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SYNTHESIS OF ALLYL VINYL SILANES. PREPARATION OF 12-(DIMETHYLSILA)SQUALENE

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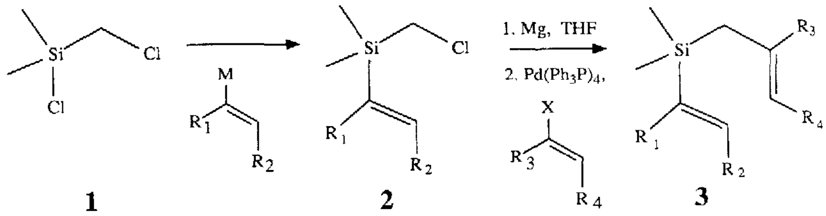
Summary: A general method for the preparation of mixed allyl vinyl dimethylsilanes uses the sequential coupling of two different alkenylmetallics to (chloromethyl)dimethylchlorosilane. This method is applied to synthesize the 12-dimethylsila analog of squalene.

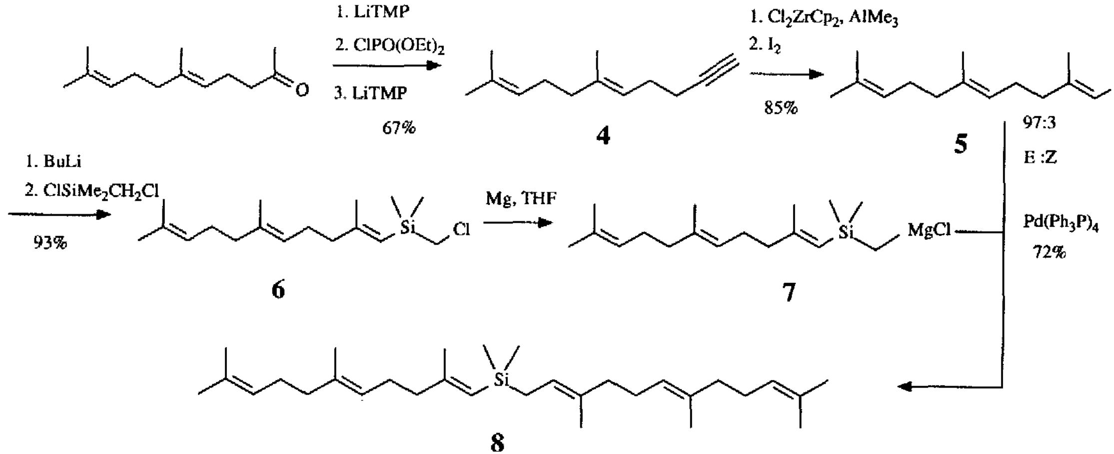
Although both allylsilanes and vinylsilanes are readily prepared and useful reagents in organic synthesis[1], no general methods were available in the literature for the synthesis of silanes bearing both an allylic and a vinylic moiety.[2] Compounds of this type have particular interest for us for the study of beta-silicon-accelerated cationic cyclizations.[3] In addition, the availability of a variety of allyl vinyl silanes could stimulate anew the examination of the sila-Cope rearrangement.[2a] We now describe a general route to the preparation of allyl vinyl dimethylsilanes **3** from (chloromethyl)dimethylchlorosilane (**1**) via the palladium-catalyzed coupling of an alkenyl or aryl iodide with the alkenyl(chloromethyl)silane **2**. Furthermore, we illustrate the practical utility of this procedure to synthesize the 12-dimethylsila analog of the polyolefinic triterpene squalene.



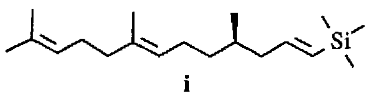
Negishi and co-workers described the coupling of (chloromethyl)trimethylsilane to a variety of alkenyl halides as a general approach to allylsilanes.[4] Thus, tetrakis(triphenylphosphine)palladium is employed as a catalyst for the coupling of the magnesium reagent of the silane with an alkenyl halide. We chose the parent (chloromethyl)dimethylvinylsilane **2a** (R_1 = R_2 = H) to explore the generality of the coupling reaction with alkenyl and aryl halides.

Table I illustrates representative examples of the coupling reaction. Aryl iodides and *(E)*-1-alkenyl bromides and iodides couple efficiently to give the allyl vinyl silane products.[5] In contrast, *(Z)*-1-alkenyl iodides and 2-bromostyrene couple with lower efficiency, which we attribute to steric congestion in the palladium-olefin complex. Additionally, *(Z)*-1-alkenyl iodides give reductive coupling to alkenyl(trimethyl)silane products.** Indeed, the reduced reactivity of the *(Z)* isomers allows kinetic enrichment in *(E)*-allyl silane products **3** in the cases of β-bromostyrene and the trisubstituted alkenyl iodides.

