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A Quantitative NMR Method for Silyllithium Analysis

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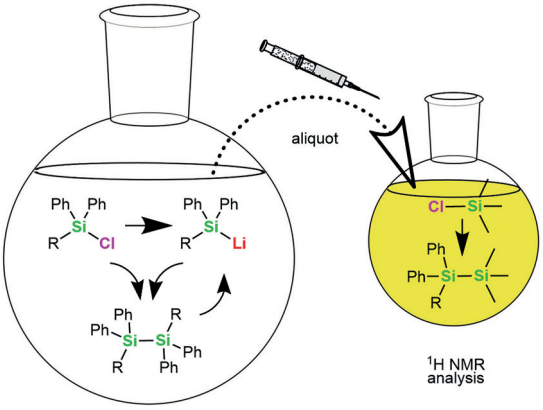

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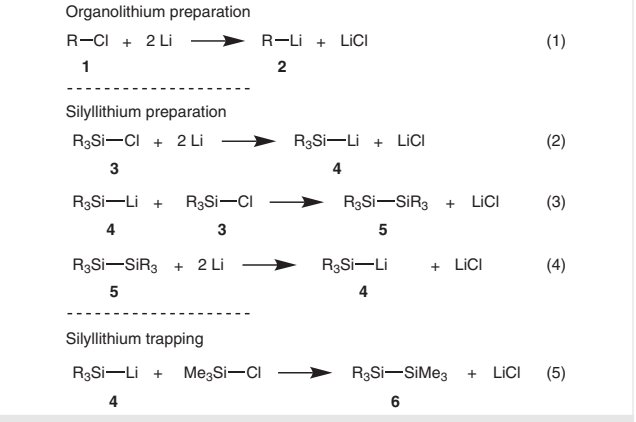
Abstract A rapid and extremely simple method for silyl anion analysis is presented. The progress of silyllithium reagent preparation can be determined by quenching an aliquot with neat chloro(trimethyl)silane, evaporation, dilution with $CDCl_3$, and direct proton NMR analysis. This procedure is fast, simple, and allows for identification and relative quantification of the starting reagent, intermediates, and the silyllithium product.

Key words silicon, lithium, lithiation, organometallic reagents, halogens, hydrides

Silyl anion reagents have received extensive attention[1,2] since Kraus and Eatough first reported their preparation in 1933,[3] and they have enjoyed an expanding use in synthesis. The importance of these reagents is based on the many roles of silicon as a masked hydroxy group,[4–10] an electrophile-directing group,[4] and an α-anion-stabilizing group,[11–13] as well as their use in construction of organosilanes themselves.[14–18] Silyl anion reagents are not available commercially and therefore must be prepared, often immediately before use.

Despite the apparent analogy between the preparations of organolithium and silyllithium reagents from the corresponding chlorides, the latter preparation is more complicated (Scheme 1). The preparation of organolithium reagents from the halide (Scheme 1, equation 1) begins with two electron transfers at the metal surface to the halide, leading directly to the organometallic.[19] When these reactions are conducted with very reactive halides such as benzyl or allyl chlorides, significant coupling can occur, leading to a terminal dimeric byproduct.[20–22] Similarly, during the conversion of a chlorosilane **3** into a silyllithium **4** (Scheme 1, equation 2), the initially formed silyllithium **4** rapidly reacts with the starting chlorosilane **3** to form a disilane **5** (Scheme 1, equation (3). In a subsequent step, disilane **5** undergoes reduction to give the silyllithium reagent **4** (Scheme 1, equation 4).[23,24] The reduction of disilane **5** is often slower than reduction of chlorosilane **3**.[23] The heterogeneous nature of this reaction and the difficulty in ascertaining its end point prompted us to consider options for determining the stage of this conversion.



Scheme 1 Conversion of a chlorosilane to a silyllithium reagent is more complicated than the corresponding carbon version. Trapping of the silyllithium product with TMSCl yields a stable derivative.

In general, only phenyl-substituted silanes are used when silyllithium reagents are prepared from a chlorosilane, because in the absence of the phenyl group, the dimer **5** does not undergo reductive cleavage. In addition to chlorosilanes, fluorosilanes[25] and hydridosilanes[16,26,27] can also be used to prepare phenyl-substituted silyllithium reagents, and we have recently revisited the lithium reduction of alkoxysilanes as a route to silyllithium reagents.[28] Dimer **5** is believed to play a role in these syntheses as well.

