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A Succinct Method for Preparing the Stork−Jung Vinylsilane Robinson Annulation Reagent

Jeananne A. Singletary, Hubert Lam, and Gregory B. Dudley*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390

gdudley@chem.fsu.edu

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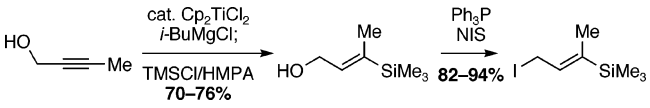


The Stork−Jung vinylsilane reagent (**1**) is prepared in two steps and in good overall yield. This provides rapid and efficient access to a useful methyl vinyl ketone surrogate.

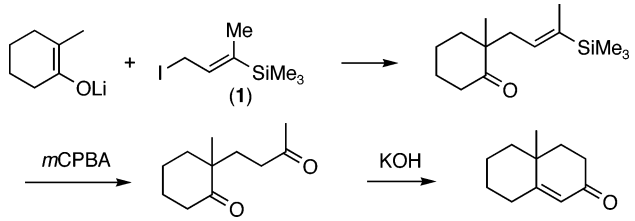
The Robinson annulation has been a cornerstone method in organic synthesis since its establishment in the early part of the 20th century.[1] In its simplest form, it comprises three steps: Michael addition of an enolate nucleophile to an α,β-unsaturated ketone, aldol cyclization, and finally dehydration to afford the cyclohexenone product.[2]

As part of an ongoing synthetic project in our Laboratory, we wished to prepare the Michael adduct between an unstabilized cyclohexanone enolate and methyl vinyl ketone (MVK), the prototypical electrophilic partner for the Robinson annulation. Although polymerization of MVK competes with direct addition, modified reagents ("MVK equivalents")[2] have been developed for effecting such transformations. Of these, the Stork−Jung vinylsilane (**1**) quickly emerged as the optimal reagent for our purposes.[3,4]

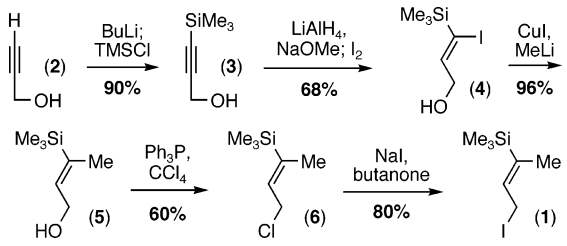
Vinylsilane **1** is particularly well suited to the alkylation of regiospecifically generated, unstabilized enolates. After alkylation, the vinylsilane may be treated with *m*CPBA to afford the ketone, which is poised for cyclization and dehydration.

Unfortunately, vinylsilane **1** is not as simple to prepare as other MVK equivalents. Scheme 2 illustrates the original route to **1**.[2a,5] Alternative approaches have been described (via alcohol **5**),[6] but the Stork−Jung synthesis

SCHEME 1. Stork-Jung Robinson Annulation



SCHEME 2. Original Synthesis of the Stork-Jung Vinylsilane (1)



(with minor modifications) remains the commonly employed procedure.[7]

We envisioned that titanium-catalyzed hydromagnesiation of 2-butynol (**7**) according to Sato's protocol,[8] followed by trapping with trimethylsilyl chloride (TMSCl), would provide efficient access to vinylsilane **5**. Two key obstacles had to be overcome. First, 2-butynol was not proven to be a reliable hydromagnesiation substrate.[9] Second, the viability of TMSCl as the electrophilic partner was unclear.[10] Most examples of the Sato reaction have involved propargyl alcohols with larger hydrocarbon appendages (e.g., 2-octynol) and reactive electrophiles such as aldehydes, iodine, or (after solvent exchange) iodomethane.[8] Nonetheless, the appeal of a simple, one-pot synthesis of alcohol **5** encouraged us to investigate this further.[11] We report herein the results of our investigations.

Table 1 presents our initial screening of hydromagnesiation conditions. Indeed, 2-butynol (**7**) appears to be less reactive than more lipophilic propargyl alcohols. Under the original Sato conditions (entry 1),[8] significant amounts of recovered **7** were observed. We hypothesized that this apparent decrease in reactivity is related to poor solubil-

(1) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.

(2) Reviews: (a) Gawley, R. E. *Synthesis* **1976**, 777. (b) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(3) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682.

(4) For a recent application of this and a related reagent, see: Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123.

(5) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684.

