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Carbon Alkylation of 2-Phenylthio-1,3-cyclopentanediones

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CARBON ALKYLATION OF 2-PHENYLTHIO-1,3-CYCLOPENTANEDIONES

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ABSTRACT

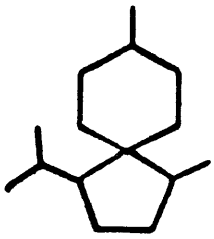
The intent of this work was to investigate the carbon alkylation of 2-phenylthio-1,3-cyclopentanedione. The 2-alkyl-2-phenylthio-1,3-cyclopentanediones are precursors to the 2-alkylidene-1,3-cyclopentanedione systems, a highly reactive and synthetically useful intermediate. Allyl bromide and methyl vinyl ketone adducts were prepared. The preparation of 2-alkyl-2-phenylthio-5,5-dimethyl-1,3-cyclohexanedione analogs was also accomplished. Ozonolysis of the allyl side chain was also investigated. In addition to preparing and characterizing the carbon alkylated precursors, attempts were made to cyclize the methyl vinyl ketone adduct.

CARBON ALKYLATION OF

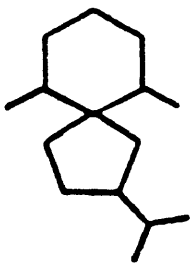
2-PHENYLTHIO-1,3-CYCLOPENTANEDIONES

INTRODUCTION

The 2-alkylidene-1,3-cyclopentanedione (1) system is a versatile synthetic intermediate owing to its potential for carbon-carbon bond formation. This system provides for the introduction of a functionalized cyclopentanedione moiety via a variety of reactions (Scheme 1). The synthetic importance of this system becomes apparent in light of the current emphasis on the synthesis of cyclopentanoid natural products. Trapping the alkylidene intermediate as a Diels-Alder adduct (Reaction 1) provides a route to the spiro[4.5]decane ring system.[1] The spiro[4.5]-decane sesquiterpenes have been the target of much synthetic effort. The basic spirocyclic carbon skeleton encompasses several types of natural products, including the acoranes and spirovetivanes. Specific synthetic

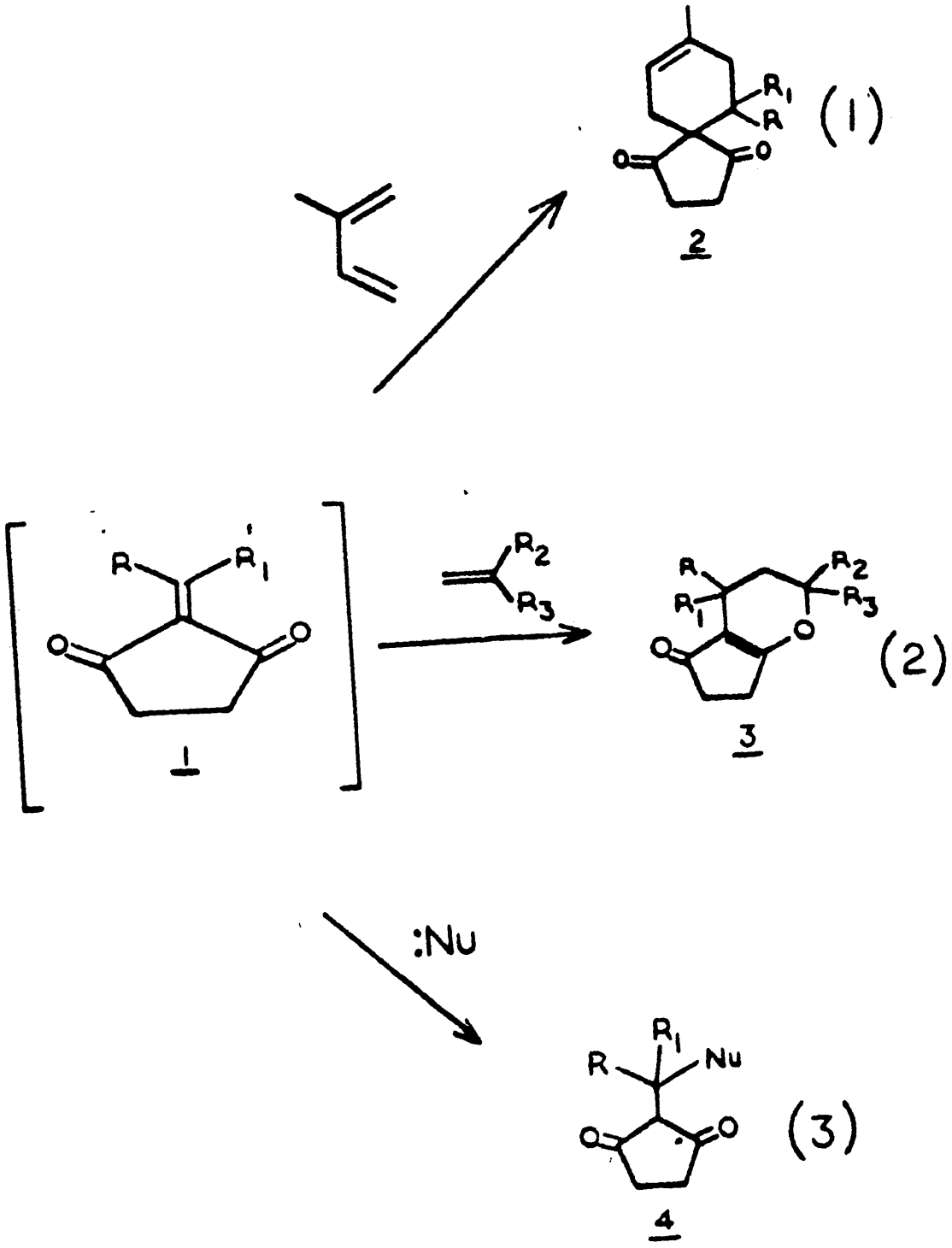


ACORANES



SPIROVETIVANES

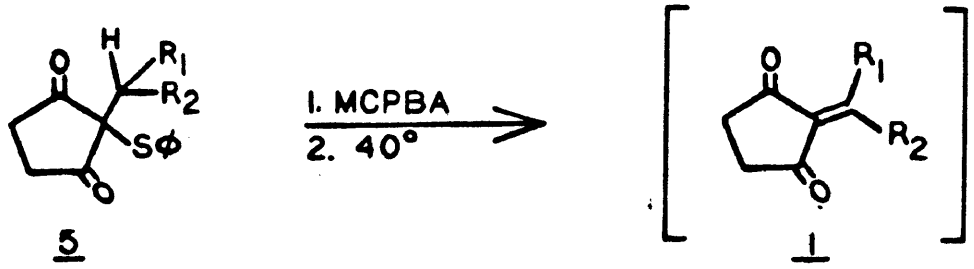
routes to these natural products have been developed.[2] In addition, the versatility of these spirocyclic compounds as synthetic intermediates has



SCHEME 1

been exploited in the synthesis of more complex systems such as quadrone[3] and prostaglandin analogs.[4] The enormous synthetic utility of these intermediates makes the development of a general route to flexibly functionalized spiro[4.5]decane ring systems highly desirable.

Literature examples of ene-diones such as 1 are rare. A very few derivatives have been reported.[5] Recently, a general method for the preparation of these systems has been developed (Scheme 2).[1] This

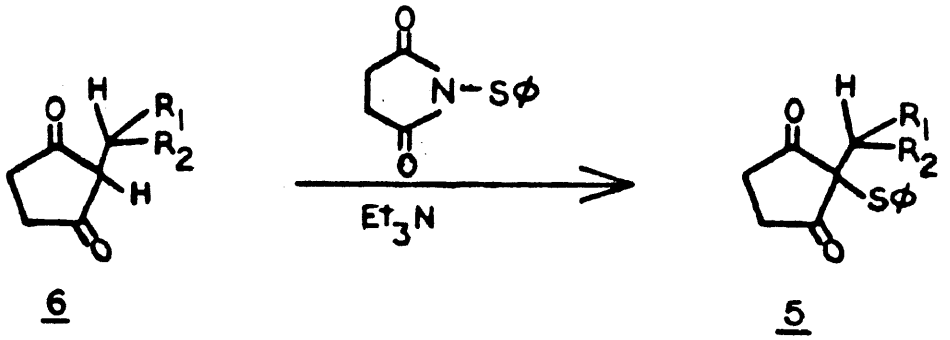


5 1

SCHEME 2

method involves the oxidative elimination of phenylsulfenic acid from sulfide 5 to generate the desired ene-dione. Preparation of the 2-alkyl-2-phenylthio-1,3-cyclopentanedione (5) precursors is a key step in the synthesis of the 2-alkylidene-1,3-cyclopentanediones (1). One route to these precursors involves the sulfenylation of 2-alkyl-1,3-cyclopentane-diones (Scheme 3).[1] This method has some disadvantages, the principal one being the difficulty encountered in preparing the 2-alkyl-1,3-cyclo-pentane-dione precursors (6). Alkylation of 1,3-cyclopentanedione at the 2-position is especially difficult. Alternatively, condensation of open chain

