylic phosphonium salts or by reaction between $\alpha,\beta$-unsaturated aldehydes and methylene ylide (Figure 22).

$$
\begin{align*}
&\text{R} \quad \text{PPh}_3 \\
\text{HCHO} &\rightarrow \\
&\text{R} \quad \text{PPh}_3 \\
\text{CH}_2 &\text{PPh}_3 \\
&\text{R} \\
\end{align*}
$$

Figure 22: 1,3-Dienes from the Wittig reaction

Both (Z)-allylic phosphorus ylides$^{69-71}$ and (Z)-$\alpha,\beta$-unsaturated aldehydes$^7$ give dienes retaining the original (Z)-configuration in Wittig reactions.

In Wittig-Horner reactions$^{71,73}$, configurationally homogenous allylic diphenyl phosphine oxides react with carbonyl compounds leading to dienes with preservation of the configuration in the phosphine oxide, eg. 41 - 42 (Figure 23).
Figure 23: Wittig-Horner reaction

Some steric control over the newly-formed double bond in the Wittig reaction is possible using "salt-free" conditions, such as in the synthesis of diene 44 from 43 and acrolein \(^7\) (Figure 24).

Figure 24: Wittig reaction with high stereoselectivity

An advantage of the Wittig-Horner approach to dienes is that the diastereoisomeric intermediates it produces are cry-
stalline and separable by chromatography and crystallization. Elimination with sodium hydride then gives dienes with high stereospecificity.

Reaction of the (diphenylphosphino)allyltitanium reagent \textbf{45} with aldehydes gave \textit{\(\alpha\)-erythro-}adduct \textbf{46} exclusively which may be directly converted to the \(\beta\)-oxido phosphonium salt of type \textbf{47} with methyl iodide.\textsuperscript{75} The betaines stereoselectively lead to (Z)-1,3-dienes via a "Wittig" cycloelimination in yields from 32 - 89% and E/Z ratios averaging 5:95\textsuperscript{76} (Figure 25).

\textbf{Figure 25: Wittig-Horner olefin synthesis via organo-titanium reagents}
Using the lithio derivative from allyldiphenylphosphine, the same reaction in tetrahydrofuran (THF) - HMPA solution formed the (E)-1,3-diene\textsuperscript{76} with E/Z ratios in the range 90:10 to 95:5 in yields from 41 - 88\%.

5. Eliminations from saturated diols and unsaturated alcohols and derivatives

Dienes are produced via elimination from saturated 1,3- and 1,4-diols, and \(\alpha,\beta\)-unsaturated alcohols and their derivatives, eg. halides and esters.\textsuperscript{77-79}

Spangler\textsuperscript{80} developed a simple route to conjugated dienes from dehydration of allylic alcohols under mild conditions using methyltriphenyloxyphosphonium iodide in HMPA.

Short\textsuperscript{81} used a novel 1,4 Hofmann elimination to prepare S-trans-dienes \textsuperscript{48} from amines (Figure 26).

![Figure 26: Hofmann elimination route to 1,3-dienes](image)

\(\beta,\gamma\)- Unsaturated \(\delta\)-hydroxycyclohexenecarboxylic acids \textsuperscript{49} undergo decarboxylative elimination when treated with N,N-di
methylformamide (DMF) dioneopentyl acetal$^{82}$ (Figure 27). This approach presents an expeditious method for the regio-specific preparation of cyclohexa-1,3-diene derivatives without isomerization of the double bond.

Figure 27: Decarboxylative elimination route to 1,3-dienes

Two additional methods for the synthesis of cyclohexa-1,3-dienes are based on the reactions between enolate anions and vinylic phosphonium salts.$^{83,84}$

Yasuda$^{85}$ developed a highly stereospecific procedure involving a 1,4 dehydration of allylic alcohols to 1,3-dienes. This multistep sequence utilizes the highly regio- and sterspecific isomerization of oxiranes into allylic alcohols with aluminum amides$^{86}$ (specifically conversion of 2,3-epoxy alcohols 50 to 3-ene-1,2-diols 51 (Figure 28)).
Figure 28: 1,3-Dienes from 1,4 dehydration of allylic alcohols

The diol was converted to the 1,3-diene by a mixture of copper (I) bromide, phosphorus tribromide and zinc.

Reich\(^{87}\) regiospecifically converted allylic alcohols to 1,3-dienes by sequential sulenate-sulfoxide [2,3] sigmatropic rearrangement and syn elimination (Figure 29). The overall stereochemistry in cyclic systems was cis, but trans in acyclic compounds. This simple procedure requires moderate temperatures and mildly basic conditions (Et\(_3\)N) and the reaction is tolerant of functional groups. Limitations are of two types: (1) if the [2,3] sigmatropic equilibrium favors sulenate too strongly, the reaction will be sluggish and may give poor yields; (2) if the allyl carbonium ion formed by ionization of allyl sulenate is exceptionally stabilized, yields or regioselectivity may be poor.
Figure 29: 1,3-Dienes via Sigmatropic rearrangement and elimination

Sodium hydroxide (NaOH) and iodine convert allylic 1,1-disulfoenes to (E,E) and (E,Z) 1-arenesulfonyl 1,3-dienes with the stereochemical composition of 85/15, (E,E) to (E,Z). This 1,4 elimination of benzenesulfinic acid requires mild conditions and gives yields from 15 - 77% (Figure 30).

Figure 30: Stereoselective synthesis of aronesulfonyl-1,3-dienes
Treatment of acetoxy sulfones 56 gave (E,E) 2-arenesulfonfyl 1,3-dienes 57 via basic elimination of acetic acid. Powdered NaOH in dioxane or ether gave approximately 90 - 93% (E,E) and 7 - 10% (E,Z) in 50 - 78% yields (Figure 31).

\[
\begin{align*}
\text{56} & \quad \xrightarrow{\text{OR}_1} \quad \text{(E,E)} \quad \text{57} \quad \text{(E,Z)}
\end{align*}
\]

Figure 31: Dienes from acetoxy sulfones

Regio- and stereoselective coupling between trimethylsilyl allyl carbanions and aldehydes can be achieved with an additive "M": use of dicyclopentylboron chloride or ethylaluminum dichloride as "M" gives predominantly the threo isomer 59 while use of tributyltin chloride - boron trifluoride affords the erythro isomer exclusively. 89 Erythro- or threo- 59 can then be stereoselectively converted into (E) or (Z)-1,3-dienes (60) by the method of Hudrik and Peterson 90 (Figure 32). The additive "M" completely changes the normal \( \gamma \)-stereoselectivity to \( \alpha \)-selectivity. 91
Figure 32: Stereoselective synthesis of 1,3-dienes using trimethylsilyl allyl carbanions

Reactions of aldehydes with 1,3-bis(trimethylsilyl)propenyl anion with magnesium bromide (MgBr₂) or trimethyl borate gave stereoselectively the alcohols 62, which can be transformed stereospecifically to either (1E,3E) or (1E,3Z)-1-trimethylsilylbuta-1,3-dienes 63 92 (Figure 33).

Pd-catalyzed 1,2 elimination of methylvinylcarbinol acetates allows a regioselective synthesis of 2-substituted 1,3-butadienyl compounds of high isomeric purity (86 - 98%) in yields from 61 - 66% 93 (Figure 34).
Figure 33: Utility of bis(trimethylsilyl) reagents in 1,3-diene synthesis

64 a,b) / (PPh₃)₄Pd, toluene, Δ

65 a) = myrcene

65 b) = (E)-farnesene

Figure 34: Use of Palladium in stereoselective formation of 1,3-dienes
The four stereoisomeric 1-carbamoyloxy 1,3-alkadienes have recently been prepared with stereoselectivities up to 99.7% using aluminum or titanium-mediated addition to aldehydes followed by stereospecific Peterson elimination. ⑨④

6. **Diene Synthesis employing pericyclic reactions**

![Diene Synthesis Diagram](image)

**Figure 35: Preparation of 1,3-dienes via pericyclic reactions**

Figure 35 summarizes various methods of generating dienes through pericyclic reactions. ⑨⑤ A common way of producing dienes is the thermolysis or photolysis of cyclobutenes ⑥⑥ via a thermally allowed conrotatory or photochemically allowed disrotatory electrocyclic process.
Figure 36: 1,3-Dienes from electrocyclic cyclobutene ring opening

Exposure of cis-2,3-disubstituted cyclobutenes 71 to heat produces (E,2) dienes 72; the trans isomers 73 which would give (E,E) or (Z,Z) dienes, open to afford only the less sterically hindered (E,E) dienes 74. Ring opening under photochemical conditions gives the opposite results.

A mild and stereospecific diene synthesis relies on the facile [4 + 2] cycloreversion of a dihydro-oxathiin 2-oxide 75\textsuperscript{96} (Figure 37). The reaction proceeds, at least 120°C lower than the more common method based on the thermolysis of cyclic sulfones 76\textsuperscript{97} (Figure 38).
worm moth, Diparopsis Castanea Hmps exemplifies this tech-
nique\textsuperscript{98} (Figure 39).

\begin{equation}
\begin{align*}
\text{CH}_2_\text{Ph}_3 & \rightarrow \\
\text{CH}_2_\text{OAc} & + \text{CH}_2_\text{OAc}
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{lig. SO}_2 & \rightarrow \\
\text{CH}_2_\text{OAc} & + \text{CH}_2_\text{OAc}
\end{align*}
\end{equation}

\textbf{Figure 39: Purification of diene mixtures using reversible
cycloadditions}

Despite the extensive array of 1,3-diene synthesis avail-
able, practical difficulties arise which limit their synthet-
ic potential. The stereochemistry of the diene is difficult
to predict in some of these regiospecific reactions. Some
methods require air-sensitive, sophisticated, or costly organo-
metallic reagents whose chemoselectivity is poor. Others req-
uire drastic conditions and/or suffer from low stereoselectiv-
ity and are limited to the isolation of symmetrical or term-
inal dienes. Despite the availability of many reagents for
olefination reactions, there still exists a need for new methods for stereoselective routes to conjugated 1,3-dienes under mild conditions.

Interest in the stereospecific and regiospecific preparation of conjugated 1,3-dienes stimulated McIntosh and coworkers to investigate a general method for the synthesis of 2,5-dihydrothiophenes. Examination of the literature revealed that the most general route to the 2,5-dihydrothiophene ring system was through ring closure.

SYNTHESIS OF 2,5-DIHYDROTHIOPHENES

Synthetic routes to 2,5-dihydrothiophenes include reduction of thiophenes, cycloadditions and condensation reactions. 99

Reductive Methods

The reduction of thiophene with sodium in liquid ammonia, using methanol as proton source\textsuperscript{100,101} forms mixtures of 2,5-dihydrothiophene 78 and 2,3-dihydrothiophene 79 (Figure 40). This method prohibits the preparation of geminally disubstituted compounds and suffers from low yields.

Thiophene was reduced with sodium and ammonium bromide to form a 55% yield of a mixture of 2,3- and 2,5-dihydrothio-
Purification of the 2,5-isomer was effected by removing the 2,3-isomer with aqueous (30%) sulfuric acid.

\[
\begin{align*}
\text{S} & \quad \text{Na/NH}_3 \\
\text{CH}_3\text{OH} & \quad \rightarrow \\
\text{S} & \quad + \\
& \quad \text{S}
\end{align*}
\]

Figure 40: The Birch reduction of thiophene

Thiophene-2-carboxylic acids\textsuperscript{104,105} have been electrochemically reduced to the corresponding 2,5-dihydrothiophene-2-carboxylic acids\textsuperscript{80} in 75 - 90% yields using 2M lithium hydroxide (Figure 41). This methodology has been applied to the stereoselective synthesis of (E)-homoallylic alcohols\textsuperscript{106} and the juvenoid pesticide methoprene.\textsuperscript{107}

\[
\begin{align*}
\text{R} & \quad \text{S} \quad \text{CO}_2\text{H} & \quad 2e^- \\
& \quad \text{R} \quad \text{2H}^+ & \quad \text{R} \quad \text{S} \quad \text{CO}_2\text{H}
\end{align*}
\]

Figure 41: Electrochemical reduction of thiophene-2-carboxylic acids to 2,5-dihydro acids
The Birch reduction of thiophene-2-carboxylic acid to 2,5-dihydrothiophene-2-carboxylic acid has been reported independently by two groups.\textsuperscript{108,109} Blenderman and Joullié\textsuperscript{110} observed that lithium/ammonia reduction of lithium carboxylate salts form substituted 2,5-dihydrothiophenes 81 in good yields (75 - 90\%) (Figure 42). They also separated and characterized the \textit{cis} and \textit{trans} forms.

