ALKYLATION OF FURAN WITH 
2-PHENYLTHIOALLYL CHLORIDE

by

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Attempts were made to accomplish \[4 + 3 = 7\] cycloadditions to furan utilizing cations generated from 2-thio substituted allyl chlorides under non-solvolytic \(S_{n1}\) conditions, in analogy to similar reactions reported for cations generated from 2-oxy substituted allyl halides. 2-Phenylthioallyl chloride was prepared from allene and benzenesulfenyl chloride. Attempts to prepare 2-acetylthioallyl chloride from acetylsulfenyl chloride and allene yielded either the desired allyl chloride or a disulfide. Attempts to trap episulfonium ion intermediates during the preparation of the 2-thio substituted allyl chlorides failed. Heterogeneous generation of the cations using silver trifluoroacetate did not yield any furan adducts, but may have resulted in esterification of the allyl chlorides. Silver trifluoromethanesulfonate was used to generate the cations under homogeneous conditions in furan solution. When 2, 6-di-tertbutyl pyridine was used to prevent the accumulation of acid, a product corresponding to that resulting from electrophilic aromatic substitution was obtained. Other bases either yielded tars or apparently reacted with the allyl chlorides. The vinyl sulfide product, 2-phenylthio-3-(2-furyl)-1-propene, was
synthesized independently from 2-phenylthioallyl chloride and lithium di-2-furylcuprate, and was hydrolized to 1-(2-furyl)-2-propanone. The possible use of 2-phenylthioallyl chloride as a synthetic equivalent to acetone is discussed. Projected investigations of the reactions of 2-phenylthioallyl chloride with cuprates, as Grignard reagents, or as cuprates are illustrated.
INTRODUCTION

Various synthetic approaches have been utilized in the syntheses of seven membered rings by the cycloaddition of a four carbon fragment with a three carbon fragment. Such approaches might be used to synthesize 8-oxabicyclo-[3.2.1.]-oct-6-ene-3-one (I) which is a key intermediate in a proposed synthesis of loline.

![Chemical structure of I](attachment://structure.png)

The earliest entry into this ring system was reported by A. W. Fort who obtained (II) in 18% yield as shown below:

![Chemical reaction](attachment://reaction.png)
Cookson et al.\textsuperscript{2} found that reduction of di-$(\alpha$-bromo-benzyl) ketone with sodium iodide in the presence of furan yielded a mixture of cis and trans (II).

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

\[+\text{NaI} \rightarrow \]

\[\text{II}
\]

They speculated that the reactive intermediate might involve an equilibrium of cyclopropanone (IIIA), allene epoxide (IIIB) and 1,3 dipole (IIIC).

\[
\begin{align*}
\text{III} & \quad \Leftrightarrow \\
\text{IIB} & \quad \Leftrightarrow \\
\text{IIIC}
\end{align*}
\]

Posner and Sterling\textsuperscript{3} reported a 20\% yield of (II) from reaction of di-$(\alpha$-bromobenzyl) ketone in furan at \(-78^\circ\text{C}\), with lithium dimethyl cuprate.

Turro and co-workers\textsuperscript{4} reported cycloadditions of conjugated dienes with substituted cyclopropanones.
However, cyclopropanone itself did not undergo the cycloaddition reaction.

H. M. R. Hoffman and co-workers\(^5\) have investigated cycloaddition reactions employing allyl cations as the three carbon fragments. They were able to achieve the first synthesis of the parent compound, (I), using 2-methoxyallyl bromide as a precursor for the allyl cation and furan as the diene:

\[
\text{Cyclopropanone} + \text{allyl bromide} \stackrel{\text{AgOC\textsubscript{CF\textsubscript{3}}} \text{Na\textsubscript{2}CO\textsubscript{3}}}{\longrightarrow} \text{bicyclic ketone (I)}
\]

This reaction resulted in a 15% yield of the bicyclic ketone (I). More recently Hoffmann et al.\(^6\) and Noyori and co-workers\(^7\) have reported more efficient preparations of (I). The recent preparation of (IV)\(^8\) offers another potential route to (I).
Hoffmann et al. have pointed out the lower reactivity of 2-methoxyallyl bromide compared to the corresponding 2-alkylallyl halides. This was not surprising given the previously reported rate retardations observed for 3 oxygen substituents in solvolysis reactions. However, if the cycloadduct formed via an intermediate carbonium ion such as (V), stabilization by the α oxygen substituent could be an important factor in the cycloaddition.

Cation stabilization by a β sulfur atom is well known. Stabilization by an α sulfur substituent is analogous to such stabilization by oxygen. Thus it seemed that the sulfur analogs of the 2-methoxyallyl cation might afford higher yields of cycloadduct in reactions similar to those reported by Hoffmann et al.
Compounds with the general structure (VII) provide precursors for allyl cations such as (VI) and are accessible by addition of sulfenyl halides to allene. Such compounds were prepared and experiments were investigated in which the cations formed from these compounds under non-solvolytic $S_{n1}$ type conditions would be trapped by furan.

\[ \text{CH}_2=\text{C} \equiv \text{CH}_2 + \text{RSX} \rightarrow \text{C=C=CR}_2 \text{RX} \stackrel{?}{\rightarrow} \text{C=C=CR}_2 \text{R}^+ \]
RESULTS AND DISCUSSION

