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Cyclopropanol Chemistry

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Contents

I. Introduction and Scope

Two brief reviews of the chemistry of cyclopropanols and some of their derivatives appeared in 1968;[2,3] however, the extensive work which has been done in these and related areas since that time seems sufficient to warrant a thorough, updated review. The present manuscript, which covers the literature through May 1973, provides a summary of the methods of preparation of cyclopropanols and their derivatives, describes the wide variety of ring openings of these compounds (and applications of such reactions in the synthesis of other organic compounds), and attempts to relate the chemical behavior of the cyclopropanols to that of their nitrogen and sulfur analogs.

Ring-opening reactions of cyclopropanols which result from the action of electrophiles have been reviewed recently elsewhere[4] and are surveyed only briefly here for completeness. The section on ring openings involving carbon–oxygen bond breaking is discussed briefly as well, since an exhaustive review of this subject would require full consideration of the solvolytic behavior of other cyclopropane derivatives; such a study is clearly beyond the scope of this review.

II. Synthesis of Cyclopropanols and Their Derivatives

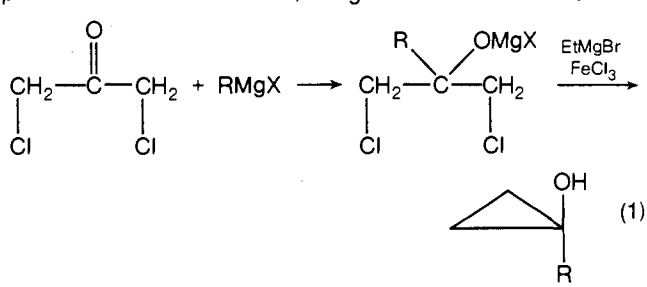
For purposes of this review it is convenient to divide this section according to the following compound types: cyclopropanols, 1,2-cyclopropanediols, and cyclopropyl ethers or esters. While there are synthetic methods which are common to the intermediate steps in many of these (in particular, carbenoid additions to carbon–carbon double bonds), there are some methods which are unique to each group. The great diversity in the methods available ensure that cyclopropanols, or their derivatives, of nearly any structure can be prepared.

A. Cyclopropanols

1. From 1,3-Dihalo Compounds

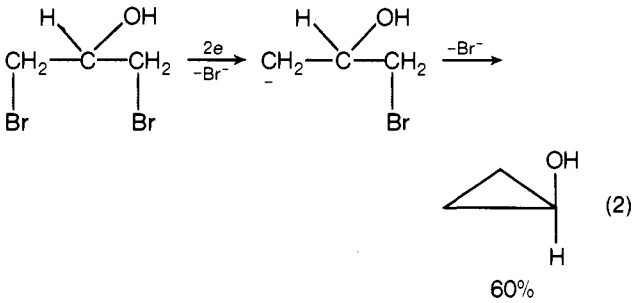
The simplest method for the synthesis of cyclopropanol is that accidentally discovered by Cottle, *et al.*,[5] which involves the reaction of epichlorohydrin with magnesium bromide, ethylmagnesium bromide, and ferric chloride. Although the original workers were not able to obtain the alcohol in more than 87% purity, the application of more modern separation techniques gives analytically pure product in moderate yield.[6] In view of the simplicity of the procedure and the availability of the starting materials, this is the method of choice for cyclopropanol itself.

Cyclopropanols substituted only in the 1 position are best synthesized by a modification of this method. Epichlorohydrin has been shown to react with $MgBr_2$ to form the magnesium salt of 1-bromo-3-chloro-2-propanol; analogous salts are available by Grignard additions to 1,3-dichloroacetone.[7] If this type of salt is then treated with a Grignard reagent in the presence of ferric chloride,[8] ring closure occurs. Yields of



(1)

60% or greater of the 1-substituted cyclopropanols can easily be obtained. The main precaution to be observed in these reactions (as with other preparations of the alcohols) is to avoid undue contact of the cyclopropanols with acids or with bases in the presence of protic solvents. The method should be applicable to the synthesis of more highly substituted cyclopropanes, but such syntheses do not seem to have been attempted. A further modification of the 1,3-dihalo-2-propanol route to cyclopropanols has recently been reported, however, by Gerdil;[9] dehalogenation is accomplished by an electrochemical process and provides cyclopropanol in good yield.

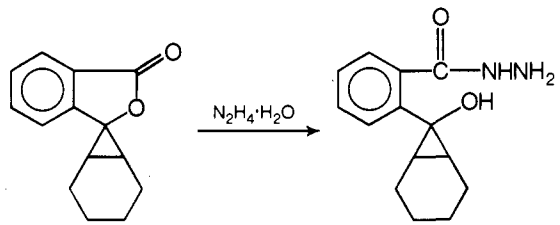


(2)

2. By Cleavages of Esters and Ethers

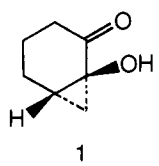
Some years ago it was shown that cyclopropyl acetate could be hydrolyzed to give cyclopropanol;[6,10] the yield is improved if the ester cleavage is performed with lithium aluminum hydride (53%) or, more conveniently, by use of methyllithium. The method has general utility since a wide variety of cyclopropyl acetates are available or accessible from the carboxylic acids (see section II.C).

Although the ester cleavage reactions have generally involved cyclopropyl acetates, several different types of cyclopropyl esters have been used to prepare the alcohols. For example, a variation of this method has been reported by Staab and Ipaktschi;[11] in this, a lactone is cleaved by hydrazine hydrate to give the cyclopropanol directly. In general, basic



(3)

cleavage of a cyclopropyl ester gives the cyclopropanol in good yields; however, Paukstelis and Kao[12] have reported one instance in which the cleavage reaction is attended by a skeletal rearrangement which takes precedence over cyclopropanol formation. Thus the alcohol **1** is only a minor product of acetate cleavage.



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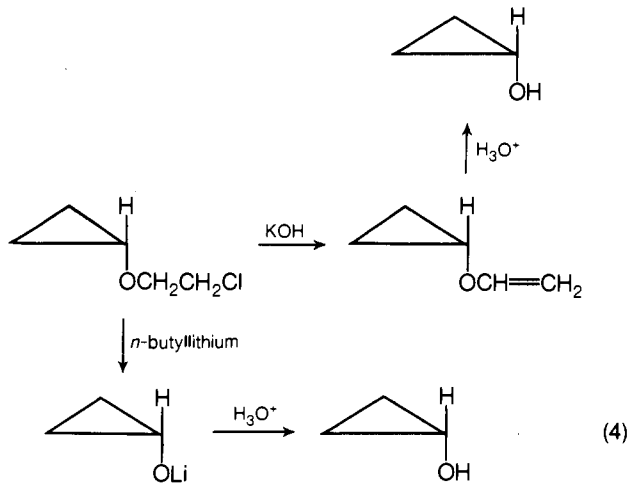
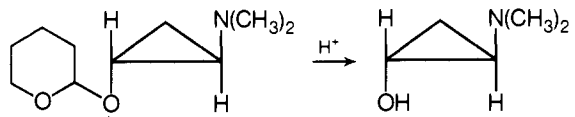
Schöllkopf and his coworkers were the first to develop the ethers as a means of preparing cyclopropanols, and the early work in this area has been reviewed.[3] The problem inherent in such a synthetic route is to find an R group which can be removed under sufficiently mild conditions that the three-membered ring is not opened concurrently; the first substituent which was found to meet these conditions was the β-chloroethyl group (eq 4). The method has been used to prepare secondary cyclopropanols and can be used to prepare



(4)

some tertiary systems as well. Templeton and Wie[13] have used the *n*-butyllithium route to prepare a tertiary steroidal cyclopropanol.

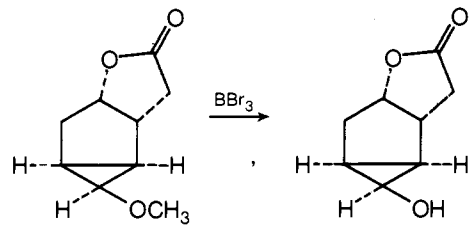
The tetrahydropyranyl group can be easily removed under mild conditions, and two research groups have begun to use it as a protecting group. Thus, Armstrong and Cannon[14] have prepared the 2-aminocyclopropanol in eq 5 by this route, and



(5)

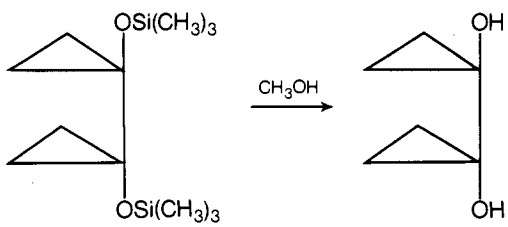
Birch and Keeton[15] have reported the preparation of some tricyclic compounds containing a cyclopropanol by this method.

In at least one instance a cyclopropyl methyl ether has been successfully cleaved and converted to the corresponding cyclopropanol. Corey and his coworkers[16] have performed the transformation in eq 6 by low-temperature reaction with boron tribromide.



(6)

The cleavage reactions of trimethylsilyl ethers (first used to prepare the 1,2-diols, as discussed in section II.B) promise to be particularly useful in the preparation of very reactive cyclopropanols, since the cyclopropanols can be generated under exceptionally mild conditions. Conia and Denis[17] have used this method to prepare 1,1′-dihydroxybicyclopropyl (eq 7).



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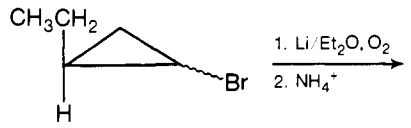
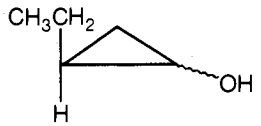
3. By Oxygenation or Oxidation Reactions

In the process of reinvestigating and verifying the Cottle procedure for cyclopropanol synthesis,[5] Roberts and Chambers[18] selected an independent method for synthesis of the

alcohol in which cyclopropylmagnesium chloride was oxygenated. This method gave very poor yields (9%) of the alcohol but helped to confirm Cottle's earlier work. More recently, Longone and Wright[19] have modified the oxygenation reaction by using cyclopropyllithiums rather than Grignard reagents. The reaction of cyclopropyllithium in this way gives a moderate yield of cyclopropanol, but most other such reactions give good yields of the expected cyclopropanols. Interestingly, the isomer ratio of the starting halide does not govern the distribution of alcohol isomers as the sequence in eq 8 shows.



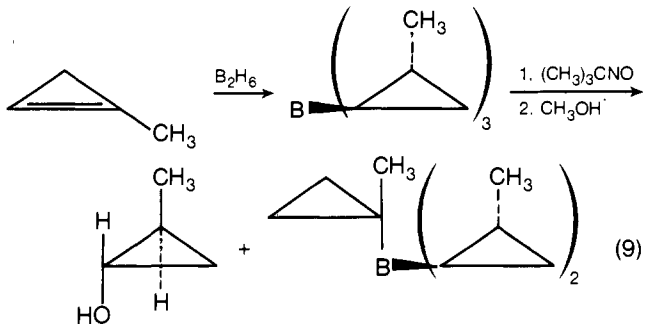
cis/trans = 3/2



(8)

cis/trans = 1/2

Three recent reports have shown that cyclopropanols may be obtained by oxidation of cyclopropylboron compounds. Koster and his coworkers[20] generated these precursors by reaction of cyclopropenes with diborane; the boron compounds were then oxidized with trimethylamine oxide and the cyclopropanol was obtained by methanolysis (eq 9). A variation of this procedure has been reported in which BH_3 is added to a methylenecyclopropane[21] (eq 10). The yield of cyclopropanol is high when the exocyclic carbon atom is disubstituted, but the reaction fails to give a cyclopropanol when this atom bears a single substituent.



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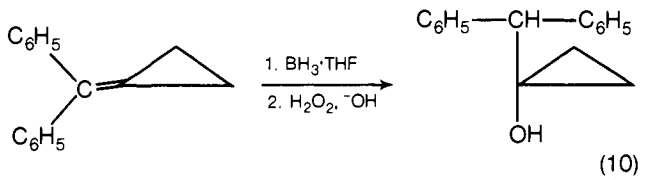
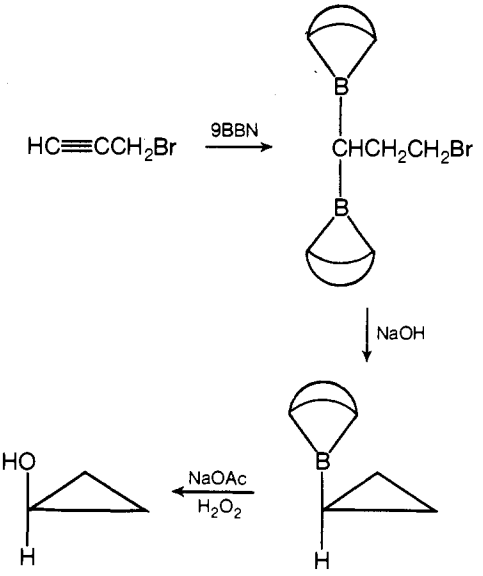


(10)

Brown and Rhodes[22] formed the 9-borabicyclo[3.3.1]nonane (9-BBN) derivative of cyclopropane and converted it to cyclopropanol in high yield (eq 11). It seems probable that this method can be extended to the synthesis of other cyclopropanols and that the oxidation procedure in this latter method may be applicable to the Koster method.

4. *From Cyclopropanones and Their Derivatives*

Cyclopropanols may also be formed by addition reactions to cyclopropanones; the preparation of the cyclopropanones and the early work describing the preparation of a number of geminal bifunctional cyclopropanols has been reviewed.[23] The compounds of this type which have been used most in synthesis are the hemiketals and hemiacylals formed by direct addition to cyclopropanones (eq 12). The cyclopropanone hemiketals have generally been prepared by reactions of a ketene with a diazoalkane followed by addition of an alcohol. A different synthetic route has recently been reported by Fry and Scoggins;[24] these workers prepared methyl hemiketals by electrochemical reductions of some α,α'-dibromo ketones in the presence of methanol.



