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Review

SILOXYCYCLOPROPANES. USEFUL SYNTHETIC INTERMEDIATES

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Contents

Introduction

In this article, the methods of preparing siloxycyclopropanes and their use in organic synthesis will be reviewed. Siloxycyclopropanes (or cyclopropyl silyl ethers) are highly reactive to various reagents, especially to electrophiles, because of the strained ring and the electron donating substituent on it. Though reactive, these compounds are thermally stable. In addition, the design of various interesting synthetic reactions taking advantage of the characteristic properties of the organosilicon group is possible. The important properties of the organosilicon moiety relating to the reactivity of siloxycyclopropanes are the donation of electrons by Si through a σ-bond, the stabilization of a cation at a βposition to Si, the susceptibility of Si towards nucleophilic attack and the neutrality of R_3SiX formed as a by-product of this reaction.

We will first describe how we have come to be engaged in the chemistry of siloxycyclopropanes. General methods for the preparation of enol silyl ethers and their use for the selective generation of lithium enolates were reported in 1968 by Stork et al. and 1969 by House et al. [1,2]. It may be now stated that these works have triggered the explosive development [3] of the application of organosilicon compounds in organic synthesis. At that time, however, silicon was rather an exotic element to most organic chemists. Impressed by the simplicity of the structure of enol silyl ethers, we started a few years later our research program on the use of enol

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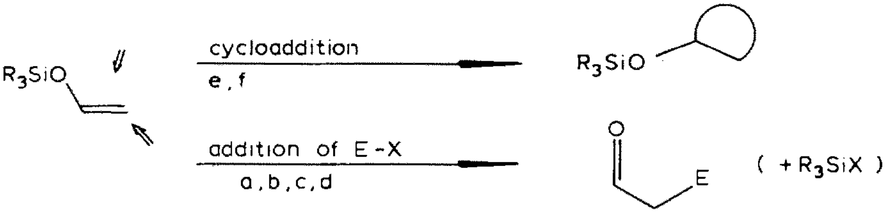
silyl ethers as the synthetic equivalent of enols. Our prime objective was to demonstrate the basic reaction patterns which might be useful in planning further applications. In the few years following, we were able to illustrate some fundamental types of reactions of enol silyl ethers: (a) addition of a carbon free radical [4], (b) addition of a sulfur free radical [5], (c) addition of a carbon electrophile [6,7], (d) addition of a sulfur electrophile, (e) [2 + 1] cycloaddition [8], and (f) [2 + 2] cycloaddition [9], as shown in Scheme 1.

SCHEME 1



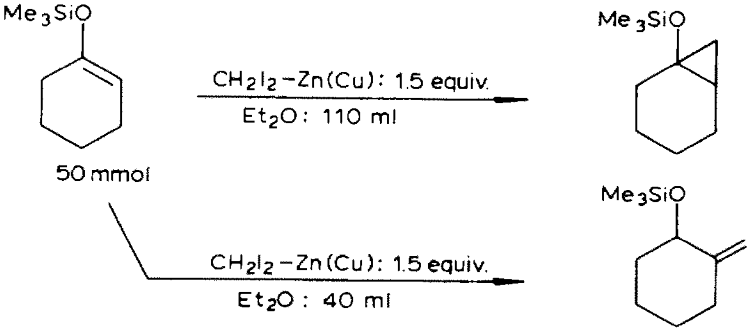
The products arising from the simplest cycloaddition reaction (e) of enol silyl ethers are siloxycyclopropanes, which have in turn been proved to be another type of useful intermediates in synthesis. A thorough coverage of the chemistry of siloxycyclopropanes has been attempted in this review. Conia and Ito have summarized their own work on this subject elsewhere [10].

It should be mentioned that the development of the chemistry of siloxycyclopropanes would have been much slower without the knowledge accumulated in the chemistry of cyclopropanols [11] and alkoxycyclopropanes [12].

1. Preparation of siloxycyclopropanes from enol silyl ethers and zinc carbenoids

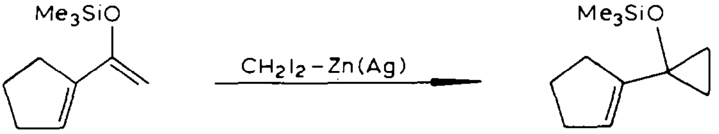
Siloxycyclopropanes can be most conveniently obtained by the Simmons-Smith reaction of enol silyl ethers. When carrying out the Simmons-Smith reaction (Zn-Cu/CH_2I_2), two experimental precautions must be followed. First, since siloxycyclopropanes are rather labile towards acids, aqueous HCl work-up, a usual method in Simmons-Smith reactions, must not be employed; otherwise hydrolysis of the products to cyclopropanols and 2-methylketones may take place. We recommend work-up with aqueous NH_4Cl for the removal of zinc iodide [8]. Secondly, the amounts of solvent are important for the preparation of 1-siloxy-bicyclo[*n*.1.0]al-