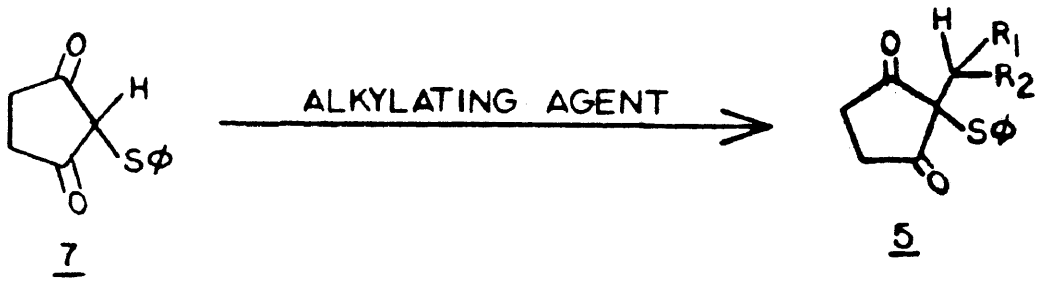
compounds to yield the desired 2-alkyl-1,3-cyclopentanediones (6) involves



6 5

SCHEME 3

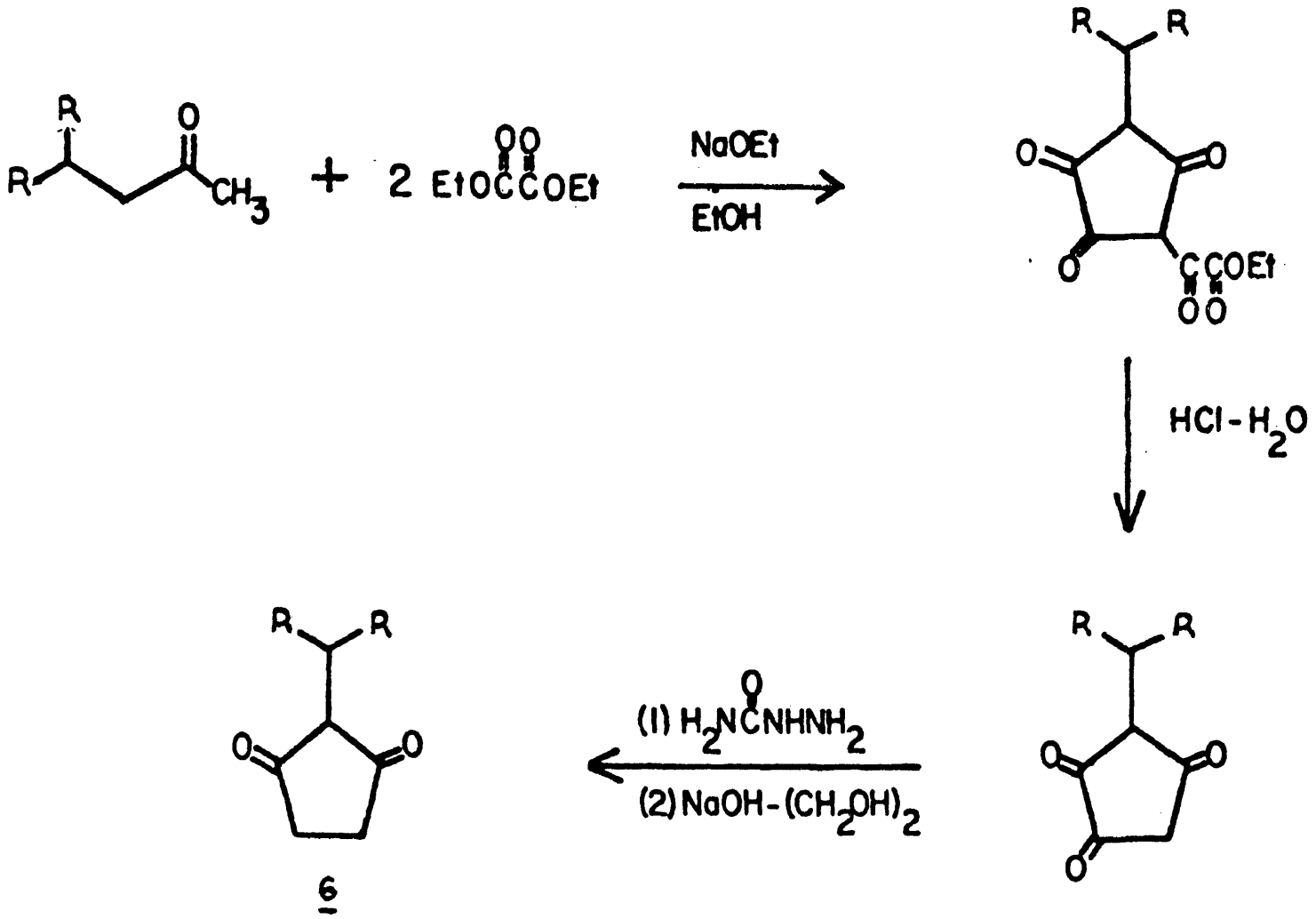
several steps with the concomittant material losses (Scheme 4).[6] A complimentary method for preparing 5 involves the carbon alkylation of 2-phenylthio-1,3-cyclopentanedione (Scheme 5). This second method has the



7 5

SCHEME 5

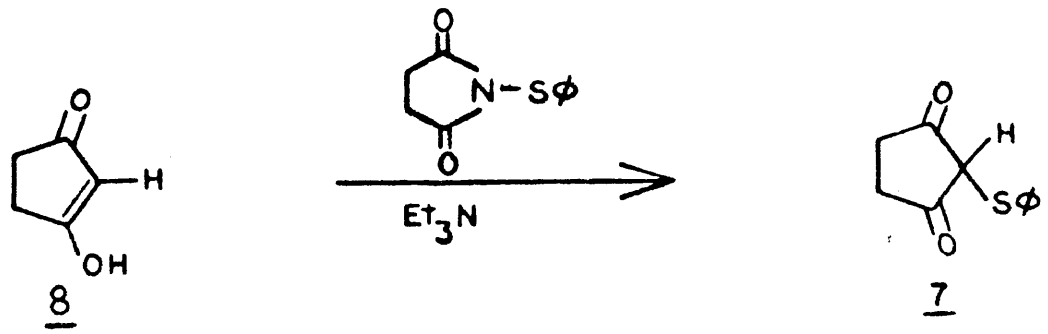
advantage of being a more convergent route. This allows the introduction of the sulfenylated cyclopentanedione system (7) into a complex molecule.


R
O
R
CH3
+ 2 EtOCCOEt
NaOEt
EtOH
R
R
O
O
O
CCOEt
OO
HCl-H2O
R
R
O
O
O
R
R
O
O
(1) H2NCNHNH2
(2) NaOH-(CH2OH)2

6

SCHEME 4

This eliminates having to build the cyclopentanedione around a complex substituent or having to risk losing a precious precursor in an alkylation process. Sulfide 7 is readily prepared in good yields (90%) by the sulfenylation of 1,3-cyclopentanedione with N-phenylthio-succinimide (Scheme 6).[1,7,8] The ability to introduce sulfide 7 into

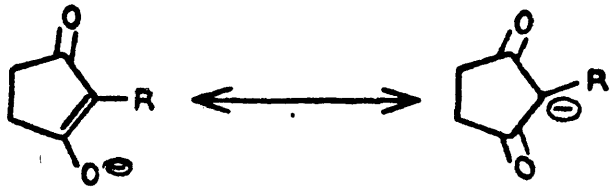


SCHEME 6

a complex system via alkylation provides a synthetic equivalent for the 2-alkylidene systems (1). The alkylation of 7, however, is complicated by competition between C- versus O-alkylation. Conditions must be chosen which facilitate C-alkylation and inhibit O-alkylation as much as possible in order to achieve an optimum yield of the desired C-alkylated product. An understanding of the factors affecting C- versus O-alkylation is necessary in order to be able to select appropriate reaction conditions.