The two-stage reaction sequence for silyl anion formation, with its slower second reduction step, makes determination of the reaction status important. Depending on the starting silane, the reaction scale, the lithium source, the metal surface area, and the procedure used for cleaning the metal surface, we have found that the time required for complete conversion of a starting silane into a silyllithium reagent can vary from hours to days. Direct titration of the silyllithium solutions is often limited to total base, or one can use the classic, but rather laborious, double-titration method.[29–31] The double-titration method is more complex for organosilanes than for organolithium reagents, a situation eloquently discussed by Fleming and co-workers.[24,32] ^{29}Si NMR spectroscopy can also be used to follow the course of silyllithium formation,[33–35] but this technique is not routinely available in many laboratories. The use of silyllithium reagents is often conducted with an excess of the reagent, but this is wasteful and potentially expensive.

We report here a straightforward and effective ^{1}H NMR method for evaluating the progress of a silyllithium preparation. This procedure involves addition of an aliquot of the reaction mixture to neat chloro(trimethyl)silane, which rapidly converts any silyl anions into the corresponding trimethylsilyl-terminated disilane, (Scheme 1, Equation 5). The resulting mixture is evaporated and analyzed by ^{1}H NMR spectroscopy.[36,37]

When this technique is used, at any given point during the reaction there are only three possible components, **3**, **5**, and **6**, in the product mixture, and generally only two of these are observed. In the ^{1}H NMR spectrum of **6**, the nine-proton trimethylsilyl singlet is cleanly separated from other signals, including other methyl groups on phenyl-substituted silanes, and it can be integrated accurately. For example, the ^{1}H NMR methyl singlets for R_3Si = $PhMe_2Si$ have chemical shifts of δ = 0.61 (**3**, X = Cl), 0.35 (**5**), and 0.38 and 0.10 ppm (**6**); when R_3Si = Ph_2MeSi, the singlets appear at δ = 0.87 (**3**, X = Cl), 0.69 (**5**), and 0.59 and 0.15 ppm (**6**).[38–40]

The application of this protocol to chloro(methyl)diphenylsilane **7** is illustrated in Figure 1. When we stirred a solution of **7** in THF at ambient temperature with a suspension of lithium metal shot, cleaned by using the Fleming procedure,[16,24] and we analyzed an aliquot of the mixture, we found that all of the chlorosilane had been consumed in less than an hour, and the solution contained almost exclusively the dimer **8**, with a trace of the TMS-capped silyl anion product **9**.[41,42] After 90 minutes, a TMSCl-quenched aliquot contained approximately a 1:3 mixture of the disilane **8** and product **9**. After an additional hour, the reaction was essentially complete, with **9** being almost exclusively produced from quenching of the aliquot. This is seen clearly in the NMR spectra, and is also illustrated in the first graph. Repetition of this experiment under identical conditions with fluoro(methyl)diphenylsilane gave a similar result, but required more than six hours for the reaction to run to completion (second graph, see Supporting Information for progressive aliquots of this reaction).

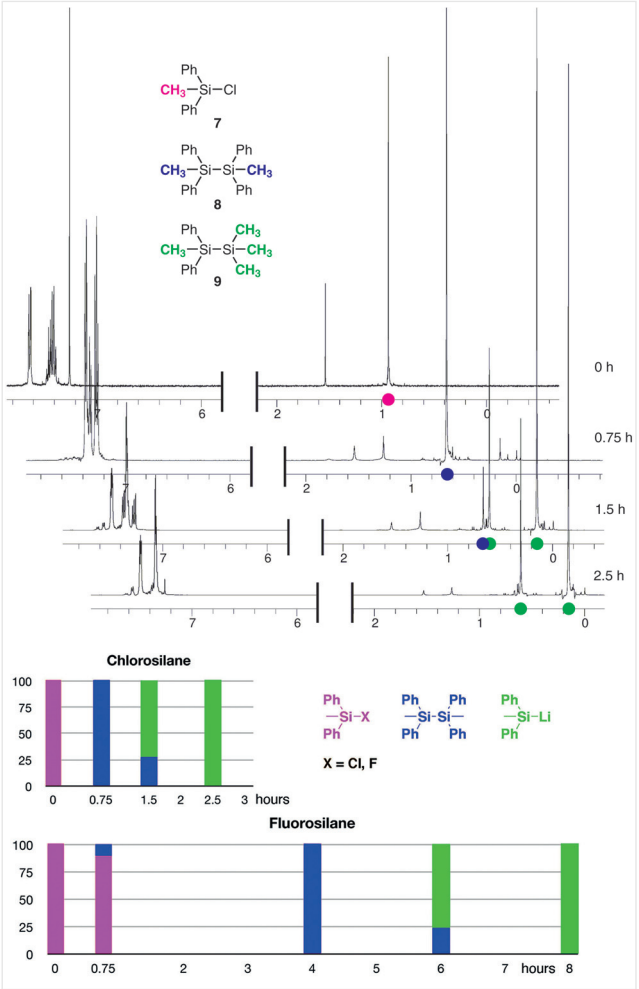


Figure 1 Reaction progress for conversion of choro- and fluoro(methyl)diphenylsilane to the corresponding lithium reagents, determined by 500 MHz ^{1}H NMR spectroscopy