Silasqualene **8** was prepared as outlined in the Scheme below. Geranylacetone was converted to the kinetic enol phosphate[6] (1.05 equiv. lithium tetramethylpiperidide (LTMP), -78 °C, 1 h; quench at -78 °C to 20 °C with 1.1 equiv. $ClPO(OEt)_2$), which was then added to 2.1 equiv. of LTMP to afford, after aqueous workup, geranylacetylene **4**[7] in 67% yield. Next, *syn* methylzirconation[8] of the alkyne using the zirconocene dichloride (1.1 equiv.)-trimethylaluminum (2.2 equiv.) reagent at 0 to 20 °C for 10 h, followed by 1.2 equiv. of iodine in THF at 0 °C afforded the (*E*)-vinyl iodide **5** in 85% yield (*E:Z* ratio, 97:3). The lithium reagent was prepared from the pure *(E)*-vinyl iodide isomer using 1.1 equiv. of *n*-butyllithium in diethyl ether at -78 °C for the metal-halogen exchange[9], and was coupled[10,11] with 1.1 equiv. of (chloromethyl)dimethylchlorosilane[12] at -78 to -30 °C and quenched at -30 °C to give vinylsilane **6** (93%). Finally, the magnesium reagent **7** generated at 20 °C from the (chloromethyl)vinyl silane **6** with 1.5 equiv. of Mg powder in THF was added to $Pd(PPh_3)_4$ at 20 °C, followed by coupling[5] with a second unit of the vinyl iodide **5** (20 °C, 12 h) to give the TLC- and capillary GC-homogeneous 12-silasqualene **8** in 72% yield.[13]

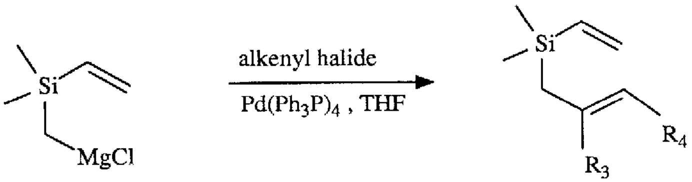


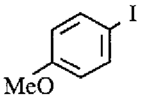
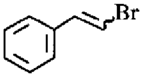
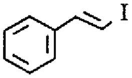
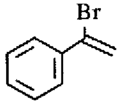
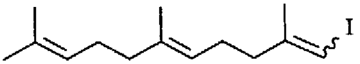
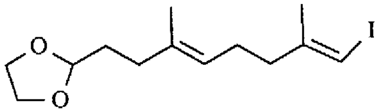
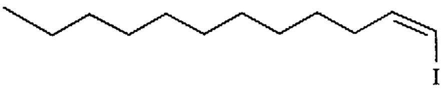
** The abnormal reductive coupling process is stoichiometric in palladium and appears to compete favorably with normal reductive elimination for *(Z)*-alkenyl halides. The structure of the adduct (i) for Entry 5 (Table 1) clearly showed an *(E)*-alkenyl(trimethyl)silane (d 5.61, d, *J* = 18.5 Hz, 1H; d 5.98, dt, *J* = 18.5, 6.7 Hz, 1H) and a new methyl doublet (d 0.86, d, *J* = 6.7 Hz, 3H).



i

Table 1. Palladium-catalyzed coupling to give allyl vinyl silanes



Entry	Alkenyl or Aryl Halide	R-X:R_4Si Ratio	Isolated Yield*
1		1:1	70%
2	 E:Z = 96:4	0.5:1	77% E:Z > 99:1
3		0.75:1	80%
4		0.5:1	5%
5	 E:Z = 75:25	1:1	55% (E), [10%]
6	E:Z = 97:3	0.5:1	60% (E), [5%]
7		0.5:1	62%
8		0.5:1	75%
9		0.5:1	38% (Z), [12%]

*Isolated yields are calculated based on the limiting alkenyl iodide. Numbers in brackets are abnormal alkenyl(trimethyl)silane coupling products.

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References and Notes

1. (a) Chan T.H. and Fleming, I., *Synthesis*, **1979**, 761-786; (b) Colvin, E.W. *Silicon in Organic Synthesis*, R.E. Krieger Publishing Co., Malabar, FL, 1985; (c) Hosomi, A., *Acc. Chem. Res.*, **1988**, *21*, 200-206.

