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SYNTHETIC ORGANIC REACTIONS BY MEANS OF REACTIVE NUCLEOPHILES GENERATED THROUGH REARRANGEMENT OF A SILYL GROUP

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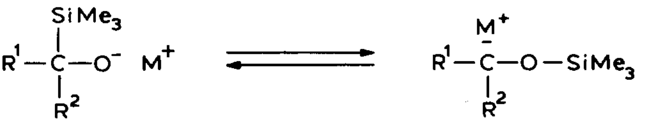
Summary

Under basic conditions, 1-(trialkylsilyl)-allylic and -propargylic alcohols have been shown to undergo 1,2-rearrangement of a silyl group from carbon to oxygen to generate the corresponding 3-siloxyallyl and allenyl anionic species. Their synthetic utilities as homoenolate equivalents are described. Furthermore, by using a 3-silyl-4-penten-1-ol system, anionic species have been generated through a similar 1,4-rearrangement of a silyl group and their synthetic use is also discussed.

Introduction

Through the pioneering work of several organosilicon chemists, it has been well recognized that the strong affinity of the trialkylsilyl group for hard bases such as the oxide anion has sometimes allowed the facile transfer of a silyl group [1]. In particular, 1,2-rearrangement of silicon from carbon to oxygen has been well documented as the Brook rearrangement [2]. If this phenomenon takes place generally on organosilicon compounds bearing hydroxy groups, it appears to be quite attractive from the synthetic standpoint because reactive carbanionic species may be easily generated through such a rearrangement. However, the requirements for this transfer have not been elucidated systematically from the synthetic point of view. Even if such a rearrangement process is kinetically favored, the equilibrium appears to be thermodynamically favored on the left-hand side of eq. 1, on the basis of the much greater electronegativity of oxygen. Several factors such as electronic



$$R^1-\overset{SiMe_3}{\underset{R^2}{C}}-O^-\ M^+ \rightleftharpoons R^1-\overset{M^+}{\underset{R^2}{\bar{C}}}-O-SiMe_3 \qquad (1)$$

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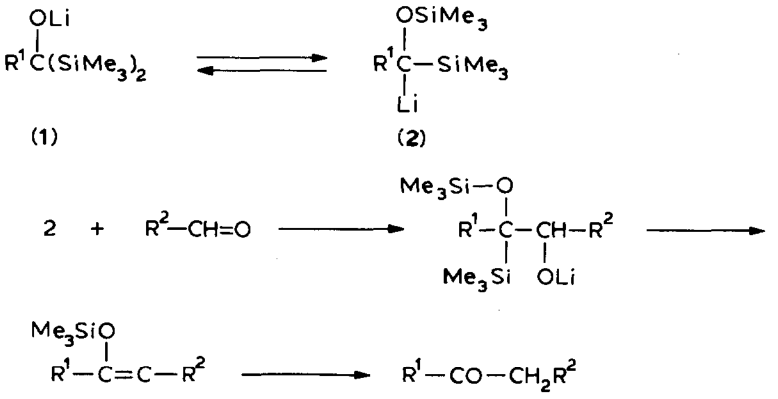
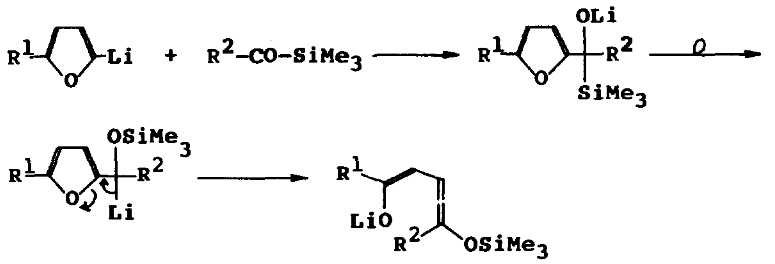
and steric effects as well as the role of the cationic part may be involved in determining the equilibrium composition. In order to clarify the synthetic utilities of the carbanionic species generated through intramolecular rearrangement of a silyl group from carbon to oxygen, we have studied the behavior of several kinds of alcohols bearing the trimethylsilyl group, under basic conditions.