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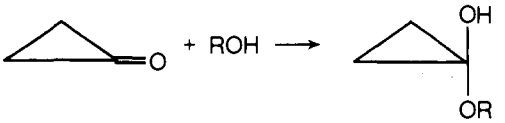
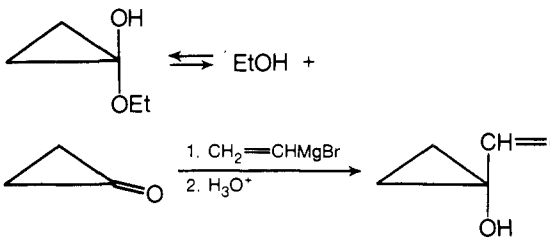


(12)

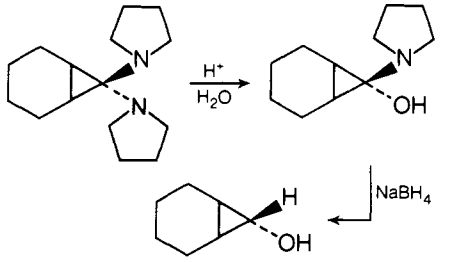
R = alkyl or acyl

Wasserman and his coworkers, over a period of several years, have synthesized a variety of unusual 1-substituted cyclopropanols by addition reactions involving cyclopropanone derivatives, particularly the hemiketals. With the latter compounds the synthetic method is dependent upon a small amount of cyclopropanone present in solution in equilibrium with the hemiketal.[25] A variety of 1-substituted cyclopropanols have been prepared in this way[26] (eq 13).



(13)

Smuszkowicz and his coworkers[27] have used an aminal derived from a cyclopropanone to good advantage in the synthesis of *endo*-7-norcaranols (eq 14). Wasserman and Baird[28] have studied these systems further and suggest that the transformations are due to the intermediacy of the iminium ion **2**.



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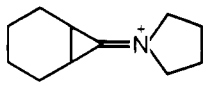

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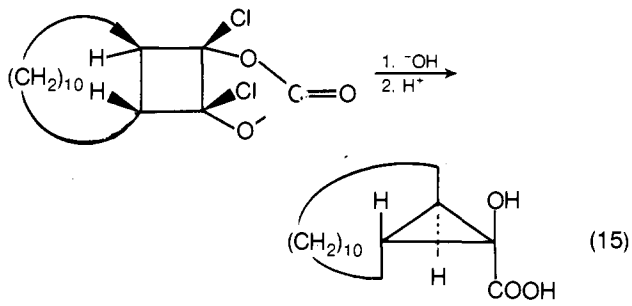
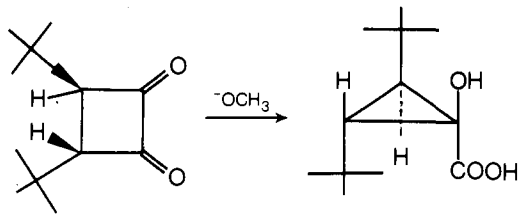
5. By Ring Contraction Reactions

The use of suitable cyclobutane derivatives to prepare cyclopropanols substituted at the 1 position by a carboxyl group has been reported recently by several groups. Scharf and Klar[29] have used a carbonate to prepare an unusual bicyclic system (eq 15).



(15)

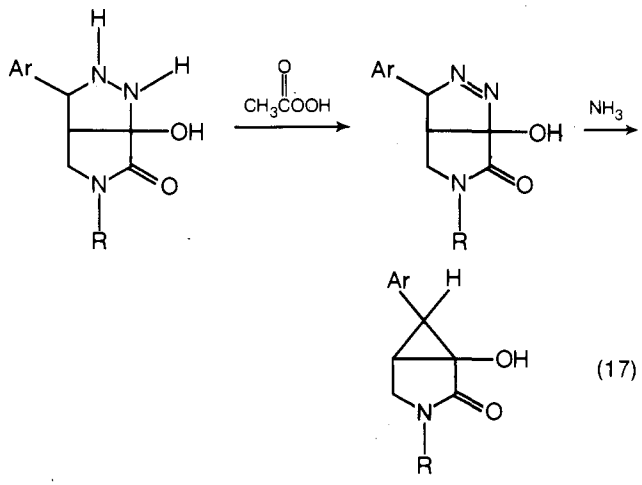
Syntheses of cyclopropanols from 1,2-cyclobutanediones have been reported by three groups. The *trans*-di-*tert*-butyl isomer shown in eq 16 undergoes a benzilic acid type rearrangement when treated with methoxide ion;[30] the reaction gives a single product, presumably with the two *tert*-butyl groups trans to one another.



(16)

The second report describes the conversion of 1,2-cyclobutanedione to 1-hydroxycyclopropane-1-carboxylic acid by the action of either acid or base[31] or water alone.[32]

A different type of ring contraction has been reported by Southwick and his coworkers[33] which is related to the pyrazoline method for cyclopropyl acetate synthesis (see section II.C):

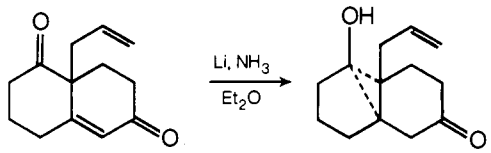


(17)

6. By Miscellaneous Other Methods

Several methods for cyclopropanol synthesis have been reported which do not easily fit into any of the above categories. Some of these should prove to be useful in the synthesis of particular types of cyclopropanols.

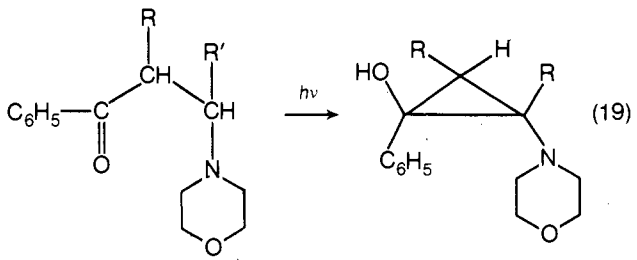
Internal addition of a carbanion to a carbonyl group can, in properly chosen systems, lead to cyclopropanols (see section III.B for a full discussion of this type of reaction). An ingenious and potentially very useful variation of this reaction has been reported[34] in which the carbanion is generated by reduction of an α,β-unsaturated ketone (eq 18). A second group[35] has



(18)

reported evidence for the intermediacy of cyclopropanols in reductions of α,β-unsaturated ketones under Clemmensen conditions.

Several reports have appeared involving photochemical routes to cyclopropanols. The parent compound has been identified as a minor component from the photolysis of butyrolactone.[36] In a second study, high yields of cyclopropanols are reported from the photolyses of 3-morpholinopropiophenones in dioxane (eq 19).[37] In each case the reaction appar-

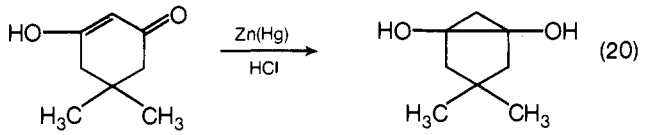


(19)

ently provides a single isomer; however, the stereochemistry of these products has not yet been established. More recently, Gull, Wehrli, and Jeger have reported the formation of a tertiary cyclopropanol from uv irradiation of an 11-oxo-Δ^{14}-5α-pregnene derivative.[38]

B. 1,2-Cyclopropanediols

The first suggestions of the formation of *vic*-cyclopropanediols comes from work on Clemmensen reductions of β-diketones.[39-41] Staschewski formulated the first product as a diol as illustrated in eq 20 in the reaction of dimedone.

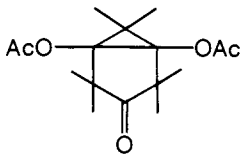


(20)

There was soon disagreement about subsequent steps in the sequence with Wenkert and Kariv pointing out that acid-catalyzed ring rupture of the diol would be expected (see section III.A) to yield an α-ketol. Further work by Baker and Davis[42] on β-diketones in the homocamphor series lent support to this mechanism since the expected α-ketols could be isolated by steam distillation during the course of the reaction. If the reductions were carried out for long periods of time without product removal, no α-ketols could be found. More recent work, by Curphey and McCartney,[43] on the reduction of hexamethyl-1,3,5-hexanetrione gave further support to the Wenkert mechanism since an α-ketol could be isolated in this case as well. Chuang and Scott have also reported isolation of an α-ketol under Clemmensen conditions.[44]

Curphey and his group continued their work on the behavior of 1,3-diketones by studying the electrochemical reduction of 2-methyl-2-acetylcyclohexanone,[45] the system studied by

Wenkert and Kariv under Clemmensen conditions. The anions of the expected epimeric cyclopropanediols were trapped as the diacetates by using acetic anhydride. Reduction of the trione they had studied earlier[43] and trapping in the same way gave the following diacetate **3**. Curphey and McCartney later



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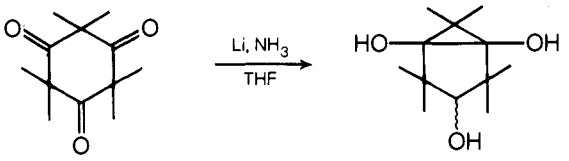
reduced this triketone in the presence of trimethylsilyl chloride and obtained the bis(trimethylsilyl) ether in high yield.[46] Addition of water to the electrolysate gave the air-sensitive diol.

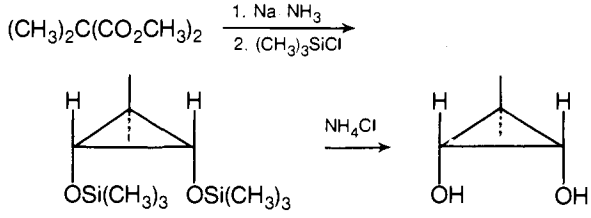
Reusch and Priddy have studied the reduction reactions of the hexamethyl-1,3,5-cyclohexanetrione under various conditions. Clemmensen reduction[47a] of the triketone gave the *vic*-cyclopropanediol in 80% yield, whereas reduction with lithium in THF–ammonia afforded the triol shown in eq 21.[47b]



(21)

Evidence for the intermediacy of the *vic*-diols has also been presented by LeGoaller and his coworkers[48] from their studies of the reduction of 3,3-dimethyl-2,4-pentanedione by sodium metal. The trapping agent employed was trimethylsilyl chloride.

The most recent report of a preparation of a 1,2-diol comes from work by Ainsworth and Chen.[49] These workers have prepared 3,3-dimethyl-*cis*-1,2-cyclopropanediol by the route in eq 22. The stereochemical results of the reduction of



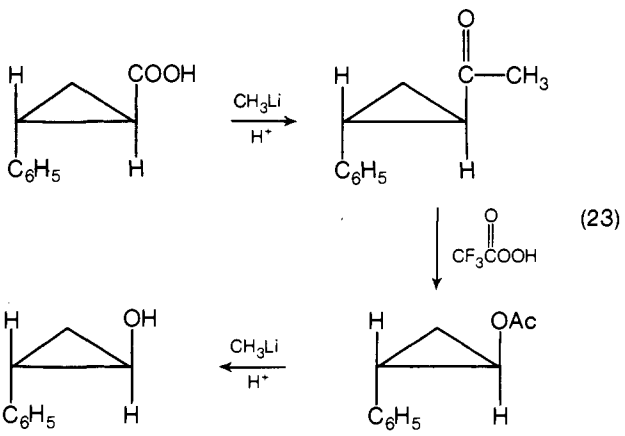
(22)

this acyclic compound are particularly interesting in view of the fact that the reductions studied by Curphey, *et al.*,[45] led to mixtures containing both cis and trans isomers.

C. Cyclopropyl Ethers and Esters

With care, esters of cyclopropanols can be hydrolyzed to the parent alcohol without ring opening. As a consequence, a method which leads to the synthesis of a cyclopropyl ester may be used to prepare the alcohol as well.

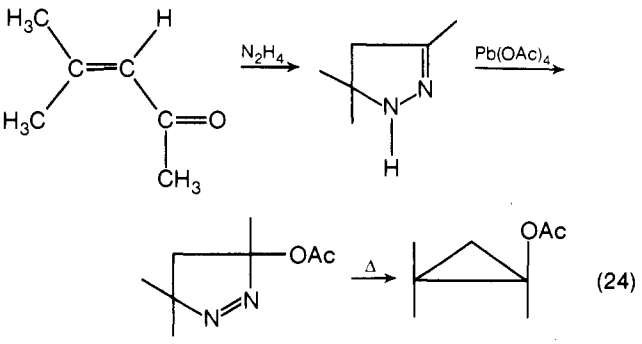
Cyclopropyl acetates became readily available when Emmons and Lucas[50] showed that methyl cyclopropyl ketones could be oxidized under Baeyer–Villiger conditions to these esters. Any group larger than methyl gives rise, almost exclusively, to esters of cyclopropanecarboxylic acids.[51] Methyl cyclopropyl ketones, in turn, are available in high yield from reaction of cyclopropanecarboxylic acids with methyllithium. A typical reaction sequence is shown in eq 23.[52] The reactions occur in high yield and are stereospecific, and the starting acids are generally easy to obtain in isomerically pure form. For the synthesis of a single pure isomer of a cyclopropanol this is often the sequence of choice. The acids are crystalline, nmr methods are available for assignment of



(23)

stereochemistry, and the alcohol can be stored as its ester until just before use.

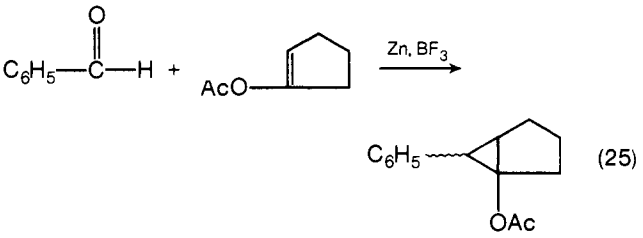
An extremely simple synthesis of a number of cyclopropyl acetates has been developed by Freeman.[53] The sequence involves the addition of hydrazine to an α,β-unsaturated ketone, oxidation of the resulting pyrazoline by lead tetraacetate, and subsequent decomposition of the azo compound to a cyclopropane derivative (eq 24). When applied to mesityl



(24)

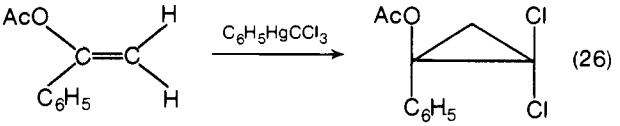
oxide, as shown in eq 24, the reactions proceed in good yield and can be carried out on a moderate-sized scale.