![Chemical structure](image)

\textbf{Figure 42: Birch reduction of lithium carboxylate salts}

Thiophene and 2-ethylthiophene\textsuperscript{111} were reduced to the corresponding 2,5-dihydrothiophenes 82 in 41 - 70\% yields with zinc in trifluoroacetic acid (Figure 43). The contaminant tetrahydrothiophene 83 was separated by preparative gas liquid chromatography (GLC).

2,5-dihydrothiophenes 86 and 87 have been prepared from diketo-sulfides by an intramolecular reductive coupling reac-
tion using a low valent titanium reagent (McMurry coupling) (Figure 44). Symmetrically substituted diketo sulfides are prepared by reaction of \( \alpha \)-haloketones with sodium sulfide. Unsymmetrically substituted diketo sulfides are obtained by reaction of \( \alpha \)-haloketones with \( \alpha \)-mercapto ketones.

![Chemical structure diagram]

**Figure 43:** Reduction of thiophene with zinc in trifluoroacetic acid

\[
2 \text{R}_1\text{C} = \text{C} = \text{R}_3 \xrightarrow{\text{Na}_2\text{S}} \text{R}_1\text{O} = \text{C} = \text{R}_2 \xrightarrow{\text{TiCl}} \text{R}_1\text{O} = \text{C} = \text{R}_2 \xrightarrow{\text{Zn}} \text{R}_1\text{O} = \text{C} = \text{R}_2
\]

\( X = \text{Cl, Br} \)

**Figure 44:** Synthesis of 2,5-dihydrothiophenes from diketo sulfides with a TiCl\(_2\) - Zn reagent
2-acyl-2,5-dihydrothiophenes 88 were synthesized in 44 - 82% yields from 2-acylthiophenes utilizing the Birch reduction followed by alkylation 113 (Figure 45).

\[
\begin{align*}
&\text{R}_2 & & \text{Na/ NH}_3 & & \text{NH}_4\text{Cl} & & \text{R}_3\text{X} \\
&\text{EtOH} & & & & & \rightarrow & & \text{R}_2 \\
&\text{R}_1 & & & & & & & \text{R}_3 & & \text{MeI} \\
& & & & & & & & \text{n-C}_4\text{H}_9\text{Br} \\
&\text{Br} & & & & & & & & & & \text{PhCH}_2\text{Br}
\end{align*}
\]

\[R_3X = \text{PhCH}_2\text{Br} \]

88

Figure 45: Birch reduction of 2-acylthiophenes

Cycloadditions

Kellogg 114,115 used dipolar cycloadditions to prepare several substituted 2,5-dihydrothiophenes (Figure 47). He was interested in the preparation and reactions of "thiocarbonyl ylides" 89 (Figure 46).

\[
\begin{align*}
&\text{89} & & \leftrightarrow & & \text{90}
\end{align*}
\]

Figure 46: Thiocarbonyl Ylide resonance forms
Figure 47: Routes to 2,5-dihydrothiophenes via thiocarbonyl ylides
1,3-Thiadiazolidine 91 could be dehydrogenated with diethyl azodicarboxylate to form the thiadiazoline 93. The most general method proceeded via the chlorinated azo compound 92. 2,5-dihydrothiophenes 94 were synthesized in good yields by the in situ reaction of the dipolarophile, dimethyl acetylenedicarboxylate with the thiocarbonyl ylides generated from 93 (Figure 47). The observed cis/trans ratio was 20:80 when $R_1 = H$ and $R_2 = \text{Ethyl (Et)}$ in 94 (Figure 47).

The Schönberg reaction of diazomethane with diethyl thioacetate 95 has recently been utilized to give thia diazoline 96 as an alternative route to 2,5-dihydrothiophene derivatives 116 (Figure 48). Dipolar cycloaddition of the presumed thiocarbonyl ylide 97 to dimethyl acetylenedicarboxylate at 0 - 5°C gave a low yield of dihydrothiophene 98.

$$\text{Et}_2\text{C}=\text{S} + \text{CH}_2=\text{N}=\text{N} \rightarrow \begin{array}{c}
\begin{array}{c}
\text{Et} \\
\text{Et}
\end{array}
\end{array}$$

95

$$\text{MeO}_2\text{C} \begin{array}{c}
\text{S} \\
\text{Et}
\end{array} \begin{array}{c}
\text{Et} \\
\text{MeO}_2\text{C} \text{CC} = \text{CCO}_2\text{Me}
\end{array}$$

98

$\text{MeO}_2\text{CC}=\text{CCO}_2\text{Me}$

97

Figure 48: The Schönberg reaction in 2,5-dihydrothiophene synthesis.
Huisgen showed that a thiadiazoline could be formed in high yield from the low temperature addition of diazo-methane to thiobenzophenone (Figure 49). This decomposed above 30°C to give the corresponding thiocarbonyl ylide. Good yields of dihydrothiophene adducts (70%) can only be obtained by dipolar cycloaddition reactions using the preformed thiadiazoline.

\[
(C_6H_5)_2C=S + \text{THF} \rightarrow \text{DMAD} \rightarrow \]

\[
\text{MeO}_2C \quad \text{CO}_2Me
\]

Figure 49: Dihydrothiophenes from thiocarbonyl ylides

Condensation Reactions

Thioglycolates condense with \( \alpha,\beta \)-unsaturated ketones or \( \beta \)
-dimethylaminoketones to produce hydroxy-tetrahydrothiophenes 102 which dehydrate to 2,5-dihydrothiophenes 103 118,119 (Figure 50).

![Chemical structures](image)

**Figure 50:** 2,5-dihydrothiophene synthesis by thioglycolate condensation

A Michael reaction of sulfide ion to 104 followed by
Nucleophilic displacement of the chloro group yields 105.

Both 2,5- and 2,3-dihydrothiophenes can be formed from the common 3-ketotetrahydrothiophene\textsuperscript{120} (Figure 51).

![chemical structure](image)

Figure 51: Dihydrothiophenes from 3-ketotetrathiophenes

2,5-dihydrothiophene is formed in 98\% yield from vinylacetylene and sodium hydrosulfide\textsuperscript{121} (Figure 52). Only the preparation of 2,5-dihydrothiophene itself gave good yields.

The addition of sulfur dichloride to 2,4-hexadiene followed by elimination of the isomeric dichloride mixture produces the desired 2,5-dihydrothiophene\textsuperscript{122} but in poor overall
yields (12 - 13%). A 9:1 mixture of E:Z-108 was obtained from Z,E-107.

\[
\begin{align*}
\text{NaSH} + \text{CH}_3\text{CH}_3\text{C} & \xrightarrow{\text{DMSO}} \left[ \begin{array}{c} \text{HS} \\ \text{CH}_3 \text{CH}_3\text{C} \end{array} \right] \\
& \rightarrow \text{CH}_3\text{CH}_3\text{SCH}_3
\end{align*}
\]

Figure 52: 2,5-Dihydrothiophenes from vinylacetylene

\[
\begin{align*}
\text{CH}_3\text{CH}_3\text{C} & \xrightarrow{\text{SCl}_2} \left[ \begin{array}{c} \text{CH}_3 \\ \text{CH}_3\text{SCH}_3 \end{array} \right] \\
& \xrightarrow{\text{Cr(OAc)}_2} \text{CH}_3\text{CH}_3\text{SCH}_3
\end{align*}
\]

Figure 53: 2,5-Dihydrothiophenes from 2,4-hexadiene

2,5-Dihydrothiophenes of general structure 112 have been prepared from 109\textsuperscript{123} or 113\textsuperscript{124} as outlined in Figure 54 in 49 - 71% yields. More highly substituted 2,5-dihydrothiophenes 114 were synthesized\textsuperscript{125} in low yields by the sequence shown.
in Figure 55.

Figure 54: 2,5-Dihydrothiophenes by multistep cyclizations

Figure 55: Takaya's synthesis of 2,3,4-tri-substituted 2,5-dihydrothiophenes
3-Acetamido-2,5-dihydrothiophenes\textsuperscript{126} \textsuperscript{116} were obtained by heating N-acetyl-S-(\alpha\textsuperscript{-ketoalkyl})cysteines \textsuperscript{115} with acetic anhydride at 130°C for one hour (Figure 56).

![Chemical structure](image)

\textsuperscript{115} a \ R_1, R_2 = -(\text{CH}_2)_4 \\
\textsuperscript{115} b \ R_1 = \text{Ph}, R_2 = \text{H} \\
\textsuperscript{116} a \ 80\% \\
\textsuperscript{116} b \ 28\%

Figure 56: Field's synthesis of 2,5-dihydrothiophene derivatives

Treatment of cis-1,4-dichloro-2-butene\textsuperscript{127} with sodium sulfide produced a 2:1 mixture of 2,5-dihydrothiophene \textsuperscript{117} and vinylthiirane \textsuperscript{118} (Figure 57). Because these products could not effectively be separated by distillation, excess sulfide anion was used to destroy the vinylthiirane yielding 35 - 38% of pure 2,5-dihydrothiophene. Alternatively, purification of \textsuperscript{117} could be effected by conversion to the sulfoxide or crystallization.

Interest in the total synthesis of the vitamin biotin \textsuperscript{125} has led to considerable development in the chemistry of 2,5-dihydrothiophenes.

During Japanese investigations\textsuperscript{125,128} of biotin, \textsuperscript{119} was
reacted with urea or ethyl carbamate to give an amino-substituted dihydrothiophene 120 or with diazomethane to afford the methyl vinyl ether 121 (Figure 58).

Figure 57: 2,5-Dihydrothiophenes using cis-1,4-dichloro-2-butene

Figure 58: Japanese routes to biotin via 2,5-dihydrothiophenes
One ingenious enantioselective approach to the synthesis of biotin precursor 124 utilizes 2,5-dihydrothiophene-1,1-dioxide as the starting material. Intramolecular cyclization of the urea 123 provides the means for effective cis diamination of 122 (Figure 59).

\[ \text{122} \rightarrow \text{123} \rightarrow \text{124} \]

\[ \text{BnN} \quad \text{BnN} \quad \text{BnN} \]

\[ \text{S} \quad \text{S} \quad \text{S} \]

\[ \text{O}_2 \quad \text{O}_2 \quad \text{O}_2 \]

(60% yield)

\[ \text{125} \]

\[ \text{Bn = Bcnzyl} \]

Figure 59: Synthesis of biotin 125 from a 2,5-dihydrothiophene sulfone

The protected form of sesquiterpene \( \alpha \)-farnesene 126 was synthesized (Figure 60) in one step by direct deprotonation
of 2,5-dihydro-3-methylthiophene-1,1-dioxide 127 followed by alkylation with geranyl bromide.\textsuperscript{130} Thermolysis of 130 by preparative glc gave a single product 126. Thus, 3-methyl-3-sulpholene 127 can be used as an isoprene-anion equivalent 129. The synthesis is regioselective, efficient and short. This methodology has also been applied to the preparation of hydroindans and hydronaphthalenes.\textsuperscript{131}

\textbf{Figure 60: Stereoselective one-step synthesis of }\textit{\alpha}-\textit{farnesene}
French researchers have developed a simple method for the stereoselective preparation of (E)-1-substituted-1,3-dienes\textsuperscript{132} and (E,E)-1,4-disubstituted-1,3-dienes\textsuperscript{133} by a thermal SO\textsubscript{2} extrusion from substituted-2,5-dihydrothiophene-1,1-dioxides \textsuperscript{132}, generated by a retro-Diels-Alder reaction (Figure 61). This procedure is quite general and has been applied to the selective syntheses of $\alpha$-functionalized conjugated dienes such as alcohols\textsuperscript{134}, ketones, esters, amides, aldehydes\textsuperscript{136}, and 1,3,5-trienes.\textsuperscript{135} The yields are excellent (ca. 85\%) and the stereoisomeric purities are high((E,E) 95\%). The method was used in the synthesis of several natural products.\textsuperscript{132,133,135}

![Figure 61: Stereoselective synthesis of (E,E)-1,3-dienes via SO$_2$ extrusion from sulfolenes](image)

\textsuperscript{131}  \textsuperscript{132}  \textsuperscript{133}  \textsuperscript{134}  \textsuperscript{135}  \textsuperscript{136}
A general method of 2,5-dihydrothiophene synthesis\textsuperscript{137-142}
has been developed employing the cyclization of α-mercapto-
carbonyl compounds\textsuperscript{133} with vinylphosphonium salts \textsuperscript{134} (Figure 62). This synthesis was successful for alkylated compounds \textsuperscript{135}. 3-Carboalkoxy-2,5-dihydrothiophenes could not easily
be made by this route, but the use of Wittig-Horner reagents
\textsuperscript{137} allowed the preparation of these materials \textsuperscript{137} (Figure 63).

