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CARBENE CHEMISTRY. STEREOSELECTIVE SYNTHESIS OF HALOALKENES

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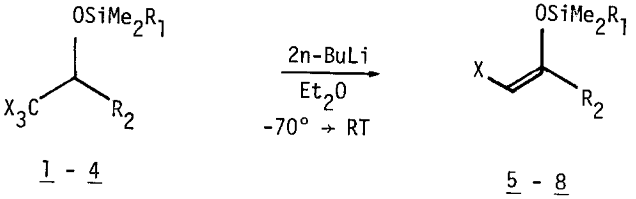
Abstract:

Hydrogen migration in halocarbenes provides a stereoselective method for preparation of (Z)-haloalkenes.

Haloenol silyl ethers are compounds of recent synthetic interest as precursors to enolate equivalents of high reactivity.[1] They may also serve as enolonium equivalents in a nickel-catalyzed coupling[2] with Grignard reagents to provide alkyl enol ethers. The methods for preparation of these compounds leave much to be desired.[3] Though they are generally obtained in good (>95% Z) geometric purity by a bromination-dehydrobromination sequence, volatility often precludes their isolation in high yield. In the course of examining carbene reactions of haloalkyl silyl ethers, we have discovered that hydrogen migration is a very facile process, leading to haloenol silyl ethers in high yield and excellent stereochemical purity.[4]

The typical reaction is outlined in Eq. 1.



(1)

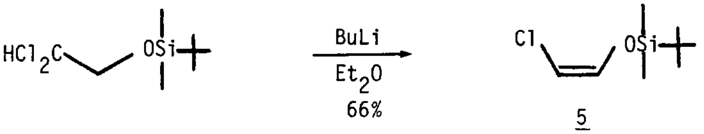
Starting[5] Material	X	R_1	R_2	Yield	Product
1	Cl	t-Bu	H	68%	5
2	Br	Me	H	86%	6
3	Br	t-Bu	H	92%	7
4	Cl	t-Bu	CH_3	96%	8

Table

The rearrangement is conducted initially at low temperature with stirring to room temperature overnight. This long warming period seems to be necessary to avoid the isolation of reduction products, despite the acknowledged instability of dihaloalkyllithiums. Two equivalents of n-BuLi are required, the second presumably to dehydrohalogenate the butyl halide product of transmetalation. The yields for the conversion to haloalkene are excellent (Table).

In all of the cases examined, the stereoselection in the formation of disubstituted alkene is great. The Z-products 5-7, as evidenced by a 4 Hz vicinal coupling constant in the ^{1}H NMR spectrum, are the only stereoisomers detectable. Furthermore, the trisubstituted alkene 8 appears to be formed with equally high stereoselection, and is tentatively assigned the Z configuration. A 1.1 Hz ^{1}H allylic coupling constant and a ^{13}C NMR spectrum consisting of only 6 lines lead to these conclusions (vide infra).

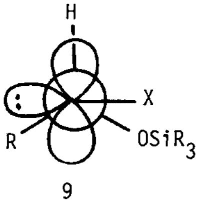
It is also possible to generate haloalkenes from the corresponding dihaloalkyl silyl ethers (Eq. 2).



(2)

Since the mechanism here is presumably deprotonation (β-elimination would not be expected to be cis-stereospecific) to produce the dichloroalkyl lithium, only a single equivalent of strong base is necessary.

The reasons for the extraordinary stereoselection observed in these hydrogen migrations are not immediately apparent. Considerable theoretical basis[6] allows the transition states 9 and 10 to be drawn.