Addition of benzenesulfenyl chloride (VIII), which was best prepared by the chlorination of thiophenol,\textsuperscript{13} to allene afforded 2-phenylthioallyl chloride (IX). As reported by Mueller and Butler,\textsuperscript{14} this adduct could not be purified. Distillations performed at a variety of pressures yielded no fractionation of the crude reaction mixture. Chromatography on silica gel, Florisil, and neutral alumina resulted in decomposition of the adduct.

\[
\text{VIII} + \text{CH}_2=\text{C}=\text{CH}_2 \rightarrow \text{IX}
\]

In the hope of securing a more stable and hence purifiable 2-thioallyl chloride, the preparation of 2-acetylthioallyl chloride was studied. Mueller and Butler\textsuperscript{14} reported that the mono-adduct (XI) of acetylthiosulfenyl chloride (X) and allene could be purified. Perhaps a similar mono-adduct (XIII) of acetyl sulfenyl chloride (XII) and allene could be prepared and purified.
An additional consideration was the possibility that the acetylthio group could facilitate cation formation by neighboring group participation as shown in Scheme I.

Acetyl sulfide was prepared from thiolacetic acid according to the reported method, and was converted to (XII) using the procedure of Böhme and Clement. Using the procedure of Mueller and Butler, attempts were made to prepare (XIII). Mueller and Butler noted the relatively slow reaction between (X) and allene. A similarly slow reaction between (XII) and allene was observed. When...
the addition mixture was stirred at -30°C for four hours, the color of the sulfenyl chloride persisted. Even after stirring the mixture at room temperature for up to ten hours, (XII) was not consumed completely.

A pmr spectrum of the reaction mixture contained signals which might correspond to the expected adduct (XIII). However, the integration of the acetyl protons was twice that expected for (XIII). This was probably attributable to the presence of diacetyl disulfide which could have formed by disproportionation of (XII). Small amounts of what corresponded to di-adduct (XIV) and regio-isomeric adduct (XV) were also evident together with an additional unidentified component.

Böhme et al. reported that the addition of (XII) to ethene yielded the disulfide (XVI) rather than the expected sulfide (XVII).
Possibly this example follows a similar reaction course:

The proton chemical shift values for the main adduct were identical to those reported for the addition of \( (X) \) to allene.\(^\text{14} \) Unfortunately, purification of the reaction mixture by distillation, as per Mueller and Butler\(^\text{14} \) failed in this case. The scale of the reaction was not sufficiently large to obtain fractionation of the
mixture and as with (IX), chromatography on all adsorbents utilized resulted in decomposition of the adduct.

As indicated above, addition of sulfenyl halides to unsaturates proceeds via episulfonium ion intermediates (XVIII).

![Chemical Structure](image)

It was this stabilization by sulfur as a neighboring group which we hoped would improve the yield of cycloadduct in this system relative to that achieved by Hoffmann et al. Experiments were undertaken to test the possibility of trapping an episulfonium intermediate during the preparation of (XI) or (IX), i.e., to see if the synthesis of the allyl chlorides and the desired cycloaddition reactions could be combined in a "one-pot" approach.

To this end (XII) was added to allene in the presence of furan. Silver trifluoroacetate and sodium carbonate were also included in the reaction mixture. By precipitating chloride ion with the silver salt, it was
hoped that one could sufficiently extend the lifetime of the episulfonium ions to permit trapping by the furan. The sodium carbonate was included, as per Hoffmann et al.\textsuperscript{5} to scavenge any acid which might be formed, as for example:

\begin{align*}
\text{O} + \text{SR} & \rightarrow \text{XIX} \\
& \rightarrow \text{XX}
\end{align*}

Under these heterogeneous conditions considerable polymerization was observed, resulting in most cases in an intractable tar. The reaction mixtures on work-up, yielded yellowish oils which became tarry (even under an inert atmosphere at -20°C) before one could scan their pmr spectra.

Similar procedures were performed using (VIII) in place of (XII). Again considerable polymerization occurred. A pmr spectrum of the methylene chloride extract of this reaction mixture was obtained. The major absorptions were 64.79 (2H, broad s); 5.39 (1H, broad s); 5.59 (1H, broad s); 7.4 (broad multiplet). The ir spectrum (carbon tetrachloride solution) contained carbonyl absorptions at 1680-cm\textsuperscript{-1} and 1780-cm\textsuperscript{-1}. Thin layer chromatography
indicated that the reaction mixture contained diphenyl disulfide but no other products were separated. Hoffmann and co-workers,\textsuperscript{5,19} have reported chemical shifts of 64.67 and 4.78 for the methylene groups in esters (XXI) and (XXII) respectively.

\[ \text{XXI} \quad \text{XXII} \]

The similar "methylene" chemical shift in this reaction mixture together with the carbonyl absorptions suggested the possibility of esterification of (IX) to yield either (XXIII) or (XXIV) or a mixture of these or some other esters.
A control experiment was performed in which furan was omitted from the reaction mixture. This experiment yielded somewhat simplified spectra which contained the same major pmr signals and also the same carbonyl stretching frequencies in the ir which were observed with the furan present. Whatever the major products were in this complicated system, it was concluded that no furan had been incorporated in them.

One additional experiment was performed before abandoning the "one-pot" approach. Benzenesulfenyl chloride and silver trifluoroacetate were observed to react with each other. One possible sequence of events in this system is shown below.\textsuperscript{20,21} This scheme can account for

\[
\text{Scheme III}
\]

the observed instability of the reaction products, the
observed formation of disulfide in the reaction mixtures, and can partially account for the spectra. It is apparent that the materials are incompatible for successful "one-pot" cycloaddition.