Carbenoid additions to enol esters represent, in principal, one of the most direct ways to prepare a cyclopropyl ester. Simmons and Smith first reported the addition of iodomethyl zinc iodide to vinyl acetate to form cyclopropyl acetate in 30% yield,[54] but extensions of this work to more complicated systems have not met with as much success. Some phenyl-substituted cyclopropyl acetates have been formed in moderate yields by a different type of carbenoid reaction (eq 25).[55]



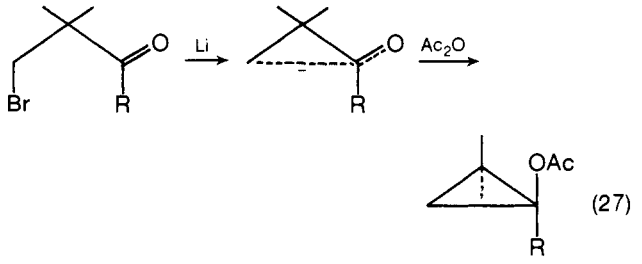
(25)

Parham and his coworkers[56] have thus far been the most successful in adding a carbenoid to an enol acetate. The reaction shown in eq 26 proceeds in 70% yield.



(26)

A different method of synthesis of cyclopropyl acetates has been described by Hamon and Sinclair;[57] reaction of a β-halo aldehyde or ketone with an alkali metal followed by acylation affords the acetate in 40–60% yield (eq 27). The car-



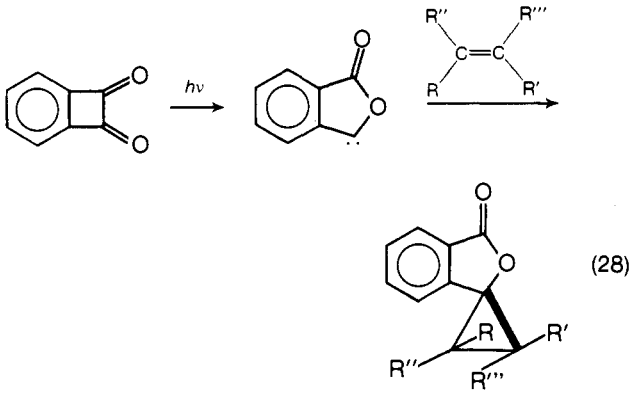
(27)

bonyl compound in this case must be one which has no α-hydrogens; therefore, the method is somewhat less general than that of Freeman[53] described above.

Longone and Miller have converted cyclopropyl Grignard reagents to their benzoates by the action of benzoyl peroxide.[58] These reactions proceed in rather low yield, however.

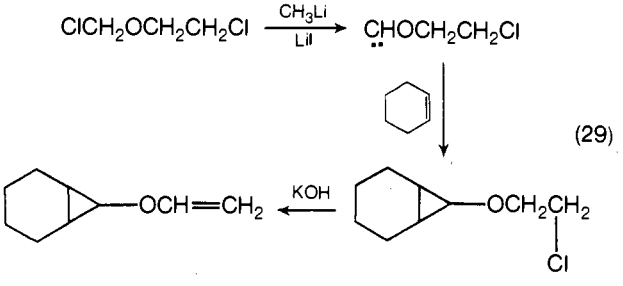
The reduction of a *gem*-dibromocyclopropane with chromium(II) acetate has been reported to give isomeric cyclopropyl acetates as major reaction products.[59]

An unusual photochemical route to cyclopropyl esters has been reported by Staab and Ipaktschi[11] (eq 28).



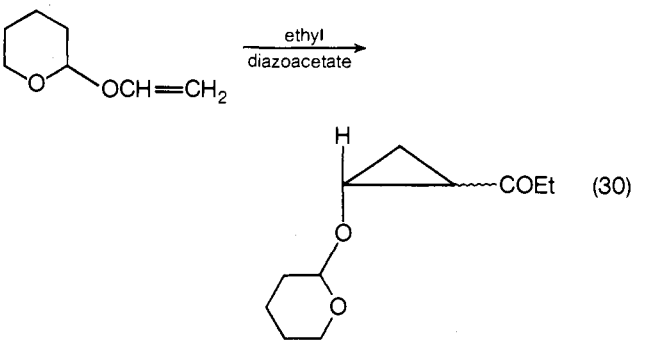
(28)

If a cyclopropyl ether is to be useful for the synthesis of a cyclopropanol, it must be readily hydrolyzable under mild conditions. Schöllkopf and his group[3] developed the cyclopropyl vinyl ethers as useful substrates from which the cyclopropanols could be generated; however, these are limited since they are useful only for preparing cyclopropanols unsubstituted at the 1 position. The vinyl ethers are prepared *via* eq 29.



(29)

More recently there have been two types of cyclopropyl ethers developed which show promise of general use as cyclopropanol precursors (or as protecting groups for such compounds); these are the 2-tetrahydropyranyl (THP) and trimethylsilyl ethers. The first of these has been successfully used by two groups recently to prepare cyclopropanols. Thus Birch and Keeton[15] have added dichlorocarbene to systems such as **4** and obtained both the mono and bis carbene adducts. Armstrong and Cannon[14] have prepared the tetrahydropyranyl ethers according to eq 30. Other transformations

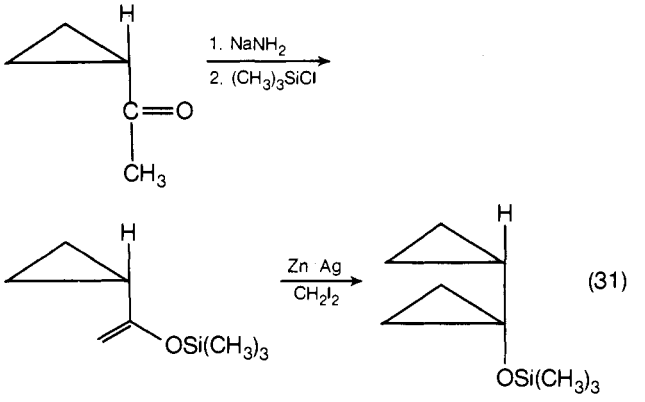


(30)

were then performed on the resulting bifunctional compounds as described in section V.

The trimethylsilyl ethers have been particularly useful in syntheses leading to the *vic*-cyclopropanediols as indicated in section II.B above. There are other ways in which these ethers may be used, however, and the chemistry of these compounds is developing rapidly.

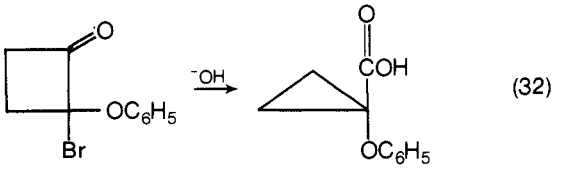
Conia has recently prepared a silyl ether of 1-hydroxybicyclopropyl by the route shown in eq 31.[60] The resulting ether



(31)

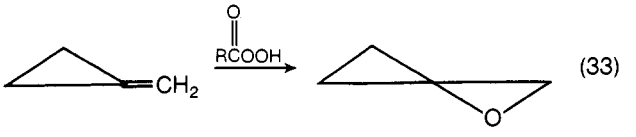
was converted in good yield to the 1-chloro derivative by reaction with thionyl chloride; only 7% of the ring-opened chloride was obtained. The preparation of other silyl ethers of cyclopropanols and the conversion of these to cyclobutanones has also been reported by Conia, *et al.*,[61] these reactions will be discussed in more detail in section IV.

The formation of cyclopropyl ethers by ring contraction reactions of the type shown in eq 32 have been studied by several groups; these and other such ring contraction reactions have recently been reviewed.[62]



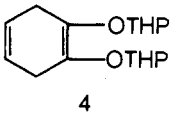
(32)

An unusual class of cyclopropyl ethers, the oxaspiropentanes, have been prepared and are being studied by two groups; Salaün and Conia have prepared the parent compound as shown in eq 33.[63] Trost and Bogdanowicz[64] have



(33)

prepared oxaspiropentanes *via* eq 34 in very high yields. These workers have then used the resulting oxaspiropen-



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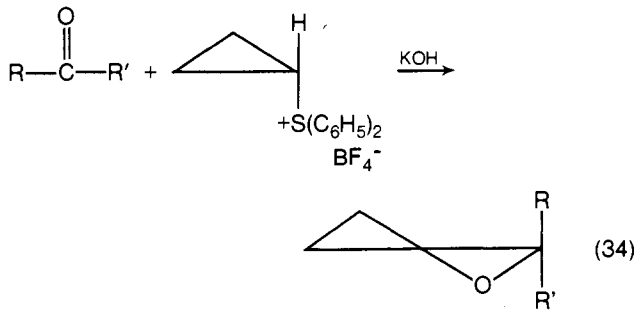
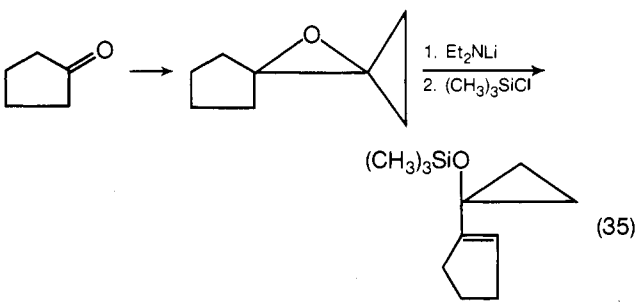


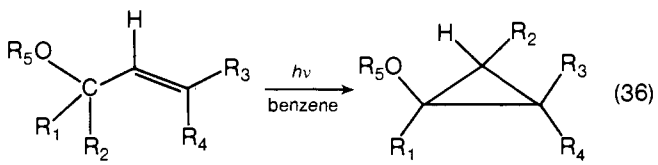
(34)

tanes to prepare silyl ethers of cyclopropanols (eq 35).[65] The uses of the oxaspiropentanes will also be discussed in detail in section IV.



(35)

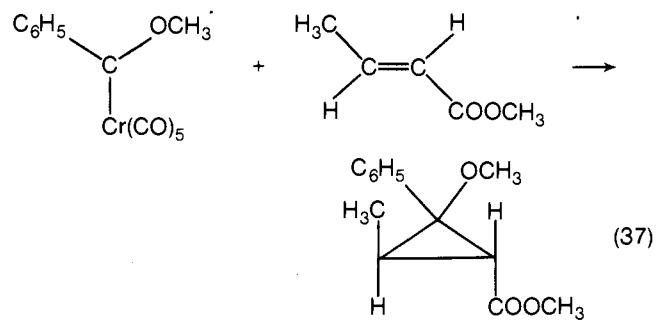
A route to other cyclopropyl ethers, recently reported by Brophy and Griffin,[66] proceeds easily and gives good to excellent yields of the product ethers. In these, an allyl ether is photolyzed in benzene solution for about 36 hr and the cyclopropyl ether results as shown in eq 36. One attempt to pre-



(36)

pare a cyclopropanone ketal by this method was unsuccessful.

Organometallic routes to cyclopropyl ethers have been developed by Fischer and Dotz. In the first report,[67] a mixture of the isomeric ethers shown in eq 37 was obtained in 60%



(37)

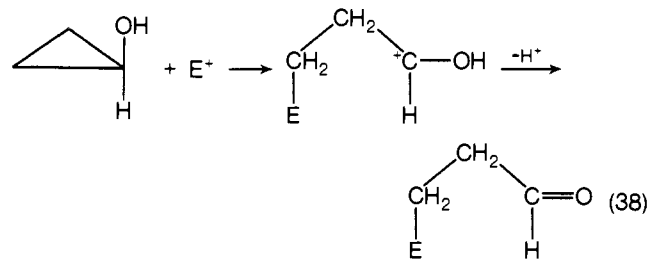
yield. The second report then dealt with reactions of this chromium–carbene complex and some vinyl ethers;[68] in this series of reactions, cyclopropane derivatives were obtained only when ligand displacement was effected by means of added carbon monoxide.

III. Ring-Opening Reactions of Cyclopropanols and Their Derivatives

For purposes of discussion it is convenient to divide the reactions of cyclopropanols and their derivatives into five types: reactions induced by electrophiles, reactions initiated by base, reactions initiated by O–X homolytic bond cleavage (X = H or NO), pyrolysis and photolysis reactions, and reactions involving C–O heterolytic bond cleavage. The first group of reactions has recently been discussed in a comparative review of cyclopropanols and cyclopropanes[4] and will not be presented in detail again here.

