Tetrahedron Letters, Vol.31, No.37, pp 5265-5268, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ORGANOSILICON RADICAL-INDUCED CYCLIZATION REACTIONS

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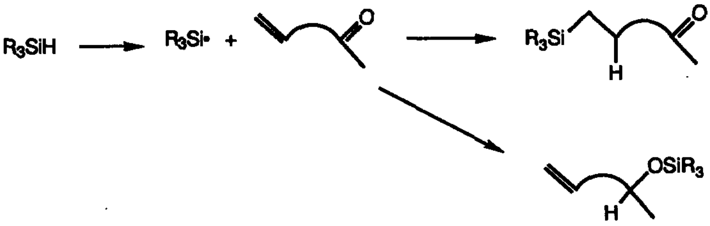
Summary: The first examples of selective additions of organosilicon radicals are reported. Trichlorosilyl radicals preferentially attack the carbonyl oxygen atom, while triethylsilyl radicals preferentially attack alkenes. Carbon-carbon bond formation to produce both monocyclic and bridged bicyclic systems is possible.

The use of organotin radicals in organic chemistry has increased enormously in recent years. In large part, this increase is due to the recognition that reagents such tributyltin hydride and hexaphenylditin can be employed as synthetic tools for the construction of complex organic molecules. This research has been collated in excellent reviews by Hart[1] and Curran[2] and in a timely book by Giese.[3] In contrast to the attention given to organotin radicals, almost no synthetic attention has been accorded to organosilicon radicals.[4] In view of the propensity of organosilicon reagents to form silicon-oxygen bonds, there is good potential for identifying interesting chemoselective reactions.

The addition of organosilanes to alkenes and, to a much lesser extent, to carbonyl groups is a well-precedented reaction. Wilt[5] and Eaborn[6] have reviewed the additions of various organosilicon radicals to alkenes and to carbonyl compounds. Fundamental contributions by Ingold[7] have laid the groundwork for the research described herein. The addition of organosilicon radicals to alkenes is much more facile than the analogous reaction of alkenes with alkyl radicals.[8] The substituents on the silicon atom greatly affect the rate of the addition reaction. In general, electron-withdrawing substituents increase the rate of addition of organosilicon radicals to both alkenes and carbonyl groups.

Despite the wealth of data on organosilicon radical additions to simple alkenes, *no study of the chemoselectivity of addition of organosilicon radicals to compounds containing isolated alkene and carbonyl units has been reported.* Moreover, *no preparative study of organosilicon radical addition to* *isolated dienes has been reported.* Since these were obviously pivotal aspects for the extension of this methodology to the synthesis of natural products, these questions were explored first. In order to examine whether substituents on the silicon atom would influence chemoselectivity, we used both trichlorosilane and triethylsilane in the initial studies. In each experiment, di-t-butyl peroxide (0.5 eq) was used as the radical source. The reaction was allowed to proceed at 140°C in an argon atmosphere in a sealed tube with the substrate (1 eq) and the silane (4 eq) in dry benzene (0.5 M). Reactions were conducted on scales ranging from one to ten millimoles.

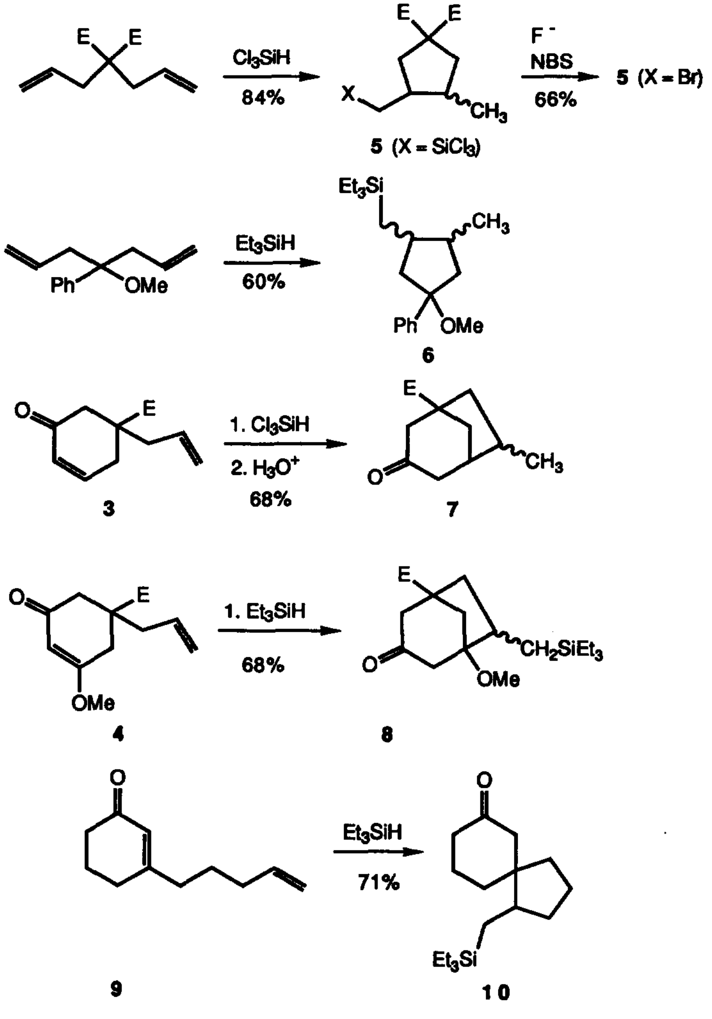


All of the substrates were set up for a 5-hexenyl radical cyclization. Compound **3** must form a bicyclo[3.2.1]octan-3-one by a relatively strained transition state. This is perhaps the most difficult case in that both 1,4-addition to the conjugated enone moiety and addition to the monosubstituted alkene are possible competing reactions. Compound **3** was formed by the alkylative Birch reduction[9] of 3-methoxybenzoic acid followed by hydrolysis and isomerization of the Birch reduction product (1N HCl/THF) and esterification with diazomethane. Compound **9** was prepared by the addition of the Grignard reagent derived from 5-bromo-1-pentene[10] to cyclohexenone followed by PCC-mediated rearrangement of the allylic alcohol and oxidation.

As the results in Scheme 1 indicate, cyclizations occur in good to excellent yields with both dienes and olefinic ketones. Trichlorosilane is the silane of choice for the selective addition to the ketone carbonyl group. The trichlorosilyl radical is more electroplilic than the trialkylsilyl radical. This facet undoubtedly accelerates the addition to the carbonyl group. In contrast, triethylsilane reacted preferentially with the alkene. Addition to the alkene was always in the anti-Markownikov sense. Notably, ester groups do not react under these conditions. This was somewhat surprising, in that Baldwin and coworkers had reported a useful ester-to-ether transformation using trichlorosilane.[11] Kumada has recently demonstrated that the trichlorosilyl group is a synthetic equivalent for the OH, Cl and Br groups.[12] As shown in Scheme 1, the Kumada reaction can also be performed on **5**.

Recently, Beckwith and Enholm have reported an interesting and related cyclization wherein a cyclopentanol was formed by the reaction of an olefinic ketone or aldehyde with tributyl tin hydride. They prepared several fused bicyclic and tricyclic ring systems in very good yield[13].

Scheme 1



E = CO_2Me

The reactions described above constitute the first examples of chemoselectivity in organosilicon radical additions to olefinic ketones. Carbon-carbon bond formation to generate monocyclic and bridged bicyclic ring systems opens the way for continued extension of this methodology to more complex systems.

Acknowledgement: We thank the donors of the Hermann Frasch Foundation for support of this research.

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(Received in USA 5 June 1990)