SCHEME 2

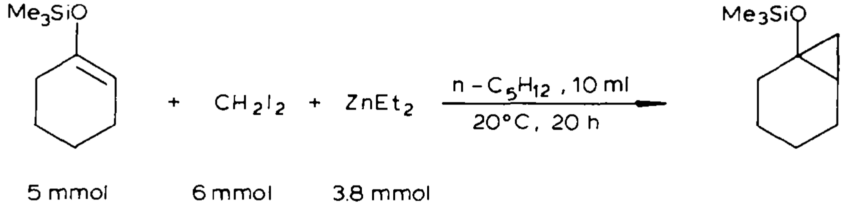


kanes. The employment of the 'dilute' reaction conditions in which the ratio of the amounts of enol silyl ether (mmol) to the solvent (ether) (ml) is adjusted to less than 1/2 (mmol/ml) has proved to be effective in avoiding further isomerization of siloxycyclopropanes to silyl ethers of 2-methylenecycloalkanols by the zinc iodide produced [13]. When required, such allylic isomers can be prepared by simply changing the relative amounts of the solvent in the reaction (Scheme 2) [13].

Coincidentally three groups besides us (Conia et al., Goaller et al., and Rubottom et al.) have also studied independently the same cyclopropanation [14]. Conia et al. applied their modified Simmons-Smith reaction (Zn-Ag/CH_2I_2) to the synthesis of various siloxycyclopropanes including 1-vinyl-substituted siloxycyclopropanes.

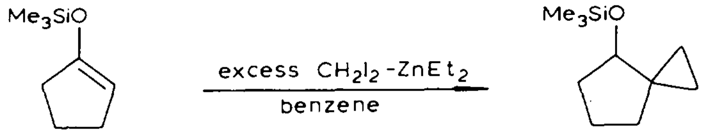


We have also found that diethylzinc-methylene iodide ($ZnEt_2/CH_2I_2$) [15] is another useful reagent for the cyclopropanation of enol silyl ethers [16]. Generally, the reaction proceeds faster and affords higher yields of siloxycyclopropanes compared with the Simmons-Smith reaction. The use of a hydrocarbon solvent such as pentane proved to be quite effective to suppress further isomerization of siloxycyclopropanes.

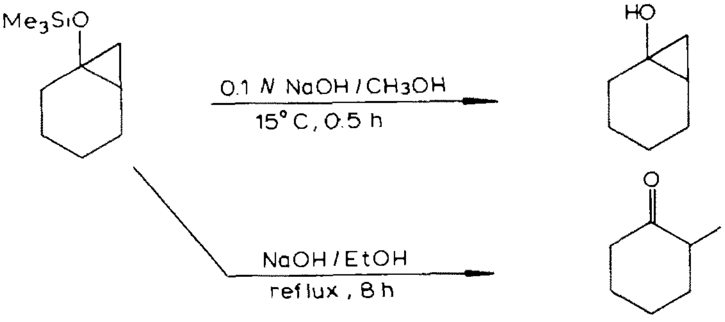


One problem in using $ZnEt_2/CH_2I_2$ lies in the extremely slow reaction with enol silyl ethers of acetophenone and 2-acetylfuran. Miyano et al. recently reported cyclopropanation of enol silyl ethers by $ZnEt_2/CH_2ClI/O_2$ [17]. This oxygen technique can be applied to the cyclopropanation of the unreactive (towards $ZnEt_2/CH_2I_2$ but not towards Zn-Cu/CH_2I_2) enol silyl ethers mentioned above, for which the reagent $ZnEt_2/CH_2I_2/O_2$ gave better results [18].

When 1-siloxycycloalkenes were treated with $ZnEt_2/CH_2I_2$ in ether or benzene, silyl ethers of spiro alkanols, which resulted from three-step-reaction (cyclopropanation, isomerization, and cyclopropanation), were obtained as products. Thus, one-pot synthesis of 4-siloxyspiro[*n*.2] alkanes ($n = 4{,}5$) from 1-siloxy-cycloalkenes can be attained by using excess amounts of $ZnEt_2/CH_2I_2$ and relatively small amounts of benzene as the solvent [14].

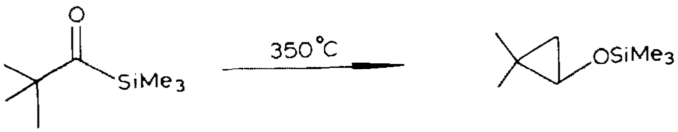


Upon treatment with acids or bases, siloxycyclopropanes can be readily converted into cyclopropanols under mild conditions [8,14] or 2-methyl ketones under more forcing conditions [14].