The anions of 1,3-dicarbonyls belong to a class of nucleophilic systems termed ambident anions which are susceptible to nucleophilic

attack at either of two alternative positions. From the charge distribution of the enolate anion, the possibility of reaction at the

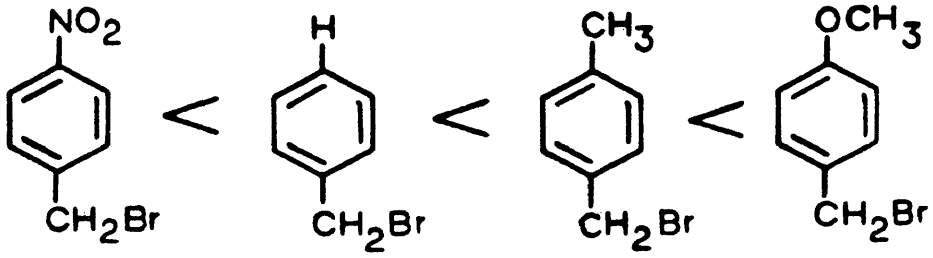


oxygen and carbon is apparent. Other examples of ambident anions include the phenoxide and nitrite anions. Gompper[9] has proposed two basic principles which describe the behavior of ambident nucleophilic compounds toward electrophilic reagents. First, a polar electrophilic reagent favors reaction at the site of highest electron density in an ambident nucleophilic compound. As the difference in the charges of the negatively and positively charged sites increases, the rate of the reaction increases while reactions at other nucleophilic sites are suppressed. Second, if the electrophilic reagent has little or no positive charge, bond formation at the most polarizable center is favored. Some of the strongest evidence regarding these principles and the factors affecting the position of alkylation in ambident anions has been compiled by Kornblum[10] from studies of the reactions of metal nitrites and alkyl halides. The nitrite anion has the capability of bond formation at the nitrogen or oxygen to yield nitroalkanes and alkyl nitrites respectively (Scheme 7). According to

$$R\text{–}X \xrightarrow{AgNO_2} R\text{–}NO_2 + R\text{–}ONO$$

SCHEME 7

Kornblum, the course of the reaction depends on the degree of Sn1 or Sn2 character present in the transition state. In going from primary to tertiary halides, the yield of nitroalkane decreases while the yield of the nitrite ester increases. This is attributed to electrostatic considerations. The oxygens of the anion share the negative charge, therefore, nitrite ester formation would be favored by alkyl halides which more easily form carbonium ions. Kinetic studies also support this, showing tertiary halides to be more reactive than primary halides in reactions with silver nitrite. A series of benzyl bromides studied also gave supporting evidence. In going from the



nitro substituted bromide to the methoxy substituted bromide, the stability of the carbonium ion increases. This increase in stability corresponds to an increase in reaction rate and nitrite ester formation. Preference for alkylation on the oxygen, therefore, is related to a higher degree of Sn1 character in the transition state.

The reactions of alkyl halides with metal nitrites also exhibit some Sn2 characteristics. Steric effects are observed in that neopentyl iodide gives essentially no reaction. Primary halides do react. No rearrangements are known in this type of reaction. Optical-

ly active secondary halides react with silver nitrite to yield nitroalkanes and nitrite esters with inversion of configuration in both products. This indicates that, even though secondary halides have more Sn1 character, the two modes of reaction, Sn1 and Sn2, are not occuring independently. Rather, the transition state possesses varying degrees of Sn1 and Sn2 character. When there is greater Sn2 contribution, alkylation on the nitrogen is enhanced.

From these results, Kornblum has concluded that the alkylation of ambident anions occurs on the atom of highest electronegativity when the Sn1 character is dominant. Conversely, an increase in Sn2 character increases alkylation at the atom of lower electronegativity. The Sn1 type of reaction is governed by electrostatic forces. A large carbonium ion component in the transition state would then enhance bond formation at the most electronegative site. In the Sn2 transition state, bond formation is a more important driving force. Since a less electronegative atom shares electrons more readily, a large Sn2 component in the transition state would favor alkylation at the site of lower electronegativity. The proportion of Sn1 and Sn2 character is affected by the nature of the alkylating agent. An alkyl halide which more easily dissociates into ions would increase the degree of Sn1 contribution. Kornblum asserts that these conclusions are generally applicable to other ambident anions. Reactions of acetoacetic ester yield increased carbon alkylation with Sn2 conditions and increased oxygen alkylation under Sn1 conditions.

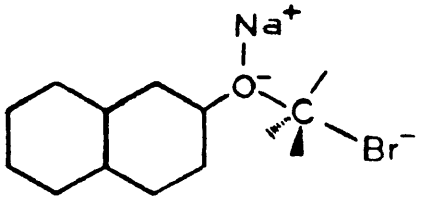
In alkylation reactions of ambident anions, the reactants include not only the anion and the electrophilic reagent, but also the solvent and the cation associated with the anion. The interaction between the

solvent and the other reactants is an important factor in the position of alkylation. The nature of the counterion also affects the position of alkylation. In ambident anions such as phenoxide and enolate anions, oxygen alkylation is favored when the oxygen is as free as possible.[11] Solvents or cations which bind up the oxygen site favor alkylation at the less electronegative site. Choosing conditions for alkylation requires some understanding of the manner in which solvents and cations interact with the other reactants.

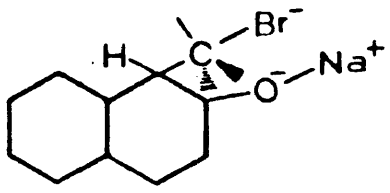
Solvents can be classified as protic or aprotic. Protic solvents have acidic hydrogens bonded to electronegative atoms such as oxygen or nitrogen. Aprotic solvents do not have such protons and therefore are not capable of solvating anions through hydrogen bonding. As the hydrogen bonding capability of the solvent increases, alkylation at the less electronegative site is favored. As the oxygen becomes increasingly shielded by solvent molecules, its availability to attack by an electrophilic reagent is decreased. Kornblum,[12] in a study of solvent effects on the alkylation of phenols, coined the term "selective solvation" to describe this solvent behavior. Ordinarily, the salts of phenols or p-alkyl phenols give oxygen alkylated products in a wide variety of solvents. Kornblum[13] found that, in good hydrogen bonding solvents such as water, phenol, or fluorinated alcohols, substantial yields of the carbon alkylated products could be obtained. This is attributed to the selective solvation of the oxygen of the phenoxide anion and enhanced solvation of the leaving group of the alkylating agent.

Another property of solvents which affects the position of alkylation is the dielectric constant of the medium. The dielectric

constant reflects the ability of a solvent to accommodate separation of charge by decreasing electrostatic attractions between ions. The aprotic solvents can be further classified as polar or nonpolar. The polar, aprotic solvents have higher dielectric constants and are better insulators. Protic solvents are also polar with high dielectric constants. However, identical reactions carried out in a protic solvent and a polar aprotic solvent of similar dielectric constant usually give different results.[14] The reaction is generally faster in the polar aprotic solvent than in the protic solvent. Again, this is attributed largely to the difference in hydrogen bonding capabilities of the two types of solvents. Because polar aprotic solvents do not strongly solvate anions, the nucleophilicity of the anion is enhanced as compared to anions in protic solvents. Hydrogen bonding in protic solvents stabilizes the anion and lowers its reactivity. The importance of the dielectric constant becomes apparent in comparing reactions carried out in polar and non-polar aprotic solvents. In a study of naphthoxide ions, Kornblum[15] has concluded that, within the aprotic group of solvents, the yield of carbon alkylated product increases with a decrease in the dielectric constant of the solvent. This behavior is attributed to differences in charge separation in the transition states and the ability of the solvent to accommodate this charge separation. The transition state for oxygen alkylation is



O-Alkylation T.S.



C-Alkylation T.S.

linear. Assuming that the reaction involves ion pairs, the transfer of charge from oxygen to bromine must be accomplished against the attractive force of the sodium ion which is relatively remote from the bromine. In a low dielectric medium, the attractive force between the bromine and sodium ion is at a maximum. The necessary removal of charge from the vicinity of the sodium ion to the distant bromine is disfavored. In a high dielectric medium, the solvent shields the departing bromine ion from the attractive force of the sodium ion, thereby accommodating the separation of charge and lowering the energy of the transition state. Oxygen alkylation is therefore facilitated by a solvent with a high dielectric constant and inhibited by a low dielectric medium. The carbon alkylation transition state is non-linear with the sodium ion and bromine proximate to one another. Due to comparatively little separation of charge, the transition state is relatively insensitive to dielectric effect. Carbon alkylation is favored by solvents with low dielectric constants because a force opposing oxygen alkylation is maximized.