\textbf{Figure 62: }Synthesis of 2,5-dihydrothiophenes by a combined Michael addition and Wittig olefination sequence

\textbf{Figure 63: }Use of Wittig-Horner reagents in 2,5-dihydrothiophene synthesis
α-Mercaptoaldehydes 138 also add to α,β-unsaturated aldehydes to give mixtures of 2,5-dihydrothiophene-3-carboxyaldehydes 139 and corresponding thiophene products 145 (Figure 64).

**Figure 64:** Use of α,β-unsaturated aldehydes in 2,5-dihydrothiophene synthesis

The thermolysis of 2,5-dihydrothiophene-1,1-dioxides (sulfolenes) is a concerted, fragmentation reaction in which orbital symmetry control is the dominant stereodirective factor. 146 This thermal decomposition has wide applicability in the stereospecific synthesis of substituted 1,3-dienes. Woodward - Hoffmann selection rules for a linear cheletropic process 147 predict that the thermal fragmentation of sulfolene should occur in a completely regiospecific and stereospecific disrotatory manner. 148-150 Experimental verification with the cis- and trans-2,5-dimethyl-sulfolenes 151 (Fig-
ure 65) leads to the conclusion that the reaction is mechanism-istically concerted.\textsuperscript{152}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{diagram.png}
\caption{Thermolysis of (Z) and (E)-2,5-dimethyl-2,5-dihydrothiophene sulfones}
\end{figure}

Thermolysis of \textit{cis}-2,5-dimethylsulfolene gives \textit{trans}, \textit{trans}-2,4-hexadiene, while \textit{trans}-dimethylsulfolene gives \textit{cis}, \textit{trans}-2,4-hexadiene with greater than 99.9\% stereospecificity.\textsuperscript{150}

This linear [4n] cheletropic extrusion of SO\textsubscript{2} proceeds with complete stereospecificity\textsuperscript{153} (Figure 66).

Sulfone thermolysis temperatures vary from 100\textdegree{}C - 200\textdegree{}C depending on the stability of the adduct.\textsuperscript{146}

Five membered cyclic sulfones are easily prepared from
1,3-dienes\textsuperscript{146} and \textit{SO}_2 or by oxidation of the parent dihydrothiophene.\textsuperscript{154}

\[ \text{disrotatory} \]

\textbf{Figure 56: Linear cheletropic extrusion of \textit{SO}_2}

As previously noted, past research in this group has established an efficient synthesis of 2,5-dialkyl-2,5-dihydrothiophenes and the stereochemistry of these compounds has been shown to be predominantly \textit{cis}. The presence of a C-3 alkyl substituent lowers the \textit{cis}-selectivity. It was of interest to determine the effect of a 3-carboalkoxy group on the stereochemistry of dihydrothiophene formation and therefore ultimately on the stereochemistry of the dienes derived from them.
CHAPTER 2

RESULTS AND DISCUSSION

The stereochemistry of formation of non-carboxylated dihydrothiophenes has been determined in this laboratory.\textsuperscript{141} These dihydrothiophenes were converted to conjugated 1,3-dienes by thermolysis of the corresponding sulfones.

Cis-2,5-dialkyl-2,5-dihydrothiophenes were formed in preference to the trans isomers in the reaction between vinylphosphonium salts and α-mercaptocarbonyl compounds. Incorporation of increasingly bulky groups at C-3 of the ring led to relative increases in the amount of trans isomer. It was concluded that the substituent trends suggested a steric basis for this effect.

The mechanism for the cyclization reaction\textsuperscript{138} involves the conjugate addition of thiolate ion\textsuperscript{140} to the polarized double bond of the phosphonium salt\textsuperscript{141} followed by an intramolecular Wittig reaction of the ylide (Figure 67). The first step of this sequence is known to be reversible.\textsuperscript{141} Recently,\textsuperscript{155} oxaphosphetanes\textsuperscript{142} have been observed as intermediates in this reaction, but it is not yet clear what the origins of the observed stereoselectivities are and whether the traditionally assumed betaines\textsuperscript{143} play some role.\textsuperscript{156} Such knowledge would, of course, lead to better control over product stereochemistry.
Based on the assumption that betaine decomposition was irreversible\textsuperscript{157}, product stereochemistry would be determined by structural influences on the transition state for this step. Models suggest that the ring is nearly planar at this point and all substituents are eclipsed. Thus, a stereochemical model (Figure 68) for dihydrothiophene formation where C-2 and C-5 substituents were \textit{trans} to the phosphorus atom, was devised. This would minimize the steric interactions and result in the formation of the favored \textit{cis}-2,5-dialkyl-2,5-dihydrothiophenes. Based on experimental evidence, it was predicted that this steric discrimination should decrease as the steric bulk of \( R \), \( R' \) and \( X \) increase.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Suggested mechanisms of dihydrothiophene formation using \( \alpha \)-mercaptocarbonyl compounds and vinylphosphonium salts.}
\end{figure}
Theoretically, four diene isomers (E,E; Z,Z; E,Z; and Z,E) can be isolated from sulfone pyrolysis.

Mock\textsuperscript{158} developed a model to explain the fragmentation of the 3-thiabicyclo[3.1.0]hexane 3,3-dioxido ring system to 1,4-dienes. Masse\textsuperscript{159} extended this model to explain the analysis of products derived from the cis- and trans-2,5-dihydrothiophene sulfones.

The two disrotatory modes available from the thermolysis of the cis-2,5-dihydrothiophene sulfones lead to (E,E)- and (Z,Z)-dienes (Figure 69). It is evident from these models that steric problems are encountered when R and R' rotate inward
towards each other. Therefore, sulfone pyrolysis follows the more favorable path involving outward rotation and the (E,E)-diene is the sole isomer produced.

![Chemical structures](image)

**Figure 69: Pyrolysis of cis-sulfones**

Similarly, Figure 70 depicts the two modes of disrotatory opening from the thermal decomposition of the trans-2,5-dihydrothiophene sulfones. Rotation of the group at C-2 causes an eclipsing interaction with the C-3 substituent in the second mode. This problem does not occur in the first mode. Experimental evidence supports the model's prediction that the trans-2,5-dihydrothiophene sulfones isolate the (Z,E)-diene and not the (E,Z)-diene.

The formation of non-carboxylated dihydrothiophenes from vinylphosphonium salts is thus a stereoselective process, especially when the steric bulk of the substituents at C-3 was not too large.
Figure 70: Pyrolysis of trans-sulfones

Our research goals were to determine the stereochemistry of formation of carboxylated dihydrothiophenes and investigate the thermal stereochemical stability of these dienes. These 3-carboxylated 2,5-dihydrothiophenes were synthesized from α-mercaptocarbonyl compounds and vinylphosphonates\textsuperscript{143,144} (Figure 71). The significance of these functionalized dihydrothiophenes is illustrated by their facile conversion, via the corresponding sulfones, to substituted 2-carbomethoxy-1,3-butadienes.\textsuperscript{143}

Initially, several assumptions must be made regarding the thermolysis of 2,5-dihydrothiophene sulfones.

1. Diene formation from non-carboxylated dihydrothiophene sulfones is disrotatory and stereospecific. We are assuming
that the presence of a 3-carbomethoxy group in the sulfone
does not affect this stereochemistry of SO₂ elimination.

2. Although cis-2,5-disubstituted 2,5-dihydrothiophenes
can give two isomers (E,E and Z,Z) via disrotatory opening,
only the (E,E) isomer is formed due to steric factors. The
assumption is made that this is also true for cis-2,5-disub-
stituted 3-carboxylated dihydrothiophenes.

3. The dienes do not undergo sterochmical isomerization
on the 'glc.'

4. The sulfone pyrolysis on the glc give diene mixtures
which reflect the dihydrothiophene stereochemistry.

5. If pot pyrolysis gives different diene ratios than direct glc decomposition ratios, then isomerization is occurring during the pot reactions.

\[ \text{Figure 71: Synthesis of 3-carbomethoxy-2,5-dihydrothiophenes} \]
The preparation of α-mercaptocarbonyl compounds from their α-halo precursors using hydrogen sulfide and base are established procedures.\textsuperscript{160,161} The α-mercaptocarbonyl compounds exist as dihydroxy-1,4-dithianes and are insoluble in the usual organic solvents.\textsuperscript{138,161} These dimers are often used as sources of α-mercaptocarbonyl reagents under basic conditions which serve to catalyze monomer formation and promote condensation and cyclization.\textsuperscript{162} Traces of acid easily dehydrate these dimers to transannular ethers which are unreactive.\textsuperscript{161}

Phosphonate was prepared by an Arbuzov reaction between triethyl phosphite and methyl bromoacetate (Figure 72). In the "classical" Arbuzov or Michaelis - Arbuzov reaction, a nucleophilic phosphorus (III) reagent and an α-halo ester, usually during prolonged heating and without a solvent giving an organophosphorus (V) compound with alkyl transfer. Considerable evidence exists for an ionic mechanism involving the quaternary intermediate "quasiphosphonium salt" \textsuperscript{154}. The bromide counter anion has a high nucleophilic reactivity towards saturated carbon and therefore rapid dealkylation occurs. The process is helped by the formation of the strong P=O bond.

We obtained good yields (80 - 85\%) of \textsuperscript{155} which had proton nuclear magnetic resonance (\textsuperscript{1}H nmr) data consistent with the proposed structure and with literature values. A set of overlapping quartets (J = 7 Hz) at 4.07 parts per million
(ppm) and 4.25 ppm indicate the presence of two -QCH₂ groups.
The methyl ester singlet appears at 3.7 ppm. A doublet at 2.93 ppm (J = 22 Hz) confirms the presence of two protons adjacent to phosphorus. This large coupling constant (J) is typical for coupling between ¹H and phosphorus-31 (³¹P). The proton-phosphorus coupling constant in a similar system¹⁶⁷, CH₃C(O)-CH₂PO(OR)₂ is 23 hertz (Hz). A triplet at 1.37 ppm (J = 7 Hz) indicates the six protons of the ethyl group. The nmr and infrared (ir) data indicate that 155 exists predominantly in its keto form.

\[(\text{EtO})_3P: + \text{CH}_3\text{OC-CH}_2\text{Br} \rightarrow \triangle \rightarrow \text{[(EtO)}_2P-\text{CH}_2\text{COCH}_3 + \text{EtBr}\]

\[\text{155} + \text{154}\]

*Figure 72: The Mechanism of formation of Methyl Diethylphosphonoacetate*
Vinylphosphonates 168-170 have been prepared in good yields utilizing a selenoxide elimination\textsuperscript{172} or via a cyclic titanate ester.\textsuperscript{171} These costly reaction sequences use phosphoryl selenides,\textsuperscript{170} the rather unpleasant selenophenol,\textsuperscript{169} phenylselenyl bromide\textsuperscript{168,169} or titanium tetrachloride.\textsuperscript{171}

We chose to synthesize vinylphosphonates 147 and 148 using a literature procedure\textsuperscript{143} based on a Knoevenagel-type condensation (Figure 73). This synthetic method was operationally simpler, showed wide generality, and the reagents were readily available.

\[
\begin{align*}
\text{(EtO)}_2\text{P-CH}_2\text{-C-OCH}_3 + \text{RCHO} & \xrightarrow{\text{C}_6\text{H}_6, \ \Delta \ \text{reflux with}} \text{(EtO)}_2\text{P-CH}_2\text{-C-OCH}_3 + \text{RCHO} \\
\text{155} & \xrightarrow{\text{H}_2\text{O}} \text{147} \ (R=\text{Ph}) \\
& \xrightarrow{\text{148}} \text{R=\text{i-Pr}}
\end{align*}
\]

**Figure 73: Vinylphosphonates synthesized**

The Knoevenagel condensation\textsuperscript{166,173-175} is effected by treating the aldehyde with an active methylene compound, the phosphonate 155, in the presence of catalytic amounts of an
amine (piperidine), and acetic acid. The reaction is run in refluxing benzene with the azeotropic removal of water. The mechanism is thought to involve the intermediate formation of an electrophilic iminium salt 156 from the aldehyde and the amine (Figure 74). Subsequent reaction of this salt with the enol, derived from the phosphonate produces an intermediate amino compound 157 which in turn forms the vinyl phosphonate by elimination of the amine.