1,2-Bis-siloxycyclopropanes are most conveniently obtained by [2 + 1] cycloaddition reaction of enediol bis-silyl ethers with zinc carbenoid reagents [19].

Formation of siloxycyclopropanes by thermolysis and photolysis of acylsilanes, shown by Brook et al. [20a] and by Dalton et al. [20b] respectively, seems interesting but lacking in generality.

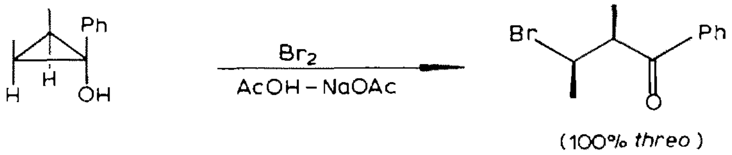


Several functionalized siloxycyclopropanes, which are synthetically useful, are also available by the [2 + 1] cycloaddition route. The preparative methods for them will be mentioned in Section 3 with their synthetic applications. Synthetic methods for siloxycyclopropanes not using [2 + 1] cycloaddition are rather limited and they will be also mentioned in Section 3.

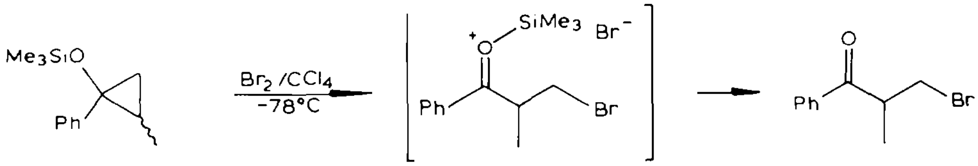
2. Reaction of siloxycyclopropanes with electrophilic reagents

(a) Reaction with bromine

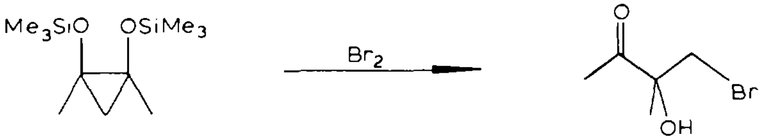
Cyclopropanols, the parent compounds, readily undergo ring opening with halogenating agents including bromine to give β-halogenated ketones [21]. Reaction with bromine usually occurs with inversion of configuration at bromo-substituted carbon atom.



To make this type of reaction synthetically useful the development of a synthetic equivalent of cyclopropanols is highly desirable, since they are neither readily available for synthetic purposes nor stable to heat. We thought that siloxycyclopropanes would be the best compound for this purpose; this is in fact the case. Namely, the reaction of siloxycyclopropanes with bromine in carbon tetrachloride proceeded smoothly at −78°C to give the desired β-bromo ketones in quantitative yields [22]. The reaction system is maintained essentially neutral and trimethylsilyl bromide, a by-product, can be removed easily by evaporation. Ring opening occurs preferentially at the least substituted carbon and this may be attributed to the least hindered site of attack by bromonium ion.

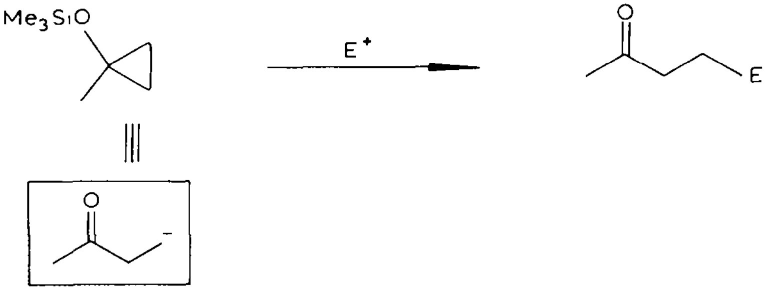


Bromination of 1,2-bis-siloxycyclopropanes has been reported by Goaller et al. and more recently by Breitkeil et al. [19a,23]. The bis-siloxycyclopropanes, readily available from 1,2-bis-siloxyethylenes, also undergo a similar type of site-selective ring opening to give α-hydroxy-β-bromo ketones in good yields.



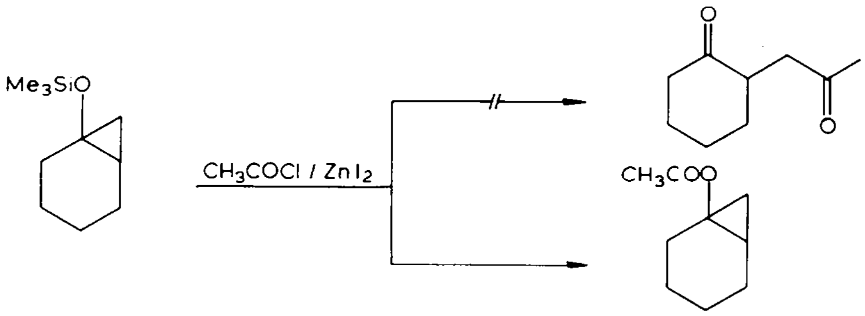
(b) *Reaction with carbon electrophiles*

Considerable efforts have been directed to the development of β-acyl anion or homoenolate anion equivalents [24]. If the attack of a carbon electrophile takes place at the carbon of a siloxycyclopropane in the same manner as bromination does, the siloxycyclopropane must be a useful β-acyl anion equivalent.