The effect of the cation on the position of alkylation also becomes apparent in aprotic solvents. Aprotic solvents with high dielectric constants have the ability to solvate cations, leaving the anions relatively free. This favors oxygen alkylation. Even if the cation is associated with the anion in an ion pair, the shielding effects described above still favor oxygen alkylation. In protic solvents, the effect of the cation is reduced due to the generally high dielectric constant of the medium. However, the hydrogen bonding capability of protic solvents overrides any tendency toward oxygen alkylation because of selective solvation of the oxygen atom. Alkyl-

ations of the naphthoxide anion in methanol and ethanol showed little variation in product ratios with different cations. In non-polar solvents, the attraction between cation and anion is significant. Ion pairs and ion aggregates are likely to exist. This favors carbon alkylation by binding up the oxygen. In alkylations of the naphthoxide anion,[15] carbon alkylation increases in the following cation sequence: $R_4N^+ < K^+ < Na^+ < Li^+$. As the size of the cation decreases, it becomes more tightly held by the oxygen, therefore, inhibiting oxygen alkylation. This same cation sequence holds for both polar and non-polar aprotic solvents. In a polar, aprotic medium, however, there is a leveling effect observed. Cation solvation is also a function of ionic size. While the smaller, more tightly held lithium cation favors carbon alkylation in the ion pair, it is also more strongly solvated by the solvent molecules. This favors oxygen alkylation, thereby reducing the cation effect.

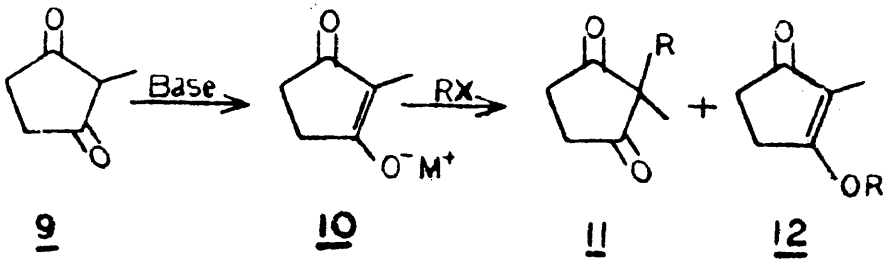
As mentioned earlier, the nature of the alkylating agent is also a factor in the position of alkylation. High Sn2 reactivity favors carbon alkylation. Generally, steric factors are more important in carbon alkylation with bulky groups favoring oxygen alkylation. Leaving group effects are also important. Leaving groups such as BF_4^-, ClO_4^-, and TsO^- give high oxygen to carbon alkylation ratios.[11] This can be attributed to "symbiosis",[16] the tendency of hard ligands to flock together at a site of displacement. Since oxygen is harder than carbon, the harder leaving groups assist in oxygen alkylation.

Strong evidence in support of these principles and applicable to the cyclopentanedione system has been compiled by Schick[17] in a study of the alkylation of 2-methyl-1,3-cyclopentanedione. The regio-

selectivity of the alkylation was found to be dependent on the nature of the solvent and the structure of the alkylating agent (Table 1). The solvent effects observed for these alkylations are in agreement with the principles previously discussed. The polar, protic solvent (water) decreased the amount of oxygen alkylated product. Aprotic, polar solvents increase the amount of oxygen alkylation. Regarding the alkylating agent, carbon alkylation was favored by alkyl halides with sp^2 or sp hybridized carbon atoms in the β position. Again, this is as expected from the general principles cited. The unsaturated alkyl groups are "softer" compared to the saturated primary alkyl halides. Since the carbon site is also softer than the oxygen, soft alkyl groups and leaving groups favor carbon alkylation. Schick also attributes these alkylating agent effects to the degree of Sn2 reactivity. The saturated primary alkyl halides have lower Sn2 reactivity than the unsaturated alkyl halides and therefore favor oxygen alkylation.

In choosing alkylating agents for use in the preparation of the 2-alkyl-2-phenylthio-1,3-cyclopentanediones (5), the synthetic utility of the alkyl group must be considered in addition to the degree of carbon alkylation possible. In the case of the synthesis of the spiro[4.5]decane sesquiterpenes, synthetic versatility is a must due to the large number of substitution patterns observed in this class of natural products. Unsaturated alkylating agents appear to be promising. Allyl halides favor carbon alkylation and the allylated product can be modified, for example, by ozonization to the aldehyde (Scheme 8). The aldehyde functionality provides tremendous synthetic flexibility. Other possibilities include Michael acceptors such as methyl

TABLE 1

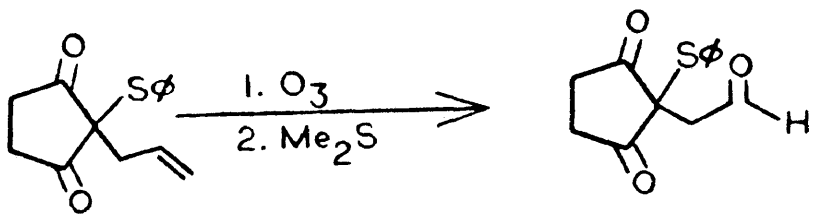


9 10 11 12

RX	SOLVENT	C-alkyl : O-alkyl
$n\text{-}C_4H_9I$	H_2O	1 : 3.7
	Acetonitrile	1 : 4.0
	HMPT	1 : 6.5
	DMSO	1 : 8.0
	DMF	1 : 9.3
$n\text{-}C_3H_7I$	H_2O	1 : 2,5
	DMF	1 : 8.6
C_2H_5I	H_2O	1 : 1.6
	DMF	1 : 4.6
CH_3I	H_2O	1 : 0.15
	DMF	1 : 1.2
$H_2C{=}CH\text{-}CH_2Br$	H_2O	1 : 0.14
	DMF	1 : 0.74
$HC{\equiv}C\text{-}CH_2Br$	H_2O	1 : 0.16
	DMF	1 : 0.52

Schick, et al., Tetrahedron 38, 1279 (1982).

vinyl ketone. This alkylating agent contains a "soft" π-system which,

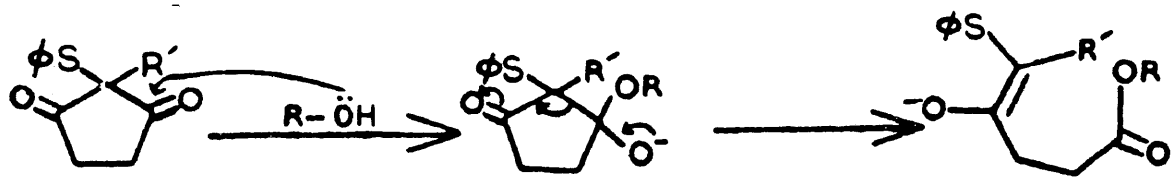


13 14

SCHEME 8

again, enhances carbon alkylation. The carbonyl containing methyl vinyl ketone also provides for the introduction of a variety of functional groups into the molecule.

In summary, the carbon alkylation of the phenylthio cyclopentanedione (7) is the method of choice for gaining entry into the 2-alkylidene-1,3-cyclopentanedione (1) systems. This carbon alkylation is favored by alkyl halides with high Sn2 reactivity and soft, polarizable alkyl groups and leaving groups. Protic solvents or non-polar aprotic solvents enhance carbon alkyation. One possible



SCHEME 9

difficulty with protic solvents is the tendency of the cyclopentanediones to undergo a retro-Claisen ring cleavage (Scheme 9). In view of this, non-polar aprotics appear to be a better solvent choice. Experimental results pertaining to the carbon alkylation of 2-phenylthio-1,3-cyclopentanedione (7) and its synthetic utility are discussed in the following section.

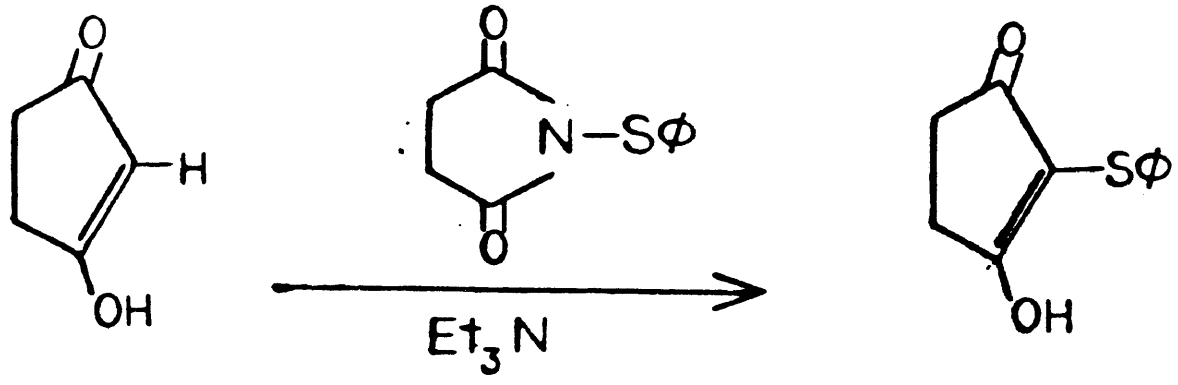
RESULTS AND DISCUSSION

Phenylthio Preparation

The preparation of the desired 2-alkyl-2-phenylthio-1,3-cyclopentanedione precursor (5) is accomplished by reaction of the sulfide (7) with an appropriate alkylating agent. Sulfide 7 is readily

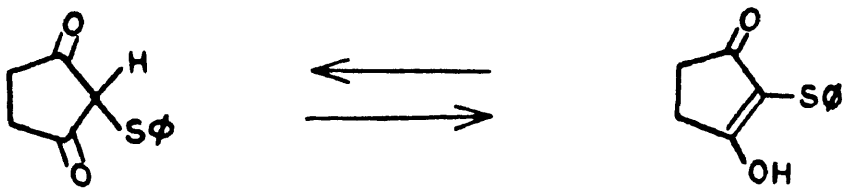
7 5

prepared by phenylsulfenylation of 1,3-cyclopentanedione (8) with one equivalent of N-phenylthio succinimide (NPTS) in triethylamine and



8 7

benzene. Sulfide 7 can be obtained in good yields (87%) as white crystals from ethyl acetate. The melting point range is 197.6-198.6°C. The solubility of sulfide 7 is limited due to the enolic character of the compound. Strong intermolecular forces (hydrogen



bonding) give the compound a polymeric form which decreases solubility.