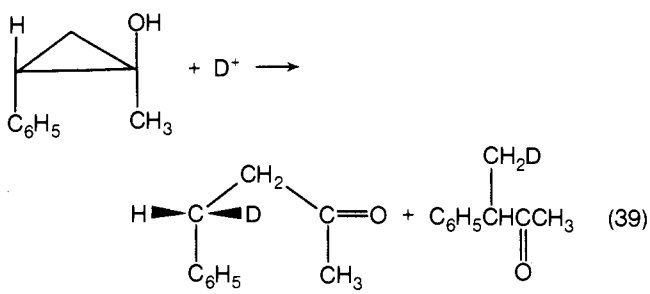
A. Reactions Induced by Electrophiles

Cyclopropanols, in common with other cyclopropane derivatives, undergo ring cleavage reactions when treated with electrophiles (eq 38). Thus the alcohols, their ethers, and es-



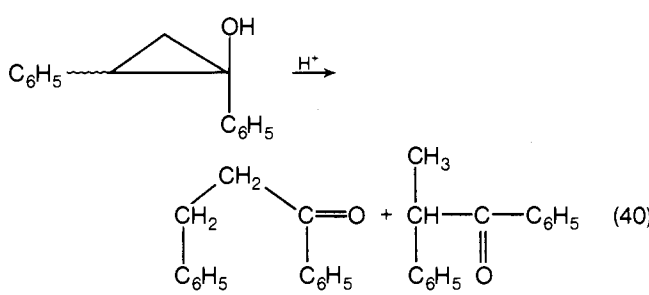
(38)

ters react readily with acids, mercuric salts, and (particularly the alcohols) halogenating agents. With acids the reaction generally occurs with retention of configuration at the site of electrophilic attack,[52] but one example of ring opening of a cyclopropyl methyl ether with inversion is known.[69] As dem-



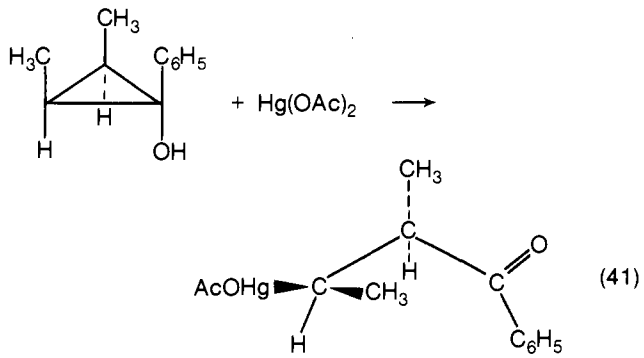
(39)

onstrated by these reactions, a mixture of products generally results from opening of unsymmetrical cyclopropanols with the product resulting from proton attack on the least substituted carbon predominating. The major exception thus far noted is the reaction of 1,2-diphenylcyclopropanol in which 1,2-bond cleavage far exceeds 1,3-cleavage in both cis and trans isomers (eq 40).[70] Cyclopropanols and their derivatives react



(40)

readily with mercuric acetate in either acetic acid or methanol.[71] The stereochemistry of the resultant organomercurial depends strongly upon the substitution pattern of the substrate; attack occurs most readily on the least substituted bond in the molecule with ring opening in the direction of the carbinol carbon. If bonds are equally substituted, attack on a cis-disubstituted bond proceeds more readily than on a trans bond. Thus, *trans*-2,3-dimethyl-1-phenylcyclopropanol (eq 41) gives products with 90% inversion of configuration whereas *trans*-2,3-dimethylcyclopropanol opens with 90% retention of configuration (eq 42). Mercuric acetate ring opening is, compared to that induced by acid, highly sensitive to steric hindrance. As an example, ring opening of 2-methyl-1-



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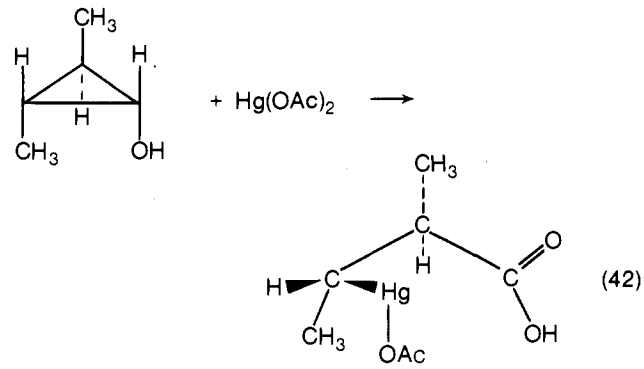
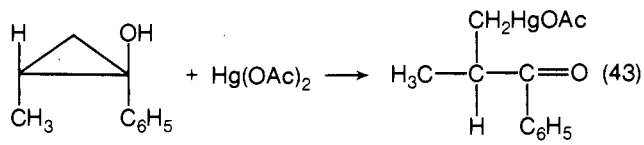


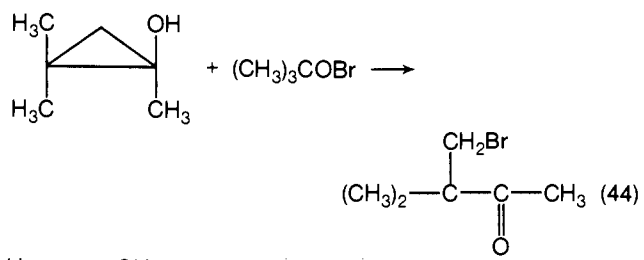
(42)

phenylcyclopropanol with $Hg(OAc)_2$ gives 97% C_1–C_3 cleavage compared to a nearly 50:50 mixture of C_1–C_2 and C_1–C_3 cleavage by protons (eq 43).[52]



(43)

Cyclopropanols are observed to react readily with halogenating agents.[72] With bromine or chlorine the corresponding hydrogen halide is a by-product of the opening and may compete with the halogen as the electrophile. For that reason *tert*-butyl hypohalite or *N*-bromosuccinimide gives cleaner products. Halogen openings seem to be more sensitive to electronic effects than either proton or mercuric ion openings. As indicated below, 1,2,2-trimethylcyclopropanol gives exclusively C_1–C_3 cleavage with *tert*-butyl hypobromite (eq 44), but *trans*-2-phenyl-1-methylcyclopropanol is cleaved exclusively adjacent to the phenyl group (and with inversion, eq 45). Both protons and mercuric ions give mainly C_1–C_3 cleavage with either alcohol. Ring openings with halogenating agents generally do not occur readily on cyclopropyl ethers and esters.[72]



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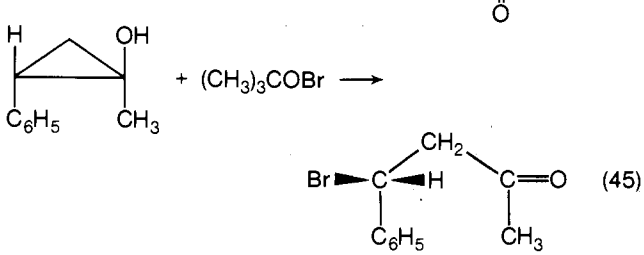


(45)

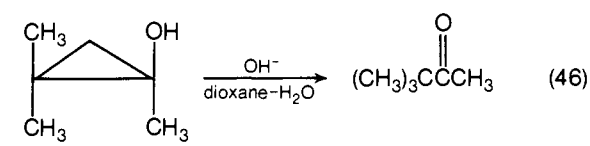
In reactions with protons or mercuric salts, the ethers are generally 10 to 100 times less reactive than the corresponding alcohols. Toward halogenating agents this reactivity difference is much larger, so much so that the products often do not survive the reaction conditions or side reactions occur.

We conclude then that electrophilic openings of cyclopropanols can occur cleanly and stereospecifically and give promise of developing into useful synthetic reactions (see section IV below).

B. Reactions Induced by Base

The first preparation of cyclopropanol[5b] resulted in a product shown later to be contaminated with propionaldehyde. The rearrangement occurs with particular ease in the presence of base, and even attempts to dry the alcohol over potassium carbonate resulted in its conversion to 2-methyl-2-pentenal, the aldol product of propionaldehyde. Since base cleavage of cyclopropyl esters offers a potential synthetic route to cyclopropanols, an investigation of the acetates was undertaken to determine the relative rates of ester cleavage and ring opening.[10] The results of the kinetic studies indicated that cyclopropanol is comparatively stable under conditions required to cleave the acetate with ring opening to the aldehyde occurring slowly.

Further studies of the reactions of cyclopropanols in the presence of base have indicated that the ring opening occurs more readily toward the ring carbon atom which can best stabilize a negative charge.[52,72,73] The examples in eq 46 and 47 are illustrative. Studies of the stereochemistry of the ring-



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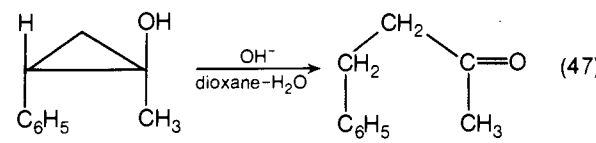
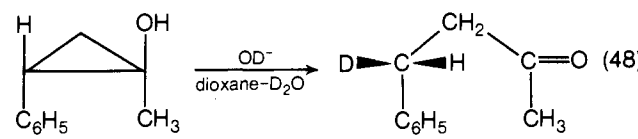


(47)

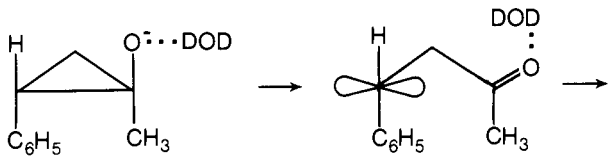
opening reactions of cyclopropanols were initiated with the *trans*-2-phenyl-1-methyl cyclopropanol (eq 47). In dioxane–D_2O the ring-opening proceeds with inversion of configuration at the benzylic carbon atom (eq 48).[52] These results suggest-

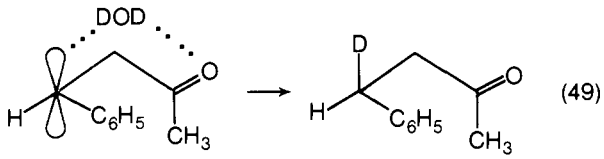


(48)

ed that an SE1 reaction, such as Cram and his coworkers had studied,[74] might be involved. A carbanion intermediate is formed in the rate-determining step of the SE1 reaction, but, although the solvent is one Cram had shown to give predominant inversion, the high stereospecificity observed in the cyclopropanol opening seemed to argue against a "free" carbanion. As a result of his own studies of the stereochemical course of the ring opening reactions of cyclic alcohols, Cram[75] has recently suggested a "rotation mechanism" as an alternative means of accounting for the inversion observed in the previous studies of the *trans*-2-phenyl-1-methyl alcohol (eq 49).

At about the same time that the work with the *trans*-2-phenyl-1-methylcyclopropanol appeared, Nickon[76] reported the results of a study of the base-catalyzed opening of the alcohol in eq 50. Although the solvent used here had demonstrated a marked tendency to give retention in the systems studied by Cram, it gave inversion exclusively with the nortri-





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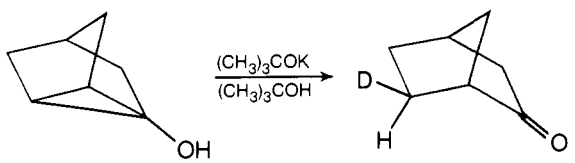
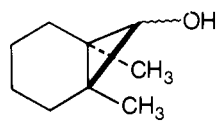


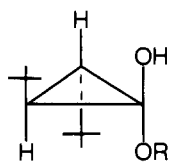
(50)

cyclic system. Wharton and Bair reported[77] that the products formed in the ring openings of the exo and endo alcohols **5**



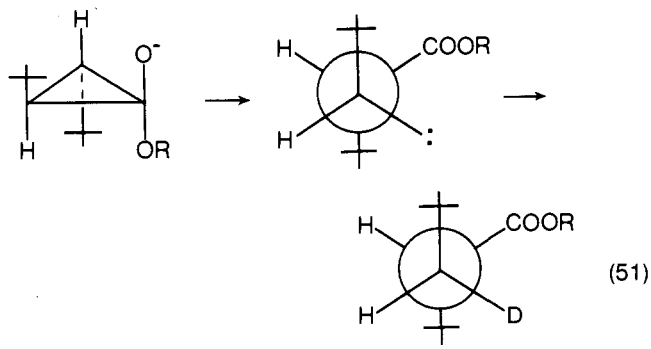
5

were those which would have been expected from predictions based on Cram's work; these cyclopropanols open with retention in *tert*-butyl alcohol and give inversion in ethylene glycol. Wharton has suggested that the inversion observed in Nickon's system may be attributed to a steric preference of the norbornyl system for exo attack. More recently Wharton and Fritzberg have examined the ring-opening reactions of hemiketals derived from *trans*-2,3-di-*tert*-butylcyclopropanone[78] (**6**). These are observed to open with predominant re-



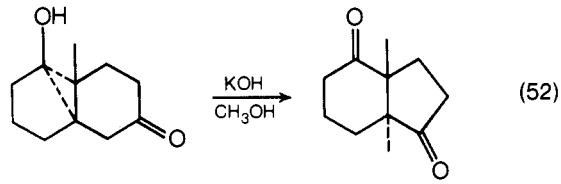
6

tention in both CH_3OD–CH_3ONa and $DOCH_2CH_2OD$–$DOCH_2CH_2ONa$, although according to Cram's results the former should give *retention*, the latter *inversion*. The unusual geometry of these systems may be responsible for their behavior in solvents predicted to give opposite stereochemical results. Capture of the intermediate carbanion before inversion can occur is thought to be aided by the conformational stability of the anion (eq 51).



(51)

The unusual behavior of the cyclopropanol shown below in the presence of acid or base has been studied by Reusch and his coworkers.[79] In the presence of methanolic KOH, the reaction takes the course shown in eq 52. The rearrangement has been rationalized in terms of equilibrating cyclopropylalkoxide ions and solvent capture of the more stable one (eq 53). The "normal" course for base-catalyzed ring opening



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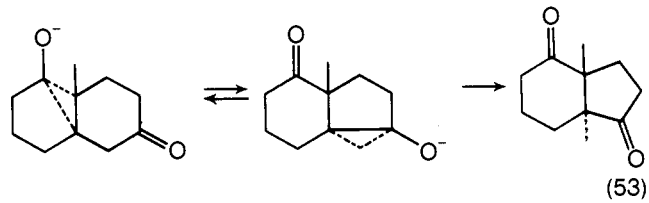
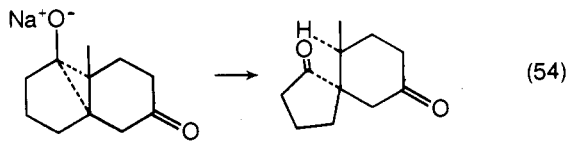


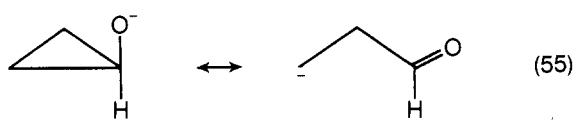
(53)

of the alcohol could be effected by converting the substrate to its sodium salt (by NaH) followed by quenching with methanol;[79b] the spiro ketone obtained in this reaction results from retention in the protonation step (eq 54).