Figure 74: Mechanism of the Knoevenagel-type condensation between Benzaldehyde and Methyl Diethylphosphonoacetate
This condensation is not stereoselective but yields mixtures of cis and trans isomers. This stereochemical result is unimportant since the subsequent reaction with α-mercapto-carbonyl compounds does not depend on the geometry of the double bond.

Vinylphosphonate 147 was obtained in 65 - 70% yields and the nmr data was consistent with literature values. A downfield signal at 7.38 ppm confirms the presence of the phenyl ring and the olefinic hydrogen. A quintet at 4.2 ppm indicates the four methylene protons attached to oxygen. The methyl ester singlet appears at 3.8 ppm. The upfield triplet at 1.35 ppm can be assigned to the six methyl protons of the two ethyl esters. Glc indicates the presence of the E/Z isomers in approximately equal amounts. The mass measurement gives the molecular ion at 298 m/e, corresponding to C₁₄H₁₉O₅P.

Vinylphosphonate 148 was obtained in better yields (ca. 90%) and was a diastereoisomeric mixture by glc and carbon-13 (¹³C) nmr. The thermodynamically more stable E isomer was thought to be the predominant isomer because of the steric bulk of the isopropyl group. Several attempts were made to purify this material but without success. One of the reasons for this failure was the similarity of boiling points of starting material and product. The nmr and mass spectra (ms) data were consistent with the proposed structure. A downfield doublet of doublets at 6.66 ppm (J = 23 and 10 Hz) indicate the
presence of the vinyl proton. There is long-range coupling in the $^1$H nmr spectrum of 148. The proton-phosphorus coupling constants are large and observable through at least four bonds. $^{176,177}$ The alkene proton is downfield due to the two electron-withdrawing groups, $\equiv C=P=O$ and $\equiv C=O$. A multiplet at 4.03 confirms the presence of the four methylene protons of the ethyl groups. The methyl ester appears as a singlet at 3.74 ppm. The allylic methine proton of the isopropyl group occurs upfield as a multiplet at 2.94 ppm. A triplet at 1.31 ($J = 6$ Hz) confirm the presence of the six methyl protons of the ester. An upfield doublet at 1.01 ppm ($J = 7$ Hz) represents the six methyl protons of the isopropyl group. The ir spectrum has bands at 1726, 1256 and 1380 cm$^{-1}$ indicative of an $\alpha,\beta$-unsaturated $\equiv C=O$ ester, $\equiv C=P=O$ and $\equiv C(CH_3)_2$. $^{178}$ $^{13}$C nmr data for vinylphosphonate 148 are given in Table 1.

An attempt to make the vinylphosphonate with $R = CH_3$ (Figure 73), using acetaldehyde or the imine derived from cyclohexylamine and acetaldehyde, was unsuccessful. The ms and gic indicated that the starting phosphonate 155 was the sole product.

2.5-Dihydrothiophene Synthesis

Dihydrothiophenes 149 - 153 were prepared using a tandem Michael/Horner-Emmons sequence $^{143,144}$ with $α$-mercaptocarbon-
yl compounds 144 – 146 and vinylphosphonates 147 and 148 (Figure 71).

**TABLE 1**

<table>
<thead>
<tr>
<th>$^1^3$C Nmr data for Vinylphosphonate 148</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>C-1</td>
</tr>
<tr>
<td>15.6</td>
</tr>
<tr>
<td>15.9</td>
</tr>
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</table>

The Michael addition$^{179}$ involves the nucleophilic addition of thiolate ion to the carbon-carbon double bond of the $\alpha, \beta$-unsaturated carbonyl compound, the vinylphosphonate (Figure 75). In this Horner-Emmons modification of the Wittig reaction, a resonance-stabilized phosphonate cation reacts intramolecularly with the carbonyl to produce the dihydrothiophene. Electron-withdrawing $\alpha$-substituents are generally required at the carbanion centre before preparative yields of olefin can be obtained.$^{180}$ This is because of the poorer sta-
bilitating effect of the phosphoryl group. The high stability of phosphorus ylides $158a-158b$ (Figure 76) derives from $p\pi-\sigma\pi$ bonding involving back-donation of the negative charge from the ylide carbon into the vacant $d$-orbital of the phosphorus atom.

Figure 75: Suggested Mechanism of formation of 3-carbomethoxy-2,5-dihydrothiophenes
The α-anion of a phosphonate is considered to be a resonance hybrid with three contributing structures (Figure 77).

Structures 159 and 161 also utilize an empty 3d-orbital on the phosphorus atom. Electron-withdrawing groups on the phosphonate lead to delocalization of the negative charge with subsequent loss of reactivity. Back donation from oxygen leads to a decrease in stabilization in phosphonate carbamions 162.
The Horner-Emmons olefination shows a preference for formation of the more stable (E)-olefins. However, recent developments suggest that considerable control of stereochemistry is possible.

The mechanism is analogous to that of the conventional Wittig reaction, which is still controversial.\textsuperscript{182,183} It is conceivable that the betaine is an intermediate and may be in equilibrium with the oxaphosphetane (Figure 75).

The Horner-Emmons reaction has several advantages over the conventional Wittig reaction.

1. Phosphonate carbanions are more nucleophilic than the usual Wittig reagents.
2. The water-soluble phosphate ion formed from the phosphonates allows much easier separation of the olefin from the reaction mixture.
3. Phosphonates are cheap and readily available from the Arbuzov reaction.

The results of the dihydrothiophenes synthesized are summarized in Table 2. The spectral data and physical properties are listed in Tables 3, 4 and 7.

Dihydrothiophene \textsuperscript{149} had nmr and ir data consistent with the proposed structure and with literature values.\textsuperscript{144} A downfield singlet at 7.19 ppm indicates the presence of the five phenyl protons. The vinyl proton appears as a multiplet at 6.97 ppm. The allylic proton attached to C-2 is a multiplet at 5.45 ppm. A multiplet at 4.00 ppm can be assigned to the
two allylic protons attached to C-5. The singlet at 3.57 ppm confirms the presence of the methyl ester protons.

Although the crude yields of 150 were generally quantitative, losses were incurred during chromatography. This is not surprising as very polar solvents were not employed to simply eliminate colored impurities as stated in the original paper. Gradual increases in solvent polarity was tedious and often resulted in poor yields, though purer 2,5-dihydrothiophenes were produced.

The proton nmr of 150 supported the proposed structure. The five phenyl protons appear downfield at 7.20 ppm. A multiplet at 5.50 ppm can be assigned to the allylic proton at C-2. The allylic proton attached to C-5 appears at 4.40 ppm. The singlet at 3.50 ppm confirms the methyl ester. The vinyl methyl is a singlet located at 2.17 ppm. The upfield doublet at 1.43 ppm (J = 7 Hz) represents the allylic methyl group.

The ir absorption at 1717 cm\(^{-1}\) indicates the ester C=O. The mass measurement gives the molecular ion at 248 m/e, corresponding to C\(_{14}\)H\(_{16}\)O\(_2\)S. A loss of the ester \((-\mathrm{CO}_2\mathrm{CH}_3\)) is the only significant feature in the mass spectrum.

The \(^1\)H and \(^13\)C nmr spectra indicate that 151 exists as a diastereoisomeric mixture. Two downfield singlets at 7.27 and 7.30 ppm represent the five phenyl protons. The allylic proton attached to C-2 appears as a multiplet at 5.45 ppm. The multiplet from 4.63 - 4.00 ppm confirms the other allylic pro-
ton at the ring junction. Two singlets at 3.40 and 3.47 ppm characterize the methyl ester. The eight protons of the fused six-membered ring are represented by the multiplet from 2.50 - 1.30 ppm.

The proton nmr spectrum of 152 substantiates the proposed structure. The vinyl proton appears downfield at 6.83 ppm as a multiplet. The multiplet at 4.57 - 4.30 ppm indicates the presence of the allylic proton at C-2. The methyl ester occurs as a singlet at 3.70 ppm. The two allylic protons attached to C-5 are represented by a multiplet at 3.65 ppm. The methine proton of the isopropyl group is a multiplet at 1.30 ppm. Two upfield doublets at 0.97 and 0.80 ppm (J = 7 Hz) can be assigned to the two isopropyl methyl groups. The isopropyl group shows a strong doublet, centred at 1380 cm\(^{-1}\) in the ir spectrum. The mass measurement gives the molecular ion at 186 m/e, corresponding to \(\text{C}_9\text{H}_{14}\text{O}_2\text{S}\). Quantitative yields were usually obtained but using longer reflux times. The bulky isopropyl group may offer some resistance to intramolecular ring closure of the phosphonate anion and hence retards the rate of reaction.

The condensation of 145 with 148 gave after nine days at reflux the nonandione 163 and starting material. This is a substitution product between the solvent, methylene chloride and mercaptan 145 (Figure 78). The two protons adjacent to the sulfurs appear as a singlet at 3.28 ppm, superimposed on
a quartet representing the other two methine protons. A singlet at 2.12 ppm indicated the presence of the two methyl groups to the carbonyl carbons. The two methyl groups in the 3- and 7-position occur as a doublet \( J = 7 \text{ Hz} \) at 1.28 ppm.\(^{176}\) The ir absorption at 1708 cm\(^{-1}\) seems reasonable for a saturated ketone. The molecular ion at \( m/e = 220 \) confirms the preceding evidence for \( 163 \).

A small yield of \( 153 \) (31\%) was obtained as a mixture of diastereoisomers. The nmr data supports the proposed structure. A downfield multiplet at 4.38 ppm represents the allylic proton attached to C-2. The other allylic methine proton on C-5 appears from 4.20 - 3.93 ppm. The methyl ester appears as a singlet at 3.65 ppm. A broad singlet at 2.01 - 2.55 ppm indicated the vinyl methyl and the isopropyl methine proton. The doublet at 1.36 \( (J = 7 \text{ Hz}) \) confirms the presence of the allylic methyl group. The two upfield doublets at 0.90 and 0.76 ppm can be assigned to the gem-dimethyl protons of the isopropyl group. The isopropyl group is characterized in the ir by a doublet centred at 1380 cm\(^{-1}\). The mass measurement gives the molecular ion at \( m/e = 214 \), corresponding to \( \text{C}_{11}\text{H}_{8}\text{O}_{2}\text{S} \).