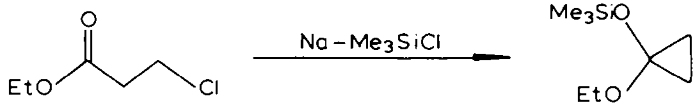


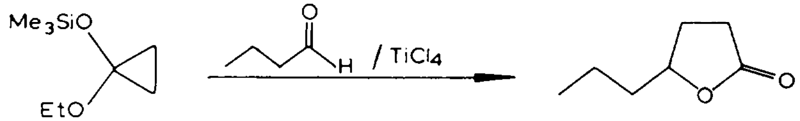
We attempted the reaction of siloxycyclopropanes with acid halides in the presence of zinc iodide [25]. The products obtained, however, were cyclopropyl esters which resulted from the preferential attack of the carbon electrophile at oxygen. In the hope of achieving the desired carbon–carbon bond formation, we studied in vain the reactions of siloxycyclopropanes with carbon electrophiles derived from aldehydes and Lewis acids.

Interestingly, Kuwajima and Nakamura have reported that the doubly electron-donating 1-ethoxy-1-siloxycyclopropane, prepared by reductive silylation of ethyl β-chloropropionate using the sodium and trimethylchlorosilane system [26], reacted with aldehydes in the presence of titanium tetrachloride to give γ-lactone derivatives [27]. Mechanistically, however, this reaction may not involve the ring opening with a



carbon electrophile, since the intermediacy of β-titano esters formed via electrophilic ring opening with titanium tetrachloride is strongly suggested [28]. The related reactions to give β-metallo ketones will be covered in the following section.



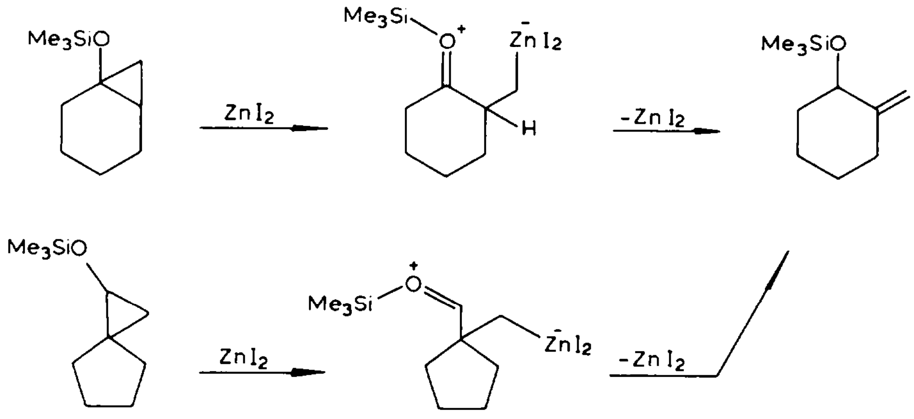


Since a variety of carbon electrophiles are now available, we believe there still remain possibilities of finding useful carbon–carbon bond-forming reactions at positions β to carbonyls using siloxycyclopropanes.

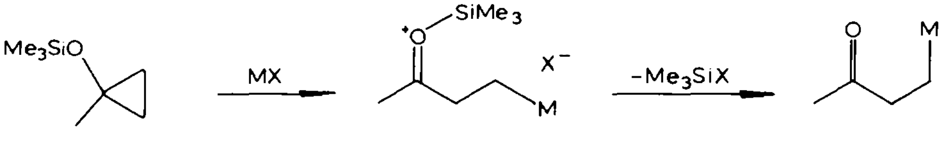
(c) *Reaction with metal salts as electrophiles*

The zinc iodide-promoted isomerization of siloxycyclopropanes discovered in the study of the Simmons-Smith reaction of enol silyl ethers takes place with ring opening at the peripheral cyclopropane carbon and subsequent 1,2-migration of hydrogen or carbon atom [13,29]. For this isomerization reaction the following mechanistic rationale involving an ionic intermediate is suggested (Scheme 3). The intermediate cation may be stabilized not only by oxygen but also by trimethylsilyl group at the β position. The corresponding alkoxy analogous undergo similar isomerization only reluctantly [30].