(54)

Since cyclopropanol may be regarded as the simplest homoenol, the cyclopropylalkoxide ion is one of the pair of anions which constitute the most fundamental type of homoenolate anion[80] (eq 55). The ring-opening reactions of some cyclopropanols in base are explicable in terms of free carbanions, thus giving credence to the belief that resonance of the above type (or an equilibrium mixture consisting of ions related to the above pair) describes the character of the anion better than the alkoxide ion alone. some attempts have been made to produce the alkoxide–carbanion pair by generating a carbanion center β to a carbonyl group in a system capable of closing to the cyclopropyl alkoxide; the first of these was a study of the behavior of optically active camphenilone at high temperatures in the presence of strong base. To account for the observation that racemization as well as deuterium incorporation occurs, Nickon and Lambert have suggested the sequence in eq 56. Homoenolate anions have recently been suggested to be intermediates in the rearrangements of some



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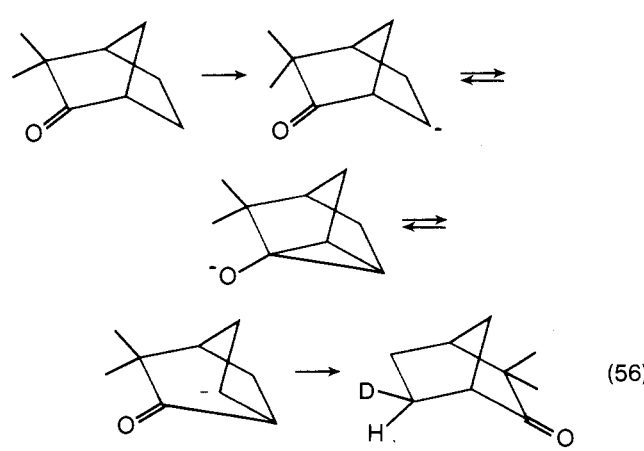
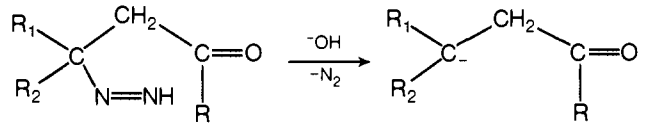


(56)

4,5-disubstituted homocubyl derivatives. As with Nickon's system, exo addition of the proton (with inversion) was confirmed when the rearrangements were performed in deuterated solvent.[81]

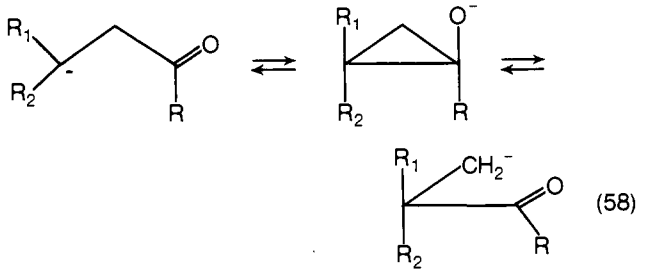
Hamon and Sinclair[57] generated homoenolate ions by the action of an alkali metal on a β-halogenated aldehyde and a related ketone. Acylation of the resulting anions gave cyclopropylacetates in yields of about 50%.

Freeman[82] has used a very different type of system to provide evidence for the intermediacy of homoenolate ions of the above type; the base-catalyzed hydrolysis of 3-acetoxy-Δ^1-pyrazolines is thought to involve a diimide (eq 57), which



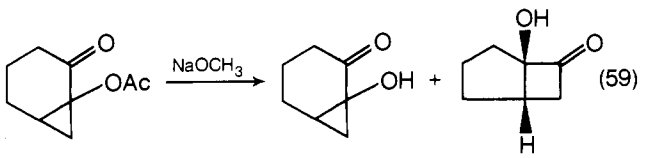
(57)

would be expected to decompose as shown. The resulting carbanion could then equilibrate with the cyclopropyl alkoxide (eq 58). It was shown that, when R = R_1 = R_2 = CH_3, the



(58)

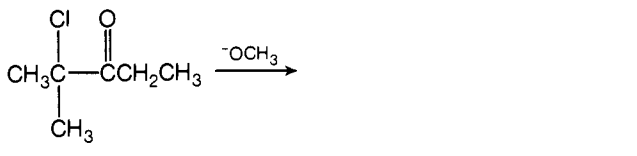
major reaction product is pinacolone together with a lesser amount of methyl isobutyl ketone. The base-catalyzed hydrolysis of 1,2,2-trimethylcyclopropyl acetate was shown to give a 90:10 mixture of these two ketones with the pinacolone again predominating, and, more recently, the base-catalyzed opening of the corresponding cyclopropanol has been shown to yield pinacolone exclusively.[72] These results thus support the suggestion that a homoenolate ion is responsible for the behavior of the pyrazolines in base. The alcohol studied by Reusch[79] seems to be the only one reported thus far in which structurally different homoenolate ions can be obtained from a single cyclopropanol. However, Yates[83] and his coworkers have rationalized the base-catalyzed rearrangement of an α-diketone in terms of equilibrating homoenolate ions, and the base cleavage of the acetate[12] (eq 59) takes a course which suggests intermediate homoenolate ions.



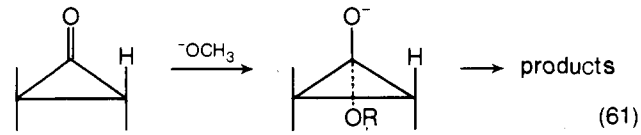
(59)

major product

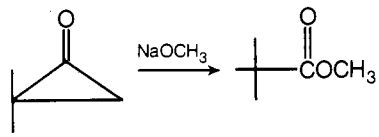
The base-induced reaction of α-halo ketones, in which skeletal rearrangements of the type shown in eq 60 occur, are known as Favorskii rearrangements,[84] and there is good evidence that many of these proceed through cyclopropanone intermediates.[85] The reaction of the chloro ketone (eq 60) has been suggested to proceed by way of the intermediates shown in eq 61. Reaction of 2,2,3-trimethylcyclopropanone with methoxide ion gives essentially the same product mixture as is obtained from the chloro ketone.[86] It was further demonstrated that the methyl hemiketal of the cyclopropanone afforded the same ring-opened esters in approximately the same yields as in the reactions of the cyclopropanone.



84% 16% (60)

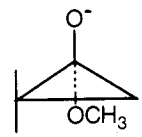


(61)

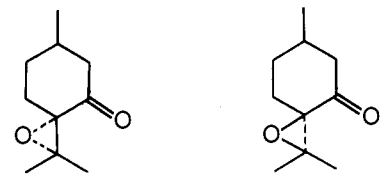


(62)

Turro and Hammond[87] have shown that the dimethylcyclopropanone opens in the presence of sodium methoxide (eq 62). The direction of ring opening of this cyclopropanone parallels that of 1,2,2-trimethylcyclopropanol (in which preferential opening toward the primary center is observed[72]); the cyclopropyl alkoxide **7** must be an intermediate. The lack of specificity observed in the ring opening of the trimethylcyclopropanone (or its hemiketal) has been attributed to the lower energy difference involved in secondary *vs.* tertiary carbanions; ring opening to the tertiary center thus became competitive with opening to the secondary center.



7

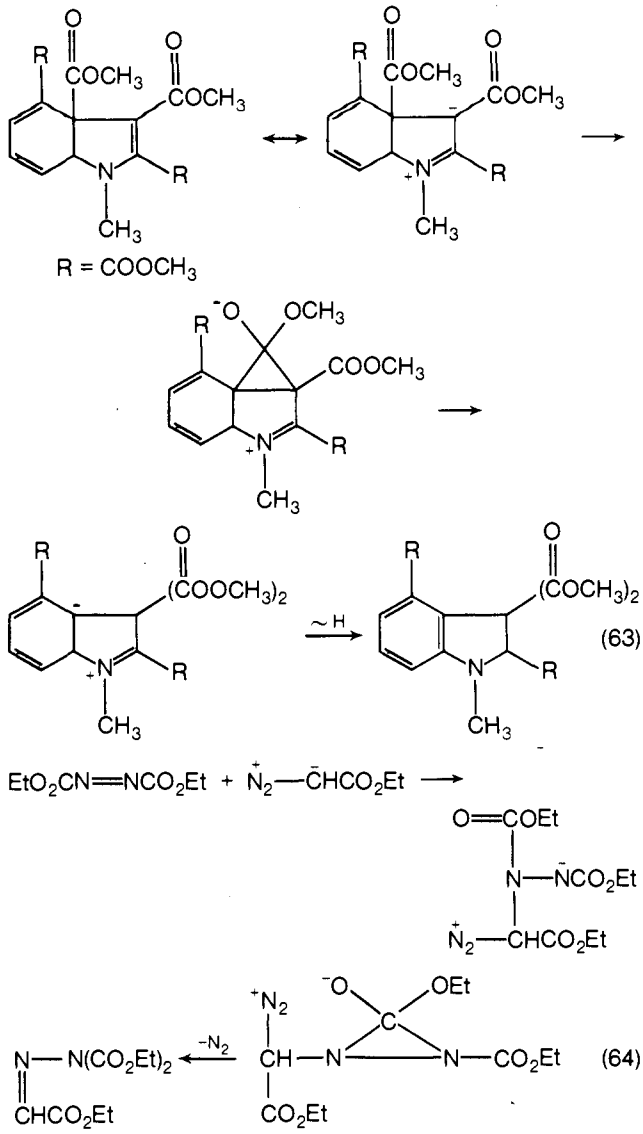


8 **9**

The Favorskii rearrangements of the stereoisomeric pulegone oxides **8** and **9** have been studied by Reusch and Mattison;[88] the reaction products result from both possible modes of cyclopropanone cleavage and retention of configuration is obtained with either isomer in protonation of the tertiary center resulting from "abnormal" opening. The latter results are in accord with predictions based on Cram's work[74] for the solvent system used.

The base-catalyzed ring opening of a *vic*-cyclopropanediol has been reported by Chen and Ainsworth;[49] the results are rationalized in terms of a normal base opening of a cyclopropanol followed by Cannizzaro reaction of the resulting aldehyde.

Some reactions in which an ester group is seen to migrate have been rationalized in terms of cyclopropyl alkoxides or related intermediates; the examples in eq 63 and 64 are illustrative.[89] Cyclopropyl alkoxides have also been implicated in the rearrangement of methylmalonyl coenzyme A to succinyl coenzyme A.

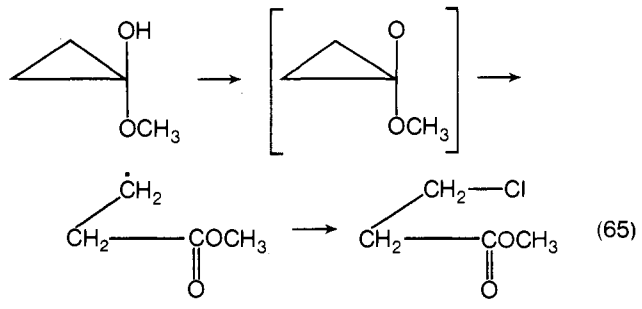


(63)

(64)

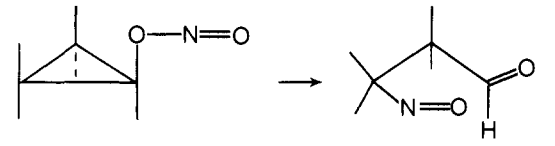
C. Reactions Initated by O–X Bond Cleavage

The first attempts to generate and directly observe cyclopropoxy radicals were described by Schaafsma, Steinberg, and deBoer.[90] They found that treatment of cyclopropanone hydrate (or the corresponding methyl hemiketal) with one-electron oxidants such as Ag^+, $Cu,^{2+}$ or Fe^{3+} give ring-opened radicals which can be detected by esr spectroscopy (eq 65); no evidence was obtained for the suspected intermediate cyclopropoxy radical. Other cyclopropanols have since been allowed to react with ferric chloride, and with these also, the products are best rationalized in terms of a non-stereospecific path in which ring opening is followed by ligand transfer of chlorine to the radical.[91,72] These reactions thus take a completely different course than the ones involving positive bromine, in which inversion of configuration is observed.

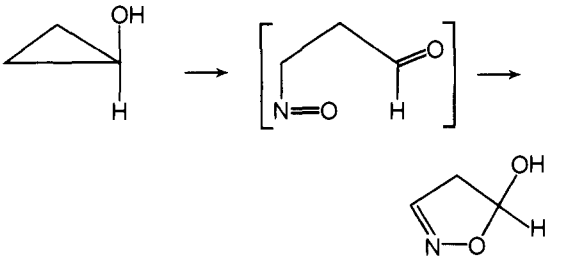


(65)

A second possible route to cyclopropoxy radicals was suggested by the observation that alkoxy radicals are generated in the decomposition reactions of nitrite esters;[92] furthermore, the nitrite esters of a series of cyclic alcohols had been studied, and it was thought desirable to compare the behavior of cyclopropyl nitrites with these. Aliphatic nitrite esters are decomposed by heating (typically at temperatures near 200°) while the corresponding cyclopropanol derivatives are found to be much more reactive.[93] The tetramethylcyclopropyl nitrite, for example, has a half-life of about 1 hr at −45° and reacts as shown in eq 66. Reaction products from these alcohols are usually nitroso monomers or dimers; however, in several instances in which the nitroso group is attached to a primary or secondary carbon atom, reaction products resulting from tautomerism have been observed (eq 67).



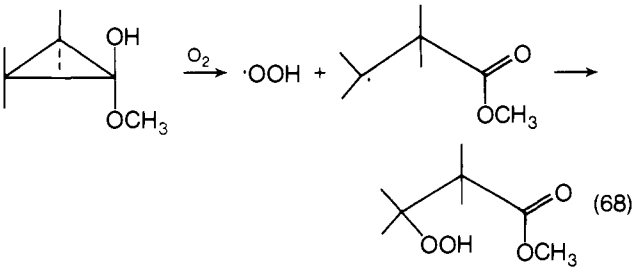
(66)



(67)

Two explanations have been advanced to account for the rate enhancement observed in the thermal decompositions of these nitrite esters relative to their aliphatic counterparts: (a) that a lower energy of activation is needed, since the cyclopropoxy radical may have some of the unusual stability attributed to the cyclopropylcarbinyl cation, or (b) that carbon–carbon bond breaking is concerted with the breaking of the O–N bond and that rate enhancement is a result of energy release accompanying ring opening and carbonyl group formation. The second of these is presently favored, since compounds having substituents at the 2 position are observed to be less thermally stable than the unsubstituted compounds; this order of reactivity is expected if some radical character is developed in the transition state.

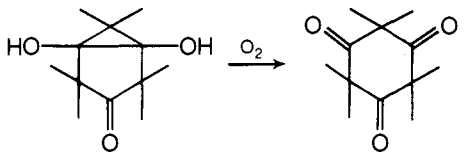
Cyclopropanols which can form stable free radicals by C_1–C_2 bond cleavage are subject to oxidation by ground-state molecular oxygen.[94] The reactions proceed according to eq 68, although the β-hydroperoxy compound rapidly cyclizes to a hydroxy dioxolane when a ketone results from ring opening. The reactivities of cyclopropanols toward molecular oxygen parallel those of the corresponding nitrite esters toward thermolysis; the hemiketal shown above is completely oxidized after about 24 hr and is the most reactive compound yet examined.