A two-step strategy was investigated next. Utilizing the procedure of Hoffman et al.\textsuperscript{5} but substituting (IX) for 2-methoxyallyl bromide yielded inconclusive results. A white solid, presumed to be silver chloride, precipitated immediately upon addition of silver trifluoroacetate to the furan solution of (IX). As with the findings of Hoffman and co-workers,\textsuperscript{5} the reaction mixture was very tarry. A pmr spectrum of the reaction mixture contained, in addition to several new signals, primarily signals corresponding to the starting material (IX).

Hoffman et al.\textsuperscript{19} have pointed out the possible importance of heterogeneous reaction conditions in their cycloaddition reactions. If the absorption of the cation and diene on the surface of the silver salt played an important role in the cycloaddition, then perhaps the substitution of an \(-\text{S} - \phi\) grouping for the \(-\text{O-CH}_3\) grouping exceeded the steric requirements of the adsorption site. Also in contrast to the methoxy system, possible co-ordination between silver and sulfur would destabilize the bicyclic carbonium ion (XIX). In any case, it seemed that in this system, heterogeneous reaction conditions were not advantageous.
Efforts were directed toward development of homogeneous conditions.

A solution of silver trifluoroacetate was prepared in a mixture of furan and benzene. To this stirring, homogeneous solution was added (IX). As with the heterogeneous reaction conditions, a white precipitate formed immediately. After twenty hours, the solid was filtered from the reaction mixture and rinsed with methylene chloride. The filtrate was concentrated on a rotary evaporator to yield a yellow oil.

The recovered solid was shown (by ir) to contain some unreacted silver trifluoroacetate. The bulk of the material was insoluble in water but completely soluble in ammonia. This strongly suggested that the bulk of the solid was silver chloride.

The pmr spectrum of the liquid residue contained signals with the same chemical shifts as (IX), while the infrared spectrum contained ester absorptions. Further characterization of this material could not be accomplished because of its rapid (within thirty minutes) decomposition to tar. Under these reaction conditions, no incorporation of furan was observed, but esterification of (IX) by trifluoroacetate anion was possible. Treatment of the liquid residue with silver nitrate solution yielded no precipitation, thus indicating the absence of unreacted (IX).
As Hoffmann et al. have pointed out, the selection of the anion in the silver salt can have an important effect on the outcome of these reactions. In an attempt to use less nucleophilic counter ions, silver tetrafluoroborate and silver trifluoromethanesulfonate were studied.

Silver trifluoromethanesulfonate (XXIX) was prepared using the known procedure and was found to be completely soluble in furan. To a solution of this silver salt in furan was added (IX), dropwise at room temperature. Upon the addition of the first few drops of (IX), a violent, exothermic reaction was observed which resulted in a viscous tar. An ethereal extract of this tar was treated with aqueous bicarbonate, dried and concentrated to yield an oil whose pmr spectrum consisted of 61.75(s), 3.95(s), 6.05(m), 6.2(m), and 7.35(m). Thin layer chromatography indicated at least four components were present in the mixture. No fractionation of the mixture was obtained by bulb to bulb distillation. Unfortunately, no structural assignments were possible for these products.

The appearance of the pmr signals at 66.05 and 6.2, corresponding to the region where furan β protons absorb, suggested incorporation of furan in the product mixture. No base had been used in this reaction mixture. One could envision proton elimination taking place in this
system, whether cycloaddition or electrophilic substitution occurred:

$$\text{XXV}$$

In the case of the trifluoromethanesulfonate anion, the strong acid which would accumulate almost certainly would polymerize furan, vinyl sulfide (XXV), and bicyclic ether (XXVI). If acid-catalyzed decomposition were responsible for the observed tar formation, the use of a non-nucleophilic base should solve this problem.

2, 6-Di-tert-butyl-pyridine (XXVII) was selected as a base which would satisfy the requirement. The first experiment with (XXVII) employed silver tetrafluoroborate as a source of Ag(I) ion. A stoichiometric amount of (XXVII) was added to a solution of silver tetrafluoroborate in furan and then (IX) was added dropwise. Unlike previous experiments, no white precipitation was observed; a brownish gel-like material formed. A work-up identical to that used for the previous silver trifluoromethanesulfonate
experiment yielded an oil whose pmr spectrum was identical to that of (IX). There was no evidence suggesting incorporation of furan in the product mixture nor was there any indication of reaction between (IX) and (XXVII).

To a solution of (XXIX) in furan a solution of (IX) and (XXVII) in furan was added dropwise at room temperature. A white precipitate immediately formed. No change in temperature of the reaction mixture was noted, nor was there any tar formation.

After forty-eight hours, the unreacted furan was evaporated at room temperature, the residue taken up in ethyl acetate and filtered to remove the precipitated silver salts. A pmr spectrum of the oil obtained from concentration of the filtrate contained signals corresponding to (IX), (XXVII) and new signals at 63.4, 5.0, 5.1, 6.0, and 6.2. Further work-up of the crude mixture was undertaken: a water wash was used to remove di-tert-butyl-pyridinium-trifluoromethanesulfonate; washings with up to 5% aqueous hydrochloric acid did not remove unreacted (XXVII), but following these washes pmr signals corresponding to (IX) disappeared. Stronger acid washes were not attempted because of the acid sensitivity of the reaction mixture.