SCHEME 3

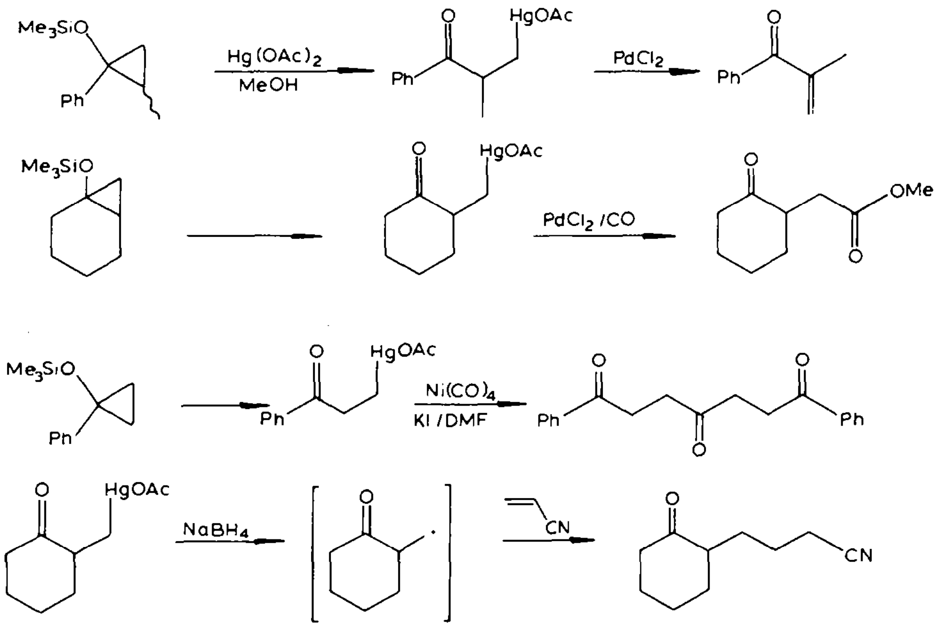


In general, if a metal ion is sufficiently electrophilic to cause ring opening and the counter anion is capable of removing the trialkylsilyl group, the reaction of siloxycyclopropanes with the metal salt should offer a new methodology for generating β-metal-substituted ketones. Although β-metal-substituted ketones appear to be quite attractive intermediates to perform a variety of types of bond formation reactions β to carbonyls, no satisfactory entry for them is available so far. In this context, the formation of β-mercuric ketones from the reaction of cyclopropanols with mercuric acetate reported by DePuy et al. was quite indicative [31].



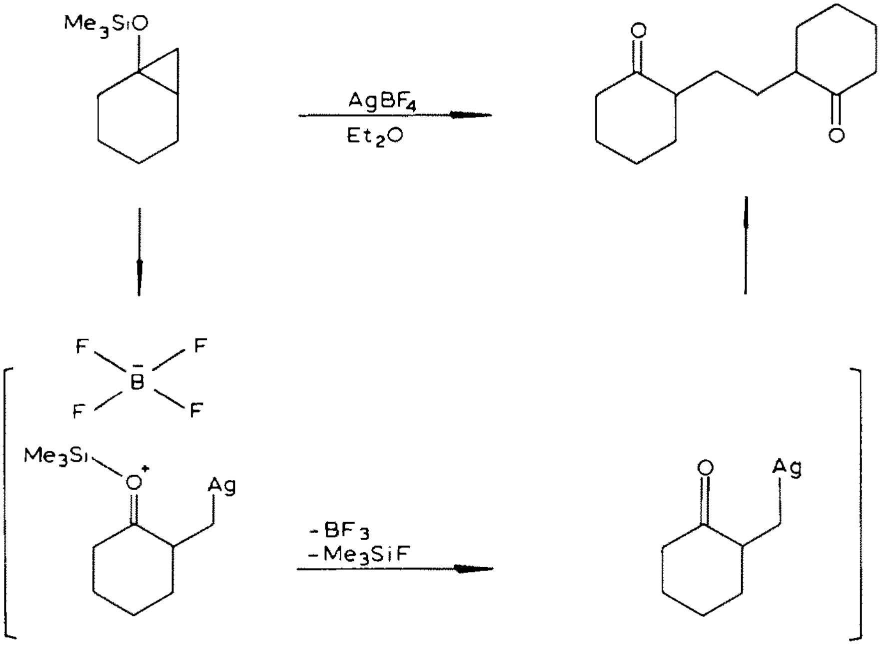
Indeed, siloxycyclopropanes readily undergo site-selective ring opening at the least hindered site with mercuric acetate to afford quantitative yields of β-acetoxymercuric ketones [32]. The reaction is usually completed within 30 minutes and the evaporation of solvent gives essentially pure products. Although the β-mercuric ketones obtained are fairly stable toward carbon electrophiles, they can serve as precursors of more reactive β-metallo ketones via transmetallation. Thus, α-methylene ketones or 1,4-keto esters were obtained by treatment with palladium dichloride [31] and 1,4,7-triketones with nickel tetracarbonyl [33] (Scheme 4). Generation of β-acylalkyl radicals from β-mercuric ketones and the reaction of the radicals with olefins have been reported recently [34].