The application of this procedure to hydridosilane **10** is shown in Figure 2. In this case the disappearance of starting **10** can be followed by monitoring the single hydrogen on silicon at δ = 4.9 ppm (triplet), however, this coupled proton signal is much less prominent than the trimethylsilyl signal at δ = 0.17 ppm for the TMS-capped product **11**, formed from the silyl anion.[43] It is noteworthy that the chemical shifts of the signals for the methoxymethyl protecting group are not greatly affected by this reaction sequence and cannot be used to monitor progress. Of additional note, for this particular reaction, little or no evidence for a disilane intermediate was observed.

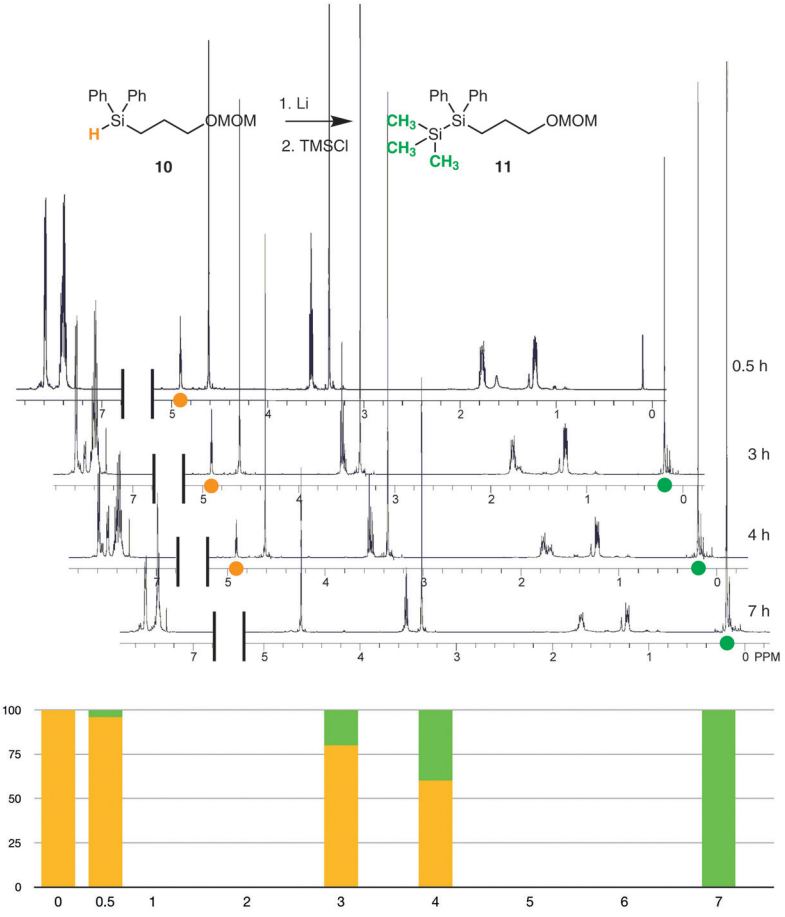


Figure 2 Monitoring the conversion of silane **10** into the corresponding lithium reagent (500 MHz ^{1}H NMR)

As the application of silyl anion chemistry continues to expand, we believe this simple experimental technique will provide a useful protocol for monitoring these key intermediates.

The examples described here were run on a relatively small scale (1 mmol in 3.3 mL of solvent) and the aliquots used were arbitrarily set at 0.2 mL. The signal-to-noise ratio of the nine-proton trimethylsilyl singlet in the product suggests that much smaller analysis aliquots might provide high-quality data on the progress of a reaction.

The simple protocol described here, illustrated with three different substrates, permits rapid and quantitative monitoring of the progress of silyl anion formation. Three reducible groups on silicon are used: chloro, fluoro, or hydrido. Monitoring a reaction by ^{1}H NMR using a nine-proton TMS monitoring group results in a very sensitive analytical method. The rapid reaction of anions with chloro(trimethyl)silane allows the use of a five-minute reaction time and thus provides a fast reaction analysis. We have found this method to be extremely useful in our studies,[28] and we expect that others will as well.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590902.