The reaction between \( 146 \) and \( 148 \) gave only recovered starting material even on prolonged reflux in boiling chloroform.
Figure 78: Formation of 4,4-dithia-3,7-dimethyl-2,8-nonan-dione
### TABLE 2

Dihydrothiophenes Synthesized

<table>
<thead>
<tr>
<th>Mercaptan</th>
<th>Phosphonate Number</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>144</td>
<td>147</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>47</td>
</tr>
<tr>
<td>145</td>
<td>147</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>Ph</td>
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<tr>
<td>146</td>
<td>147</td>
<td>H</td>
<td>-(CH₂)₄⁻</td>
<td>Ph</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>148</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>i-Pr</td>
<td>100</td>
</tr>
<tr>
<td>145</td>
<td>148</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>i-Pr</td>
<td>31</td>
</tr>
</tbody>
</table>

a) mp 70 - 71°C

b) mp 60 - 61°C (recrystallized from n-hexane)
\begin{table}
\centering
\caption{Spectral Data for Dihydrothiophenes}
\begin{tabular}{|c|c|c|}
\hline
\textbf{Number} & \textbf{IR} & \textbf{NMR} \\
\hline
149 & 3020, 1725, 1650, 1275. & 7.19 (s, 5), 6.97 (m, 1), 5.45 (m, 1), 4.00 (m, 2), 3.57 (s, 3). \\
\hline
150 & 2925, 1717, 1436 1281, 1232. & 7.20 (s, 5), 5.50 (m, 1), 4.40 (m, 1), 3.50 (s, 3), 2.17 (s, 3), 1.43 (d, 3, J = 7). \\
\hline
151 & 2950, 1715, 1285, 1265. & 7.27, 7.30 (2s, 5), 5.45, (m, 1), 4.63-4.00 (m, 1), 3.40, 3.47 (2s, 3), 2.50-1.30 (m, 8). \\
\hline
152 & 2925, 1722, 1436, 1380, 1260, 1195. & 6.83 (m, 1), 4.57-4.30 (m, 1), 3.70 (s, 3) 3.65 (m, 2), 1.30 (m, 1), 0.97, 0.80 (2d, 6, J = 7). \\
\hline
153 & 2961, 1717, 1434, 1380, 1214, 1067. & 4.38 (m, 1), 4.20-3.93 (m, 1), 3.65 (s, 3) 2.55-2.01 (bs, 4), 1.36 (d, 3, J = 7), 0.90, 0.76 (2d, 6, J = 7). \\
\hline
\end{tabular}
\end{table}

\textit{Note:}

a) most intense peaks
b) see experimental for coding
TABLE 4

**Sulfones Prepared**

<table>
<thead>
<tr>
<th>Dihydrothiophene</th>
<th>R</th>
<th>Product</th>
<th>M.P. (°C)</th>
<th>Yield(%)</th>
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</thead>
<tbody>
<tr>
<td>149</td>
<td>Ph</td>
<td>164</td>
<td>169-171</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(dec)</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>Ph</td>
<td>165</td>
<td>110-112a</td>
<td>23</td>
</tr>
<tr>
<td></td>
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<td>(dec)</td>
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<tr>
<td>151</td>
<td>Ph</td>
<td>166</td>
<td>117-120a</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>(dec)</td>
<td></td>
</tr>
<tr>
<td>152</td>
<td>i-Pr</td>
<td>167</td>
<td>78-80a</td>
<td>63</td>
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<td></td>
</tr>
<tr>
<td>153</td>
<td>i-Pr</td>
<td>168</td>
<td></td>
<td>69</td>
</tr>
</tbody>
</table>

a) recrystallized from n-hexane

![chemstruct](image-url)
TABLE 5

Spectral Data for Sulfones

<table>
<thead>
<tr>
<th>Number</th>
<th>IR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>NMR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>164&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1735, 1460, 1335, 1200.</td>
<td>d7.41 (m,6), 5.46 (bs,1), 4.33 (d, 2, J = 4), 3.90 (s,3).</td>
</tr>
<tr>
<td>165&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2937, 1713, 1313, 1237, 1136.</td>
<td>7.32 (m,5), 5.20 (m,1), 3.95 (m,1), 3.58 (s,3), 2.37 (s,3), 1.63 (d,3, J = 7).</td>
</tr>
<tr>
<td>166</td>
<td>3056, 2880, 1719, 1317, 1245, 1166.</td>
<td>7.05 (m,5), 5.20-4.97 (m,1), 3.75-3.45 (m,1), 3.45, 3.52 (2s,3), 2.28-1.05 (m,8)</td>
</tr>
<tr>
<td>167</td>
<td>2977, 1723, 1436, 1325, 1257, 1228, 1199.</td>
<td>7.12 (m,1), 4.00-3.77 (m,3), 3.77 (s,3), 2.60-1.94 (m,1), 1.14 (d,6, J = 7).</td>
</tr>
<tr>
<td>168&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2964, 1721, 1436, 1310, 1234, 1139, 1080.</td>
<td>—</td>
</tr>
</tbody>
</table>

a) most intense peaks
b) see experimental for coding
c) KBr pellet
d) in CF₃COOD solution
e) mixture of sulfone and sulfide
### TABLE 6

**Analytical Data for New Products**

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<th>Number</th>
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<td></td>
<td>C</td>
<td>H</td>
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<tr>
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<td>165</td>
<td>59.98</td>
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<td>5.92</td>
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<td>167</td>
<td>49.52</td>
<td>6.46</td>
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</table>
### TABLE 7

**13C Spectra of Alkylated 3-Carbomethoxy-2,5-dihydrothiophenes and related sulfones**

**Chemical Shifts**

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<thead>
<tr>
<th>Number</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>COOCH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>CO</th>
<th>C-4'CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>C-5'CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>149</td>
<td>57.1</td>
<td>139.1</td>
<td>(141.3</td>
<td>38.1</td>
<td>52.0</td>
<td>164.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>164</td>
<td>74.7</td>
<td>138.6</td>
<td>146.0</td>
<td>55.7</td>
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<td>134.3, 134.1,</td>
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<td>9.7</td>
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### TABLE 7 (cont'd)

#### Chemical Shifts

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<th>C-5</th>
<th>COOCH$_3$</th>
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<td>163.4</td>
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<td>141.1</td>
<td>37.3</td>
<td>51.7</td>
<td>164.2</td>
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<tr>
<td>167</td>
<td>70.0</td>
<td>(138.8)</td>
<td>(134.5)</td>
<td>56.7</td>
<td>52.4</td>
<td>163.2</td>
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<tr>
<td>153</td>
<td>60.8</td>
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<td>51.9</td>
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![Chemical Structure](image)

<table>
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<th>C-7</th>
<th>C-8</th>
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<tr>
<td></td>
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<td>31.0 (21.8) (15.2)</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>29.8 18.9 18.9</td>
</tr>
</tbody>
</table>

C-4 Me: 14.6
C-5 Me: 21.6
C-4 Me: 21.9

a) under phenyl signal
Preparation of Sulfones and Their Thermolysis

Dihydrothiophenes 149 - 153 were oxidized to sulfones 164 - 168 (Table 4) using m-chloroperbenzoic acid (MCPBA). The spectral data and physical properties are summarized in Tables 5, 6 and 7. The $^{13}$C resonances are within acceptable limits for the structures proposed 164 (Table 7).

The protons at C-2 and C-5 experience pronounced downfield shifts in $^1$H and $^{13}$C nmr due to the fact that the sulfur atom has been converted to the more electron-withdrawing sulfone.

The $^1$H nmr data of sulfone 164 is consistent with literature values. 144 A downfield singlet at 7.41 ppm can be assigned to the phenyl ring protons and the vinyl proton. A broad singlet at 5.46 ppm represents the allylic methine proton at C-2. The two allylic protons at C-5 appear as a doublet ($J = 4$ Hz) at 4.33 ppm. The methyl ester occurs at 3.90 ppm as a singlet.

Sulfone 165 has nmr data consistent with the proposed structure. A downfield multiplet at 7.32 ppm indicates the presence of the phenyl ring. The allylic methine protons at C-2 and C-5 occur as multiplets at 5.20 and 3.95 ppm respectively. The methyl ester appears as a singlet at 3.58 ppm. The vinyl methyl occurs at 2.37 ppm as a singlet. An upfield doublet ($J = 7$ Hz) represents the allylic methyl protons.
The IR spectrum has bands at 1313 and 1136 cm\(^{-1}\), indicative of the asymmetric and symmetric \( \text{SO}_2 \) stretching patterns. A mass measurement gives the molecular ion at 280 m/e, corresponding to \( \text{C}_{14} \text{H}_{16} \text{O}_4 \text{S} \). Evident in the mass spectrum is sulfoxide formation. Incomplete oxidation could account for the low yield (23%) of sulfone 165. Yields might be improved by increasing the reaction time or using a full two equivalents or more of peracid. A loss of oxygen is the only significant feature in the mass spectrum.

The \(^1\text{H}\) and \(^13\text{C}\) nmr data of 166 indicate a mixture of diastereoisomers. A downfield multiplet at 7.05 ppm confirm the presence of the phenyl ring. The allylic methine protons at C-2 and C-7a appear as multiplets at 5.20 - 4.97 and 3.75 - 3.45 ppm respectively. The methyl ester occurs as two singlets at 3.45 and 3.52 ppm. A multiplet at 2.28 - 1.05 ppm represents the eight protons of the fused six-membered ring. The \( \text{SO}_2 \) stretching absorptions occur at 1166 and 1317 cm\(^{-1}\) in the IR spectrum. The molecular ion at 306 m/e corresponds to \( \text{C}_{16} \text{H}_{18} \text{O}_4 \text{S} \).

Several equivalents of MCPBA were necessary to achieve a 63% yield of sulfone 167. The bulky isopropyl group must sterically hinder the oxidation process. The \(^1\text{H}\) nmr data is consistent with the proposed structure. A downfield multiplet at 7.12 ppm represents the vinyl proton. The allylic methine proton at C-2 and the two allylic protons at C-5 appear as a
multiplet at 4.00 - 3.77 ppm. The methyl ester is located at 3.77 ppm as a singlet. The isopropyl methine proton is a multiplet at 2.60 - 1.94 ppm. An upfield doublet at 1.14 ppm (J = 7 Hz) indicates the presence of the gem-dimethyls. The ir has bands at 1325 and 1132 cm\(^{-1}\), indicative of \(\text{SO}_2\) stretching. Noteworthy in the mass spectrum is the corresponding diene (m/e 154) and the molecular ion at 218 m/e, corresponding to \(\text{C}_9\text{H}_{14}\text{O}_4\text{S}\).

An attempt to oxidize dihydrothiophene 153 resulted in the formation of a mixture of sulfoxide and sulfone 168 according to ms and ir. Preparatively useful yields of the sulfone were not obtained in this instance.

Sulfones 164 - 167 were decomposed by direct injection into the glc and the diene ratios were determined (Table 9). The 1,3-dienes prepared are summarized in Figure 79. As the dienes were not separated, it is not possible to rigorously assign stereochemistries. The results of the diene analysis from the pot pyrolyses are incorporated into Tables 9 - 13. Spectral data are recorded in Table 8. The dienes undergo isomerization in the pot reactions and therefore, the ratios recorded for the pot pyrolyses do not reflect accurately the stereoselectivity. In contrast, the direct ratios probably reflect a more accurate picture.
Figure 79: 1,3-Dienes prepared
<table>
<thead>
<tr>
<th>Dihydrothiophene</th>
<th>Sulfone</th>
<th>Diene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>NMR&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>164</td>
<td>169</td>
<td>2924(s), 2852(s), 1723(m), 1520(s), 1463(m), 1256(m), 1248(m), 1221(m), 1142(m), 1125(m), 1037(w), 935(w), 800(w), 750(w), 712(w), 699(w).</td>
<td>7.5-7.0 (m,5), 6.65 (s,1), 6.75-5.13 (m,3), 3.85, 3.80 (2s, 3).</td>
</tr>
<tr>
<td>150</td>
<td>165</td>
<td>170</td>
<td>2950(m), 2923(m), 1713(s), 1448(m), 1434(m), 1253(s), 1242(m), 1207(m), 1193(m), 1177(m), 1096(m), 975(w), 850(w), 776(m), 692(m).</td>
<td>7.3-7.0 (m,6), 5.17 (m,1), 3.70, 3.53 (2s, 3), 2.9, 1.9 (2d, 3, J=2 Hz), 1.43, 1.37 (2d, 3, J=7 Hz).</td>
</tr>
<tr>
<td>151</td>
<td>166</td>
<td>171</td>
<td>2929(s), 1718(s), 1436(m), 1248(s), 944(w), 881(w), 840(w), 690(m).</td>
<td>7.57 (s, 1), 7.46-7.13 (m, 5), 6.45 (s, 1), 6.0-5.5 (m, 1), 3.78, 3.75 (2s, 3), 2.3-1.7 (m, 4), 1.7-1.0 (m, 4).</td>
</tr>
<tr>
<td>152</td>
<td>167</td>
<td>172</td>
<td>2959(s), 2930(s), 2870(s), 1720(s), 1620(m), 1600(m), 1580(m), 1463(s), 1436(s), 1370(m), 1306(m), 1249(s), 1196(s), 1157(s), 1097(m), 1077(m), 1030(m), 945(m), 783(m), 753(m), 695(m).</td>
<td>a) no stereochemistry implied, b) see Experimental for coding.</td>
</tr>
<tr>
<td>Sulfone</td>
<td>Direct Injection</td>
<td>Pot Pyrolyses&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>------------------</td>
<td>--------------------------</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Ratio</td>
<td>Time (hrs)</td>
<td></td>
</tr>
<tr>
<td>164</td>
<td>72:28&lt;sup&gt;c&lt;/sup&gt;</td>
<td>49:51</td>
<td>4.0</td>
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<tr>
<td></td>
<td></td>
<td>23:77</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>165</td>
<td>13:77:10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>14:76:10</td>
<td>2.6</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>12:82:6</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>166</td>
<td>45:55&lt;sup&gt;e&lt;/sup&gt;</td>
<td>50:50&lt;sup&gt;f&lt;/sup&gt;</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>167</td>
<td>80:20&lt;sup&gt;g&lt;/sup&gt;</td>
<td>45:55</td>
<td>20.0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Isomer eluted first is recorded first