SCHEME 4

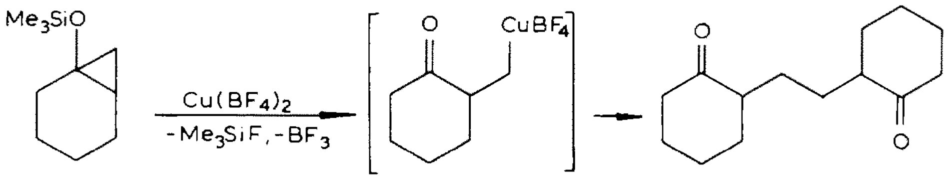


An attempt to generate silver β-acylalkyls has been carried out based on the same strategy. When a siloxycyclopropane was treated with silver tetrafluoroborate in ether, rapid oxidation took place to give a 1,6-diketone and reduced silver [35]. Again, selective ring opening occurred at the least substituted cyclopropane carbon. A mechanistic rationale of this coupling reaction requires a *β*-silver-substituted ketone as an intermediate (Scheme 5).

SCHEME 5



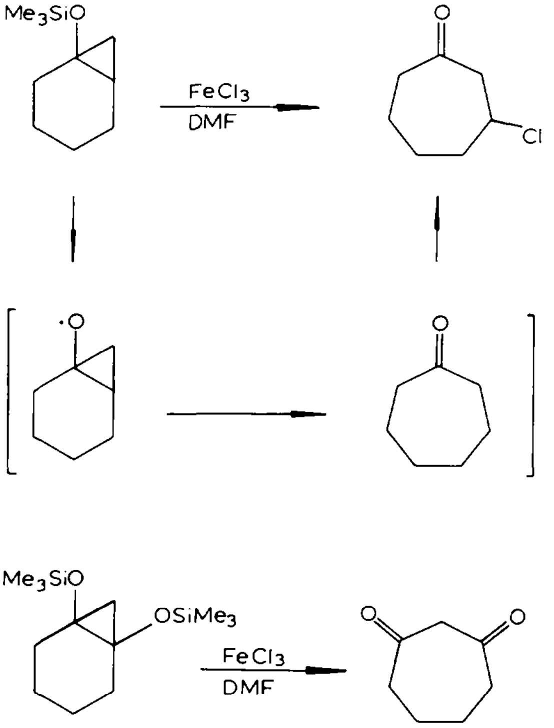
Interestingly, copper(II) tetrafluoroborate, $Cu(BF_4)_2$, reacted with siloxycyclopropanes similarly to give 1,6-diketones in high yields. The reaction can be conducted using a variety of solvents (EtOH, i-PrOH, AcOEt, Et_2O, etc.) without effecting the yields. Although the intervention of *β*-acylalkylcopper seems most likely, more studies are required to clarify the mechanism of these reactions [35].



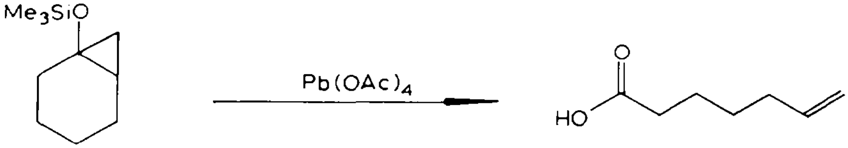
Since the strategy mentioned above has proved to be promising, efforts to generate other *β*-metal substituted ketones and their application to bond formation at the *β* position to carbonyls are in progress in our laboratory.

Ferric chloride-($FeCl_3$)-induced chlorination of cyclopropanols has been reported by DePuy et al. [36]. In contrast to other electrophilic ring-opening reactions, chlorination with ring opening occurs at the most substituted rather than the least substituted cyclopropane carbon, and this reaction has been explained by a one-electron transfer mechanism. Ito et al. have studied the reaction of $FeCl_3$ with siloxycyclopropanes. The cyclopropane ring of 1-siloxy-bicyclo[*n*.1.0]alkanes undergoes cleavage at the most substituted carbon atom to give higher β-chlorinated ketones in good yields. The latter can be readily converted to enones by a base. Similarly, 1,2-bissiloxycyclopropanes afford 1,3-diones with central bond cleavage. Application of the reaction to the synthesis of *d,l*-muscone or macrocyclic 1,3-dione synthesis has also been reported (Scheme 6) [37,38].

