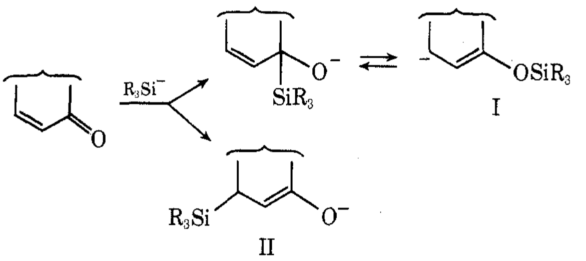
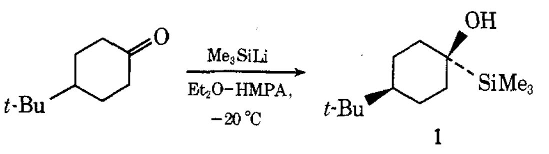
Conjugate Addition of Trimethylsilyllithium. A Preparation of 3-Silyl Ketones

Summary: Trimethylsilyllithium is readily prepared by adding methyllithium to hexamethyldisilane in hexamethylphosphoramide (HMPA); this reagent undergoes rapid 1,4 addition to cyclohexenones at low temperature to give enolates of 3-silyl ketones (II).

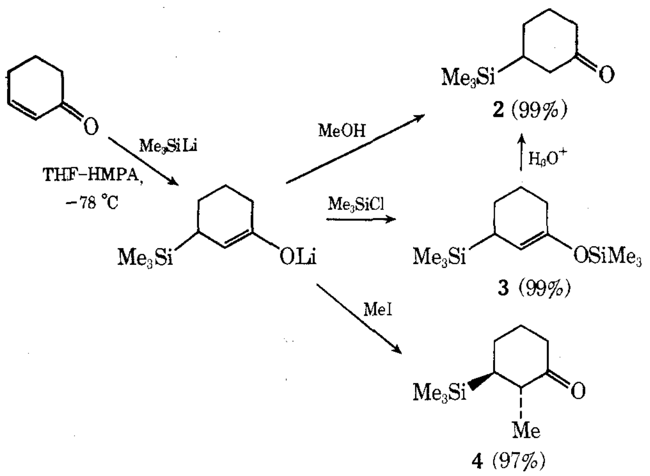
Sir: Since the late 1950's, it has been known that silyl anions[1] undergo smooth addition to a variety of organic electrophiles[2] including ketones, epoxides, and halides. However, we know of no report of the reaction of these reagents with simple α,β-unsaturated carbonyl compounds.[3] The result of such a reaction is of special interest since it could lead via 1,2 addition to an allyloxy carbanion[4] (I) or via 1,4 addition to a regiospecific enolate of a 3-silyl ketone[5] (II). In this communication, we report an extremely convenient preparation of trimethylsilyllithium and a study of its addition to representative α,β-unsaturated ketones.



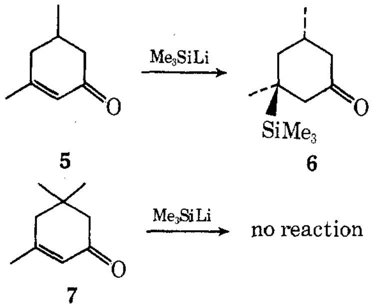
Trimethylsilyl alkali metal compounds have been prepared traditionally by a metal exchange reaction between an alkali metal and bis(trimethylsilyl)mercury.[6] However, the lengthy preparation[7] required for the latter compound and the inherent danger of handling volatile mercury compounds make this route to trimethylsilyl anions unattractive. More recently, cleavage of hexamethyldisilane by sodium or potassium methoxide has been used to prepare trimethylsilylsodium or -potassium.[2d,e] However, the sodium and potassium reagents have been reported[8] to be less effective in addition reactions with carbonyl compounds than the corresponding lithium compounds. We therefore sought a convenient preparation of trimethylsilyllithium. We have found that 1.25 equiv of hexamethyldisilane[9] react rapidly with an equivalent of methyllithium in HMPA (0 °C, 15 min) to produce a deep red solution of trimethylsilyllithium and inert tetramethylsilane (TMS). Utilization of methyllithium appears complete since addition of excess 4-*tert*-butylcyclohexanone to the reagent in ether yields no methylcarbinol. Instead, a single product, the crystalline alcohol **1** (mp 90.5–91.5 °C), is produced. The stereochemistry of **1** is assumed to be that which would result from less hindered equatorial attack by a trimethylsilyl anion.[10] It should be mentioned here that the latter reaction is very sensitive to the nature of the solvent. Replacing ether by tetrahydrofuran, for example, resulted in significant by-product formation.