(68)

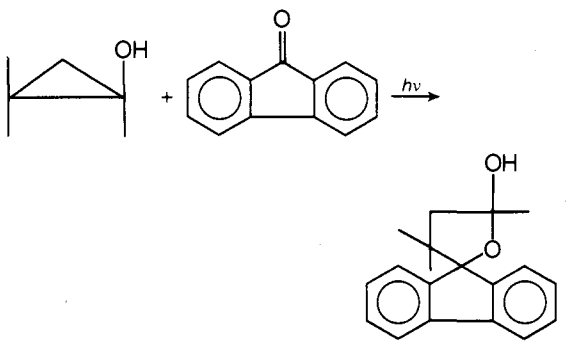
Similar oxidation reactions of 2,2-dimethylcyclopropanone methyl hemiacetal have recently been reported by deBoer, *et al.*[95] In these, oxygen, *tert*-butyl hydroperoxide, or di-*tert*-butyl peroxalate as used as the hydrogen abstraction agent, and CIDNP effects were observed when any of these agents were added to an nmr sample of the cyclopropanol.

Reusch and Priddy[96] have studied the air oxidations of *vic*-cyclopropanediols and have found that these compounds are even more reactive than simple cyclopropanols. With the diols, the reactions products are 1,3-diones and the reaction (eq 69) proceeds to completion in about an hour.



(69)

A detailed study of the oxidations of cyclopropanols by photoexcited aryl ketones has recently been reported.[97] Quantum yield studies indicate that the cyclopropanols react with high efficiency and are comparable to reactive substrates such as benzhydrol. In general, the products obtained from highly substituted cyclopropanols result from disproportionation of the intermediate alkyl radicals. Some aryl ketones which do not normally function as hydrogen abstraction agents, such as fluorenone, have been found to react readily with cyclopropanols. The reaction products with fluorenone differ markedly from those obtained with other ketones and result from dimerization of the fluorenone ketyl with the ring-opened alkyl radical of the cyclopropanol (eq 70).

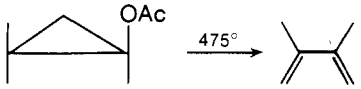


(70)

From all of the above studies it seems clear that the O–X bond of cyclopropanols or their derivatives (X = H or NO) undergo homolytic fission much more easily than the analogous bonds of aliphatic alcohols.

D. Pyrolysis and Photolysis Reactions

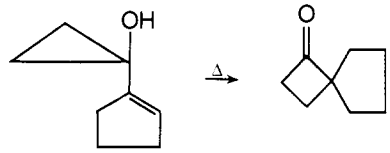
Some time ago, a brief examination of pyrolytic eliminations of cyclopropyl acetates was done to determine if cyclopropenes could be prepared in this way. The pyrolysis of 1,2,2-trimethylcyclopropyl acetate[98] proceeds according to eq 71. With further studies of other cyclopropyl acetates it



(71)

was possible to reject a concerted mechanism for these eliminations (such as the one which is operative in other pyrolytic eliminations[99]) in favor of one in which homolytic C_2–C_3 bond breaking initiates the reaction. In support of this, the nature of the products obtained from 1-phenylcyclopropyl acetate (in which C_1–C_2 bond breaking would be preferred) is completely different from those obtained from simple alkyl-substituted cyclopropylacetates.

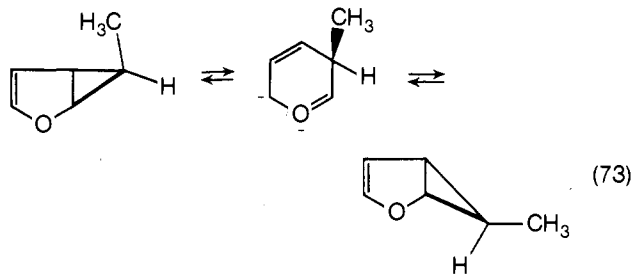
In the course of their studies of other synthetic routes to vinylcyclopropanols, Salaün and Conia[100] have found that thermal ring enlargements occur in which the 1-vinylcyclopropanols are converted to cyclobutanone derivatives (eq 72).



(72)

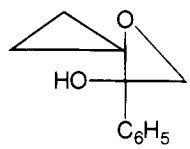
The rearrangements proceed in nearly quantitative yield when the cyclopropanol is heated to 100°. Deuterium-labeling studies suggest that the reaction takes place by an intramolecular cis addition to the double bond.

A preliminary report of the thermolysis reactions of some homofurans suggests that the rearrangements of these compounds take place by concerted processes which lead eventually to ring-opened products.[101] The authors suggest that equilibrium is established among the three systems in eq 73, any of which can subsequently open to form a dienal.



(73)

Photolysis of an α-cyclopropoxyacetophenone has been reported to yield acetophenone, cyclopropanone (in low yield), and a cyclization product **10**.[102] Darling and Turro[103]



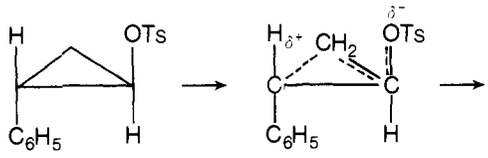
10

have recently reexamined this reaction with some 2,3-dimethyl-substituted derivatives and found that the main components are cyclization products such as **10**, together with the cyclopropyl ethers resulting from isomerization of the cyclopropane ring.

E. Reactions Involving Carbon–Oxygen Bond Breaking

In their early studies of the behavior of cyclopropanol and its derivatives, Roberts and Chambers[18] showed that cyclopropyl tosylate undergoes acetolysis at an exceedingly slow rate at 175°; ring cleavage results, in which the carbon oxygen bond is also severed and allyl acetate is obtained as the final product.

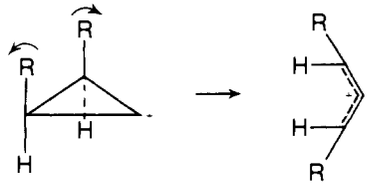
The solvolytic behavior of several cyclopropyl tosylates was reexamined some years later by DePuy and his coworkers.[104] The first systems examined, 1-arylcyclopropyl tosylates, were shown to solvolyze faster than the unsubstituted compound and no 1-arylcyclopropyl acetates were formed, although such compounds are stable under the solvolysis conditions used. The tosylates from both *cis*- and *trans*-2-phenylcyclopropanol were also examined and found to react faster than the unsubstituted compound;[105] these results were contrary to expectations based on the usual inductive effect of a phenyl group, and the mechanism outlined in eq 74 was suggested to accomodate the results. In this, ring opening is suggested to be concurrent with loss of the tosyl-



$$C_6H_5—\overset{+}{C}HCH{=}CH_2 \quad OTs^- \qquad (74)$$

ate leading to a partial positive charge on the benzyl carbon atom in the transition state; thus a phenyl group in either a cis or trans position can stabilize the transition state and enhance the rate of solvolysis.

From orbital symmetry considerations Woodward and Hoffmann[106] predicted that the electrocyclic transformation in which a cyclopropyl cation is converted to an allyl cation would occur in disrotatory fashion. Thus, for those systems which possess cis substituents at C_2 and C_3, two different disrotatory modes are allowed (eq 75 and 76). On steric



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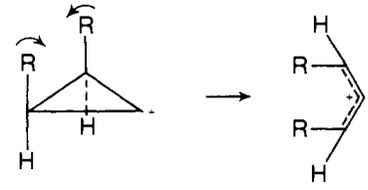
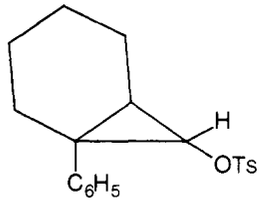


(76)

grounds it would appear that formation of the trans,trans cation would be preferred by such systems.

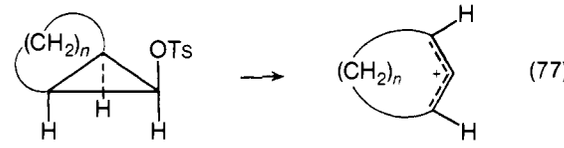
Additional results indicated that *cis*-2-phenylcyclopropyl tosylate solvolyzed faster than the corresponding trans compound, suggesting that the particular disrotatory path a system would take might depend upon the stereochemistry of the leaving group. The norcaranyl tosylate **11**, in which out-



11

ward rotation of the trans groups is impossible, was prepared in order to test the postulate that a distinct preference for this mode of ring opening existed. As predicted, the norcaranyl tosylate was observed to be very unreactive under conditions which easily solvolyzed the other 2-phenyl systems.[105]

The most extensive kinetic investigations are those of Schleyer and Schöllkopf and their coworkers; the early work by these investigators has been reviewed[3] and will simply be summarized here. Detailed studies of the rates of solvolysis of 2,3-disubstituted cyclopropyl tosylates were undertaken in order to test the postulates regarding their relative rates. The acetolysis rate of *trans,trans*-2,3-dimethylcyclopropyl tosylate was found to be 4500 times that of the corresponding cis,cis isomer. Also, the 2,2-dimethyl compound reacted at about the same rate as the *cis,trans*-2,3-dimethyl isomer; the latter results were expected since, in each case, one methyl group must rotate outward and the other inward. In addition to these simple systems some additional bicyclo[*n*.1.0.] systems were studied. With the endo series the kinetic results reflect differences in stabilities of the cationic products, the system having $n = 3$ solvolyzing about 400 times faster than the

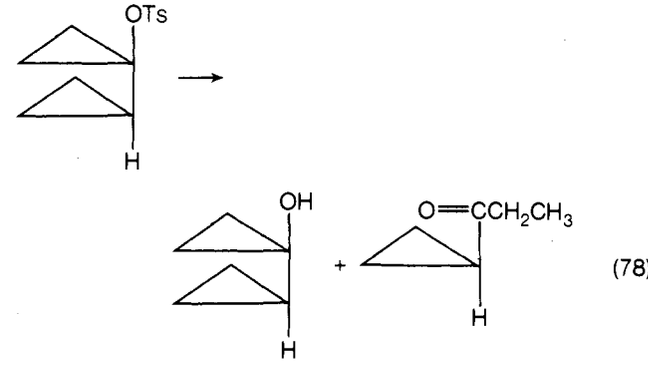


(77)

system with $n = 4$. In the exo series, opposite kinetic results were obtained and the system having $n = 3$ was inert under conditions which gave acetolysis products with the others. In this series when $n = 4$ the exo norcaranyl acetate was obtained in about the same yield as *cis*-cyclohexyl-1,3-diacetate. These results have been rationalized in terms of a "semi-open" intermediate, with the diacetate being formed by acetic acid addition to the strained and highly reactive trans olefin. When $n > 4$ the allyl character of the intermediate ion predominates, and no bicyclic products result. The results obtained from these studies amply demonstrated the utility of the initial postulates.

More recently, Schleyer and his coworkers[107] have studied the solvolytic behavior of some highly unreactive cyclopropyl systems by employing the much more active trifluoromethanesulfonate leaving group. With this, the exo compound with $n = 3$ in the series described above could be solvolyzed and was shown to be 26,000 times slower then cyclopropyl triflate.

Jewett and Howell[108] prepared 1-cyclopropylcyclopropyl tosylate and studied its solvolytic behavior. The main products from reaction in aqueous acetone were the unrearranged alcohol (63%) and an isomeric ketone (24%) (eq 78). When



(78)

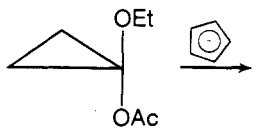
the reaction was conducted in the presence of calcium carbonate, the product mixture consisted of unrearranged alcohol (59%) and 2-cyclopropylallyl alcohol (41%). This product mixture was then subjected to conditions of the unbuffered hydrolysis and gave the same product distribution as the tosylate; these results support the belief that the ketone does not arise by homoketonization of the alcohol.

IV. Synthetic Uses of Cyclopropanols and Their Derivatives

A wide variety of cyclopropanols has been prepared in recent years, and the synthetic utility of these compounds and their derivatives is being examined by several groups.

In their early studies of cyclopropanone derivatives, Wasserman and Clagett[25] investigated the reactions of the acetate **12** and cyclopropanone ethyl hemiketal with various nucleophilic agents. Following one of these, an unusual ring expansion reaction was observed (eq 79).

More recently, Wasserman and his coworkers have extended their studies of ring expansion reactions with related systems. The reactions of 1-vinylcyclopropanol and the corresponding ethynyl compound with electrophilic agents con-



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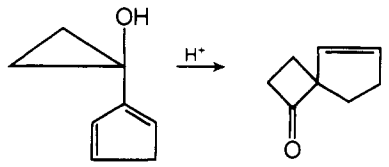
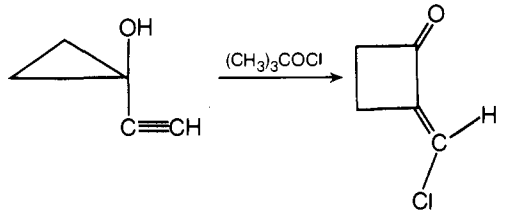


(79)

20% overall yield

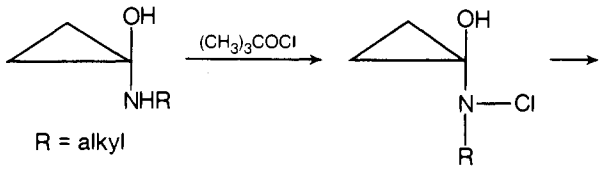
vert these compounds to cyclobutanone derivatives also (eq 80).[26b]



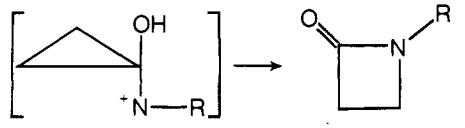
(80)

60%

Reaction of the ethyl hemiketal of cyclopropanone with sodium azide afforded a β-lactam in low yield. Later studies then showed that the β-lactams could be formed in better yields from aminals or carbinolamines; reaction 81 is illustrative.[28,109]

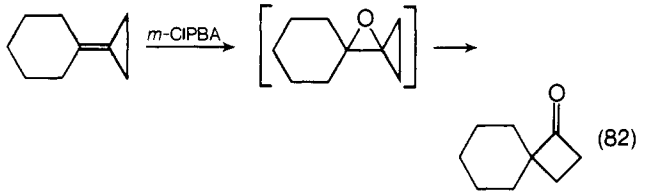


R = alkyl



(81)

The synthetic uses of oxaspiropentanes are being studied and developed by two groups. A cyclobutanone was obtained by Trost from a reaction (eq 82) thought to involve an inter-

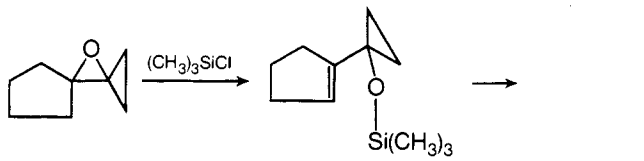


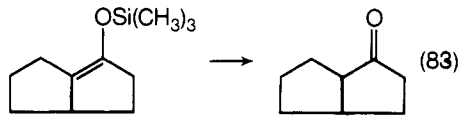
(82)

mediate oxaspiropentane.[110] Salaün and Conia[63] then reported the preparation of the parent compound and indicated that its isomerization to cyclobutanone could easily be effected by LiI.