SCHEME 6



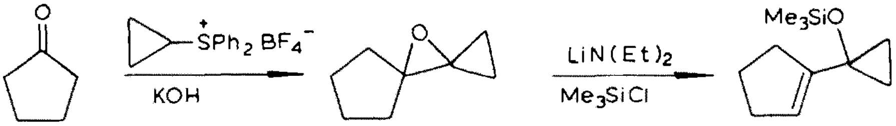
Rubottom et al. have recently reported the oxidative cleavage of siloxycyclopropanes with lead tetraacetate ($Pb(OAc)_4$) to afford olefinic carboxylic acid derivatives [39]. In this case both central and peripheral bonds are cleaved. Thus, it is rather difficult to speculate on the mechanism of the initial bond-breaking reaction.



3. Synthesis via functionalized siloxycyclopropanes

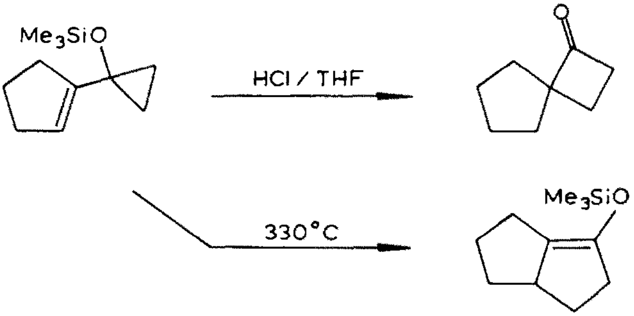
(a) Thermal and acid-promoted rearrangement of 1-vinylsiloxycyclopropanes

Two routes are available for the preparation of 1-vinylsiloxycyclopropanes. One is the regioselective cyclopropanation of dienol silyl ethers reported by Conia et al., which has been described in Section 1 [10a,14a]. An alternative route shown by Trost et al. employs oxaspiropentanes, obtained by condensation of diphenyl sulfonium-cyclopropylide with ketones [39].



These two groups independently studied thermal and acid-promoted rearrangement of 1-vinylsiloxycyclopropanes. Hydrolysis under acidic conditions afforded cyclobutanone derivatives, while thermolysis at 330°C resulted in vinylcyclopropane-cyclopentene rearrangement to give enol silyl ethers of cyclopentanones, both in quantitative yields (Scheme 7) [10a,40]. For this vinylcyclopropane rearrangement, the activation energy is estimated to be 44 kcal/mol which is 7 kcal/mol less than that for the corresponding vinylcyclopropane without the siloxy substituent [41].

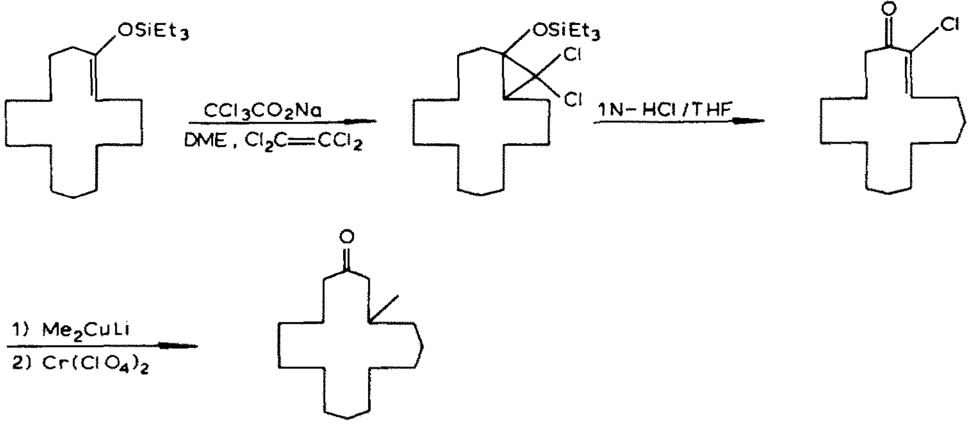
SCHEME 7



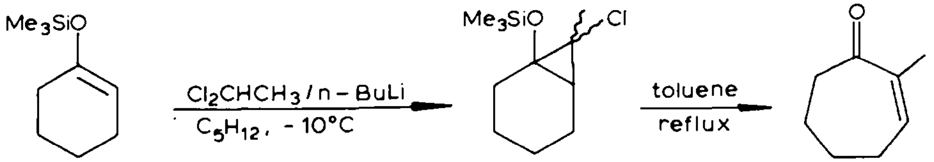
(b) Halogen-substituted siloxycyclopropanes

Enol silyl ethers react with dichloro- or dibromo-carbenes to give *gem* dihalosiloxycyclopropanes in good yields. Stork and Macdonald utilized the dihalocarbene adduct of 1-triethylsiloxycyclotetradecene as a key intermediate in the synthesis of *d,l*-muscone from cyclododecanone [42]. Under solvolytic conditions the adduct underwent central bond cleavage to give the ring-expanded enone, which was subsequently treated with lithium dimethyl cuprate, followed by reduction with chromium(II) perchlorate to give *d,l*-muscone (Scheme 8).