<sup>b</sup> Toluene at reflux

<sup>c</sup> In CF<sub>3</sub>CH<sub>2</sub>OH, glc (Column B, 119 °C), average of 5 injections

<sup>d</sup> In CHCl<sub>3</sub>, glc (Column B, 119 °C), average of 3 injections

<sup>e</sup> In CHCl<sub>3</sub>, glc (Column B, 149 °C), average of 3 injections

<sup>f</sup> Average of 3 injections

<sup>g</sup> In CHCl<sub>3</sub>, glc (Column A, 149 °C), average of 2 injections

<sup>h</sup> Injection port temperature 267 °C
Direct injection into the glc of sulfone 164 gave two compounds as determined by glc in a ratio of 72:28 (Table 9). After twenty hours in refluxing toluene and chromatography using silica gel, the isomeric ratio reversed to 13:87. This mixture was predominantly one isomer by glc and nmr. Only one methyl ester singlet appears at 3.82 ppm. A singlet at 7.59 ppm is similar to a calculated value of 7.64\(^{185}\) for E/Z 169. This sample corresponds to the second peak on the glc (Column B, 119°C) representing the second isomer eluted. This evidence seems to fit the pyrolysis data as it is reasonable that the more thermodynamically stable isomer would be favored after twenty hours. This would make the 2-isomer the kinetic product on direct injection.

The \(^1H\) nmr of the crude pyrolysate E/Z mixture had a multiplet at 7.5 - 7.0 ppm for the five phenyl protons. The vinyl proton attached to the carbon bearing the phenyl group appears downfield as a singlet at 6.65 ppm. This would correspond to the 2-isomer as the calculated value for this proton is 7.04 ppm.\(^{185}\) The same proton corresponding to the E-isomer occurs at 7.59 ppm. The other three vinyl protons appear as a complex multiplet at 6.75 - 5.13 ppm. The methyl ester occurs as two singlets at 3.80 and 3.85 ppm. The \(^13C\) nmr confirm the presence of a mixture of E- and 2-isomers. The ir spectra are uninformative except for the ester carbonyl absorption at 1723 cm\(^{-1}\). The ms of the crude pyrolysate has the molecular ion at 188 m/e, corresponding to diene 169.
and thiophene 173 at m/e 218. Thiophene formation must have occurred during the oxidation of dihydrothiophene 149 (Figure 80).

![Chemical structures]

**Figure 80: Peracid Oxidation of 2,5-dihydrothiophene resulting in thiophene formation**

A Diels-Alder dimer was also present as suggested by a peak at m/e 376 in the mass spectrum. The amount of this product as indicated by glc may not be reliable since the Diels-Alder re-
action is reversible and some could revert to the monomer in the injection port. It is interesting to note that diene 174 only exists as a dimer.

E-1-phenyl-butadiene-2-carboxylic acid 175 has been prepared in the literature\textsuperscript{187,188} but no nmr was reported. No direct comparisons were useful therefore.

Direct injection of sulfone 165 gave three compounds as determined by glc in a ratio of 13:77:10 (Table 9). This ratio did not change much after five hours in refluxing toluene (12:82:6). After chromatography, the ratio was 6:72:22 (Column B, 119°C). A downfield multiplet at 7.3 - 7.0 ppm indicates the presence of the five phenyl protons and the vinyl proton attached to the carbon bearing the phenyl group.
Because this proton is at low field, it is possible that the major isomer is \((E, E)\)-170. A multiplet at 5.17 ppm can be assigned to the other vinyl proton. The O-methyl hydrogens appear as two singlets at 3.70 and 3.53 ppm. A third O-methyl ester is visible superimposed on the \(-\text{OCH}_3\) signal of the major isomer. Two doublets at 2.0 and 1.9 ppm \((J = 2 \text{ Hz})\) represent the protons of the non-terminal vinyl methyl group. The protons of the terminal methyl group are indicated by two doublets \((J = 7 \text{ Hz})\) at 1.43 and 1.37 ppm. No conclusions can be drawn from the ir spectrum. The ms shows the molecular ion at 216 m/e corresponding to dienes 170. The gc/ms gives three peaks, one major and two minor. That all three are isomers is evident from their identical mass spectra. The molecular ion of the diene was present in all three fractions. The base peak occurs at m/e 157 \((\text{M-\text{COOCH}_3})\).

Woodward - Hoffmann\textsuperscript{147} rules predict that thermolysis of sulfone 165 gives four isomers (Figure 81). The importance of steric factors in this decomposition is revealed by the fact that 2-165 produces only the \((E, Z)\)-isomer and no \((Z, E)\) despite the fact that the reaction is allowed in a concerted sense. Two isomers are possible from the thermolysis of \(E\)-165, \((Z, Z)\) and \((E, E)\) and both of these are produced in the reaction. Both minor isomers are formed in essentially the same percentage, i.e. 13:10. If the proposed model is applied in this case (Figure 84), that means cis or 2-165 is favored in the
2,5-dihydrothiophene's transition state. Therefore, the major isomer is probably the E/Z stereochemistry. Nmr chemical shifts give conflicting results when compared to the model's predictions. At this time, we are unable to specify the stereochemistry definitely.

Figure 81: Pyrolysis of cis- and trans sulfones 165
Direct injection of sulfone 166 gave two compounds as determined by glc in a ratio of 45:55 (Table 9). The pot pyrolysis ratio after ten hours in refluxing toluene was 50:50. A singlet at 7.57 ppm corresponds to the vinyl proton attached to the carbon bearing the phenyl substituent. This proton is downfield due to resonance. A multiplet at 7.46 - 7.13 ppm can be assigned to the five phenyl protons. A singlet at 6.45 ppm probably corresponds to the terminal vinyl proton in the other isomer. The vinyl proton attached to the ring appears as a multiplet at 6.0 - 5.5 ppm. The methyl ester appears as two singlets at 3.75 and 3.78 ppm. Because the higher field –OCH$_3$ singlet is the most intense, we expect this isomer probably is (E,2) based on chemical shifts. The cyclohexyl protons appear as two multiplets at 2.3 - 1.7 and 1.7 - 1.0 ppm. The ms has the molecular ion at 242 m/e, corresponding to dienes 171.

Woodward – Hoffman rules $^{147}$ predict that only two isomers are possible from the thermolysis of sulfone 166 (Figure 82). In this case, ring constraints prevent the formation of the other diene isomers.

Direct injection of sulfone 167 gave two compounds as determined by glc in a ratio of 80:20 (Table 9). After twenty hours in refluxing toluene, the ratio was 45:55, while after chromatography, it was 60:40. Although the $^1$H integration in this case is poor, the complex pattern from 6.8 - 5.0 is clearly vinyllic. The methyl ester appears at 3.75 ppm, con-
sistent with the proposed structure. A multiplet at 3.2 - 2.3 ppm indicates the presence of the isopropyl methine proton. Two doublets at 1.20 and 1.03 ($J = 7$ Hz) represent the methyl groups of the isopropyl moiety. The ms shows the molecular ion at 154 m/e, corresponding to the dienes 172 and a Diels-Alder dimer at 308 m/e. Only two isomers are possible from the thermolysis of sulfone 167 (Figure 79). It is not possible to suggest which isomer is preferred at this stage.

![Diagram of chemical structures]

Figure 82: Thermolysis of cis- and trans-Sulfones 166
Examination of the literature\(^1\) reveals that thermal [1,5] sigmatropic rearrangements have been established in a number of cis-1,3-dienes. 1,3-dienes, in which a vinyl and alkyl group are cis, undergo a reversible thermal isomerization involving the overall 1,5-transfer of hydrogen with concomitant migration of both carbon-carbon double bonds (Figure 83). At 350 - 450°C, depending on the nature of the diene, an equilibrium mixture is approached where the thermodynamically more stable predominates (Figure 83). This anticipated problem was resolved by performing the pyrolyses of sulfones in the injection port of a gas chromatograph. This minimized pyrolysis time and thus the chance for rearrangement. However, it is unlikely that rearrangement products are formed in our work as the pyrolysis temperatures were relatively low, but this possibility cannot be ruled out at the present time.

\[ \text{Figure 83: Dienyl 1,5-Hydrogen Shifts} \]
Inspection of Table 9 shows that the two methods of analysis do not give similar results. The dienes undergo stereochemical isomerization in the pot pyrolyses. Therefore, the ratios obtained by direct injection reflect a more accurate representation of the stereoselectivity of the 1,3-diene formation. Masse assigned the stereochemistry of the 2,5-dihydrothiophenes, not 1,3-dienes, via gc. Our results appear to be similar to those obtained by Masse using vinylphosphonium salts.\(^{141}\) The cis-3-carboxylated alkyl-substituted 2,5-dihydrothiophenes are formed in preference to the trans-isomers in the reaction between vinylphosphonates and \(\alpha\)-mercaptocarboxyl compounds. Incorporation of increasingly bulky groups on the ring lead to a relative increase in the amount of trans isomer present. The 3-carbomethoxy group does not seem to have an appreciable effect on the selectivity of diene formation.

The accepted mechanism for the cyclization reaction involves the conjugate addition of thiolate anion to the activated carbon-carbon double bond of the vinylphosphonate (Figure 77), followed by an intramolecular Horner-Emmons reaction.

A transition state model similar to the one proposed by Masse is suggested to account for the observed stereoselectivity (Figure 84). Substituents at C-2 and C-5 are trans to the phosphorus atom to relieve the severe steric hindrance between eclipsing substituents. This results in preferred
formation of the cis-3-carboxylated alkyl-substituted 2,5-dihydrothiophenes. This steric discrimination should decrease as the steric bulk of \( R, R' \) and \( X \) increase.

![Chemical Structure](image)

**Figure 84: Stereochemical Model for Dihydrothiophene Formation**

The results are in agreement with this model (see Table 9) although it is not possible to rigorously assign stereochemistry to the 1,3-diene products.
CONCLUSIONS

The synthesis of 3-carboxylated alkyl-substituted 2,5-dihydrothiophenes has been shown to be a facile process and a general method has been explored. The formation of alkylated 2,5-dihydrothiophenes bearing a 3-carbomethoxy group appears to be a stereoselective process favoring cis isomers. Conversion to the sulfones and thermolysis of these derived compounds (in the injection port of a gas chromatograph) results in the formation of 1,3-dienes. These are isomerized under normal thermal conditions. Thus, a useful method for stereoselective 1,3-diene synthesis has been elucidated. The presence of the 3-carbomethoxy group does not interfere with this stereoselectivity. Furthermore, a useful group has been introduced which is of considerable value in synthesis.
**APPENDIX**

**Structures of Compounds Described in Experimental Section**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>(EtO)$_2$P(=O)(CH$_2$COCH$_3$)</td>
<td>155</td>
</tr>
<tr>
<td>(EtO)$_2$P(CO$_2$CH$_3$)</td>
<td>157</td>
</tr>
<tr>
<td>H$_2$C$_2$(O)</td>
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</tr>
<tr>
<td>C$_3$(H$_2$)(C=O)(C=SH)</td>
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<tr>
<td>CO$_2$CH$_3$</td>
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</table>

<table>
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<th>Compound</th>
<th>Number</th>
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<tbody>
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<td>158</td>
</tr>
<tr>
<td>H$_2$C$_2$(O)</td>
<td>149</td>
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<tr>
<td>C$_3$(H$_2$)(C=O)(C=SH)</td>
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<tr>
<td>CO$_2$CH$_3$</td>
<td>151</td>
</tr>
<tr>
<td>CO$_2$CH$_3$</td>
<td>152</td>
</tr>
</tbody>
</table>
Preliminary Notes

Reagent grade chemicals were used without further purification unless otherwise noted. Melting points were determined on a Fisher-Johns apparatus and are uncorrected; boiling points are uncorrected.