Initially, we examined the reaction of a lithium alkoxide of 1,1-bis(trimethylsilyl)alkanol (**1**) [3] with an aldehyde, assuming that **1** may be used as the equivalent of nucleophilic species **2**. Under equilibrium conditions, such species may be expected to react with the aldehyde to yield the corresponding enol silyl ether through 1,2-addition of **2** followed by Peterson-type elimination of the trimethylsilanol moiety. Various examinations revealed that benzylic alkoxide **1** ($R^1 = C_6H_5$) reacted with the aldehyde to give the corresponding aromatic ketone after acidic workup of the reaction mixture, but all the saturated aliphatic alkoxides (R^1 = alkyl) examined failed to react with the aldehyde to give back the starting materials. These results apparently show that a certain anion-stabilizing substituent is required to induce the equilibrium between alkoxides **1** and the carbanionic species **2**, and the phenyl group seems to satisfy this requirement.



(2)

A furan substituent of the α-position also effects the 1,2-shift of the trimethylsilyl group. On treatment of acylsilanes with furyllithium, the initially formed alkoxides undergo such a rearrangement to yield the corresponding furfurylcarbanionic species from which 5-siloxy-3,4-pentadienone enolates [4] are generated through the ring-opening reaction [5].



(3)

1. 1,2-Rearrangement of a trimethylsilyl group

(a) 1-(Trimethylsilyl)allylic alcohols. Stereo- and regio-controlled synthesis of enol silyl ethers [6–8]

Enol silyl ethers have recently been employed as one of the most useful precursors for enolate anions [9]. In most cases, they have been prepared by the generation of enolates from the parent carbonyl compounds followed by quenching with an appropriate silylating reagent. The differences between kinetically and thermodynamically favorable enolate anions have been utilized to secure the regiochemistry of the resulting enol silyl ethers [10]. However, much difficulty has been encountered in controlling regiochemical integrities where such differences are very small or negligible.

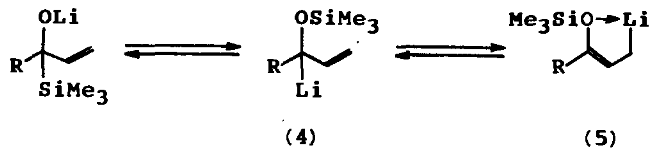
In addition to regiochemistry, much attention has been paid to the geometry of the enol derivative because it often has a marked influence on the stereochemical outcome of the reaction products, e.g. an aldol adduct [11]. A few methods have been reported so far which control the stereochemistry of enol silyl ethers [12], but the range of their application is restricted to symmetrically substituted ketones or carbonyl compounds that are enolizable on only one side.

By using 1-(trimethylsilyl)allylic alcohols (**3**), we attempted to explore another indirect methodology for determining the regio- and stereo-chemistry of enol silyl ethers. Judging from 1,1-bis(trimethylsilyl)benzyl alcohol, lithium alkoxides of **3** were expected to be in equilibrium with the corresponding 1- or 3-(trimethylsiloxy)allyllithiums **4** or **5**, presumably the latter, namely lithium homoenolates, which are favorable owing to internal coordination of the siloxy group to the metal cation.

Although such a type of alcohol **3** is not produced from the reaction of α,β-unsaturated carbonyl compounds with (trimethylsilyl)lithium [13], treatment of acyltrimethylsilanes [14,15] with vinyl Grignard reagents afforded the desired alcohols **3** in excellent yields. A slightly modified procedure developed by Cohen and Matz [16] has also been employed as a good alternative, especially for the preparation of β-substituted allylic alcohols.

Various examinations have disclosed the curious feature that the equilibrium between the alkoxide and **5** (or **4**) is too rapid to control the generation of the homoenolate species **5** on treatment of the alcohol **3** with butyllithium in THF: before complete formation of the lithium alkoxide with butyllithium, rapid equilibration allows the generation of the corresponding homoenolate **5**, which undergoes protonation with the remaining alcohol **3** to yield the enol silyl ether **6**. To control the generation of lithium alkoxide, it is important to use a non-polar solvent such as hexane where this equilibration has been blocked almost completely. Addition of THF to this hexane solution effects a rapid equilibration between the alkoxide and **5**. Treatment of the resulting solution with alkyl iodide at about −40°C afforded the corresponding enol silyl ethers **7** in good yield together with a small amount of an α-alkylation product and a dimerization product.