Addition of 2-cyclohexenone to trimethylsilyllithium in THF–HMPA (5:1) at −78 °C results in immediate disappearance of the red color of the reagent. Quenching with methanol and workup yields the known compound, 3-(trimethylsilyl)cyclohexanone[5d,e] (**2**) as the only product. Alternatively, quenching with trimethylchlorosilane produces the corresponding enol silyl ether[5e] **3**. The intermediate enolate can also be alkylated cleanly by reactive alkyl halides without equilibration. For example, addition of excess methyl iodide to the reaction mixture yields a methylated silyl ketone (spectral data given in experimental procedure) in 97% yield after bulb-to-bulb distillation. TLC, VPC, and NMR indicate this compound to be a single isomer to which the structure **4**[11] has been assigned. The regiochemistry of the alkylation follows from mechanistic considerations and from the observation of a 12% NOE enhancement of the trimethylsilyl grouping (relative to tetramethylsilane) on irradiation of the 2-methyl signal in the NMR.[12] The equatorial nature of the methyl group (and therefore the trans disposition of the two substituents) is indicated by the stability of **4** to epimerizing conditions (NaOMe, MeOH, 1 hr, 25 °C) and by a half-height peak width for each member of the methyl doublet which is only 0.3 hertz broader than tetramethylsilane.[13] Reaction of the intermediate enolate with less reactive halides (e.g., *n*-propyl iodide) gives rise to complex mixtures.

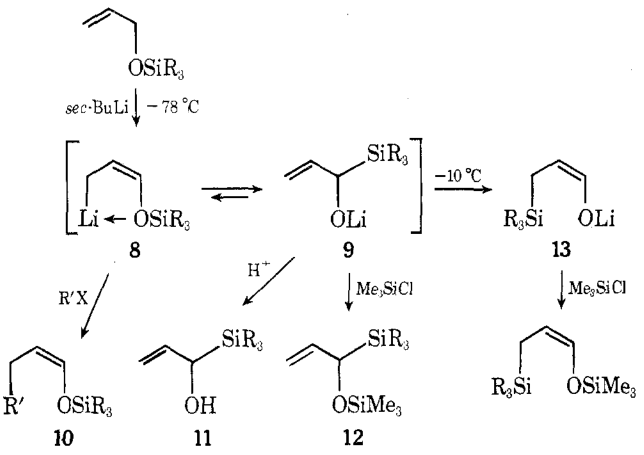


Our results with other enones indicate that the reagent has a strong preference for axial addition. For example, 3,5-dimethyl-2-cyclohexenone (**5**) leads to the silyl ketone **6** [ir (neat) 1712, 1250, 840 (br) cm^{-1}; NMR $\delta^{\mathrm{CDCl_3}}$ 0.99 (3 H, d, J = 6 Hz), 0.97 (3 H, s), −0.02 (9 H, s); MS (70 eV) 183 (parent − CH$_3$)] in 78% yield after column chromatography. The assignment of *cis*-dimethyl stereochemistry is based on the chemical shifts of the two methyl signals in the NMR. While 3-methylcyclohexanone and *cis*-3,5-dimethylcyclohexanone exhibit methyl resonances at δ 1.00, cyclohexanones with β-methyl groups constrained to be axial show signals shifted to higher field (δ 0.75–0.90).[14] Since the methyls in **6** have similar chemical shifts (δ 0.99, 0.97) which are clearly outside the high field range, these substituents have been assigned as cis diequatorial.[15] More support for the axial mode of attack is found in the reaction of trimethylsilyllithium with isophorone (**7**). Unlike the previously described reactions, the addition of isophorone to the silyllithium reagent does not result in disappearance of the red color. Instead, the reaction is incomplete even after 30 min at −78 °C. Quenching and workup as before returns a pale yellow oil which is 90–95% starting material. This result is not unexpected. Although steric effects



for equatorial attack on **5** and **7** are very similar, a severe 1,3-diaxial methyl–trimethylsilyl interaction would be expected to destabilize the transition state for axial addition to isophorone.