Infrared absorption spectra were recorded on a Perkin Elmer Model 180 instrument or a Nicolet 5-DX Fourier Transform (FT) spectrometer and are reported in wavenumbers (cm\(^{-1}\)) in the indicated solvent. The five most intense peaks and those of special significance are reported. The absorption intensities of the dienes are expressed using the following code system: w = weak (100 - 75% transmission), m = medium (74 - 40% transmission) and s = strong (39 - 0% transmission).

\(^1\)H nmr spectra were measured on a Varian EM-360 or a Bruker WP 80 Continuous Wave (CW) spectrometer in deuterochloroform (CDCl\(_3\)) solution. Chemical shift values are quoted in delta (\(\delta\)) values in ppm with respect to tetramethylsilane as internal standard. The tabulation of nmr data follows the order: nmr (solvent), chemical shift (\(\delta\)), (multiplicity, number of protons, coupling constant). The splitting pattern of each resonance is coded: s = singlet, d = doublet,
t = triplet, q = quartet, qt = quintet, dd = doublet of doublets, m = multiplet and bs = broad singlet.

Carbon-13 ($^{13}$C) nmr spectra were run in CDC$_3$ at 22.64 MHz in the FT mode using a flip angle of 45° on a Bruker CXP-100 instrument.

Mass spectra were recorded on a Varian MAT CH-5 Double Focusing (DF) instrument equipped with electron impact (EI), field desorption (FD) and fast atom bombardment (FAB) sources. The following code was utilized: mode, mass/charge (m/c) value, % relative abundance (RA). In EI, only m/c values with %RA ≥ 30% are reported.

Gas chromatogram/mass spectra (gc/ms) were measured on a Finnigan 4000 instrument.

Microanalyses were carried out by Dr. W. Boos at Uniroyal Research Incorporated, Guelph, Ontario.

Unless otherwise stated, solvents were removed on a rotary evaporator at reduced pressure and the drying agents used were anhydrous sodium or magnesium sulfate.

Column chromatography utilized Aldrich neutral alumina (150 mesh, 58 Å) Brockman activity grade 1 or Merck silica gel 60 (70 – 230 mesh). Kodak chromatogram silica gel sheets with fluorescent indicator were used in thin layer chromatography (tlc).

Gas liquid chromatography (glc) analyses were conducted on a Varian Model 3700 gas chromatograph using a helium gas
flow of 1 cc sec⁻¹. Injection port temperature and detector
temperature were 267°C and 277°C respectively. The following
columns were used: A) 10" x 0.375" od 20% SE-30 on Chromo-
sorb W and B) 50 cm. x 1/8" od 5% OV-101 on Chromosorb W.

Unless otherwise specified, all reactions were performed
under an atmosphere of nitrogen. Yields are not optimized.

Benzene and toluene were distilled from calcium hydride
and stored over sodium. Benzaldehyde, isobutyraldehyde and
ethanol were distilled prior to use and dried over Fisher
molecular sieves, Type 4A (mesh 10 - 16). The petroleum eth-
er used in chromatography was low boiling (35 - 60°C). MCPBA
is Aldrich technical grade (85% pure). This has been taken
into account when calculating weights.

Part A - Preparation of Starting Material

Preparation of Phosphonates

Methyl 2-Diethylphosphonoacetate 155 was prepared according
to the method of House, Jones and Frank 163 in 85% yield;
bp 113 - 121°C/2 Torr; lit. 163 bp 113°C/9 Torr.

Methyl 2-Diethylphosphonocinnamate 147 was prepared by the
method of McIntosh and Sieler 143 in 68% yield; bp 130 - 160
°C/0.6 Torr; lit. 143 bp 160 - 165°C/1 Torr.
Methyl 2-Diethylphosphono-4-methyl-2-pentenoate 148

To a stirred solution of isobutyraldehyde (11.97 g, 0.166 mol) and phosphonate 155 (6.99 g, 0.0333 mol) in 250 mL benzene was added a mixture of 1.5 mL acetic acid and 0.50 g piperidine. The solution was heated at reflux under a Dean-Stark water separator for 5 days. The reaction was monitored by glc (Column A, 150 - 250°C) and appeared to be complete after 55 hours. Heating was continued for an additional 65 hours. The solvent was removed and the residue distilled to give 7.39 g (90%) of vinylphosphonate 148 as a mixture of diastereoisomers which was 98% pure by glc. Bp 97 - 105°C/0.5 - 1.1 Torr (yellow oil); ir (CHCl₃): 2978, 1726, 1380, 1256, 1055, 1027 cm⁻¹; H nmr (CDCl₃): 6.66 (dd, J=23, 10 Hz), 4.03 (m, 4), 3.74 (s, 3), 2.94 (m, 1), 1.31 (t, 6, J=6 Hz), 1.01 (d, 6, J=7 Hz); C nmr (CDCl₃): see Table 1; ms(FI): 265 (37), 264(100, M⁺).

Preparation of α-Mercaptocarboxyl Compounds

α-Mercaptoacetaldehyde 144 was purchased from the Aldrich Chemical Company in the form of its dimer, p-dithiane-2,5-diol (mp 149 - 150°C).

3-Mercapto-2-butane 145 was prepared according to the method of Hromatka and Haberl 160 in 55% yield. Bp 48 - 53°C/19.5 Torr; lit. bp 39°C/8 Torr.
2-Mercaptocyclohexanone \(146\) was prepared by the method of Aisinger\(^{161}\) et al. in 50\% yield. Mp 136 - 144°C (colorless powder); \(^{161}\) lit. mp 145 - 146°C (propanol or chloroform).

Part B: Preparation of Dihydrothiophenes

2-Phenyl-3-carbomethoxy-2,5-dihydrothiophene \(149\) was prepared by a variation of the literature procedure.\(^{144}\) A suspension of mercaptan \(144\) (2.5 g, 0.033 mol) in 250 mL of methylene chloride containing triethylamine\(^{-}\) (5.26 g, 0.052 mol) was heated to reflux. A solution of vinylphosphonate \(147\) (5.96 g, 0.020 mol) in 50 mL of methylene chloride was added dropwise to the refluxing solution. After 14 hours, the solution was cooled, diluted with 200 mL of methylene chloride, washed with water (2 x 100 mL), 5\% hydrochloric acid (2 x 150 mL), dried, and the solvent evaporated. The crude yellow oil (4.38 g, 100\%) was chromatographed on alumina (135 g) using 1:1 ether:petroleum ether as the eluting solvent. Fractions of 50 mL were collected. The first 300 mL contained 2.08 g (47\%) of dihydrothiophene \(149\) as colorless needles; mp 70 - 71°C; \(^{144}\) lit. mp 66 - 68°C.

2-Phenyl-3-carbomethoxy-4,5-dimethyl-2,5-dihydrothiophene \(150\)

In a similar fashion, 8.29 g of a crude pink oil was obtained from mercaptan \(145\) (1.75 g, 0.0168 mol), triethylamine
(2.21 g, 0.0218 mol) and vinylphosphonate 147 (5.0 g, 0.0168 mol) in 84 mL methylene chloride. Compound 150 (2.51 g, 60%) was eluted with 20% ether/petroleum ether from a column of neutral alumina (249 g). Continued elution with 50% ether/petroleum ether gave 0.46 g (11%) of product. This oil was triturated with cold n-hexane to give colorless needles; yield: 2.97 g (71%); mp 60 - 61°C; ir (n̄at): see Table 3; 1H nmr (CDCl₃): see Table 3; 13C nmr (CDCl₃): see Table 7; ms (FI): 249(17, M+1), 248(100, M+); (EI): 248 (100), 189(78); Anal. calcd. (C₁₄H₁₆O₂S): C 67.71, H 6.49; Found: C 67.85, H 6.55. Further elution with anhydrous ether gave unidentified yellow oils.

2-Phenyl-3-carbomethoxy-2,4,5,6,7,7a-hexahydrobenzo[b]thiophene 151:

From vinylphosphonate 147 (2.0 g, 0.00671 mol), mercaptan 146 (1.05 g, 0.00806 mol) and triethylamine (0.88 g, 0.0087 mol) in 60 mL methylene chloride was obtained 3.58 g (> 100%) of a crude orange-pink oil. Column chromatography on neutral alumina (107 g) using 1:1 ether/petroleum ether eluted 2.38 g (ca. 100%) of a yellow oil as a mixture of diastereoisomers, which was greater than 90% pure by glc (Column A, 150 - 250°C). The ir, 1H nmr, and ms were consistent with literature values for 151. 13C nmr (not previously reported) (CDCl₃):
see Table 7); ms (FI): 275(15,M+1), 274(100,M+1).

2-Isopropyl-3-carbomethoxy-2,5-dihydrothiophene 152

To a stirred solution of mercaptan 144 (1.83 g, 0.0240 mol) and triethylamine (2.96 g, 0.0293 mol) in 100 mL methylene chloride was added vinylphosphonate 148 (4.25 g, 0.0173 mol) in 50 mL of the same solvent. After 2 days at reflux, the reaction was worked up to yield 4.10 g (> 100%) of a crude oil. Chromatography on a column of neutral alumina (114 g) using 1:1 methylene chloride/ether produced 2.07 g (ca. 100%) of a yellow oil. Glc (Column A; 150 - 250°C) indicated that 152 was greater than 90% pure. ir (neat): see Table 3; 1H nmr (CDCl₃): see Table 3; 13C nmr (CDCl₃): see Table 7; ms (FI): 186(100, M+).

2-Isopropyl-3-carbomethoxy-4,5-dimethyl-2,5-dihydrothiophene 153

To a stirred solution of mercaptan 145 (1.70 g, 0.0163 mol) and triethylamine (1.78 g, 0.0176 mol) in 51 mL of methylene chloride was added vinylphosphonate 148 (2.0 g, 0.00812 mol) in 17 mL methylene chloride. The solution was refluxed for 9 days and followed by glc (Column A, 150 - 250°C). After workup, 3.20 g of a crude oil was obtained which glc (Column A, 150 - 250°C) showed to contain a 1:1 mixture of vinylphosphonate 148 and 4,6-dithia-3,7-dimethyl-2,8-nonandione 163.
along with a small amount of product. This material was chromato-
graphed on neutral alumina (125 g) using 20% ether/pet-
roleum ether as eluant. A yellow oil (0.54 g, 31%) whose
spectroscopic characteristics supported the dihydrothiophene
structure was eluted in the first 1500 mL. This material
was approximately 90% pure by glc (Column A, 150 - 250°C).
Ir (neat): see Table 3; $^1$H nmr (CDCl$_3$): see Table 3; $^{13}$C
nmr (CDCl$_3$): see Table 7; ms (FI): 215(12, M+1), 214(100,
M$^+$).

Later fractions contained starting mercaptan 145 and vinyl-
phosphonate 148. From the last fraction 0.74 g of 4,6-dithia-
3,7-dimethyl-2,8-nonandione 163 was obtained as a yellow oil.
This was a single peak on glc (Column A, 150 - 250°C) and had
a longer retention time than the product.

Compound 163. ir (CHCl$_3$): 2968, 1708, 1450, 1208, 1062 cm$^{-1}$;
$^1$H nmr (CDCl$_3$): 3.28 (m, 4), 2.12 (s, 6), 1.28 (d, 6, J=7 Hz).