References and Notes

(1) Lee, V. Ya.; Sekiguchi, A. *Organometallic Compounds of Low-Coordinate Si-, Ge-, Sn- and Pb: From Phantom Species to Stable Compounds*; Wiley: New York, **2010**.
(2) Singer, R. D. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, **2002**.
(3) Kraus, C. A.; Eatough, H. *J. Am. Chem. Soc.* **1933**, *55*, 5008.
(4) Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 1872.
(5) Krohn, K.; Khanbabaee, K. *Angew. Chem. Int. Ed.* **1994**, *33*, 99.
(6) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, *64*, 6005.
(7) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859.

(8) Tenenbaum, J. M.; Woerpel, K. A. *Org. Lett.* **2003**, *5*, 4325.
(9) Powell, S. A.; Tenenbaum, J. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 12648.
(10) Fleming, I.; Winter, S. B. D. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 2687.
(11) Itami, K.; Mitsudo, K.; Yoshida, J.-i. *Angew. Chem. Int. Ed.* **2001**, *40*, 2337.
(12) Li, L.; Navasero, N. *Org. Lett.* **2004**, *6*, 3091.
(13) James, P.; Landais, Y. *Org. Lett.* **2004**, *6*, 325.
(14) Hernández, D.; Mose, R.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 732.
(15) Hernández, D.; Lindsay, K. B.; Nielsen, L.; Mittag, T.; Bjerglund, K.; Friis, S.; Mose, R.; Skrydstrup, T. *J. Org. Chem.* **2010**, *75*, 3283.
(16) Nielsen, L.; Skrydstrup, T. *J. Am. Chem. Soc.* **2008**, *130*, 13145.
(17) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035.
(18) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403.
(19) Wardell, J. L. In *Comprehensive Organometallic Chemistry*, Vol. 1; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: Oxford, **1982**, Chap. 2, 43.
(20) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1955**, *77*, 3134.
(21) Gilman, H.; Schwebke, G. L. *J. Org. Chem.* **1962**, *27*, 4259.
(22) Seyferth, D.; Weiner, M. A. *J. Org. Chem.* **1961**, *26*, 4797.
(23) George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403.
(24) Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 1209.
(25) Sen, S.; Purushotham, M.; Qi, Y.; Sieburth, S. McN. *Org. Lett.* **2007**, *9*, 4963.
(26) Milligan, J. G.; Kraus, C. A. *J. Am. Chem. Soc.* **1950**, *72*, 5297.
(27) Gilman, H.; Dunn, G. E. *J. Am. Chem. Soc.* **1951**, *73*, 5077.
(28) Bo, Y.; Singh, S.; Duong, H. Q.; Cao, C.; Sieburth, S. McN. *Org. Lett.* **2011**, *13*, 1787.
(29) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin. Trans. 1* **1981**, 2527.
(30) Brook, A. G.; Gilman, H. *J. Am. Chem. Soc.* **1954**, *76*, 278.
(31) Gilman, H.; Klein, R. A.; Winkler, H. J. S. *J. Org. Chem.* **1961**, *26*, 2474.
(32) Fleming, I.; Roberts, R. S.; Smith, S. C. *Tetrahedron Lett.* **1996**, *37*, 9395.
(33) Krempner, C.; Chisholm, M.; Gallucci, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 410.
(34) Gaderbauer, W.; Balatoni, I.; Wagner, H.; Baumgartner, J.; Marschner, C. *Dalton. Trans.* **2010**, *39*, 1598.
(35) Zirngast, M.; Flock, M.; Baumgartner, J.; Marschner, C. *J. Am. Chem. Soc.* **2009**, *131*, 15952.
(36) **[Methyl(diphenyl)silyl]lithium from Chloro(methyl)diphenylsilane; Typical Analytical Procedure**
To a round-bottomed flask containing Li shot (41 mg, 5.9 mmol) under argon, cooled to 0 °C, was added TMSCl (0.1 mL, 0.79 mmol) in THF (2 mL), and the mixture was stirred for 30 min. The solution was removed by syringe, and the Li was washed with THF (3 × 1 mL). A solution of chloro(methyl)diphenylsilane (197 mg, 0.85 mmol) in THF (3.3 mL) was then added dropwise to the cleaned lithium shot. At intervals, aliquots (0.2 mL) of the solution were removed by syringe and added to a round-bottom flask containing chlorotrimethylsilane (0.1 mL, 0.79 mmol, ca. 16 equiv) at r.t. After mixing for 5 min, the mixture was concentrated in vacuo, taken up in $CDCl_3$ (1 mL), filtered through cotton and analyzed by ^1H NMR spectroscopy (see Ref. 44).