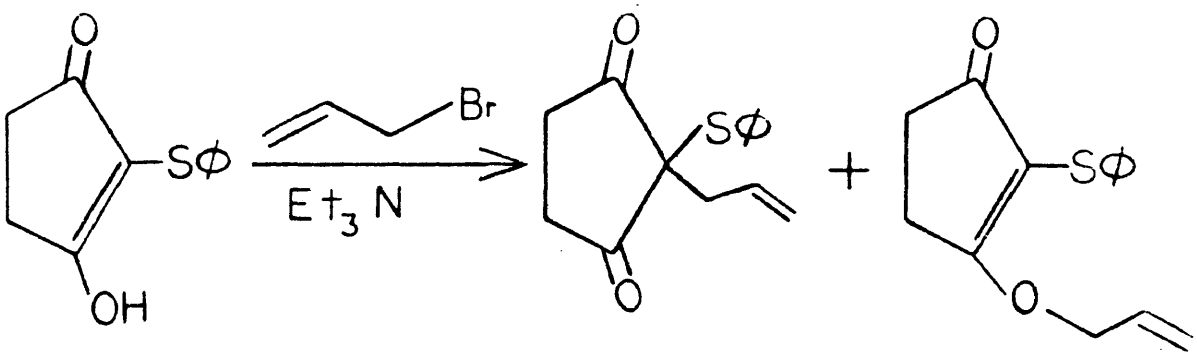
Allylations

Ideally, the alkyl groups introduced at the 2-position on the 2-phenylthio-1,3-diketone should have good synthetic flexibility. For example, when precursors such as 5 are used to gain entry into the [4.5]decane sesquiterpene ring systems (see Scheme 1), the capability of modification of the allyl groups is necessary due to the wide variety of substitution patterns within this group of natural products. To achieve carbon alkylation, the allyl halides meet the synthetic requirements, as well as the carbon versus oxygen alkylation criteria discussed in the introduction. The alkyl side chain can be modified by a variety of reactions. Ozonolysis at the double bond followed by a reductive work-up gives an aldehyde functionality which can then be modified through a variety of reactions at the carbonyl site. Electrophilic addition across the double bond also provides some synthetic

versatility. In accordance with the carbon versus oxygen alkylation criteria, the allyl group is relatively polarizable and has good Sn2 reactivity.

In accordance with the solvent effects discussed, water, a polar, protic reaction medium, was used in the initial attempts at alkylation. Aqueous preparations using allyl bromide and NaOH[18] and allyl chloride with NaBr and NaOH[19] showed no evidence of the desired product formation by NMR. This was due primarily to difficulties with solubility. Sulfide 7, and to a large degree the allyl halides, are insoluble in the aqueous medium. The starting material was recovered by filtration.

Alkylation of sulfide 7 was accomplished in benzene, a non-polar, aprotic solvent. By refluxing the sulfide with excess allyl bromide and triethylamine in benzene, a mixture of the carbon and oxygen alkylated-products was obtained. These were easily separated

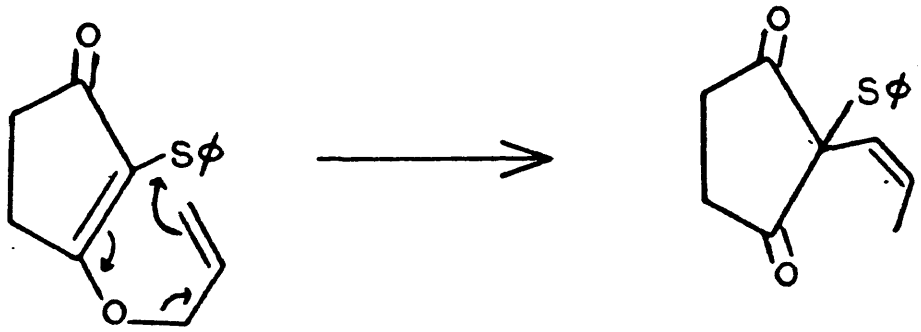


7 13 15

by column chromatography using a silica gel column with methylene chloride : hexane (50 : 50) as the solvent system. The carbon alkylated product was eluted first as an oil in about 50% yield. ^{1}H

NMR showed the vinyl side chain protons ($-CH_2-C\underline{H}=C\underline{H}_2$) as multiplets at 5.4 and 5.00 ppm. IR indicated a carbonyl absorption at 1720 cm^{-1}. There were no absorptions at 1600 cm^{-1} (=C-O-) which would indicate the presence of an oxygen alkylated impurity. The oxygen allylated product was eluted next as an oil in about a 12% yield. The spectral differences in these two compounds were quite evident. The IR spectrum for the oxygen allylated compound showed a characteristic strong absorption at 1570 cm^{-1}. In the ^1H NMR, the side chain allyl protons ($-C\underline{H}_2-CH=CH_2$) resonate farther downfield in the oxygen allylated product (4.85 ppm) than in the carbon allylated product (2.65 ppm) due to deshielding by the oxygen.

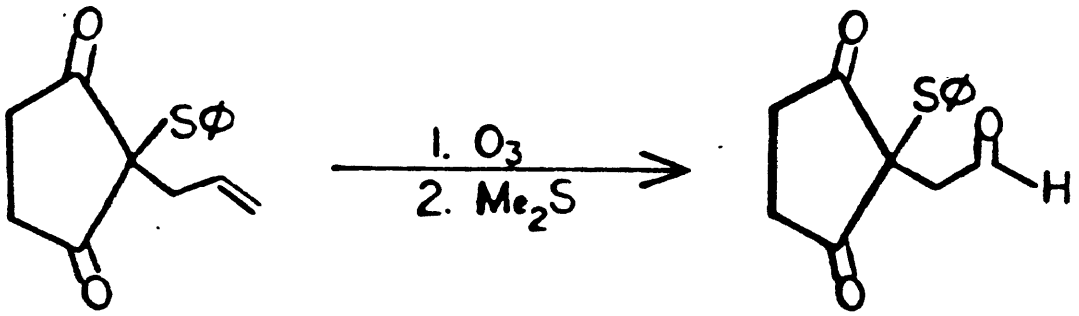
Fortunately, the oxygen allylated product can be converted to the desired carbon allylated product. This isomerization occurs thermally probably through a 3,3-sigmatropic rearrangement. Refluxing the



oxygen allylated product in toluene for three hours gave a 70% recovery of the carbon allylated product. Application of this finding to the allylation reaction itself involved carrying out the reaction in toluene with extended reflux. Following the reaction by thin layer chromatography indicated the disappearance of the oxygen allylated

product. The yield of carbon alkylated product was increased by 10%, giving an overall yield of 60%. The possibility that the alkylation occurred initially on the oxygen followed by rearrangement to the carbon alkylated product was considered. An NMR study, however, indicated both products were formed initially. Aliquots taken every fifteen minutes showed little change in proportion of carbon versus oxygen alkylated products over a period of two hours. This result argues against a mechanism involving predominant oxygen alkylation with subsequent rearrangement to C-allyl product, since, if this were the case, higher oxygen to carbon allyl ratios would be expected earlier in the reaction.