(6) (a) Altnau, G.; Rösch, L.; Bohlmann, F.; Lonitz, M. *Tetrahedron Lett.* **1980**, *21*, 4069. (b) Sato, F.; Watanabe, H.; Tanaka, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1126. (c) Audia, J. E.; Marshall, J. A. *Synth. Commun.* **1983**, *13*, 531. (d) Miller, R. B.; Al-Hassan, M. I. *Tetrahedron Lett.* **1983**, *24*, 2055. (e) Wang, K. K.; Liu, C.; Gu, Y. G.; Burnett, F. N.; Sattsangi, P. D. *J. Org. Chem.* **1991**, *56*, 1914.

(7) (a) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168. (b) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1227.

(8) (a) Sato, F.; Ishikawa, H.; Watanabe, H.; Miyake, T.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1981**, 718. (b) Sato, F.; Kobayashi, Y. In *Organic Syntheses*; Wiley and Sons: New York, 1993; Collect. Vol. VIII, p 507.

(9) A single, unoptimized example has been reported: (a) Lautens, M.; Huboux, A. H. *Tetrahedron Lett.* **1990**, *31*, 3105. (b) Lautens, M.; Zhang, C. H.; Goh, B. J.; Crudden, C. M.; Johnson, M. J. A. *J. Org. Chem.* **1994**, *59*, 6208.

(10) (a) Two examples are described in a footnote and in undisclosed yield: Kang, J.; Cho, W.; Lee, W. K. *J. Org. Chem.* **1984**, *49*, 1838. (b) For trapping with *stannyl* chlorides, which requires solvent exchange, see ref 9.

(11) In fact, Sato reported that hydromagnesiation of **3** and isomerization, followed by solvent exchange and methylation, afforded **5**,[6b] although this protocol has not supplanted two-step conversions of **3** → **5**. The method reported herein is advantageous in that silylation occurs without requiring the solvent exchange (vide infra), and **7** is more readily available than **3**.

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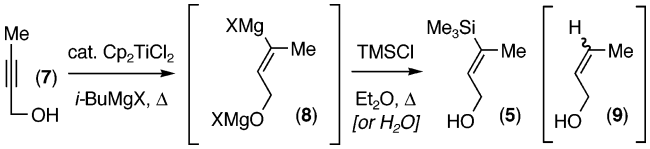
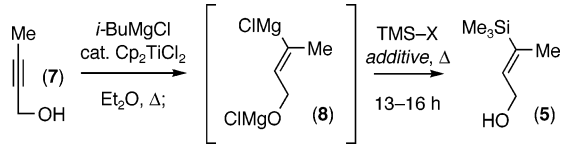
TABLE 1. Hydromagnesiation of 2-Butynol



entry	X	solvent	time (h)	bath temp (°C)	yield of **5** (%)	byproducts
1	Cl	Et_2O	4[b]	rt	–	**7**
2	Cl	Et_2O	4[b]	36–38	–	**7**, **9**
3	Cl	Et_2O	16[c]	36–38	28–35	**9**
4	Cl	Et_2O-HMPA[a]	12[c]	36–38	0	**7**
5	Cl	hexane	16[c]	68–70	27	**7**, **9**
6	Cl	Bu_2O	18[c]	80–82	nd[d,e]	–
7	Br	Et_2O	16[c]	36–38	nd[d]	**7**, **9**

[a] 2.0 equiv with respect to Mg salts. [b] Aqueous quench. [c] Followed by heating for 12–14 h with 3.0 equiv of Me_3SiCl. [d] Not determined. [e] Product contaminated with Bu_2O.

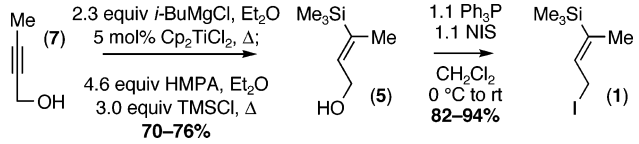
TABLE 2. Reaction of 8 with TMSCl



entry	Me_3SiX	additive	bath temp (°C)	silane **5** yield (%)[c]
1	Me_3SiCl	HMPA[a]	36–38	70–76
2	Me_3SiCl	THF[b]	58–60	50–56
3	Me_3SiCl	THF[b]–HMPA[a]	60–62	65–73
4	Me_3SiCl	THF[b]–DMPU[a]	60–62	45
5	Me_3SiCl	DMPU[a]	36–38	42
6	Me_3SiBr	THF[b]–HMPA[a]	36–38	–[d]
7	Me_3SiI	THF[b]–HMPA[a]	36–38	–[d]

[a] 2.0 equiv with respect to Mg salts. [b] Volume of THF equal to the initial volume of Et_2O added (15 mL). [c] Varying amounts of crotyl alcohol (**9**) observed in suboptimal cases. [d] No desired product (**5**) was observed in the crude product mixture.