The ylide route to the oxaspiropentanes (see section II.C) is a very versatile one, and the reaction can be accomplished with systems which have acid- or base-sensitive groups. Trost and Bogdanowicz have prepared some very unusual spiro compounds and are studying the synthetic utility of them (eq 83 and 84).[65,111] When followed by a hydrogen peroxide oxidation, the ring expansion sequence ultimately produces a lactone (eq 85).[112]

Conia and his group[61] have developed another synthetic route to cyclobutanones which involves intermediate cyclopropyl silyl ethers (eq 86–88).





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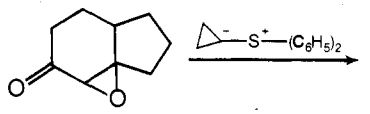

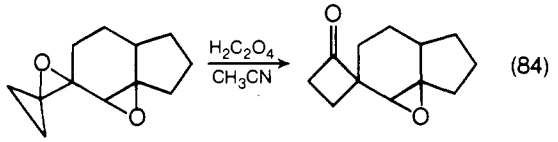

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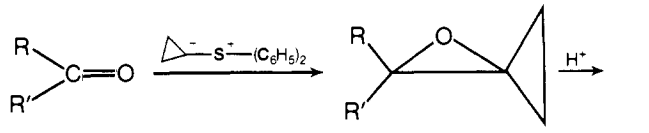

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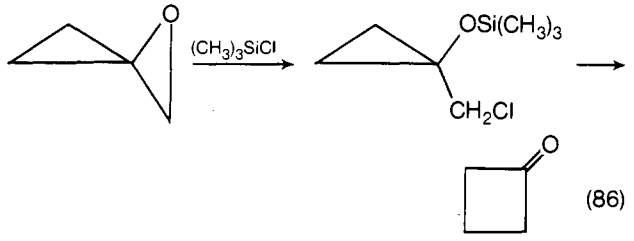

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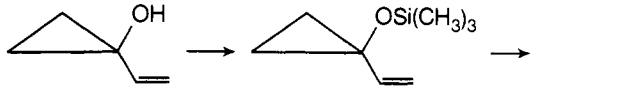

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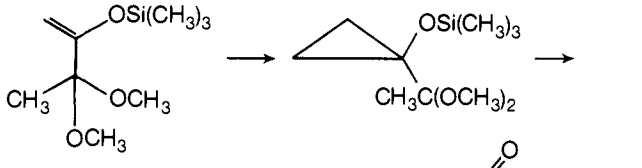
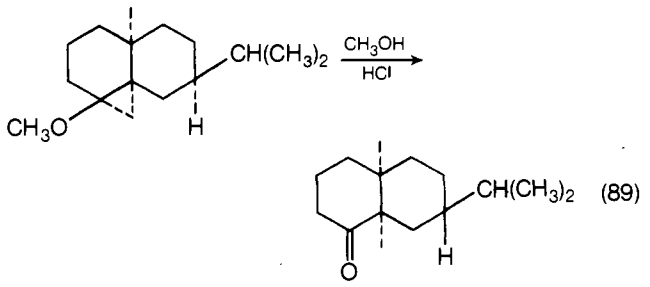


(88)

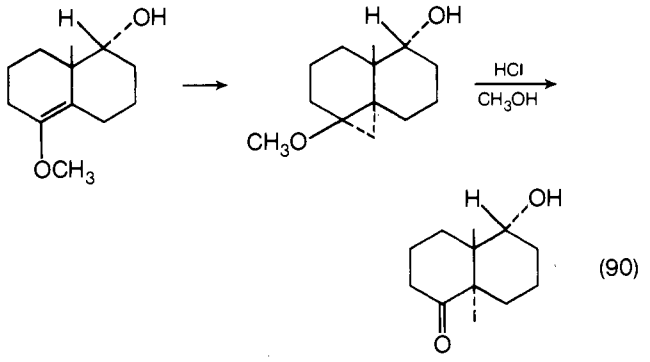
Wenkert and his coworkers[113] were the first group to demonstrate the use of the ring-opening reactions of cyclopropanol derivatives to perform highly specific synthetic transformations; the cyclopropyl ether shown in eq 89 was converted in quantitative yield to 1-valeranone. Work has been continued in this area, extending these reactions which produce a quaternary α-methyl carbonyl system to a design of terpene synthesis.[114]

Ireland and his coworkers[115] have studied similar transfor-



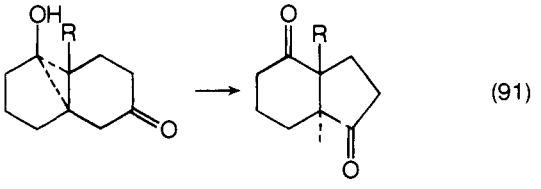
(89)

mations and developed a stereoselective synthesis of 9,10-dimethyl-*trans*-1-decalone as illustrated in eq 90.



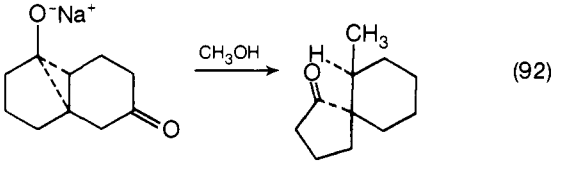
(90)

Reusch and his coworkers have made use of highly selective ring-opening reactions of cyclopropanols to obtain perhydroindan systems (eq 91).[79a] Reaction of the sodium salt of



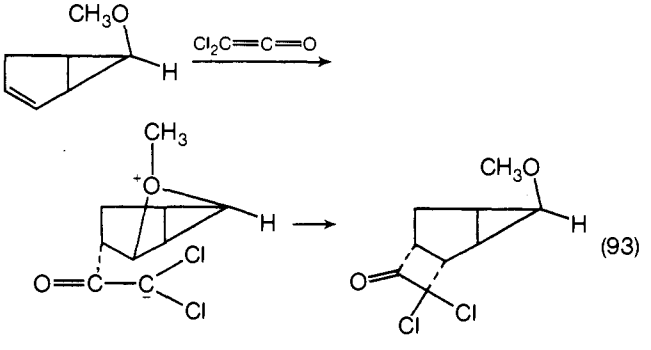
(91)

this alcohol with methanol provided an entirely different rearranged product (eq 92).[79b]



(92)

Corey and Arnold[16] have made use of the properties of a cyclopropyl methyl ether in the preparation of key intermediates for a synthesis of prostaglandins E_2 and $F_{2\alpha}$. They suggest that a cyclopropyl ether directs the course of a cycloaddition reaction with dichloroketene as shown in eq 93.



(93)

Oxidative ring opening of the cyclopropanol, produced by BBr_3 cleavage of the resulting ether, provides another important intermediate later on in the synthetic scheme.

The synthetic applications of the metal ion oxidations of cyclopropanols are being studied in detail by deBoer and his coworkers;[116] reactions of 1-methoxycyclopropanol with Cu^{2+} or Fe^{3+} in the presence of activated olefins (α,β-unsaturated ketones or dienes) are providing useful means of chain lengthening with a three-carbon unit.

V. Synthesis and Properties of Cyclopropylamines and Cyclopropanethiols

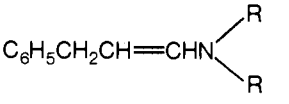
Recently there has been increasing interest in the nitrogen and sulfur analogs of cyclopropanols. While these compounds do have some properties which are similar to those of their oxygen-containing counterparts, the other heteroatoms impart some unique properties to these compounds which promise to make them versatile substrates for synthesis.

In naming the compounds in the sections below, we will use the system adopted for the cyclopropanols in which substituents at C_2 and C_3 are indicated to be cis or trans to the heteroatom.

A. Cyclopropylamines and Their Derivatives

The parent compound was first synthesized by Lipp, *et al.*,[117] in 1932, although the dimethyl derivative had been known for nearly a decade.[118] An improved synthetic route to the unsubstituted compound, which involved a Beckmann rearrangement of the benzenesulfonate from cyclopropyl methyl ketoxime, was later reported by Roberts and Chambers.[18] Interest in these compounds remained dormant for several years and then began to increase about the middle of the last decade.

Burger and his coworkers[119] have prepared and investigated the ring-opening reactions of *trans*-2-phenylcyclopropylamine and some of its N-substituted derivatives. The primary amine and its *N*-methyl derivative undergo ring opening when treated with lithium aluminum hydride, whereas the *N,N*-dimethyl analog was found to be stable; the results are consistent with a mechanism which involves proton removal by the reducing agent followed by ring opening of the anion. Methanolysis of the *N,N*-dimethyl derivative gave the ring-opened tertiary amine and a substantial amount of polymeric material; when performed in the presence of a large excess of piperidine the enamine **13** was the major product.



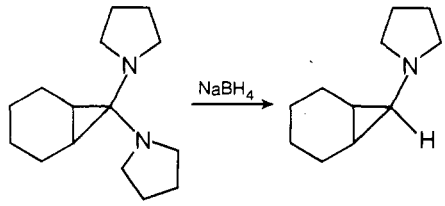
13, R = piperidine

The syntheses of several cyclopropyl and 1-bicyclo[*n*.1.0]alkylamines have been reported[120] together with interpretations of their nmr spectra. The compounds were prepared by the action of diazomethane on various enamines in the presence of cuprous chloride; yields ranging from 65 to 80% were obtained.

Kuehne and King[121] have prepared cyclopropylamines from reactions of cyclic ketone enamines with other methylene transfer agents as well as the diazoalkane–cuprous chloride method. The yields reported are usually moderate, ranging from 32 to 87%. The resulting cyclopropylamines are resistant to attack by electrophiles and do not, therefore, behave as homologous enamines. They are also more resistant to attack by electrophiles than alkoxycyclopropanes.[122] Ring opening was effected either by heating the amine in aqueous methanol at 150–170° (sealed tube) or, more easily, by refluxing in aqueous methanol to which a small amount of palladium on charcoal had been added. Protonation occurred at the least substituted carbon giving methylation products rather than ring-expanded ones; the results are consistent with a transfer of negative charge from nitrogen to a β-carbon atom in the transition state of the cleavage reaction. As expected

from the work of Burger, *et al.*,[119] these tertiary amines are also resistant to ring opening in basic media.

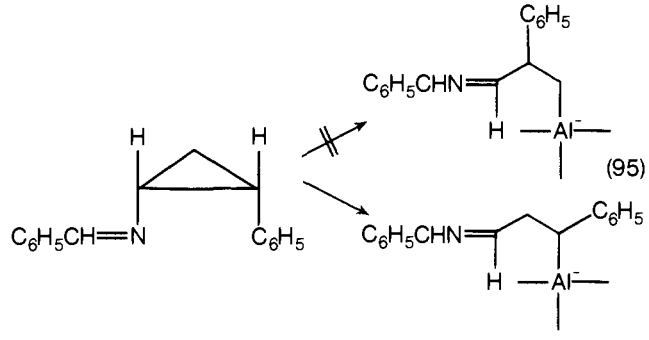
The novel synthesis of some tertiary cyclopropylamines was reported by Smuszkowicz and his coworkers[27] and was described earlier (section II); the aminal shown in eq 94 was



(94)

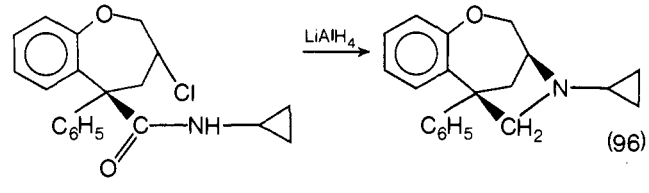
synthesized, and some of its reactions were studied. Reduction with sodium borohydride afforded the amine in high yield whereas acid-catalyzed hydrolysis gave the carbinolamine with an endo hydroxyl group. Reduction of the carbinolamine gave the endo cyclopropanol.

Recently, Bumgardner and his coworkers[123] have reported that cyclopropylamines can be prepared by reductions of the corresponding imines under mild conditions. Thus, $NaBH_4$ or the lithium analog, as well as catalytic methods using platinum, is effective in providing the cyclopropane derivatives, whereas sodium or lithium aluminum hydride cleaved the adjacent three-membered ring as well as reduced the imine. Phenyl substitution of the ring results in unidirectional cleav-



(95)

age and lends support to the suggestion that the cleavage is related to cyclopropoxy–homoenolate anion reactions, since better anion stabilization would be available at the benzylic carbon. The results with $LiAlH_4$ are in agreement with an earlier report by Zaugg and Michaels[124] in which ring opening attended imine reduction; however, these workers were able to perform a reductive cyclization of a secondary cyclopro-

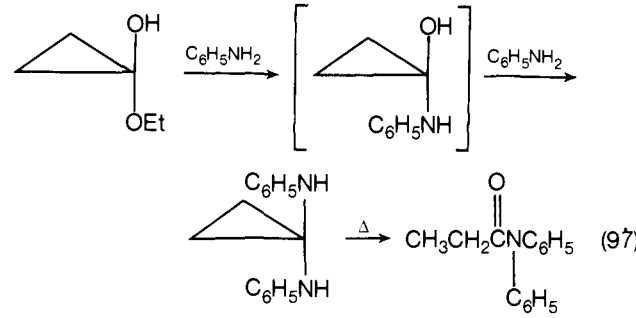


(96)

pylamide without opening the ring (eq 96). In this case the adjacent carbonyl group apparently stabilizes the anion so that ring opening does not occur.