2. (a) The *(Z)*- and *(E)*-propenyl allyl vinyl silanes were prepared by an uncatalyzed coupling reaction of the alkenyl magnesium reagent with allyldimethylchlorosilane: Slutsky J. and Kwart, H., *J. Org. Chem.*, **1973**, *38*, 3658-3660; (b) Silabenzene was generated by retro-ene reaction of 1-methyl-1-allylsilacyclohexa-2,4-diene, prepared by coupling of allylmagnesium chloride with the 1-chlorosilacyclohexadienyl precursor: T. J. Barton and G. T. Burns, *J. Am. Chem. Soc.*, **1978**, *100*, 5246.

3. See, for example, Blumenkopf, T.A. and Overman, L.E., *Chem. Rev.*, **1986**, *86*, 857-873. Exploration of the effects of the β-silyl group on *in vitro* cyclizations are in progress in our laboratory.

4. Negishi, E., Luo, F.-T., and Rand, C.R., *Tetrahedron Lett.*, **1982**, *23*, 27-30.

5. A typical procedure for the β-iodostyrene is described. Chloromethyldimethylvinylsilane (0.27 g, 0.3 ml, 2 mmol) in 1.5 ml of THF was added to Mg (0.072 g, 2 mmol) in 1.5 ml of THF. The Grignard compound was transferred via double-ended needle to $Pd(PPh_3)_4$ (0.23 g, 0.1 equiv.) in 2 ml of THF at room temperature. To this, *(E)*-1-iodostyrene (0.34 g, 1.5 mmol) in 2 ml of THF was added, and the reaction mixture was stirred at 20 °C for 12 h. Then, 3 N HCl was added, stirring was continued for 0.5 h, and the product was extracted with hexane. The hexane solution was washed (H_2O, aq. $NaHCO_3$)), dried ($MgSO_4$), and concentrated *in vacuo*. After column chromatography on silica gel with hexane 0.23 g (80%) of pure allyl vinyl silane was obtained ^1H NMR ($CDCl_3$) δ 0.075 (s, 6H), 1.68 - 1.70 (m, 2H), 5.67 (dd, *J* = 20.0 Hz, *J* = 4.0 Hz, 1H), 5.95 (dd, *J* = 14.7 Hz, *J* = 4.0 Hz, 1H), 6.16 (dd, *J* = 20.0 Hz, *J* = 14.7 Hz, 1H), 6.17 - 6.28 (m, 2H), 7.11 - 7.25 (m, 5H). All allyl vinyl silanes were characterized by FT-IR, 300 MHz ^1H NMR, 75 MHz ^{13}C-NMR, and elemental analysis. (These data are available in tabular form on request from G.D.P.)

6. Negishi, E., King, A.O., and Klima, W.L., *J. Org. Chem.*, **1980**, *45*, 2526-2528.

7. (a) Stadler, P.A. and Nechvatal, A., Frey, A.J., and Eschenmoser, A., *Helv. Chim. Acta*, **1957**, *40*, 1373-1409; (b) Corey, E.J. and Kirst, H., *Tetrahedron Lett.*, **1968**, 5041-5043.

8. Negishi, E., VanHorn, D.E., and Yoshida, T., *J. Am. Chem. Soc.*, **1985**, *107*, 6639-6647.

9. Cahiez, G., Bernard, D., and Normant, J.F., *Synthesis*, **1976**, 245-248.

10. Neumann, H. and Seebach, D., *Tetrahedron Lett.*, **1976**, 4839-4842.

11. Tamao, K., Nakajima, T., and Kumada, M., *Organometallics*, **1984**, *3*, 1655-1660.

12. Anderson, R., *Synthesis*, **1985**, 717-734.

13. Spectral data for 12-(dimethylsila)squalene: ^1H NMR ($CDCl_3$) δ 0.079 (s, 6H), 1.49 (d, *J* = 8.4 Hz, 2H), 1.56 (s, 6H), 1.60 (s, 9H), 1.68 (s, 6H), 1.78 (s, 3H), 1.95 - 2.15 (m, 16H), 5.00 - 5.25 (m, 6H); ^{13}C NMR ($CDCl_3$) δ -1.87, 15.89, 16.00, 17.67, 18.41, 21.94, 25.69, 26.55, 26.79, 26.89, 39.76, 40.03, 42.56, 120.32, 121.75, 123.98, 124.39, 124.42, 131.22, 131.26, 132.43, 134.75, 135.11, 155.00. IR (neat) 2963 -2853 (s), 1665 (w), 1616 (m), 1443 (m), 1376 (m), 1246 (m), 835 cm^{-1} (s).

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