Distillation of the reaction mixture yielded no fractionation of the mixture and no observable
decomposition. Separation was achieved by chromatography on silica gel using 10:1 (v/v) pentane to benzene as eluent. Three principal bands were obtained with $R_f$'s as follows: 0.9 corresponding to (XXVII); 0.25; and 0.2 corresponding to a furan adduct. The material with $R_f$ 0.25 yielded a pmr spectrum identical to that of (IX), but no precipitate formed upon treatment with silver nitrate. The ir contained no OH stretching absorption. This material was not characterized further but was probably the ether (XXVIII), formed as the hydrolysis product of (IX). Characterization and structural proof for the furan adduct were accomplished by a combination of chemical and spectral evidence, including independent synthesis.

\[
\begin{align*}
\text{Furan} + \text{Ph} \text{Cl} & \quad \text{XXVII} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ag} \text{SO}_2 \text{CF}_3 & \quad \text{XXIX} \\
\text{XXV} \\
\text{SPh} \text{Cl} + \text{H}_2 \text{O} & \quad \text{XVIII} \\
\text{SPh} \text{O} \text{SPh} & \quad 17 \\
\end{align*}
\]

Similar procedures using other bases did not yield any furan adducts. The use of sodium carbonate necessitated heterogeneous reaction conditions (for lack of a suitable solvent) and resulted in polymerization of the
reaction mixture. When 1, 8-bis-(dimethylamino)-naphthalene was substituted for (XXVII) a tar was again the result. Using 2, 6-lutidine or ethyl-diisopropylamine apparently yielded alkylation of the bases.

Two structures, (XXV) and (XXVI) seemed possible for the furan adduct. The initial target compound of our synthesis was 8-oxabicyclo-[3.2.1.]oct-6-ene-3-one (I). If (XXVI) was the product of our attempted cycloaddition, it was anticipated that (I) would be obtainable by hydrolysis using methods similar to those described by Corey and Shulman,²³ and Trost and Stanton.²⁴

\[
\begin{align*}
\text{HgCl}_2 & \quad \text{CH}_3\text{CN/H}_2\text{O} \\
\text{XXVI} & \quad \text{H}^-\text{Ph} \\
\text{\textarrow{\right}} & \quad \text{pTsOH} \quad \text{\textarrow{\left}} \\
\text{I} & \quad \text{\textarrow{\left}} \quad \text{\textarrow{\right}} \\
\end{align*}
\]

Scheme IV

Synthesis of (I) according to the method reported by Noyori et al.⁷ was undertaken in order to provide authentic bicyclic ketone for comparison with our hydrolysis product and also to provide a possible alternative synthesis of (XXVI). Attempts to transform (I) into
(XXVI) using thiophenol and catalytic amounts of p-toluenesulfonic acid resulted in tar formation.

Hydrolysis of the furan adduct was accomplished by treatment with an equimolar amount of mercury (II) chloride in refluxing aqueous acetonitrile (2:3, v/v) for fifty-six hours yielding (XXXII). The product of electrophilic aromatic substitution, (XXV), could be envisioned to arise either by direct substitution or by fragmentation of a bicyclic intermediate like (XXVIII).

XXVII

Scheme V

Hoffmann et al.\textsuperscript{25} have reported that the reaction of the 2-methyl allyl cation with furan yields the alkylated product (XXX):
It has also been reported that the bicyclic ketone (II) rearranges to the substituted furan (XXXI) in the presence of acid or base.\textsuperscript{26}

Similarly hydrolysis of either (XXV) or (XXVI) could yield 1-(2-furyl)-2-propanone (XXXII).
The ketone (XXXII) is reported\textsuperscript{27} to be a constituent of coffee aroma. The only published spectrum found for this compound is the infrared which appears in the Sadtler indices.\textsuperscript{28} The carbonyl absorption of the above mentioned hydrolystate (XXXII) fell at 1725 cm\textsuperscript{-1} (Figure 1). The position of the carbonyl in the published spectrum is 1690 cm\textsuperscript{-1} which is more typical of a carbonyl conjugated with an aromatic nucleus than the isolated carbonyl in (XXXII). Clearly, there was a disagreement of the infrared spectra. The pmr of our hydrolystate (Figure 2) contains absorptions at 62.05(3H,s); 3.6(2H,s); 6.2(2H, unresolved multiplet); 7.25(1H,m). The methyl and methylene absorptions reported for 3-(2-N-methyl pyrrolyl)-2-propanone are at 62.05 and 3.6 respectively.\textsuperscript{29}

An independent synthesis of (XXXII) was undertaken. The condensation of furfural and nitroethane afforded nitroalkene (XXXIII) which upon reduction using cast iron turnings and hydrochloric acid yielded (XXXII).\textsuperscript{30}
Figure 1. IR Spectrum of 1-(2-furyl)-2-propanone.
Figure 2. PMR Spectrum of 1-(2-furyl)-2-propanone.
The pmr and ir spectra and glc retention times of this material were identical to the parameters obtained for the hydrolysis product of the furan adduct. This demonstrated that the ir spectrum published in the Sadtler indices was not correctly identified.

An independent synthesis of (XXV) also seemed appropriate. 2-Furyllithium was prepared from n-butyllithium and furan and (IX) was added to the stirring suspension. The pmr of the resulting reaction mixture contained signals corresponding to (XXV) but only as a minor product. The major product of this reaction appeared to be (XXXIV). It would not be surprising for the strongly basic furyllithium to isomerize the double bond into conjugation.