This alkylation reaction proceeds in a highly stereocontrolled manner to afford the enol silyl ethers of (Z)-configuration exclusively, probably due to the fixed conformation of the homoenolate **5**. Because of the rapid and irreversible rearrangement of the homoenolate to the β-trimethylsilyl enolate [13] at higher temperature, use of less reactive alkyl bromides or chlorides is not recommended for this alkylation.



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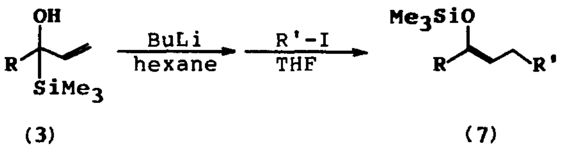
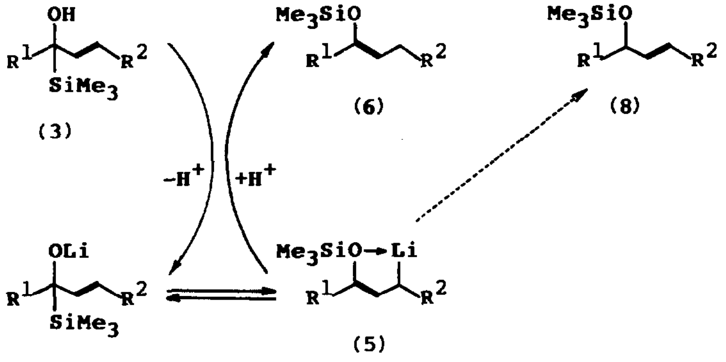


Another important feature is that the alcohol **3** undergoes isomerization to the corresponding enol silyl ether under the influence of a catalytic amount of butyllithium through the following four steps: (1) formation of the lithium alkoxide; (2) generation of the lithium homoenolate **5** via equilibration; (3) protonation of **5** with the remaining alcohol **3**; and (4) regeneration of the alkoxide. Thus, treatment of alcohol **3** with ca. 5 mol% of butyllithium in THF at ambient temperature led to the selective formation of the corresponding (*Z*)-enol silyl ether **6** in excellent yields. In contrast to the high efficacy of butyllithium as a catalyst, a Grignard reagent such as ethylmagnesium bromide proved not to be sufficient for this conversion. From the mechanistic point of view, the formation of regioisomeric enol ethers of **6** is excluded; this has been verified by experimental facts.

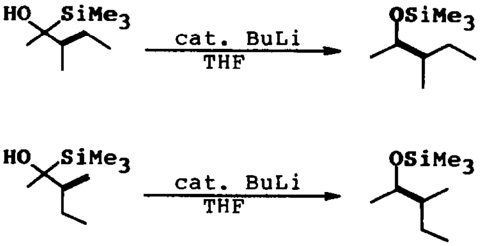
Several interesting features have been observed regarding the relationship of reactivity and selectivity with the structure of the starting alcohol **3**. With γ-unsubstituted allylic alcohols **3** (R^1 = primary alkyl; R^2 = H), the reaction usually proceeds at about −20°C within 30 min to afford the corresponding enol silyl ether **6** in a ratio of *Z*/*E* ca. 95/5. Introduction of substituents onto the β' position enhances both the reactivity and selectivity; the reaction of alcohols **3** (R^1 = secondary alkyl; R^2 = H or alkyl) takes place even at −78°C with a higher selectivity (*Z*/*E* ca. 98/2) to yield **6**. Steric overcrowding around the central carbon attached to silyl and oxide groups distinctly facilitates the rearrangement of alkoxides to the lithium homoen-



SCHEME 1

olate 5. On the other hand, for complete conversion of γ-substituted alcohols 3 (R^2 = alkyl), a higher reaction temperature, e.g. 0°C or room temperature, is usually required and a slight loss of stereoselectivity ($Z/E = 95/5-90/10$) has sometimes been observed. Furthermore, this type of alcohol usually accompanies formation of the allyl ether **8** in an appreciable extent ($< 15\%$). These are apparently attributable to both steric and electronic factors of the substituents R^2.

Conventional methods starting from parent ketones have made it impossible to control the stereochemistry of tetrasubstituted enol ethers. In contrast, this procedure has provided an excellent tool to secure the stereochemistry, even on such substrates. Typical examples are shown in eq. 5. In each case, the enol silyl ether obtained is more than 98% isomerically pure.