As mentioned previously, the ability to modify the side chain provides extended synthetic flexibility. The allyl group is subject to conversion to an aldehyde via ozonolysis. This transformation was accomplished with the 2-allyl-2-phenylthio-1,3-diketone by bubbling O_3 through a cold (-80°C) methylene chloride solution of the carbon alkylated product. Reductive workup with dimethyl sulfide gave the desired aldehyde in 43% yield. The yield was not optimized. ^1H NMR



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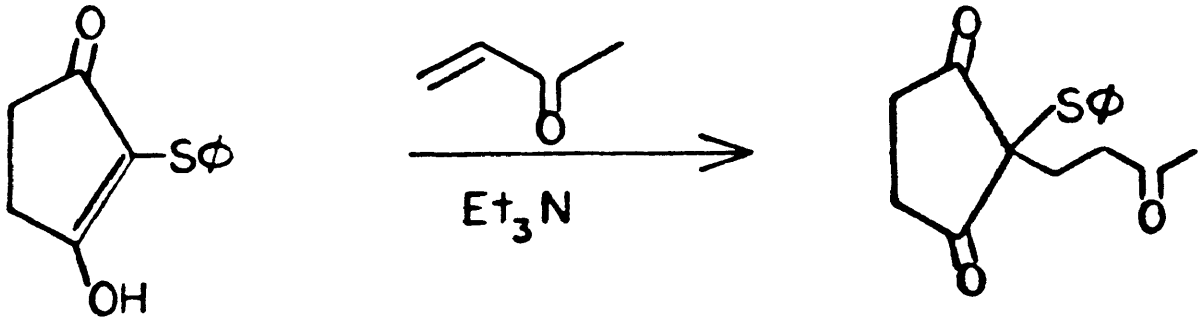
showed a somewhat broadened singlet (1H) at 9.4 ppm which is charac-

teristic of an aldehyde. The aldehyde functionality provides the desired synthetic versatility in the 2-position.

Methyl Vinyl Ketone Adduct

Another useful alkylating agent is methyl vinyl ketone. It contains a polarizable π system which should favor carbon alkylation. The resulting alkylated product would have a carbonyl functionality in the side chain, providing further synthetic possibilities. Alkylations attempted in acetonitrile and water were unsuccessful due to insolubility of sulfide 7. In both cases, the starting material was recovered.

The alkylation was accomplished in benzene with triethylamine as



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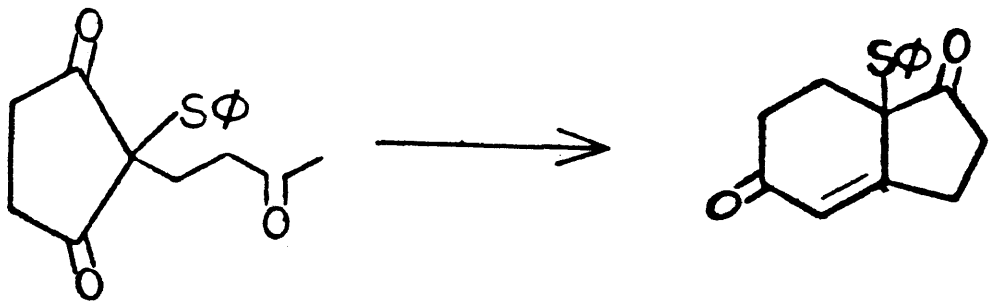
the base. The product was purified by column chromatography to give an 86% yield of an oily compound. ^{13}C NMR was consistent with the symmetry of the molecule giving the expected eleven line spectrum versus a thirteen line spectrum expected for the oxygen alkylated product.

Cyclization of the 2-oxobutyl compound (17) represents another synthetically useful route. Attempts at cyclization of the 2-oxobutyl

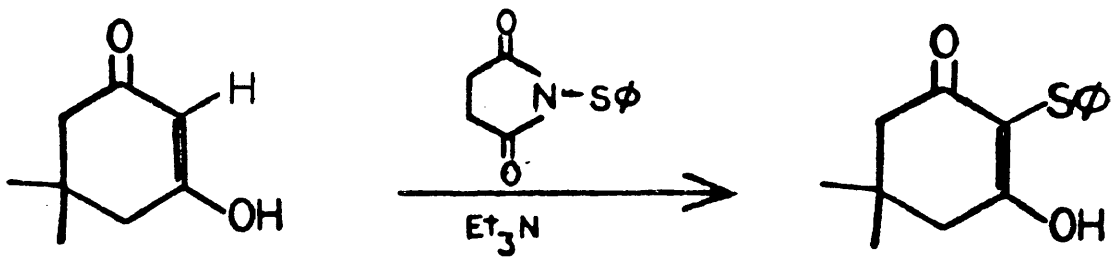


17 18

compound were unsuccessful, however. The lability of the -C-SØ bond interferes with the reaction. The nucleophile can attack at this position. The cyclopentanedione is also a good leaving group which further affects the reaction. Pyrollidinium acetate and p-TsOH catalyzed cyclizations were both unsuccessful.

Dimedone Results

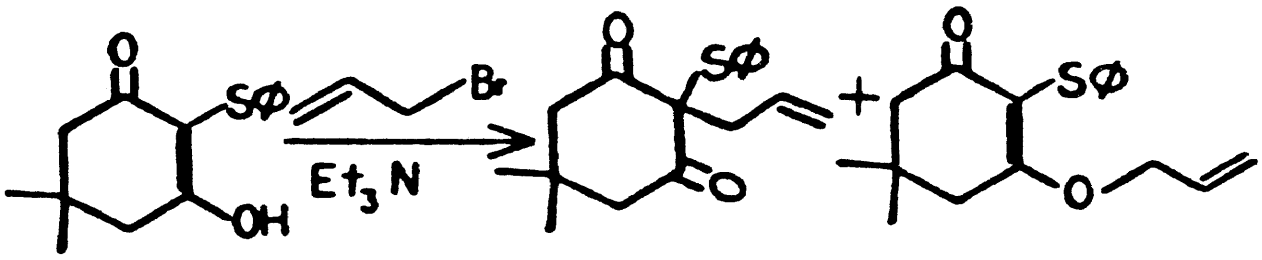
With these results available on the five-membered ring cyclopentanedione, the six-membered ring dimedone (19) was studied under similar conditions. The sulfide (20) was readily prepared in essen-



19 20

tially quantitative yields (95%) by monosulfenylation of 5,5-dimethyl-1,3-cyclohexanedione (19) as described for cyclopentanedione. The product was obtained as a white crystalline solid (m.p.: 122.0-122.5°C) by recrystallization from ethyl acetate.

The alkylation with allyl bromide is also facile and proceeds in a similar manner as the five-membered ring. Refluxing 20 with allyl bromide and triethylamine in benzene yields a mixture of carbon and oxygen allylated products. These are easily separated by column chromatography using a silica gel column and methylene chloride as the solvent. The carbon alkyl product is eluted first as an oil in 68%

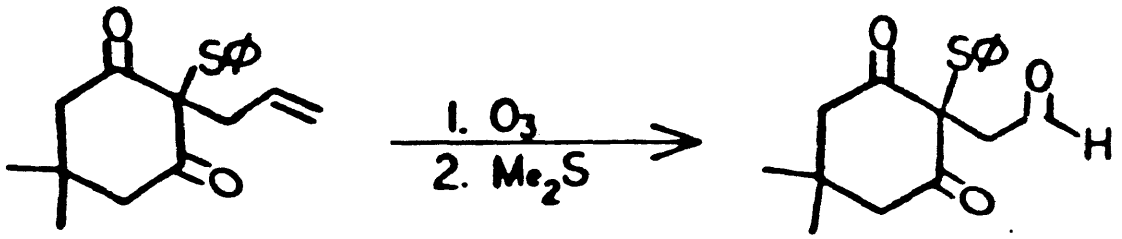


20 21 22

yield. A carbonyl absorption was present in the IR spectrum at 1705 cm^{-1}. ^1H NMR showed the vinyl side chain protons ($-CH_2-CH=CH_2$) as a multiplet at 5.30 ppm. The oxygen alkylated product is obtained as a colorless oil in about 8% yield. The IR shows the characteristic absorption at 1560 cm^{-1}. ^1H NMR shows the downfield shift in absorption of the side chain protons. The ^{13}C NMR spectra show the difference in symmetry between the two molecules with the carbon

allyl product giving a thirteen line spectrum as opposed to the fifteen line spectrum for the oxygen alkylated product.

Again, the allyl group is susceptible to ozonolysis, giving the desired aldehyde, albeit in low (10%) yield. The reaction was not as clean as the cyclopentanedione ozonolysis, mandating substantial chromatographic purification with the concomitant material loss accounting for the lower yield. Yields for the ozonolysis were not optimized.