The 2-furyllithium was again prepared and converted to the corresponding di-aryl cuprate (XXXV) using copper (I) iodide. Alkylation in an ethereal solution using (IX) yielded (XXV) in 75% yield with no (XXXIV) detectable in the pmr. Spectral parameters and glc retention times for
(XXV) were identical to the data for the furan adduct. This proved that the structure of the furan adduct is (XXV).

\[ XXXV \quad \xrightarrow{\text{CuLi}} \quad \text{SPh} \quad \xrightarrow{\text{Cl}} \quad \text{XXV} \]

Hydrolysis of (XXV) prepared via the cuprate yielded (XXXII), spectral parameters identical to the authentic material.

Attempts were made to prepare a crystalline derivative of (XXV) via Diels-Alder reactions using maleic anhydride, fumaryl chloride, and tetracyanoethylene (TCNE) as dienophiles. Reaction was observed with TCNE to yield an intensely red colored oil, but insufficient material was produced to obtain IR and PMR spectra. No reaction was observed with the other dienophiles.

The mass spectrum of (XXV) (Figure 3) contains the molecular ion at m/e 216 (100%). The first major fragmentation peak falls at m/e 135 (94%) which corresponds to the expected cleavage of an alkylated furan to the ring. Other major fragments in the spectrum were m/e 187 (20%).
Figure 3. Mass Spectrum of 2-Phenylthio-3-(2-furyl)-1-propene.
106 (78%); 91 (85%); 81 (25%); 77 (44%); 65 (18%); 39 (74%); and 28 (48%).

The pmr spectrum (Figure 4) (carbon tetrachloride solution) consists of 63.5 (2H, s); 5.0 (1H, s); 5.15 (1H, unresolved m); 6.0 (1H, d); 6.2 (1H, dd); 7.25 (6H, m); \(J_{bc} = 3.6\text{cps}\); \(J_{ab} = 1.8\text{cps}\).

The singlet at 63.5 is broadened, probably because of long range coupling with \(H_e\) and \(H_c\) whose signals at 65.0 and 6.0 respectively are similarly broadened.

The cmr signals (Figures 5 and 6) (hexadeutero-acetone solution), together with off-resonance decoupled multiplicities were as follows: (All values are ppm downfield from TMS) 636(C_h, t); 107(C_g, d); 110(C_f, d); 115(C_e, t); 128(C_d, d); 129(C_c, d); 134(C_b, d); 142(C_a, d).
Figure 4. PMR Spectrum of 2-Phenylthio-3-(2-furyl)-1-propene.
Figure 5. Broad Band Decoupled CMR Spectrum of 2-Phenylthio-3-(2-furyl)-1-propene.
Figure 6. Off-Resonance Decoupled CMR Spectrum of 2-Phenylthio-3-(2-furyl)-1-propene.
The Ir spectrum (Figure 7) contains absorptions characteristic of a mono-substituted benzene ring.
Figure 7. IR Spectrum of 2-Phenylthio-3-(2-furyl)-1-propene.
SUMMARY AND CONCLUSION

The reaction of the 2-phenylthioallyl cation with furan yields the product corresponding to electrophilic aromatic substitution rather than a cycloadduct. This result is in contrast to the cycloaddition of the 2-methoxyallyl cation to furan, but resembles the alkylation observed with the 2-methylallyl cation and furan.

The counter ion of the silver salt used to generate the cation in situ is of critical importance for the course of the reaction. Trifluoroacetate was found to be too nucleophilic to permit reaction between the cation and furan while the very weakly nucleophilic trifluoromethanesulfonate anion permitted generation of a cation with a sufficiently long life-time for furan trapping. A unique sterically hindered base is also required to protect the reaction mixture against acid catalyzed polymerization.

It is not clear whether the alkylation product is formed directly or is the result of fragmentation of an initially formed bicyclic adduct.

XXXVI

[Chemical structure]

XXXVII

[Chemical structure]
The electron withdrawing effect of the phenyl group in (XXVIII) tends to diminish stabilization of the cation by the lone pairs of the α sulfur atom. It is possible that groups with an electron donating effect could be found, such that the resulting increase in the stability of (XIX) would permit formation of a cycloadduct. A thorough investigation of the 2-alkylthio allyl cations should be fruitful.

![Chemical Diagram]

The successful use of 2-phenylthioallyl chloride as an alkylating reagent with an organo-cuprate promises a new synthetic technique with potentially great utility. The two step sequence consisting of alkylation followed by hydrolysis of the vinyl sulfide product to a ketone constitutes the synthetic equivalent of the addition of an acetone moiety positively charged at the α position:
Facile syntheses of 1,4 dicarbonyl systems may be possible; similar reactions may facilitate a synthesis of cis-jasmon e. The use of phenyl cuprate in place of furyl cuprate should provide a two step synthesis of phenyl-2-propanone which can be converted to amphetamine by reductive amination:

Other examples of difficultly obtained systems may now be accessible in fewer steps.

Alkylations of $\alpha$ halo ketones have been achieved using trialkylboranes and base $^{32}$ and by the use of Grignard reagents. $^{33,34}$ These reactions are synthetically equivalent to our alkylation with cuprates but they do not
proceed via direct displacement and are not generally applicable.