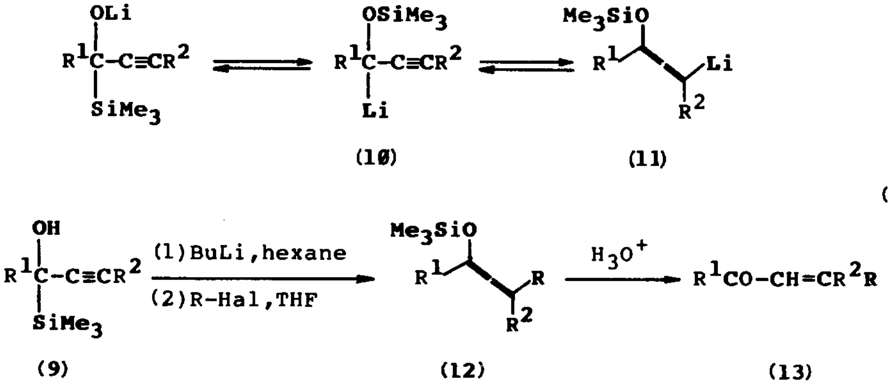
(5)

As shown already, these enol ethers can be used efficiently for stereo- and regio-specific aldol synthesis via selective transfer to the corresponding boron enolates [17].

(b) 1-(Trimethylsilyl)propargyl alcohols. Preparation of allenyl silyl ethers [18,19]

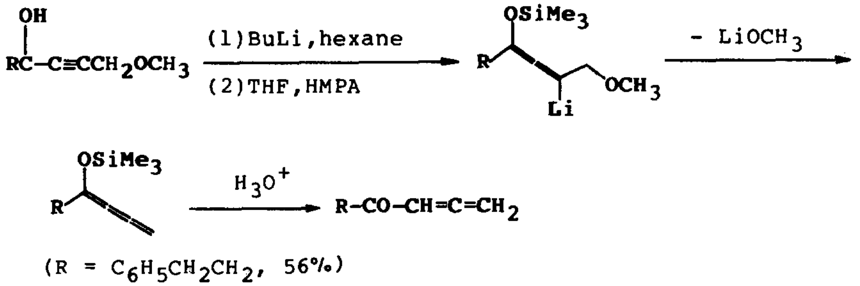
In a similar manner to 1-(trimethylsilyl)allylic alcohols **3**, an acetylenic moiety of a 1-(trimethylsilyl)propargyl alcohol **9** is also expected to effect the rearrangement of the lithium alkoxide to anionic species of propargyl silyl ether **10** or allenyl silyl ether **11**. In contrast to the cases mentioned above internal coordination of the siloxy group to the metal, which brings about thermodynamic stability, may be ruled out in the case of **10** or **11**, but anionic species of allene derivatives are expected to be very favorable in view of several reports in the literature.

Indeed, treatment of propargyl alcohol **9** with an equimolar amount of butyllithium in hexane followed by addition of THF induces the equilibration to generate



(6)

the corresponding carbanionic species **10** or **11**. Carbon chain homologation can be achieved efficiently by treating the resulting hexane-THF solution with alkyl iodide. Although two types of alkylation products may be conceivable in this case, the reaction takes place selectively at the allenic carbon to yield the corresponding α,β-unsaturated ketone **13** in an excellent yield after aqueous workup of the resulting allenyl ether **12**. An exceptional case is that where a leaving group is present at the 4-position; it undergoes facile elimination to afford an allenic ketone (eq. 7).