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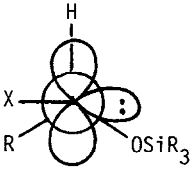

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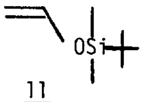
The repulsion between the lone pair at the divalent carbon and the siloxy group evidently dominates both steric and polar effects, which should disfavor 9. Alternatively, conformer 9 may be stabilized by hyperconjugation of the carbene lone pair and the low-lying C—O σ^* orbital. Previous examples of hydrogen migration in carbenes bearing π-electron withdrawing groups[7] (succinylidene → maleate) have also shown almost exclusive formation of the Z-alkene. While both chlorine and alkoxy are σ-electron withdrawing, they are π-electron donating. The latter seems to accelerate the hydrogen migration, since performing the reaction in the presence of a reactive alkene such as an enol silyl ether leads to no diversion of the carbene to cyclopropane containing products. Regardless of the explanation, electron-withdrawing groups exert a powerful influence on the course of hydrogen migration in carbenes.

We have further explored the synthetic utility of 5-8. As expected, 7 is easily transmetalated under conditions used for 6,[1] as evidenced by isolation of vinyloxy *t*-butyldimethylsilane 11 (87%) on protonolysis. Mukaiyama-type aldol condensation of 8 unsurprisingly provides a 2:1 mixture of diastereomers of the protected chlorohydrins 12.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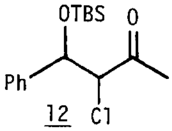

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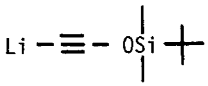

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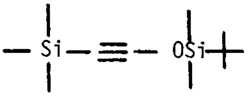
Dehydrohalogenation of 7 (2 LDA, THF, 0°C, 30 min) gives ready access to acetylide 13. Isomeric with the silyl ketene enolate of Rathke,[8] 13 is of considerably greater utility. Trapping of the anion with TMSCl (100% to 14) or cyclohexanone (98% to 15) proceeds well.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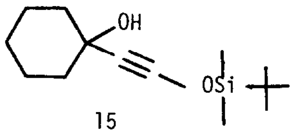

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Further conversions of these intermediates will be the subject of a future report.

Typical Procedure

To a solution of 300 mg (1.08 mmol) of 4 in 5 mL of Et_2O cooled to -70°C was added 1.35 mL (2.16 mmol) of a 1.6 M solution of *n*-BuLi in hexane. The bath was allowed to melt and the reaction mixture stirred at room temperature overnight. Precipitated lithium halide usually signaled the completion of the reaction. The reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted with Et_2O. Washing the combined organic phases with brine, drying (K_2CO_3), filtration and evaporation provided 215.1 mg (96%) of 8. ^1H NMR ($CDCl_3$): δ 0.19 (6 H, s), 0.96 (9 H, s), 1.80 (3 H, d, J = 1.1), 5.17 (1 H, m, J = 1.1). ^{13}C NMR ($CDCl_3$): δ -4.1, 18.2, 21.0, 25.6, 96.1, 149.1 ppm. *Anal*. C, H, Cl.

References and Notes

1. L. Duhammel and F. Tombret, J. Org. Chem., 46, 3741 (1981).
2. K. Tamao, M. Zembayashi, and M. Kumada, Chem. Lett., 1239 (1976).
3. M. Zembayashi, K. Tamao, and M. Kumada, Synthesis, 422 (1977).
4. The method is not limited to silyl ethers. THP-protected trichloroethanol provides Z-chlorovinyl THP ether under these conditions.
5. The silyl ethers are prepared under standard conditions (TMSCl, Et_3N, DMF; TBDMSCl, Imidazole, DMF or CH_2Cl_2) in virtually quantitative yield, except for 4, which requires a 3-day reaction time in the presence of 4-dimethylamino pyridine for complete consumption of alcohol.
6. H. F. Schaeffer, Acc. Chem. Res., 12, 288 (1979), and references therein.
7. Y. Yamamoto and F. Moritani, Tetrahedron, 26, 1235 (1970).
8. R. Woodbury, N. Long, and M. Rathke, J. Org. Chem., 43, 376 (1978).

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Note added in proof: An alternative mechanism involving β-elimination followed by stereoselective transmetalation is disfavored due to the known instability of trans-1-lithio-2-alkoxy alkenes: R. Peries, Ph.D. Dissertation, Stanford University, 1982. Acetylene formation is presumed.

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