The reagent might also prove useful as the synthetic equivalent of an acetone moiety negatively charged at the \( \alpha \) position such as in the cases of its \( \pi \) allyl complex with Ni or Fe, or as its Grignard reagent, or the organocuprate derivative. These should also provide fertile areas for future investigation,
EXPERIMENTAL

Instrumentation

Melting points were obtained in open glass capillary tubes using a Thomas Hoover capillary melting point apparatus or between microscope cover glasses using a Thermolyne microscope hot stage and are uncorrected. Proton magnetic resonance spectra were obtained using a Varian T-60 or HA-100 spectrometer with tetramethylsilane as an internal standard. Carbon-13 magnetic resonance spectra were recorded on a Bruker WH-90 spectrometer in hexadeuteroacetone with tetramethylsilane as an internal standard. Infrared spectra were taken with Perkin Elmer Models 137, 337 or Infracord spectrophotometers. Mass spectra were recorded on a Hitachi Perkin Elmer model RMU 6-E mass spectrometer at an ionizing current of 70 ev. Gas-liquid phase chromatography was performed on a Varian 1720 gas chromatograph equipped with a thermal conductivity detector, using either $\frac{1}{4}'' \times 6'$ carbowax 20M, 5% NaOH on Chromosorb W or $\frac{1}{4}'' \times 5'$ SE-30 on Chromosorb W columns.

General

All glassware was dried by baking at 120°C for at least eight hours followed by cooling in a vacuum desiccator containing anhydrous calcium sulfate. Nitrogen and argon
were dried by passage through a calcium sulfate drying
tower and were freed of residual oxygen by passing through
a tower filled with BTS catalyst from BASF.

Materials

Thin layer chromatography (TLC) was carried out
using Brinkmann HF 254 type 60 silica gel (prep plates 1mm
thick), Floridin Florisil, or Macherey Nagel neutral alu­
mina. For column chromatography, ICN 70-230 mesh silica
gel was used.

All solvents used were commercial reagent grade
chemicals. Ethyl ether and tetrahydrofuran were degassed
and dried before use by freezing in liquid nitrogen, evacu­
ating by oil pump and refilling with dry, oxygen-free argon
or nitrogen followed by distillation from lithium aluminum
hydride. Furan, carbon tetrachloride, and methylene chlo­
rude were degassed as above and dried by distillation from
calcium hydride.

Allene and chlorine were reagent grade gasses used
as obtained from Matheson. Thiophenol and thiolacetic acid
were obtained from Aldrich and were freshly distilled at
reduced pressure and placed under an anaerobic atmosphere
prior to use. Pyridine, lutidine and diisopropyl­
ethylamine were distilled under an anaerobic atmosphere
from calcium hydride. 2, 6-Di-and 2, 4, 6-tri-tert­
butyl pyridine were prepared using tert-butyl lithium from
Alfa according to the procedure of Scalzi and Golob. 6-Di-tert-butyl-pyridine was also obtained from Willow Brook and from Chemical Samples. n-Butyllithium (1.6M in hexane) and silver tetrafluoroborate were Alfa products. Silver trifluoromethanesulfonate was prepared according to the literature procedure and was recrystallized from benzene 8x and dried in a vacuum oven before use. Silver trifluoroacetate was prepared according to the procedure reported in the literature. Baker reagent grade 30 mesh zinc and Matheson-Coleman reagent cupric acetate monohydrate were used to prepare zinc-copper couple. Mercury (II) chloride was Mallinkrodt analytical range. Copper (I) iodide (98%) was obtained from Alfa and was dried with phosphorus pentoxide at 80°C and 50μ in a drying pistol.

**Benzenesulfenyl Chloride**

Benzenesulfenyl chloride was prepared from sulfuryl chloride and either thiophenol or diphenyl disulfide. A third method proved most convenient for routine use and is described in detail below.

A dry 11 3-necked round bottom flask containing a magnetic stir bar was fitted with a gas delivery tube, pressure equilibrated addition funnel and an exit hose connected to a mineral oil filled U-tube bubble valve. The apparatus was placed under a dry nitrogen or argon atmosphere, then charged with carbon tetrachloride (450 ml) and
a slow stream of chlorine was introduced under the surface of the solvent. While stirring this solution in an ice-salt bath, a solution of thiophenol (24.75g, 225 mmoles) dissolved in carbon tetrachloride (120ml) was added drop-wise. After completion of the addition, the excess chlorine was immediately removed at reduced pressure (about 35mm) by means of a water aspirator connected through a calcium sulfate drying tower. The solvent was then removed by distillation at atmospheric pressure and the residue thus obtained was distilled under oil pump vacuum to yield benzenesulfenyl chloride as a dark red-brown oil (32.0g, 98% yield): bp 95°C (23mm); pmr (carbon tetrachloride solution) δ7.4(m). Purity of the product was determined by argentometric and iodometric titrations as described below.

**General Procedure for Argentometric Titration**

The air in a 125ml Erlenmeyer flask was replaced by argon and the flask then charged with 0.1N silver nitrate (25ml), concentrated nitric acid (5ml), distilled water (20ml), and ferric ammonium sulfate indicator (2ml). The flask was sealed and weighed and a sample of sulfenyl chloride was introduced by syringe. The weight of the sulfenyl chloride was determined by difference, and the
flask contents were titrated to the faint brown end-point with a standardized solution of potassium thiocyanate.

**General Procedure for Iodometric Titration**

The air in a 125ml Erlenmeyer flask was replaced by argon and the flask was charged with 10% aqueous potassium iodide solution (20ml), concentrated hydrochloric acid (5ml), and carbon tetrachloride (10ml). Sulfenyl chloride was added by syringe and its weight determined by difference as above. The mixture was then titrated to the end-point using standardized sodium thiosulfate.