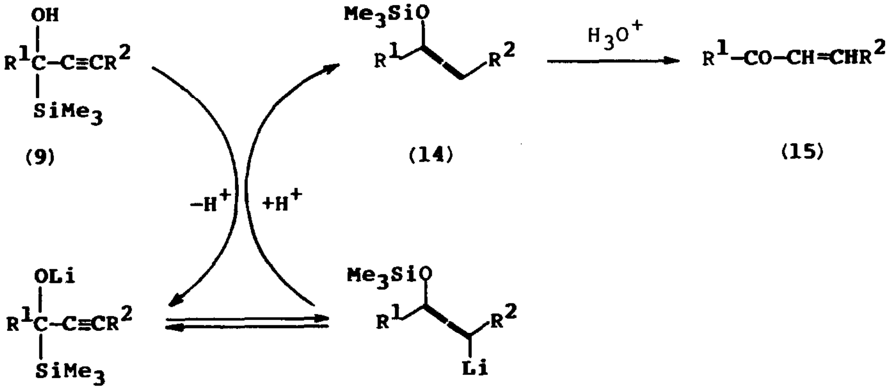


(7)

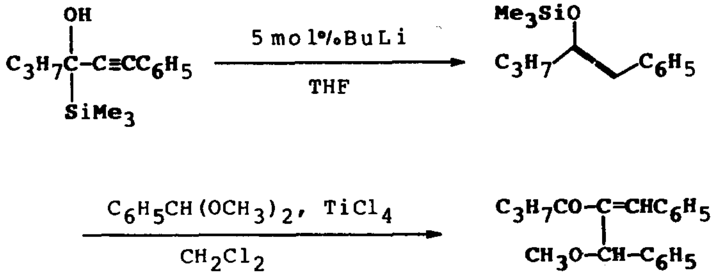
Specific conversion of the alcohol **9** to the corresponding α,β-unsaturated ketone **15** has also been effected under the influence of ca. 5 mol% of butyllithium in THF followed by acidic hydrolysis of the resulting allenyl silyl ether **14** (Scheme 2).

Protonation usually takes place selectively at the terminal allenic carbon to yield **14** in a similar manner to alkylation. Unfortunately, allenyl silyl ethers **12** or **14** are too labile to be purified by chromatography or sometimes by heating for distillation. However, the crude products obtained through alkylation or protonation are usually pure enough for further synthetic elaboration. By using such substrates, several organic substituents can be introduced onto the central carbon of the allenic linkages very efficiently. For example, crude **12** ($R^1 = C_3H_7$, $R^2 = C_6H_5$) gave the condensation product in an overall yield of 81% on treatment with a benzaldehyde acetal under the influence of Lewis acids.

Thus, starting from the propargyl alcohol **9**, this procedure allows one to effect two types of carbon chain homologation on each α- and β-carbon.



SCHEME 2

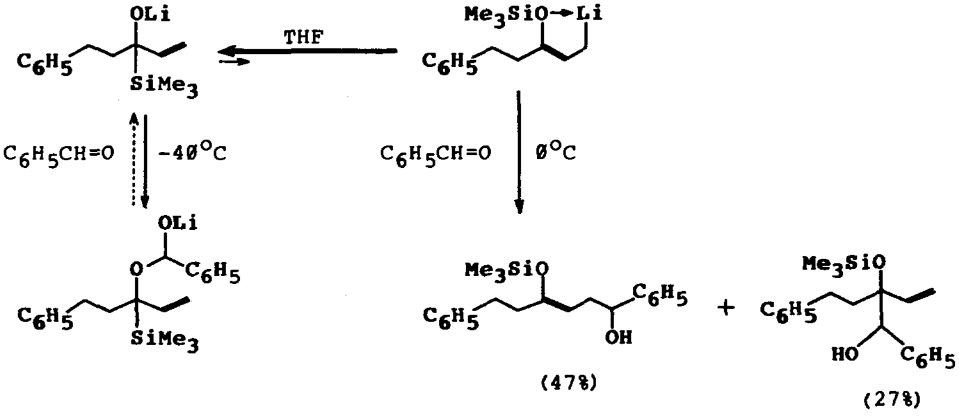


(8)

(c) Equilibrium composition between alkoxides and metal homoenolates. Stoichiometric generation of metal homoenolate equivalents