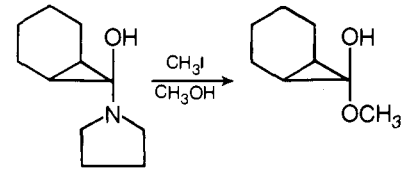
Konzelman and Conley[125] have studied the nitrous acid deamination of a series of spirocyclopropylamines prepared by Curtius rearrangements from the carboxylic acids. Spiropentylamine gave, predominantly, a mixture of 2- and 3-methylenecyclobutanol together with a small amount of a product tentatively identified as 1-vinylcyclopropanol. The other imines produced mixtures consisting principally of allylic alcohols (or dienes resulting from their dehydration) in accord with expectations from ring opening of a cyclopropyl cation as discussed in section III.

Two research groups which have been studying the reactions of cyclopropanone derivatives for several years have prepared various aminals and carbinolamines (or derivatives of these). Thus, Wasserman and Clagett[26a] reported the preparation and pyrolysis of the bis(aniline) adduct shown in eq 97. The presumed intermediate carbinolamine could not



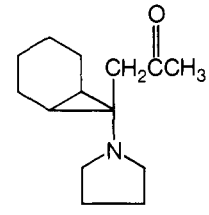
(97)

be isolated. In a later study,[28] additional work was reported on the aminal and carbinolamine reported by Smuszkowicz, *et al.*[27] Methanolysis of the aminal gave the ether in high yield, whereas the carbinolamine reacted slowly with methanol alone but gave the methyl hemiketal when methyl iodide was included (eq 98).



(98)

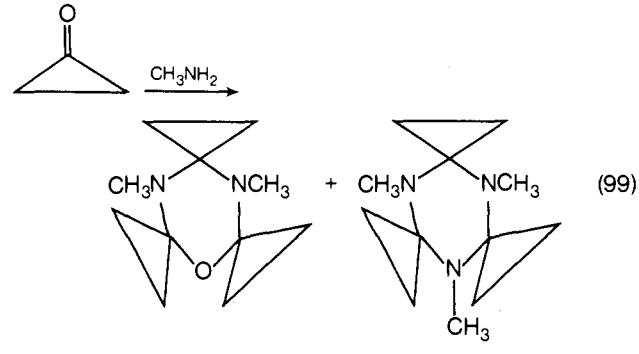
Both the carbinolamine and the aminal reacted with acetone to give the addition product **14**. As indicated earlier (sec-



14

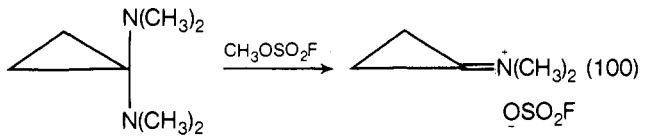
tion II.A.4), the transformations of these amines were rationalized in terms of an intermediate iminium ion. Wasserman and his coworkers have developed a synthesis of β-lactams from the carbinolamines which involves intermediate nitrenium ions;[109] the yields of the β-lactams were 38–65%. An additional instance of lactam formation from a cyclopropylamine has been reported.[126] In this case γ-lactams were produced by carbonylation of cyclopropylamine in the presence of rhodium catalysts.

DeBoer and his coworkers, in separate studies during the same period of time, have examined the reactions of cyclopropanone with aliphatic amines, principally *N*-methyl- and *N,N*-dimethylamine.[127] As shown in eq 99, polycyclic products are produced from the first amine, but the dimethyl com-

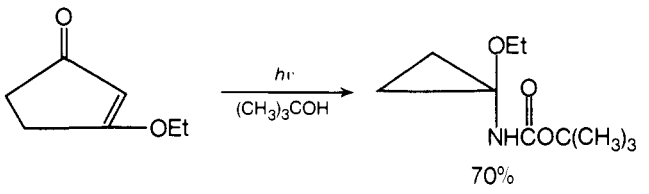


(99)

pound forms the aminal in about 40% yield. A relatively stable iminium ion has recently been prepared by deBoer and his coworkers (eq 100).[128]



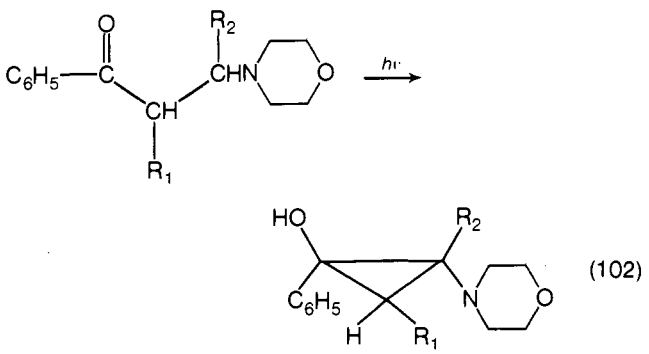
A photochemical route (eq 101) to a compound related to the carbinol amines has been reported.[129] The reaction is



(101)

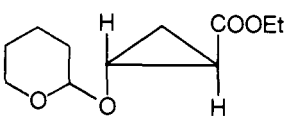
suggested to proceed by way of an intermediate cyclopropyl isocyanate.

The photochemical synthesis of several 2-aminocyclopropanols has been reported by Roth and El Raie;[37] in this a 2-amino ketone is photolyzed in dioxane and provides the amino alcohols in high yield (eq 102). It seems possible that



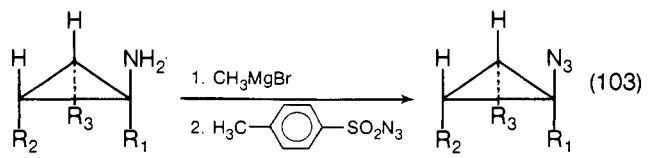
(102)

the morpholine group might be removed under mild conditions to give other cyclopropanol derivatives. Armstrong and Cannon[14] prepared 2-aminocyclopropanols by Curtius reactions on systems of type **15**. The tetrahydropyranyl group was then removed after the amino group had been formed.



15

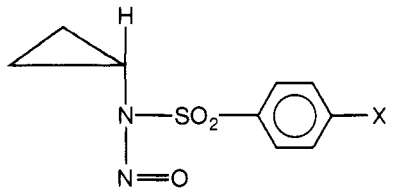
By the application of a reaction first used by Doering and DePuy[130] to prepare diazocyclopentadiene, Szeimies and his coworkers[131] have prepared a series of cyclopropyl azides from the amines in moderate yields (eq 103). The thermal



(103)

conversion of the azides is reported to provide azetines in good yield.

The nitroso compounds **16**, when photolyzed in methanol, give nitroso dimers resulting from the ring-opened radicals.[132] These results suggest that an intermediate radical, isoelectronic with a cyclopropoxy radical, may be involved.

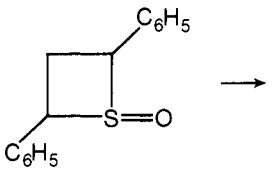


16, X = CH_3 or NO_2

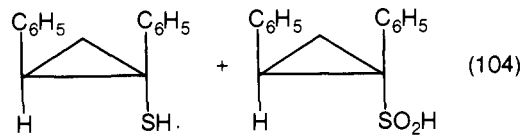
B. Cyclopropanethiols and Their Derivatives

The parent compound was first obtained[133] from the gas-phase photolysis of carbon oxysulfide in the presence of cyclopropane. The thiol is thought to result from insertion of ^1D sulfur atoms into a carbon–hydrogen bond of the cyclopropane. A more convenient preparation of the thiol has been reported by Brandsma;[134] β-chlorothioacetals, when reacted with sodium in liquid ammonia followed by careful neutralization, yield cyclopropanethiol in about 85% yield.

Isomeric thietane 1-oxides have been used to prepare a diphenyl derivative (eq 104).[135] Treatment of the corresponding

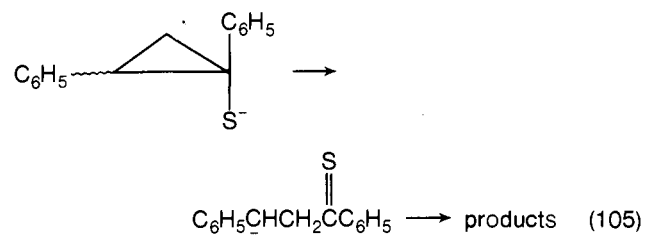


cis or trans



(104)

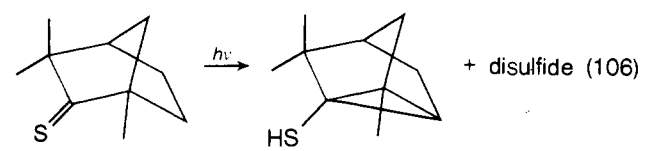
thietane with base[136] under similar conditions gave a complex product mixture thought to result from an intermediate anion such as shown in eq 105. This appears to be the only attempt



(105)

to generate the homothioenolate anion and suggests that reactions in which these can be generated are going to be complicated by the high reactivity of the thiocarbonyl group.

Blackwell and de Mayo[137] have reported the photochemical synthesis of cyclopropane thiols (eq 106). Thiocamphor



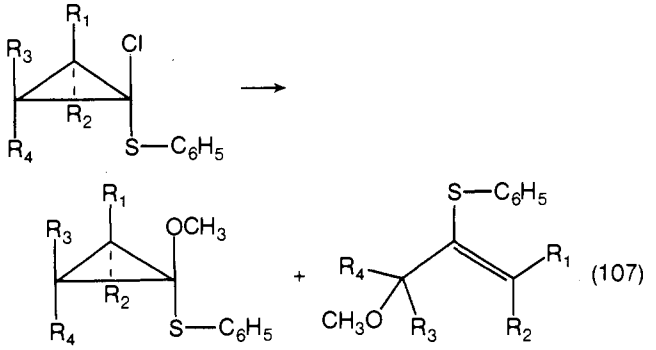
(106)

also undergoes a similar reaction, yielding the cyclopropane derivatives in about 80% yield. Such β-hydrogen abstraction reactions do not occur with the oxygen analogs of these ketones.

The thiols and their derivatives represent a departure from their oxygen and nitrogen analogs, since sulfur is a second row element and as such can make available d orbitals for stabilization. As Coffen has pointed out,[138] sulfur has the ability to stabilize an adjacent carbonium ion and carbanion simultaneously by use of 3p and 3d orbitals, respectively. The unique properties of the thiocyclopropanes promise to make

them useful substrates for synthesis as some recent work from several research groups indicates.

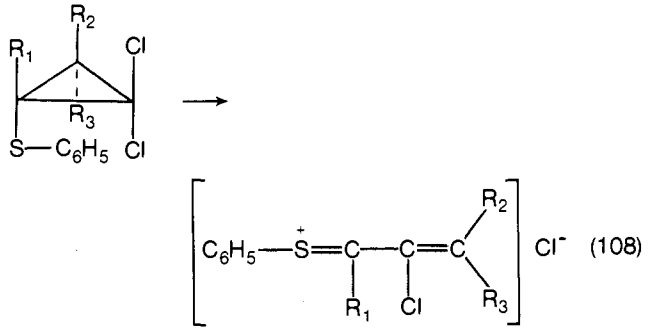
Schöllkopf and his coworkers, who have studied the solvolysis properties of 1-chloro-1-phenoxycyclopropanes,[3] have reported some of their work on the corresponding thio compounds.[139] Whereas the phenoxy group had not stabilized the developing carbonium ion to the extent that cyclopropane-containing compounds were produced, the sulfur analogs do provide substantial amounts of ring-closed products as well as the expected allyl derivatives (eq 107). Since the initial ge-



(107)

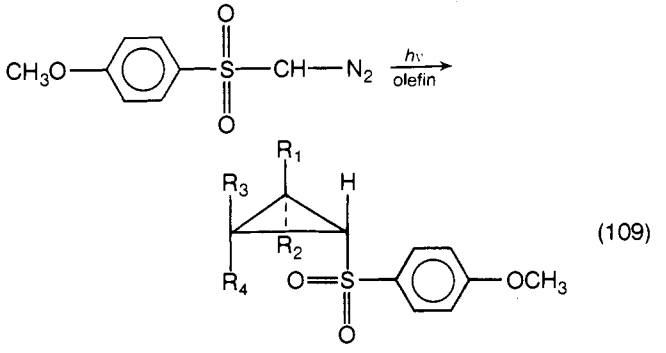
ometry is maintained in the ring-closed product, the results strongly suggest that a pyramidal ion is intermediate.

The presence of a thiophenoxy group at the 2 position of halocyclopropanes, however, enhances the ring-opening reaction by stabilizing the developing ring-opened ion (eq 108).[140]



(108)

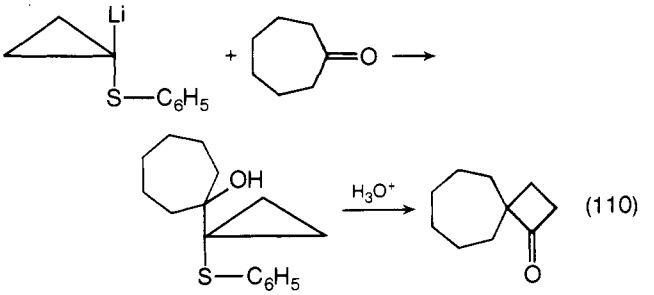
Cyclopropyl sulfones have been prepared by several different routes, some of which parallel the synthetic routes to cyclopropanol derivatives. Truce and Badiger[141] have reported their formation in moderate to good yields by reaction of dimethylsulfonium methylide with vinylic sulfones, and another group has found that the sulfones can be produced in good yield in reactions which have a high degree of stereospecificity (eq 109). This same group also prepared sulfones



(109)

by hydrogen peroxide oxidation of the corresponding thio ethers prepared by the method of Schöllkopf.[139]

Trost and his coworkers have developed the cyclopropyl thioethers (and ylides related to these) into useful reagents for spiroannelation.[112] Thus diphenylsulfonium cyclopropylide adds to Michael acceptors to give spiropentane derivatives and to simple aldehydes or ketones to give the analogous oxaspiropentanes; in each, the products are formed in high yield. This research group has also begun to develop the lithio salt of cyclopropyl phenyl ether as a useful reagent (eq 110).[142]



(110)

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