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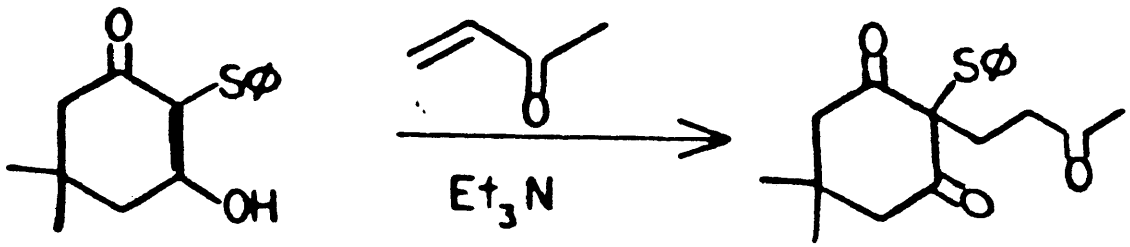
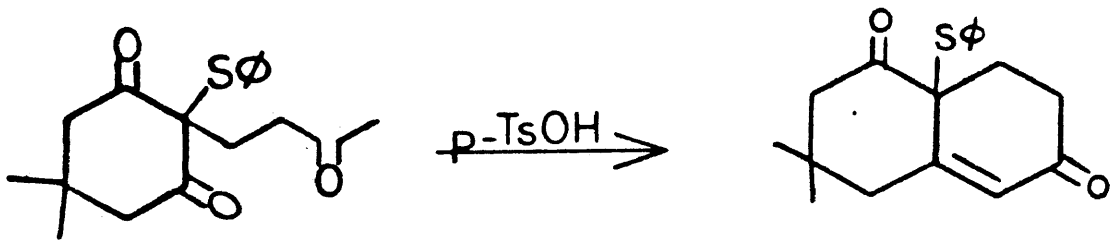
Reaction of the sulfide 20 with methyl vinyl ketone under similar conditions as those for cyclopentanedione was also successful. The



20 24

product was obtained as a white crystalline solid by crystallization from anhydrous ethyl ether in a 66% yield (m.p.: 103.3-104.2°C). ^{13}C NMR was consistent with molecular symmetry giving a fourteen line spectrum.

Attempted cyclization of the methyl vinyl ketone adduct using p-TsOH as a catalyst was unsuccessful. The six-membered ring system



24 25

is also susceptible to the same side reactions which interfere with the cyclization of the five-membered ring.

Conclusion

Preparation of the 2-alkyl-2-phenylthio-1,3-cyclopentanedione (5) precursors is a key step in the synthesis of the 2-alkylidene-1,3-cyclopentanediones (1). This alkylidene system is a versatile synthetic intermediate providing for the introduction of a functionalized cyclopentanedione moiety via a variety of reactions (Scheme 1). The preparation of the 2-allyl and 2-oxobutyl precursors has been accomplished. The allyl and oxobutyl side chains provide the syn-

thetic flexibility necessary for potential applications such as the synthesis of the spiro[4.5]decane sesquiterpenes. The 2-alkylidene-1,3-cyclopentanediones represent a novel and highly reactive class of synthetic intermediates providing a strong foundation for further investigations of the chemistry of these compounds.

EXPERIMENTAL

General

Infrared spectra (IR) were recorded on a Perkin-Elmer 1320 spectrophotometer. ^{1}H NMR and ^{13}C NMR were obtained in the specified solvent on a Varian FT-80A instrument. Chemical shifts are reported in δ units downfield from tetramethylsilane. Ozonolyses were carried out with an OREC model V350 ozonizer. HPLC was performed on a Waters HPLC instrument. Thin layer chromatography was performed on plastic sheets coated with silica gel from Eastman Kodak. Column chromatography was carried out with silica gel from J. T. Baker using the specified solvent system.

Preparation of 2-Phenylthio-1,3-cyclopentanedione (7)

Triethylamine (1 ml) was added at once to a stirred suspension of 1,3-cyclopentanedione (.605g, 6.2 mmol) and N-phenylthiosuccinimide (1.350g, 6.5 mmol) in benzene (30 ml). The resulting solution was refluxed for five hours, at which time, no N-phenylthiosuccinimide was present by TLC (silica gel with 5% ethyl acetate in methylene chloride). The reaction mixture was cooled to room temperature and concentrated under aspirator vacuum. The brown, oily residue was taken up in methylene chloride (30 ml) and poured into 25 ml of .5M H_2SO_4. The mixture was cooled (5°C) to complete precipitation of

product. The crude solid was isolated by filtration. Crystallization from ethyl acetate (180 ml) gave 2-phenylthio-1,3-cyclopentanedione (1.113g. .0054 mol, 87% yield) as a white, crystalline solid: m.p.= 197.6-198.6°C.

Preparation of 2-Allyl-2-phenylthio-1,3-cyclopentanedione (13)

Triethylamine (1 ml) was added to a stirred suspension of 2-phenylthio-1,3-cyclopentanedione (1.00g, 4.9 mmol) in allyl bromide (1 ml) and benzene (25 ml). The resulting solution was heated to reflux under nitrogen. After 1½ hours, a precipitate had formed in the reaction mixture. The reaction mixture was washed with 1M H_2SO_4 (15 ml) and 10% aqueous Na_2CO_3 (10 ml) and the organic layer dried over $MgSO_4$. The solvent was evaporated under vacuum leaving a crude yellow oil (1.06g, 88% yield). TLC (silica gel with methylene chloride : hexane solvent (50 : 50)) showed two components present. The crude sample was purified by column chromatography (silica gel with methylene chloride : hexane (50 : 50)). The first component (R_f= .64) was isolated as an oil and identified as the carbon allylated product, 2-allyl-2-phenylthio-1,3-cyclopentanedione (.60g, 2.4 mmol, 50% yield); IR ($CHCl_3$) 1760, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.35 (m, 5H), 5.45 (m, 1H), 5.00 (m, 2H), 2.65 (m, 6H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 207.78 (s), 136.99 (d), 130.99, 130.51, 129.11, 127.79, 120.26 (t), 62.18 (s), 35.17, 35 03.

A second component (R_f= .21) was identified as the oxygen allylated product (15) (.15g, 12% yield) as a colorless oil; IR ($CHCl_3$) 1685, 1570, 1270 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.15 (s, 5H), 5.85 (m, 1H), 5.25 (m, 2H), 4.85 (m, 2H), 2.70 (m, 4H); ^{13}C NMR

($CDCl_3$, 20 MHz) δ 201.43 (s), 190.81 (s), 135.25, 131.04, 128.29, 126.76, 125.06, 118.25, 108,48, 70.64, 32.86, 26.00.

Isomerization of O-allylated 2-Phenylthio-1,3-cyclopentanedione

A solution of the oxygen allylated compound (.15g, .61 mmol) in toluene (5 ml) was heated at reflux. TLC analysis (silica gel plates with methylene chloride : hexane (50 : 50) solvent) of the reaction mixture at periodic intervals showed the gradual disappearance of oxygen allylated material (R_f= .18) and the simultaneous appearance of carbon allylated product (R_f = .69). After three hours, the oxygen allylated starting material was completely consumed. The reaction mixture was cooled and the solvent removed under vacuum. The crude product was flushed through a silica gel column (methylene chloride solvent) yielding 2-allyl-2-phenylthio-1,3-cyclopentanedione (.1055g, 70% yield) as an oil.

Ozonolysis of 2-Allyl-2-phenylthio-1,3-cyclopentanedione

Ozone (5% in O_3) was bubbled through a stirred and cooled (-80°C) solution of 2-allyl-2-phenylthio-1,3-cyclopentanedione (.227g, .922 mmol) in methylene chloride (10 ml) until a blue color persisted. Excess O_3 was purged with N_2 until the effluent gave a negative test with KI/starch paper. Dimethyl sulfide (.10 ml, 1.4 mmol) was added to the reaction mixture which was then allowed to stir overnight at room temperature under a drying tube. The solvent was removed under aspirator vacuum leaving a yellow, oily residue. The crude product was taken up in methylene chloride (15 ml) and washed with H_2O (10 ml). The methylene chloride layer was dried over $MgSO_4$ and the

solvent evaporated, leaving a yellow oil (.181g, 79 %). The crude product was purified by HPLC (silica gel column, 10% ethyl acetate in methylene chloride solvent). The aldehyde (16) was obtained as an oil (.098g, .40 mmol, 43% yield); IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.40 (s, 1H), 7.45 (m, 5H), 3.57 (s, 2H), 2.87 (s, 4H).