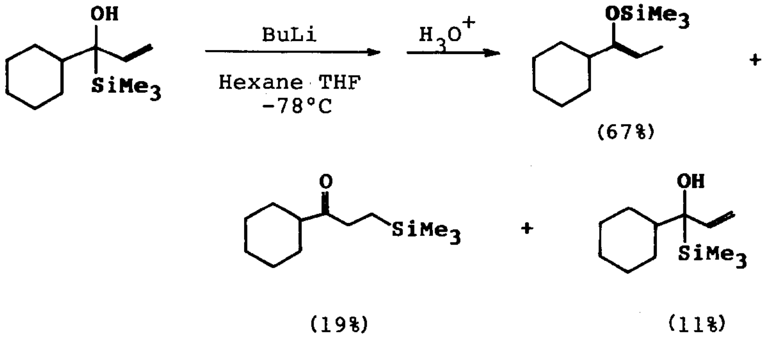
It seems to be quite important to clarify, at equilibrium, which is the more favorable species, the lithium alkoxide or the lithium homoenolate **5**. In order to estimate the equilibrium composition, a hexane-THF solution of the lithium alkoxide of **3** ($R^1 = C_6H_5CH_2$; $R^2 = R^3 = H$) prepared as mentioned earlier was quenched with dilute hydrochloric acid, giving the parent alcohol exclusively. This result clearly indicates that the equilibrium is greatly favored by the alkoxide. Such an equilibrium composition also accounts for the unusual behavior of benzaldehyde, i.e. it does not react with this alkoxide-homoenolate system at a temperature, e.g. −40°C, at which alkylation takes place quite rapidly. The addition reaction occurs at a higher temperature to give the γ-adduct and the α-adduct as shown in Scheme 3. Considering the much higher reactivity of an aldehyde to nucleophiles such as **5**, this result may be explained by assuming that the concentration of homoenolate **5** is very low at this equilibrium and most of the benzaldehyde is trapped with the predominant alkoxide as a hemiacetal to establish the equilibrium. Success in alkylation may only reflect the great difference in the reactivity between **5** and the alkoxide towards alkyl iodides; the equilibrium may move to the homoenolate side as the reaction proceeds.

However, the equilibrium composition is greatly influenced by the structure of alcohol **3**. For example, treatment of a hexane solution of lithium alkoxide (R^1 = cyclohexyl; R^2 = H) with THF at −70°C for 30 min and subsequent quenching of the reaction mixture afforded the corresponding silyl enol ether as the major product



SCHEME 3

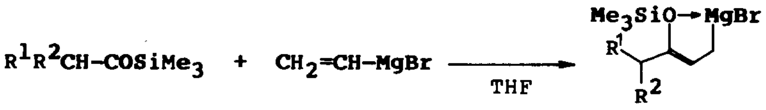
together with the parent alcohol and the β-trimethylsilyl ketone (eq. 9).



(9)

This means that substituents at the β' positions have a strong directing effect on both types of rearrangements, from an alkoxide to the lithium homoenolates **5**, and from **5** to the β-silyl enolate anion (**16**).

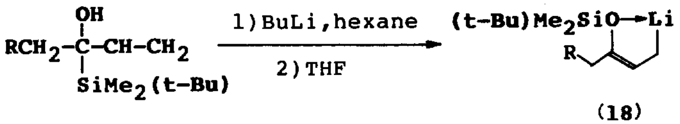
For stoichiometric generation of such metal homoenolates and their synthetic applications, there exists two serious problems to be resolved. One is the acceleration of the rearrangement of alkoxides to homoenolates, and the other is how to block the irreversible conversion of homoenolates to enolates such as **16**. Owing to the decrease in nucleophilicity of the anionic part of the homoenolates to the silyl group, the use of magnesium alkoxides has solved the latter problem, and such species as **17** can be generated almost quantitatively just by treating some α-branched acyltrimethylsilanes with vinylmagnesium bromide in THF. For example, on quenching the reaction mixture of α-ethylbutyryltrimethylsilane with vinylmagnesium bromide in THF, the corresponding enol silyl ether was obtained as a single product.



(10)

(17)

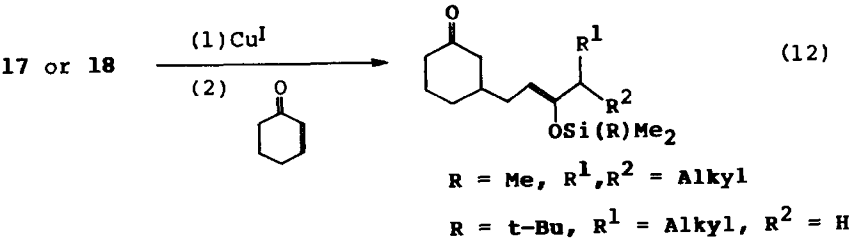
Furthermore, introduction of a t-butyldimethylsilyl group in place of a trimethylsilyl group has brought about great progress in the generation of the corresponding lithium homoenolates **18** without any assistance of sterically demanding groups. Starting from 1-(t-butyldimethylsilyl)allylic alcohols prepared from acyl(t-butyl)dimethylsilanes and a vinyl Grignard reagent, generation of the corresponding lithium homoenolates **18** has been executed almost quantitatively by controlling the reaction temperature. This is probably due to the t-butyldimethylsilyl group behaving as a sterically demanding group besides having less mobility as compared with the trimethylsilyl group.