Unlike most other conjugate additions, the 1,4 addition of trimethylsilyllithium to enones appears to be a kinetic process since 1,2 adducts like **9** are stable to the reaction conditions reported above (−78 °C). As we reported previously, allyloxy carbanions (**8**) derived from allyl silyl ethers are in rapid equilibrium with the corresponding silyl alkoxide **9**.[4] Such species may be alkylated on carbon to give **10** or they may be protonated or silylated on oxygen to give **11** or **12**. If, however, the allyloxy carbanion reagent is allowed to warm to approximately −10 °C, it undergoes irreversible rearrangement to the silyl enolate **13**.



R = Me, Et

The marked preference for a kinetic 1,4 addition with axial attack is most compatible with an electron-transfer mechanism. Other reagents (R_2CuLi and Li/NH_3) believed to react with enones by electron-transfer processes show similar regiochemistry and stereochemistry.[16,17] Further support for this mechanism is given by a number of reports which indicate that silyl anions are potent one-electron reducing agents.[18] For example, trimethylsilylsodium has been reported to reduce benzophenone and naphthalene to the corresponding radical anions and to effect reductive coupling of alkyl halides.

The following procedure for synthesis of **4** illustrates the preparation and use of the trimethylsilyllithium reagent. A solution of 0.50 ml (2.5 mmol) hexamethyldisilane[9] in 2 ml of anhydrous HMPA was cooled to 0 °C under nitrogen. Ethereal methyllithium (2 mmol) was added via syringe and the resulting deep red solution was stirred for 15 min to complete the preparation of trimethylsilyllithium. Anhydrous THF (10 ml) was added and the solution was immediately chilled to −78 °C. A solution of 144 mg (1.5 mmol) of 2-cyclohexenone in 1 ml of THF was then added dropwise. After stirring an additional 5 min, 0.5 ml of methyl iodide was injected and the mixture was allowed to warm slowly to 0 °C. The reaction mixture was poured into 50 ml of pentane and thoroughly washed with water (2 × 25 ml) to remove HMPA. Drying ($MgSO_4$) and solvent removal gave a colorless oil (308 mg). Kugelrohr distillation (1 mm, oven 80 °C) gave 268 mg (97%) of *trans*-3-trimethylsilyl-2-methylcyclohexanone (**4**): ir (neat) 1710, 1250, 853, 838 cm^{-1}; NMR δ^{CDCl_3} 1.10–2.44 (8 H, m), 1.03 (3 H, d, $J = 6.5$ Hz), 0.6 (9 H, s); MS (70 eV) 184 (15) (parent), 179 (53), 156 (9), 155 (12), 141 (19), 75 (75), 74 (22), 73 (100), 67 (20), 59 (45), 58 (32), 53 (25), 45 (90), 44 (20), 43 (78), 42 (22), 42 (62).

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W. Clark Still

Department of Chemistry, Vanderbilt University,
Nashville, Tennessee 37235

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Facile Reduction of Alkyl Tosylates with Lithium Triethylborohydride. An Advantageous Procedure for Deoxygenation of Cyclic and Acyclic Alcohols

Summary: Lithium triethylborohydride rapidly reduces *p*-toluenesulfonate esters of both cyclic and acyclic alcohols to the corresponding alkanes in excellent yields and is applicable even to tosylates derived from hindered alcohols.

Sir: Deoxygenation of alcohols to the corresponding alkanes, a frequently encountered transformation in synthetic organic chemistry, is usually achieved by the reduction of *p*-toluenesulfonate ester of the alcohol with lithium aluminum hydride.[1] Although this procedure works satisfactorily with relatively unhindered primary alcohols, the results are less favorable for the more hindered alcohols as well as for certain cycloalkanols. In such cases, the yield of the desired alkane