Preparation of 2-(3'-Oxobutyl)-2-phenylthio-1,3-cyclopentanedione (17)

Triethylamine (.5 ml) was added to a stirred suspension of 2-phenylthio-1,3-cyclopentanedione (.6182g, 3.00 mmol) in methyl vinyl ketone (1.3 ml) and benzene (25 ml). The resulting solution was refluxed under nitrogen atmosphere for six hours. The dark orange reaction mixture was washed with 1M H_2SO_4 (7 ml) and 10% aqueous sodium carbonate solution (7 ml) and dried over $MgSO_4$. The solvent was evaporated under vacuum, leaving a crude, yellow oil (.7899g, 95% yield). This was taken up in methylene chloride and flushed through a silica gel column with methylene chloride. The solvent was evaporated under vacuum to give 2-(3'-oxobutyl)-2-phenylthio-1,3-cyclopentanedione (.7115g, 2.6 mmol, 86% yield) as an oil; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.40 (m, 5H), 2.70 (m, 4H), 2.50 (m, 2H), 2.20 (m, 2H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 208.0 (s), 209.0 (s), 138.0 (d), 131.5, 130.0, 128.5, 62.0 (s), 38.0, 35.0, 30.5, 25.0.

Preparation of 2-Phenylthio-5,5-dimethyl-1,3-cyclohexanedione (20)

Triethylamine (5 ml) was added to a stirred suspension of 5,5-dimethyl-1,3-cyclohexanedione (5.017g, .0358 mol) and N-phenylthiosuccinimide (7.520g, .0363 mol) in benzene (50 ml). The resulting

solution was heated to reflux for 1½ hours, at which time, no NPTS was present by TLC (silica gel with 5% ethyl acetate in methylene chloride). The reaction mixture was cooled to room temperature and concentrated under aspirator vacuum, leaving a yellow, oily residue. The residue was taken up in methylene chloride (50 ml) and poured into 25 ml of 1M H_2SO_4. No precipitate formed. The organic layer was separated and dried over $MgSO_4$. The solvent was removed under vacuum, leaving a crude, white solid. Crystallization from ethyl acetate gave a 95% yield of 5,5-dimethyl-2-phenylthio-1,3-cyclohexanedione (8.443g, .034 mol) in four crops as a white crystalline solid: m.p. 122.0-122.5°C; IR ($CHCl_3$) 3300 (br), 1710, 1650, 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.15 (m, 5H), 2.46 (s, 4H), 1.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 134.0 (s), 128.0, 126.5, 125.0, 105.0 (s), 45.0 (t), 30.0, 28.0, 27.0.

Preparation of 2-Allyl-2-phenylthio-5,5-dimethyl-1,3-cyclohexanedione (21)

Triethylamine (1 ml) was added to a stirred suspension of 5,5-dimethyl-2-phenylthio-1,3-cyclohexanedione (.500g, 2.015 mmol) in allyl bromide (1 ml) and benzene (25 ml). The resulting solution was refluxed for 1½ hours, at which time, there was no starting dione present by TLC (silica gel with 5% ethyl acetate in methylene chloride solvent). The reaction mixture was washed with 1M H_2SO_4 (10 ml) and 10% aqueous sodium carbonate (10 ml) and dried over $MgSO_4$. Solvent was removed under vacuum leaving a crude yellow oil (.519g, 89% yield). TLC analysis (silica gel with methylene chloride solvent) showed two components present. The first component (R_f = .88) was isolated as a

pale yellow oil by column chromatography (silica gel with methylene chloride solvent) and identified as 2-allyl-2-phenylthio-5,5-dimethyl-1,3-cyclohexanedione (.395g, 68% yield); IR ($CHCl_3$) 1715, 1705, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.57 (m,5H), 5.30 (m, 3H), 2.70 (m, 6H), 1.15 (s, 3H), .8 (s, 3H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 202.01 (s), 137.09 (d), 132.59, 130.51, 129.01, 128.04, 119.86, 68.32 (s), 50.92 (t), 34.48, 30.75, 30.41, 26.03.

The second component isolated (R_f= .56) was the oxygen allyated product (.046g, 8% yield) as a colorless oil; IR ($CHCl_3$) 1650, 1560, 1290 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.15 (m, 5H), 5.75 (m, 1H), 5.20 (m, 2H), 4.65 (m,2H), 2.5 (d, 4H), 1.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 206.0, 196.0 (s), 178.0 (s), 138.0, 133.0, 130.0, 129.0, 126.0, 119.0, 69.5 (s), 51.0 (t), 41.5 (t), 32.5 (q), 29.0 (q).

Ozonolysis of 2-Allyl-2-phenylthio-5,5-dimethyl-1,3-cyclohexanedione

Ozone (5% in O_2) was bubbled through a stirred and cooled (-80°C) solution of 2-allyl-2-phenylthio-5,5-dimethyl-1,3-cyclohexanedione (.291g, 1.01 mmol) in methylene chloride (10 ml) until a blue color persisted. Excess O_3 was purged with nitrogen until the effluent tested negative with KI/starch paper. Dimethyl sulfide (.10 ml, 1.4 mmol) was added to the reaction mixture which was then allowed to stir overnight at room temperature under a drying tube. Solvent was removed under vacuum leaving a yellow, oily residue. This residue was taken up in methylene chloride (15 ml) and washed with water (10 ml). The organic layer was dried over $MgSO_4$. Evaporation of solvent left the product as an oil (.263g, 90%). The crude product was

purified by HPLC (silica gel column, 5% ethyl acetate in methylene chloride solvent) giving the aldehyde (23) as an oil (.033g, .11 mmol, 10% yield); IR ($CHCl_3$) 1700, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 9.5 (s, 1H), 7.4 (m, 5H), 3.3 (d, 2H), 3.0 (s, 2H), 2.5 (d, 2H), 1.25 (s, 3H), 1.15 (s, 3H).

Preparation of 2-(3'-Oxobutyl)-2-phenylthio-5,5-dimethyl-1,3-cyclohexanedione (24)

Triethylamine (3 ml) was added to a stirred suspension of 5,5-dimethyl-2-(3'-oxobutyl)-2-phenylthio-1,3-cyclohexanedione (3.032g, .0122 mol) and methyl vinyl ketone (7 ml) in benzene (25 ml). The resulting solution was heated to reflux under nitrogen. After 1½ hours, no dimedone starting material was present by TLC (silica gel with methylene chloride solvent). The reaction mixture was washed with 1M H_2SO_4 and 10% aqueous sodium carbonate solution and dried over $MgSO_4$. Solvent was evaporated under vacuum leaving a crude yellow oil which solidified upon standing. Crystallization from anhydrous ethyl ether gave a 66% yield of 5,5-dimethyl-2-(3'-oxobutyl)-2-phenylthio-1,3-cyclohexanedione (2.565g, .008 mol) in three crops as a white crystalline solid: m.p. 103.3-104.2°C; IR ($CHCl_3$) 1710, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 7.40 (m, 5H), 3.35 (s, 1H), 3.20 (s, 1H), 2.05 (s, 3H), 1.20 (s, 3H), .85 (s, 3H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 206.42 (s), 202.00 (s), 136.65 (d), 131.00, 130.39, 128.96, 69.12 (s), 50.59 (t), 38.81 (s), 30.52, 30.14, 29.35, 26.07, 24.26.

REFERENCES

1. P. E. Eaton and W. H. Bunnelle, Tetrahedron Letters, 23 (1984).

2. J. A. Marshall, S. F. Brady, and N. H. Anderson, Fortschr. Chem. Org. Naturs., 31, 283 (1974).

3. S. D. Burke, C. W. Murtiashaw, J. O. Saunders, and M. S. Dike, J. Am. Chem. Soc., 104, 872 (1982).

4. N. Hamanaka, H. Nakai, and M. Kurono, Bull. Chem. Soc. Japan, 53, 2327 (1980).

5. M. L. Bolte, W. D. Crow, and S. Yoshida, Aust. J. Chem., 35, 1411, (1982).

6. K. Hiroga, Chem. Pharm. Bull., 13, 1359 (1967).

7. T. Mukaiyama, Tetrahedron Letters, 5115 (1970).

8. T. Kumamoto, S. Kobayashi, and T. Mukaiyama, Bull. Chem. Soc. Japan, 45,866 (1972).

9. R. Gompper, Angew. Chem. Int'l. Ed. Eng., 3, 560 (1964).

10. N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, J. Am. Chem. Soc., 77, 6269 (1955).

11. W. J. LeNoble, Synthesis, 2, 1 (1970).

12. N. Kornblum, P. J. Berrigan, and W. J. LeNoble, J. Am. Chem. Soc., 85, 1141 (1963).

13. N. Kornblum, P. J. Berrigan, and W. J. LeNoble, Ibid., 82, 1257 (1960).

14. A. J. Parker, Chem. Rev., 69, 1 (1969).

15. N. Kornblum, R. Seltzer, and P. Haberfield, J. Am. Chem. Soc., 85, 1148 (1963).

16. R. G. Pearson, and J. Songstad, Ibid., 89, 1827 (1967).

17. H. Schick, H. Schwarz, and A. Finger, Tetrahedron, 38, 1279 (1982).

18. M. S. Newman and J. H. Manhart, J. Org. Chem., 26, 2113 (1961).

19. H. Schick, Z. Chem., 450 (1979).

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