(11)

(18)

On using an appropriate copper(I) salt, these magnesium and lithium homoenolates can be converted to the corresponding organocopper reagents [20], which have been used for selective carbon–carbon bond formation via conjugate addition to enones or for ring-opening reactions of oxiranes.



(12)

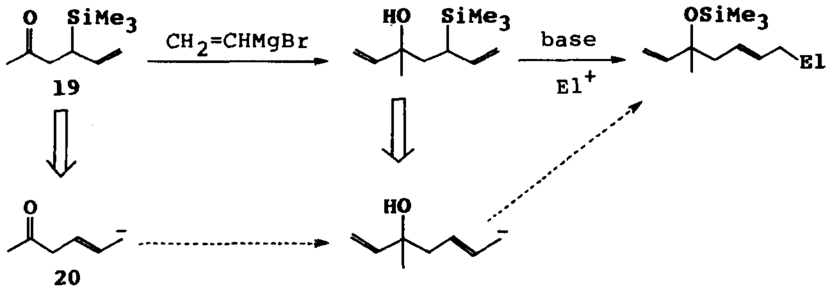
In contrast to the complication associated with alkoxides **3** and homoenolates **5**, the equilibrium between lithium alkoxides of **9** and allenyllithiums **11** has been found to be greatly favored on the side of **11** (see eq. 6), regardless of the steric factors mentioned above. In addition, since the allenyllithiums **11** are quite stable under reaction conditions where the lithium homoenolates **5** undergo rearrangement to enolates of the corresponding β-silyl ketones, these reagents can be employed as useful nucleophiles for a wide range of synthetic elaborations [21].

2. 1,4-Rearrangement of a trimethylsilyl group

α-(1-Trimethylsilylallyl) ketone as an α-alkenyl ketone equivalent [22]

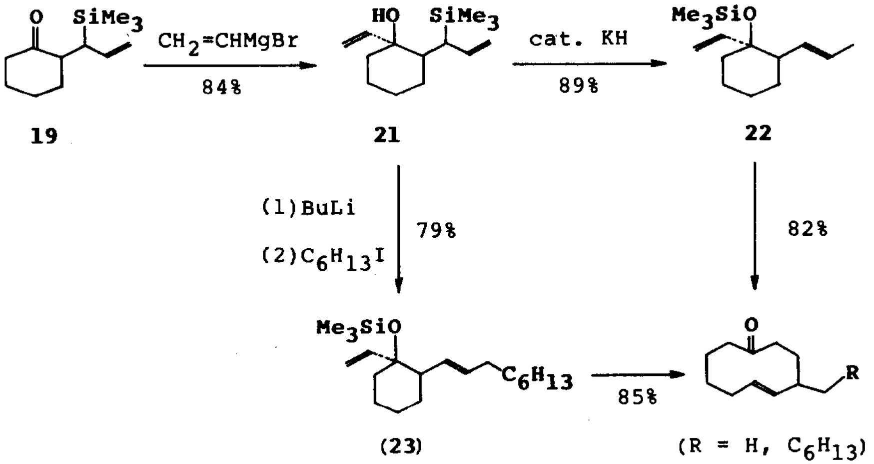
Extension of the concept described above has led us to assume that allylsilanes having a hydroxy group at a suitable position may undergo protonation or alkylation via the carbanionic species generated through equilibration with the alkoxides. In the transformation depicted in Scheme 4, the initial introduction of a vinyl group onto the ketone **19** is expected to provide a convenient method for the preparation of the 3-hydroxy-1,5-hexadiene system, a precursor for the oxy-Cope reaction. As a result, α-(1-trimethylsilylallyl) ketone **19** can be regarded as a synthetic equivalent of the α-alkenyl ketone **20**.