SCHEME 3. Two-Step Synthesis of Vinylsilane 1



ity of butynyloxy-magnesium chloride salts. The reaction with 2-butynol is heterogeneous, whereas the salts of larger propargyl alcohols are more soluble in organic media. However, switching to the magnesium bromide counterion (entry 7) and addition of hexamethylphosphoramide (HMPA, entry 4) were both deleterious. Fortunately, increases in time and temperature resulted in complete consumption of the 2-butynol (entry 3), although simple trapping with TMSCl provided the desired vinylsilane (**5**) in low to moderate yield (unoptimized).

We then focused on the silylation of hydromagnesiation intermediate **8**. Varying the reaction concentration did not have a significant effect. In contrast to the first stage of the reaction (formation of **8**), inclusion of coordinating cosolvents such as HMPA and THF at this point was beneficial (Table 2). DMPU was not a suitable replacement for HMPA. No desired product was obtained in the presence of bromide or iodide ions (entries 6 and 7), perhaps due to decomposition promoted by these harsher reagents. Crotyl alcohol (**9**, most likely from protonolysis of **8**) was identified in some instances in the crude product mixture (it is easily removed by silica gel chromatography). However, under carefully controlled conditions with freshly distilled reagents and base-washed glassware, vinylsilane **5** is produced as the only identifiable reaction product.

Entry 1 outlines the optimal conditions with respect to yield, although the yields in entry 3 are only slightly and perhaps insignificantly lower. This one-pot procedure provides vinylsilane **5** in only one step from commercially available, inexpensive reagents. Omission of HMPA (entry 2) provides the target vinylsilane in moderate yield while avoiding the health and safety concerns associated with this toxic additive. Furthermore, after a brief screening of standard conditions, the allylic alcohol was converted to the corresponding iodide with triphenylphosphine and *N*-iodosuccinimide (Ph_3P/NIS)[12] to afford the title compound (**1**, Scheme 3). The allyl iodide is somewhat unstable to storage, and we have found it most convenient to generate **1** from alcohol **5** immediately prior to use.

In conclusion, we describe a convenient, two-step procedure for preparing vinylsilane **1**. Ready access to the Stork–Jung vinylsilane Robinson annulation reagent (**1**) will be especially valuable for initial screening of the various surrogate reagents for methyl vinyl ketone in chemical synthesis.

Experimental Section

(*E*)-3-Trimethylsilanylbut-2-en-1-ol (5). To an oven-dried, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, reflux condenser, and septum was added isobutylmagnesium chloride (1.8 M in ether, 5.1 mL, 9.2 mmol, 2.3 equiv) under argon. To the Grignard solution was added bis(cyclopentadienyl)titanium dichloride (0.049 g, 0.20 mmol, 0.050 equiv) and the mixture was stirred for 20 min in an ice bath. At this temperature, 2-butyn-1-ol (0.30 mL, 4.0 mmol, 1.0 equiv) in 10 mL of ether was added dropwise in intervals over 10 min. Caution was taken with the addition as a beige-colored heterogeneous mixture formed and the mixture had a tendency to splash. Once the addition was complete, all septa were exchanged for glass stoppers and every joint was greased with silicone lubricant and wrapped with Teflon tape and Parafilm. The milky-brown reaction mixture was allowed to warm to room temperature and then placed into an oil bath and heated at reflux (36–38 °C bath temperature) for 16 h. (Note: A refrigerated circulator was used to chill the water for the condenser.) To the refluxing mixture was added hexamethylphosphoramide (3.2 mL, 18 mmol, 4.6 equiv) in 15 mL of ether dropwise over 10 min via the addition funnel, followed by a dropwise addition of chlorotrimethylsilane (1.5 mL, 12 mmol, 3.0 equiv). The reaction was maintained at reflux for 13 h. The dark brown mixture was cooled in an ice bath and then quenched with the addition of 25 mL of half-saturated ammonium chloride. The biphasic red-orange solution was washed with two 30-mL portions of saturated $NaHCO_3$ solution and the aqueous phase was extracted with two 50-mL portions of ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to leave a deep red oil that was purified by column chromatography on 16 g of silica gel

(12) We also found that displacement of the alcohol with chloride (**5** → **6**) occurs more cleanly with Ph_3P/NCS than with Ph_3P/CCl_4, although at a higher cost. See the Experimental Section.