**Method of Allene Transfer**

A 3-necked reaction flask was equipped with a magnetic stir bar, a tightly secured rubber septum, a 3-way stopcock and a connecting adapter with a stopcock between the flask and a vacuum manifold of calibrated volume. Anhydrous conditions and a nitrogen atmosphere were maintained. The flask was connected to the manifold and the entire system was evacuated with an oil pump. The flask was then closed to the manifold via the stopcock in the connecting adapter, the manifold was filled with allene and the allene was then condensed into the flask by immersing the flask in liquid nitrogen and opening the stopcock between flask and manifold. A mercury manometer directly connected to the manifold was used to record the pressure
changes from which the amount of allene condensed in the flask could be calculated. When the desired amount of allene had been condensed into the reaction flask, the flask was closed to the manifold and nitrogen was introduced through the 3-way stopcock until atmospheric pressure was reached. The 3-way stopcock was then closed and the sealed flask containing a measured amount of allene was removed from the vacuum manifold.

2-Phenylthioallyl Chloride

In a typical run, 170 mmoles of allene were condensed into the reaction vessel as described above, and after removal from the vacuum manifold, the flask was allowed to warm in a bath maintained at -60°C. Excess pressure was released as necessary. While maintaining the bath temperature at -60°C to -40°C, methylene chloride (20ml) was added by syringe followed by freshly distilled benzenesulfenyl chloride (2.41g, 16.64 mmoles) added dropwise by syringe over about twenty minutes. When the color of the sulfenyl chloride disappeared (about five to ten minutes after completion of the addition) the solvent and excess allene were removed by oil pump vacuum at ca. -10°C and a pmr spectrum was immediately obtained on the residue: δ4.02(2H); 5.25(1H); 5.58(1H); 7.25. The product was used without further purification, in most cases immediately
after synthesis. Storage under dry, oxygen free argon or nitrogen at -15°C for up to two weeks resulted in no change in the pmr spectrum.

**Attempted Preparation of 2-acetyltioallyl Chloride**

Attempts to prepare 2-acetyltioallyl chloride employed the same general procedure using acetylsulfenyl chloride\(^\text{16}\) prepared from acetyl sulfide\(^\text{15}\) in place of benzenesulfenyl chloride. Since consumption of acetylsulfenyl chloride was much slower than consumption of benzenesulfenyl chloride, these mixtures were stirred for ten hours at room temperature before removal of allene and solvent. Pmr: \(\delta2.48, 4.23, 5.65, 5.73\).

**Attempted One-pot Cycloaddition Reactions**

In the case of attempted one-pot cycloadditions, the reaction vessel was charged with equimolar amounts of sodium carbonate and silver trifluoroacetate prior to allene transfer, and furan was used in place of methylene chloride as the solvent. After addition of the sulfenyl chloride (mmoles of sulfenyl chloride = mmoles of sodium carbonate = mmoles of silver trifluoroacetate) the flask contents were warmed to room temperature and stirred while protected from light for up to fifty hours. The reactions were worked-up by extraction with methylene chloride (5x)
followed by removal of the solvent on a rotary evaporator, to yield yellowish oils. For the reactions employing acetylsulfenyl chloride, rapid decomposition prevented procurement of spectral data. Spectral parameters for the benzenesulfenyl chloride product mixture were: pmr (carbon tetrachloride solution): δ4.79, 5.39, 5.59, 7.4; ir (carbon tetrachloride solution): 1680 cm⁻¹, 1780 cm⁻¹. A control experiment utilized an identical procedure but methylene chloride was used in place of furan as the solvent. Spectral data for the control reaction were identical to those reported above.

**Attempted Two-step Cycloadditions under Heterogeneous Conditions**

The procedure was identical to the cycloaddition procedure used by Hoffmann et al.⁵ to prepare 8-oxabicyclo-[3.2.1]-oct-6-ene-3-one except 2-phenylthioallyl chloride was used in place of 2-methoxyallyl chloride.

**Alkylation of Furan**

A dry 25ml 1-necked round bottom flask equipped with a magnetic stir bar and fitted with a pressure equilibrated addition funnel was charged with silver trifluorromethanesulfonate (1.926g, 7.5 mmoles). The air in the apparatus was replaced with dry, oxygen free argon. Furan (8ml) was added to dissolve the silver salt and the flask
was wrapped in aluminum foil to exclude light. A solution of freshly prepared 2-phenylthioallyl chloride (1.384g, 7.5 mmoles) and 2, 6-di-tert-butyl-pyridine (1.433g, 7.5 mmoles) in furan (4ml) was added dropwise to the stirring silver salt solution at room temperature over about forty-five minutes. Immediate precipitation of silver chloride was observed but no temperature change occurred. The flask contents were stirred at room temperature while protected from light for sixty-six hours. The flask was then unsealed and stirred at room temperature until the unreacted furan had evaporated. The residue was taken up in ethyl acetate and filtered. The filter and precipitate were washed thoroughly with ethyl acetate and the combined filtrates were washed once with distilled water. The water wash was extracted with ethyl acetate 3x, and the combined organic fractions were dried over anhydrous magnesium sulfate. After removing the drying agent by gravity filtration and again washing the filter, the solvent was removed on a rotary evaporator. The residue thus obtained was subjected to column chromatography using 80g of silica gel on 60cm × 2.5cm of column and eluting with 5:1 (v/v) hexane to benzene. 2-Phenylthio-3-(2-furyl)-1-propene was obtained as a pleasant smelling nearly colorless oil (972 mg, 60% yield). MS: m/e 216(100%), 135(94%), 187(20%). PMR: (carbon tetrachloride solution) δ3.5(2H,s),
5.0(1H,s), 5.15(1H,m), 6.0(1H,d, J = 3.6cps), 6.2(1H,dd, J = 3.6cps and J = 1.8cps.), 7.25(6H,m). CMR: (hexadeuteroacetone solution, ppm downfield from TMS) δ36(τ), 107(d), 110(d), 115(6), 128(d), 129(d), 134(d), 142(d).