SCHEME 8



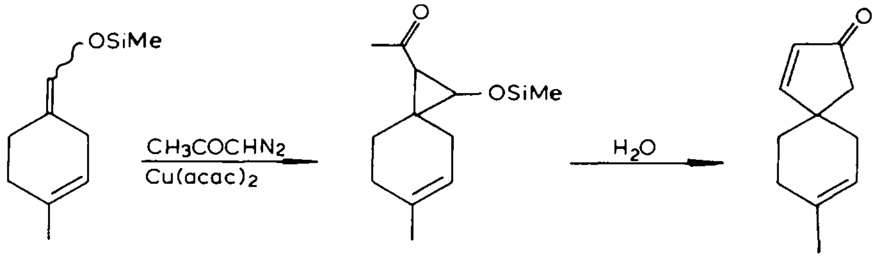
A variety of dibromocarbene adducts have been also prepared by Conia et al. [43]. By refluxing in benzene, the adducts are converted into α-bromo-α,β-unsaturated carbonyl compounds. More recently they have reported the addition of chloromethylcarbene to 1-siloxyalkenes, 1-siloxycycloalkenes, and ketenesilylacetals [44,45]. Elimination of trimethylsilyl chloride from the adducts takes place in refluxing toluene to give α-methyl enones. This process proceeds quite slowly, especially in the case of adducts in which the chloro and trimethylsilyl groups have a *cis* configuration.



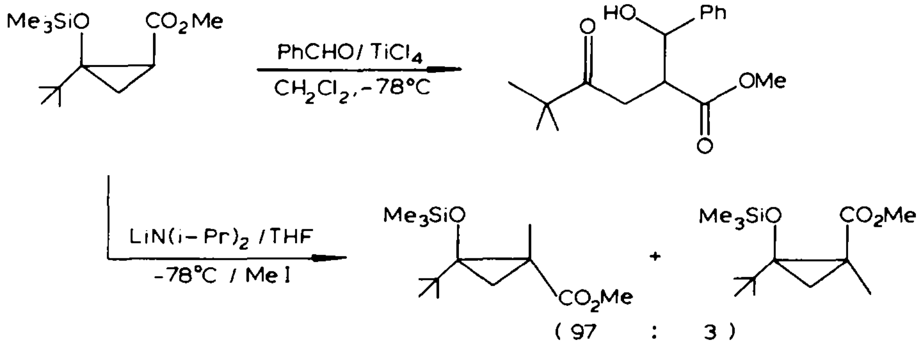
Ring opening of dichloro-1-siloxy-bicyclo[*n*.1.0]alkanes by electrolysis in alcohols in the presence of iron(III) nitrate took place at the peripheral carbon to yield α-alkoxycarbonyl cycloalkanones, except for the case of *n* = 3, where central bond cleavage predominated [46].

(c) 2-Carbonylsiloxycyclopropanes

Siloxycyclopropanes having a carbonyl group as a substituent can be obtained from the reaction of enol silyl ethers with ketocarbenoids, similarly to the case of the corresponding carbonyl-substituted alkoxycyclopropanes [47]. Treatment of such siloxycyclopropanes with aqueous acid caused hydrolysis leading to 1,4-dicarbonyl compounds, probably via the well-known cyclopropyl carbinyl cation rearrangement.

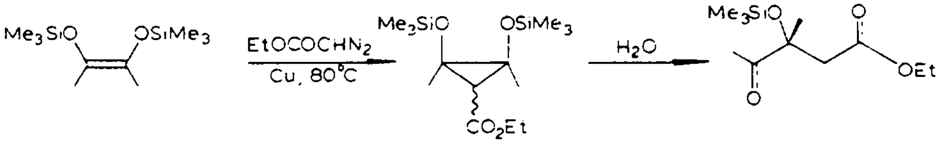


SCHEME 9



Very recently, Reissig et al. have reported the reaction of 2-methoxycarbonyl-substituted siloxycyclopropanes, prepared from enol silyl ethers and methyl diazoacetate, with carbonyl compounds in the presence of titanium tetrachloride. The carbon–carbon bond located between the donor and the acceptor groups seems labile and the γ-hydroxy-β-methoxycarbonyl ketone has been obtained [48]. For this reaction, the intermediacy of titanium ester enolates seems likely. The related reaction carried out by Kuwajima et al. has been mentioned in Section 2. Stereoselective introduction of an alkyl group at the cyclopropane carbon bearing the alkoxycarbonyl group has been also reported [49]. A pyramidal lithium ester enolate has been suggested as the intermediate (Scheme 9).

Goaller et al. have reported that enediol bissilyl ethers also react with ethyl diazoacetate/Cu to give siloxycyclopropanes, which can be converted into 2-siloxy-1,4-keto esters [19a].



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