The starting materials **19** were readily prepared by the Claisen rearrangement employing 3-(trimethylsilyl)allylic alcohols [23]. Addition of vinylmagnesium bromide to **19** afforded the substrates **21**. Although a catalytic amount of butyllithium failed to induce the expected conversion, treatment of **21** with a catalytic amount of KH (ca. 0.1 equiv) led to a clean and rapid conversion to the silyl ether **22** (89%) as a mixture of E and Z isomers (E/Z 85/15).



SCHEME 4

An alkylation reaction also proceeds quite efficiently to give a mixture of *E* and *Z* isomers of **23** in good yield, on treating **21** with an equimolar amount of butyllithium in THF and subsequent addition of an appropriate alkyl halide. In contrast to the 1,2-rearrangement discussed earlier, the use of THF did not result in any complication in the generation of the lithium alkoxide or carbanionic species in this case. This result clearly indicates that equilibrium occurs rather slowly in this 1,4-rearrangement process.

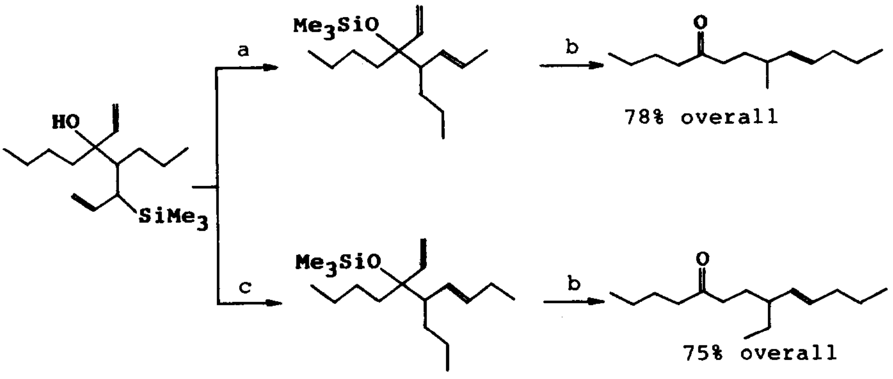


(13)

The anionic oxy-Cope rearrangement has been effected under the influence of KH and 18-crown-6 to afford the corresponding cyclodecenones in excellent yield as shown above.

Similar transformations also work quite well for an acyclic ketone derivative (Scheme 5).

This 1,4-rearrangement process also suffers distinctly from steric demanding factors, where α- as well as β-substituents appear to play very important roles in inducing the equilibration [24]. In general, lithium alkoxides of β,β-disubstituted alcohols (R^3 = alkyl; R^4 = alkyl) $HOCR^1R^2CR^3R^4CH(SiMe_3)CH{=}CH_2$ undergo alkylation at 0°C within 1 h to yield the alkylation products in more than 90%



SCHEME 5. (a) KH (0.1 equiv), THF. (b) KH, 18-crown-6, THF. (c) BuLi, THF, and then CH_3I.

yields. With β-monosubstituted tertiary alcohols (R^1, R^2, R^3 = alkyl; R^4 = H), however, the alkylation proceeds much more slowly, and it usually takes a longer period, e.g. overnight, at 0°C to complete the reaction.

Furthermore, with less substituted alcohols, the reactions become very sluggish; the alkylation reaction of β-unsubstituted alcohols did not give the corresponding product in a synthetically acceptable yield even after standing at room temperature for a prolonged period. A β-substituent works as a sterically demanding group to accelerate the transfer of a silyl group, and an α-substituent may enhance the basicity of the alkoxide to facilitate attack on the silyl group.

3. Conclusion

Thus, to determine the equilibrium composition between a metal alkoxide and a metal carbanionic species through rearrangement of a silyl group, the following two factors are in general very important: (1) anion-stabilizing substituents such as phenyl, vinyl, or acetylenic groups; and (2) steric acceleration due to overcrowding around the carbon attached to the silyl group, both of which are required to induce the equilibration efficiently. Furthermore, an enhanced basicity of the alkoxide is also needed in certain cases.

Keeping these characteristic features in mind, the appropriate choice of substrates providing such structural features will further lead to new investigations of several synthetically useful reactions.

Acknowledgement

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