Part C: Peracid Oxidation of Dihydrothiophenes

2-Phenyl-3-carbomethoxy-2,5-dihydrothiophene-1,1-dioxide 164
was prepared by the method of McIntosh and Sieler$^{144}$ in 83%
yield as colorless crystals; mp 169 - 170°C (dec); lit.$^{144}$
mp 170 - 171°C (dec); $^{13}$C nmr (not previously reported$^{144,184}$)
(CDC$_3$)$_3$: see Table 7.
2-Phenyl-3-carbomethoxy-4,5-dimethyl-2,5-dihydrothiophene-1,1-dioxide 165

A stirred solution of dihydrothiophene 150 (2.25 g, 0.00906 mol) in 45 mL methylene chloride was cooled to -10°C in an ice salt bath. To this was added MCPBA (3.12 g, 0.0154 mol) in 11 mL methylene chloride in small portions. The mixture was stirred for 3 hours at -10°C and at ambient temperature for 24 hours. After filtration, the organic layer was washed with saturated sodium carbonate solution (2 x 50 mL), dried and concentrated to give 1.44 g (57%) of a yellow oil. The residue was triturated with cold n-hexane to give 0.59 g (23%) of sulfone 165 as colorless needles; mp 110 - 112°C (n-hexane); ir (KBr pellet): see Table 5; $^1$H nmr (CDCl₃): see Table 5; $^{13}$C nmr (CDCl₃): see Table 7; ms (F1): 281(M+1), 280(100, M⁺), 264(55); (EI): 280(7), 264(M13), 157(100), 142(50); Anal. calcd. (C₁₄H₆S₄): C 59.98, H 5.75; Found: C 59.68, H 5.75.

2-Phenyl-3-carbomethoxy-2,4,5,6,7,7a-hexahydrobenzo[b]thiophene-1,1-dioxide 166

To a cooled solution of dihydrothiophene 151 (1.65 g, 0.00601 mol) in methylene chloride (30 mL) was added, dropwise and with stirring, a solution of MCPBA (2.08 g, 0.0102 mol) in 8 mL of the same solvent to produce 1.28 g (70%) of a mixture of diastereoisomers of sulfone 166 as colorless needles; mp 117 - 120°C (dec) (n-hexane); ir (CHCl₃): see Table 5; $^1$H
nmr (CDCl₃): see Table 5; $^{13}$C nmr (CDCl₃): see Table 7; ms (FI): 306(100, M⁺), 305(50); Anal. calcd. (C₁₆H₁₈O₄S): C 62.72, H 5.92; Found: C 62.32, H 5.92.

2-Isopropyl-3-carbomethoxy-2,5-dihydrothiophene-1,1-dioxide 167

To a cooled solution of dihydrothiophene 152 (2.03 g, 0.0108 mol) in methylene chloride (50 mL) was added, dropwise and with stirring, a solution of MCPBA (9.36 g, 0.0461 mol) in 50 mL of the same solvent to produce 1.51 g (63%) of sulfone 167 as colorless crystals; mp 78 - 80°C (n-hexane); ir (CHCl₃): see Table 5; $^1$H nmr (CDCl₃): see Table 5; $^{13}$C nmr (CDCl₃): see Table 7; ms (FI): 218(23, M⁺), 154(100); Anal. calcd. (C₉H₁₄O₄S): C 49.52, H 6.46; Found: C 49.44, H 6.40.

2-Isopropyl-3-carbomethoxy-4,5-dimethyl-2,5-dihydrothiophene-1,1-dioxide 168

To a cooled solution of dihydrothiophene 153 (0.15 g, 0.000709 mol) in methylene chloride (5 mL) was added, dropwise and with stirring, a solution of MCPBA (0.24 g, 0.0012 mol) in 2 mL of the same solvent to produce 0.12 g (69%) of sulfone 168. Ir and ms analyses showed that incomplete oxidation occurred and some sulfoxide was produced. Attempts to reoxidize the product using 5 equivalents of peracid reac-
ordered severe losses in the workup leading to insufficient amounts for further analysis.

Sulfone - Sulfoxide Mixture. \text{ir (neat): 2964, 1721, 1436, 1310, 1234, 1139, 1080 cm}^{-1}; \text{ms (FI): 247(9, M+1) 246(12, M+), 230(100).}

Part D: Sulfone Pyrolysis

Injection of crude sulfones 164 - 167 into the injection port of the gas chromatograph (Column B, except for 167 (Column A) effected elimination of SO₂ and the dienes were eluted. Peak ratios of the diene stereoisomeric mixtures were recorded by triangulation and compared with those derived from pot pyrolyses. Peak ratios are reported in Tables 9 - 13.

Pot Pyrolysis of Sulfones

Methyl 2-vinylcinnamate 169

Sulfone 164 (0.51 g, 0.0020 mol) was suspended in 25 mL of dry toluene and heated at reflux for 20 hours. After 2, 4, and 8 hours, aliquots were withdrawn in an attempt to distinguish the E and Z isomers by comparing nmr and ir. The solvent was removed at reduced pressure and the residue (0.22 g) chromatographed on silica (11 g) using 20% ether/petroleum ether as eluant. 20 mL fractions were collected. The first 80 mL
eluted 0.051 g of a mixture of two isomers in a ratio of 13:87 (glc: Column B, 119°C). The subsequent 40 mL eluted 0.053 g of the isomeric mixture in a ratio of 29:71 (glc: Column B, 119°C). This fraction was contaminated with thiophene which appeared as a blue fluorescent spot on tlc (ms: 218(M+) ). Later fractions (0.037 g) contained what probably is a Diels-Alder dimer (ms: 376(80)).

E/Z 169: ir (neat): see Table 8; 1H nmr (CDCl₃): see Table 8; 13C nmr (CDCl₃): 169.0, 167.7, 139.4, 135.3, 134.2, 133.2, 130.1, 129.7, 128.8, 128.4, 121.0, 116.4, 51.9; ms (FI) (crude pyrolosate): 188(100, M+), 189(72, M+1), 218(31), 219(38); (EI): 18(100), 28(36), 43(37), 129(76), 188(49), 219(36).

Methyl 2-(buten-2-yl)cinnamate 170

Sulfone 165 (0.2 g, 0.00071 mol) was suspended in 5 mL dry toluene and refluxed for 20 hours. Solvent removal gave 0.18 g of a crude oil which was chromatographed on silica gel (9 g) using 20% ether/petroleum ether as eluant. The first 400 mL eluted 0.07 g of a mixture containing three isomers, in a ratio of 6:72:22 (glc: Column B, 119°C). ir (neat): see Table 8; 1H nmr (CDCl₃): see Table 8; ms (FI): 216 (100, M+), 217(14, M+1); (EI): 18(78), 28(100), 32(25), 216 (2); gc/ms: 59, 142, 157, 216.

Further elution with 50% ether/petroleum ether, then methylene chloride gave unidentified yellow oils.
Methyl 2-(1-cyclohexenyl)cinnamate 171

Sulfone 166 (0.1 g, 0.00033 mol) was suspended in 5 mL of dry toluene and refluxed for 10 hours. The reaction was followed by tlc (5% ether/petroleum ether) and glc (Column B, 149°C). After solvent removal, the crude pyrolysate (0.1 g) was chromatographed on silica gel (25 g) using 5% ether/petroleum ether as eluant. 0.053 g of a mixture of 2 isomers (glc: Column B, 149°C) in a ratio of 49:51 was obtained in the first 350 mL of eluant; ir (CHCl₃): see Table 8; ¹H nmr (CDCl₃): see Table 8; ms (FI): 242 (100, M⁺), 243 (15, M+1); (EI): 141(68), 183(100), 242(41).

Methyl 2-vinyl-4-methylpent-2-enoate 172

Sulfone 167 (1.0 g, 0.0046 mol) was suspended in 20 mL of dry toluene and refluxed for 20 hours. The reaction was monitored by tlc (10% ether/petroleum ether) and glc (Column A, 149°C). After solvent removal, 0.32 g of the crude residue was chromatographed on silica gel (3.3 g) using 10% ether/petroleum ether as eluant. 0.20 g of a mixture of two isomers in a ratio of 60:40 was obtained in the first 320 mL; ir (neat): see Table 8; ms (FI): 154(46, M⁺), 202(85), 204 (26), 246(33, 308(54); (EI): 28(100), 79(31), 83(61), 85 (34), 139(43), 154(22), 165(39), 202(91), 204(30).
### TABLE 10

**Diene 169 Ratios\(^a\) from Pot Pyrolysis**

<table>
<thead>
<tr>
<th>Time (hrs.)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>65:35</td>
</tr>
<tr>
<td>0.6</td>
<td>66:34</td>
</tr>
<tr>
<td>1.6</td>
<td>55:47</td>
</tr>
<tr>
<td>2.0</td>
<td>54:46</td>
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<tr>
<td>3.4</td>
<td>53:47</td>
</tr>
<tr>
<td>4.0</td>
<td>49:51</td>
</tr>
<tr>
<td>4.3</td>
<td>46:54</td>
</tr>
<tr>
<td>4.6</td>
<td>46:54</td>
</tr>
<tr>
<td>7.3</td>
<td>36:64</td>
</tr>
<tr>
<td>8.1</td>
<td>35:65</td>
</tr>
<tr>
<td>15.1</td>
<td>24:76</td>
</tr>
<tr>
<td>17.6</td>
<td>27:73</td>
</tr>
<tr>
<td>18.8</td>
<td>23:77</td>
</tr>
<tr>
<td>20.0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) determined by glc (Column B, 119°C)
## TABLE 11

Diene 170 Ratios<sup>a</sup> from Pot Pyrolysis

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>14:75:11</td>
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<tr>
<td>0.6</td>
<td>13:78:9</td>
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<tr>
<td>1.4</td>
<td>13:79:8</td>
</tr>
<tr>
<td>1.9</td>
<td>15:77:8</td>
</tr>
<tr>
<td>2.6</td>
<td>14:76:10</td>
</tr>
<tr>
<td>2.8</td>
<td>15:77:8</td>
</tr>
<tr>
<td>3.6</td>
<td>13:78:9</td>
</tr>
<tr>
<td>4.2</td>
<td>13:80:7</td>
</tr>
<tr>
<td>5.2</td>
<td>12:82:6</td>
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<tr>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>20.0</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> determined by glc (Column B, 119°C)
## TABLE 12

### Diene 171 Ratios\(^a\) from Pot Pyrolysis

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>57:43</td>
</tr>
<tr>
<td>0.6</td>
<td>50:50</td>
</tr>
<tr>
<td>1.0</td>
<td>48:52</td>
</tr>
<tr>
<td>1.6</td>
<td>48:52</td>
</tr>
<tr>
<td>2.0</td>
<td>50:50</td>
</tr>
<tr>
<td>2.7</td>
<td>55:45</td>
</tr>
<tr>
<td>2.7(^b)</td>
<td>50:50</td>
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<tr>
<td>3.75</td>
<td>54:46</td>
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<tr>
<td>5.2</td>
<td>51:49</td>
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<tr>
<td>6.6</td>
<td>49:51</td>
</tr>
<tr>
<td>10.0</td>
<td>50:50(^c)</td>
</tr>
</tbody>
</table>

\(^a\) determined by glc (Column B, 149°C)

\(^b\) 2.7 hrs at reflux + 14 hrs at room temperature

\(^c\) average of 3 injections
TABLE 13

Diene 172 Ratios\textsuperscript{a} from Pot Pyrolysis

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Ratio</th>
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</thead>
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<tr>
<td>2.5</td>
<td>85:15</td>
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<td>4.5</td>
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<tr>
<td>6.25</td>
<td>81:19</td>
</tr>
<tr>
<td>10.75</td>
<td>87:13</td>
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<tr>
<td>20.0</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} determined by glc (Column A, 149°C)
REFERENCES

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95. Reference 12, pp. 119-254.


131. Ibid., 236 (1985).


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147. Reference 6a, p. 152.


152. W. L. Mock, ibid., 97, 3673 (1975).


175. Reference 78, pp. 593-599.
185. Reference 177, pp. 184-192.
186. Reference 144, p. 4432.
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