2-Furyllithium in Ether

A dry 3-necked round bottom flask containing a magnetic stir bar was fitted with a Dewar condenser, a ground glass stopper, and a tightly fitting rubber septum. The flask was flushed with nitrogen, cooled to -25°C and n-butyllithium (1.6M in hexane, 1.6ml, 2.56 mmoles), ether (4ml), and furan (0.25ml) were added by syringe. The contents were allowed to warm to room temperature and then refluxed for four hours under nitrogen. The resulting suspension of white 2-furyllithium was used immediately.

Lithium di-(2-furyl) Cuprate

A round bottom flask containing a magnetic stir bar was charged with copper (I) iodide (248mg, 1.30 mmoles). The flask was sealed with a tightly fitting rubber septum and the air replaced by dry nitrogen. The flask was cooled in an ice water bath and ether (10ml) was added. A suspension of 2-furyllithium in ether was then added dropwise by syringe. The mixture was stirred under a nitrogen atmosphere at 0°C for four hours.
Alkylation of di-(2-furyl) Cuprate

At 0°C 2-phenylthioally chloride (240 mg, 1.30 mmoles) was added dropwise by syringe to the stirring lithium di-(2-furyl) cuprate solution prepared as described above. After completion of the addition, the flask contents were stirred at 0°C for an hour and then allowed to warm to room temperature and stirred overnight. The reaction was quenched by the careful addition of distilled water (10ml). The insoluble material was removed by gravity filtration. The aqueous phase was separated and extracted with ethyl acetate (3x). The combined organic fractions were dried over anhydrous magnesium sulfate then concentrated on a rotary evaporator. The residue was subjected to preparative thin layer chromatography on silica gel, using 10:1 (v/v) hexane to benzene as eluent. 2-Phenylthio-3-(2-furyl)-1-propene was obtained as an oil (211mg, 75% yield), spectral data identical to that reported above.

Hydrolysis of 2-phenylthio-3-(2-furyl)-1-Propene

2-Phenylthio-3-(2-furyl)-1-propene (108mg, 0.5 mmoles) was dissolved in acetonitrile (3ml) and distilled water (2ml) in a nitrogen filled round bottom flask containing a magnetic stir bar. Mercury (II) chloride (136mg, 0.5 mmoles) was added and the mixture stirred at reflux
under nitrogen in an 80°C bath. Within one hour a greyish-white precipitate of mecuric sulfides began to develop. After fifty-six hours the mercuric salts were removed by gravity filtration. The flask and filter were thoroughly rinsed with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (2x). The combined organic layers were dried over magnesium sulfate and concentrated on a rotary evaporator. The residue was applied to a silica gel preparative TLC plate and eluted with 3:1 (v/v) hexane to benzene to yield 1-(2-furyl)-2-propanone (22.0mg), \( R_f \) 0.15 and recovered 2-phenylthio-3-(2-furyl)-1-propene (25.4mg), \( R_f \) 0.65. This corresponds to a 42% yield of the ketone based on consumed sulfide. Spectral parameters for the ketone are: PMR (carbon tetrachloride solution) \( \delta 2.05(3H,s), 3.6(2H,s), 6.2(2H, \text{multiplet}), 7.25(1H,m) \); IR(neat) 1725 cm\(^{-1}\).

**Authentic 1-(2-furyl)-2-Propanone**

Authentic 1-(2-furyl)-2-propanone was prepared by reduction of 1-(2-furyl)-2-nitro-1-propene as described in the literature.\(^3\)
Preparation of 8-oxabicyclo-[3.2.1.]-oct-6-ene-3-one

α, α, α', α'-Tetrabromoacetone

Acetone was distilled from anhydrous magnesium sulfate and was converted to tetrabromoacetone by the reported method. Melting point, boiling point and ir carbonyl absorptions corresponded to those reported in the literature, but the position of the singlet in its pmr spectrum in carbon tetrachloride solution varied with concentration from 66.14 to 7.0.

Diiron nonacarbonyl

Iron pentacarbonyl was converted to diiron nonacarbonyl by irradiation with a Hanovia 450 watt mercury lamp in an ice water cooled quartz immersion well.

Cis and trans-2, 4-dibromo-8-oxabicyclo-[3.2.1.]-oct-6-ene-3-one

The cyclocoupling reaction described by Noyori et al. afforded a mixture of the cis and trans dibromo ketones. The yield achieved in our hands varied from 20% to 45% using the same reaction scale reported by Noyori and co-workers.
Reduction of cis and trans-2, 4-
dibromo-8-oxabicyclo-[3.2.1]-
oct-6-ene-3-one

Zinc copper couple was prepared by the known method. The reduction was followed by thin layer chromatography, on silica gel using 5:1 (v/v) hexane to ethyl acetate. The TLC data indicated that a reaction of up to one hour was required for complete reduction, compared to the ten minute reaction time reported by Noyori.
LIST OF REFERENCES


42. R. Noyori, Professor of Chemistry, Nagoya University, private communication, February 13, 1976.