(37) Reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Alfa Aesar, or Acros Organics. Lithium (granular, 99% trace-metals basis) was purchased from Aldrich (catalogue number: 499811). Most silicon reagents were purchased from Gelest Inc. Reaction solvents were taken from a Grubbs-style Solvent Dispensing System purchased from Glass Contour or they were distilled as described in the literature.[45] Silica gel (60 Å, 170–400 mesh) or basic alumina (50–200 micron, activated) was used for flash column chromatography. Analytical TLC was performed on Analtech Uniplate Silica Gel GF (250 micron) precoated glass plates. Spots were detected by UV, iodine, or phosphomolybdic acid solution.
(38) Herzog, U. *J. Prakt. Chem.* **2000**, *342*, 379.
(39) Hosomi, A.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 248.
(40) Kashimura, S.; Ishifune, M.; Yamashita, N.; Bu, H.-B.; Takebayashi, M.; Kitajima, S.; Yoshiwara, D.; Kataoka, Y.; Nishida, R.; Kawasaki, S.-i.; Murase, H.; Shono, T. *J. Org. Chem.* **1999**, *64*, 6615.
(41) Gilman, H.; Lichtenwalter, G. D. *J. Am. Chem. Soc.* **1958**, *80*, 608.
(42) **1,1,1,2-Tetramethyl-2,2-diphenyldisilane (7)**
Granular Li shot [8 mg, 5.4 mmol, 6 equiv, in mineral oil (Aldrich)] was washed three times with hexane and transferred to a 25 mL round-bottomed flask fitted with a septum. The flask was evacuated and then filled with argon three times. THF (2 mL) was added, and the mixture was cooled to 0 °C. TMSCl (0.1 mL) was then added, the mixture was stirred for 30 min, and the solution was removed by syringe. The cleaned lithium shot was washed with THF (3 × 1 mL). A solution of methyl(diphenyl)silane (180 mg, 0.91 mmol) in THF (3 mL) was added, and the mixture was stirred at 0 °C for 8 h. To this mixture was added TMSCl (1.5 mL) and, after 5 min, the mixture was concentrated. Flash column chromatography (100:1 hexanes–EtOAc) gave a clear colorless oil; yield: 174 mg (71%).
(43) **1-[3-(Methoxymethoxy)propyl]-2,2,2-trimethyl-1,1-diphenyldisilane (11)**
Granular lithium shot [87 mg, 12.5 mmol, 14 equiv, in mineral oil (Aldrich)] was washed three times with hexane then transferred to a 25 mL round-bottomed flask fitted with a septum. The flask was evacuated and then filled with argon three times. THF (6 mL) was added, and the mixture cooled to 0 °C. TMSCl (0.3 mL) was then added, the mixture was stirred for 30 min, and the solution was removed by syringe. The cleaned lithium shot was washed with THF (3 × 3 mL). A solution of [3-(methoxymethoxy)propyl](diphenyl)silane (**10**; 259 mg, 0.90 mmol) in THF (3.0 mL) was added, and the mixture was stirred for 9 h. The solution was decanted and washed with H_2O. The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organics were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (gradient 100:1 to 10:1 hexanes–EtOAc) gave a clear, colorless oil; yield: 214 mg (60%); R_f = 0.53 (4:1 hexanes–EtOAc).
IR (neat): 3067, 2947, 2086, 1954, 1428 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.50 (m, 4 H), 7.32–7.37 (m, 6 H), 4.60 (s, 2 H), 3.50 (t, J = 6.6 Hz, 2 H), 3.34 (s, 3 H), 1.64–1.73 (m, 2 H), 1.17–1.24 (m, 2 H), 0.17 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.3, 135.4, 128.9, 128.0, 96.5, 70.7, 55.3, 25.1, 9.1, –1.1. HRMS: m/z $[M + NH_4]^+$ calcd for $C_{20}H_{34}NO_2Si_2$: 376.2123; found: 376.2123.
(44) Okinoshima, H.; Weber, W. P. *J. Organomet. Chem.* **1978**, *149*, 279.
(45) Armarego, W. L.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 6th ed.; Butterworth-Heinemann: Oxford, **2009**.