(gradient elution with 5−20% ethyl acetate in hexanes) to afford 0.43 g (76%) of **5** as a thick, pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.073 (s, 9H), 1.32 (br s, 1H), 1.71 (dt, 3H, J = 1.5, 0.7 Hz), 4.27 (dq, 2H, J = 5.9, 0.6 Hz), 5.88 (tq, 1H, J = 1.7, 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.4, 14.6, 59.5, 137.5, 139.2. IR (neat) (cm^{-1}) 3324 (OH, br), 2954 (s), 1621 (w), 1440 (m), 1404 (m), 1359 (m), 1247 (s), 1066 (s), 1013 (s), 836 (s), 749 (s), 690 (m). MS *m/z* 143.1 [65, M − H]$^+$. CH: Calcd for $C_7H_{16}OSi$: C, 58.27; H, 11.18. Found: C, 58.04; H, 10.88.

((*E*)-3-Iodo-1-methylpropenyl)trimethylsilane (1). (*E*)-3-Trimethylsilanylbut-2-en-1-ol (**5**, 0.20 g, 1.4 mmol, 1.0 equiv) and triphenylphosphine (0.40 g, 1.5 mmol, 1.1 equiv) were weighed into an oven-dried, two-necked, round-bottomed flask equipped with an argon inlet and septum. Methylene chloride (3.5 mL) was added via syringe followed by the addition of *N*-iodosuccinimide (0.34 g, 1.5 mmol, 1.1 equiv, freshly recrystallized from dioxane/carbon tetrachloride). The flask was wrapped in aluminum foil and the reaction mixture was stirred for 1 h in an ice bath and then 3 h at room temperature. When the reaction was complete (as determined by TLC), 5 mL of hexanes were added and the mixture was immediately filtered through 4 g of silica gel with the aid of 200 mL of hexanes. The filtrate was concentrated in vacuo give a thick yellow oil. (Note: Material at this stage was judged to be >95% pure by ^{1}H NMR and was suitable for use.) Subsequent filtration through 2 g of neutral alumina with 100−150 mL of hexanes and concentration in vacuo afforded 0.29 g (82%) of **1** as a pale yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 1.71 (d, 3H, J = 1.7 Hz), 3.93 (d, 2H, J = 8.4 Hz), 6.02 (tq, 1H, J = 6.4, 1.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.5, 1.2, 13.7, 134.2, 143.2. IR (neat) (cm^{-1}) 2954 (s), 1604 (w), 1437 (w), 1247 (s), 1143 (m), 835 (s). MS *m/z* 254.2 [12, M]$^+$.

((*E*)-3-Chloro-1-methylpropenyl)trimethylsilane (6). (*E*)-3-Trimethylsilanylbut-2-en-1-ol (**5**, 0.10 g, 0.69 mmol, 1.0 equiv) and triphenylphosphine (0.20 g, 0.76 mmol, 1.1 equiv) were weighed into an oven-dried, two-necked, round-bottomed flask equipped with an argon inlet and septum. Methylene chloride (3.5 mL) was added via syringe followed by the addition of *N*-chlorosuccinimide (0.10 g, 0.76 mmol, 1.1 equiv, freshly recrystallized from dioxane/carbon tetrachloride). The reaction mixture was stirred for 1 h in an ice bath, and then 4 h at room temperature. When the reaction was complete (as determined by TLC), 2.5 mL of hexanes were added and the mixture was immediately filtered through 2 g of silica gel with the aid of 100 mL of hexanes. The filtrate was concentrated in vacuo to give a thick yellow oil that was filtered through 1 g of neutral alumina with 75−125 mL of hexanes and concentrated in vacuo to afford 0.075 g (66%) of **6** as a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.081 (s, 9H), 1.76 (d, 3H, J = 1.5 Hz), 4.12 (d, 2H, J = 7.3 Hz), 5.89 (tq, 1H, J = 7.3, 1.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.4, 14.6, 59.5. 137.5, 139.3. IR (neat) (cm^{-1}) 2956 (s), 1615 (w), 1442 (w), 1405 (w), 1249 (s). HRMS calcd for $C_7H_{15}ClSi$ 162.0632, found 162.0635.

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Supporting Information Available: General experimental procedures and NMR spectra for compounds **1**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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