Studies on the 1,2-Brook Rearrangement of Bissilyl Ketones

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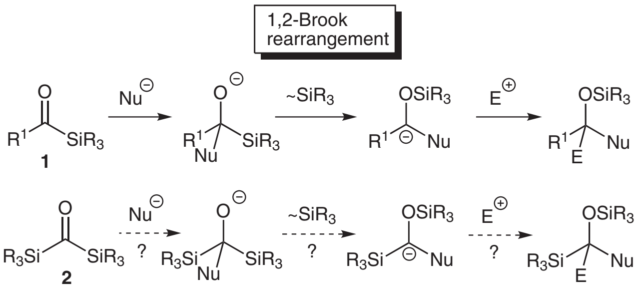
Abstract: The first 1,2-Brook rearrangements with bis(dimethylphenylsilyl) ketone, initiated after addition of different C- and S-nucleophiles, are described. The resulting, newly formed carbanion can be trapped with electrophiles thus paving the way for utilizing bissilyl ketones as formyl dianion equivalents in the future.

Key words: Brook rearrangement, bissilyl ketones, formyl anion, organolithium species, silyl migration

The intramolecular 1,2-anionic migration of a silyl group from a carbon atom to an oxygen atom is called the 1,2-Brook rearrangement.[1,2] In fact, the migratory aptitude of silyl groups comprises a family of [1,n]-carbon to oxygen silyl migrations (Scheme 1). The Brook as well as the retro-Brook rearrangements have found increasing use in organic synthesis.



Scheme 1 The 1,2-Brook rearrangement of acylsilanes and bissilyl ketones

Acylsilanes **1** are common precursors for 1,2-Brook rearrangements since nucleophiles such as organometallics smoothly add to the carbonyl group followed by silyl migration furnishing a carbanion that can be trapped electrophilically. Indeed, this process holds particular attraction because unusual carbanions can be generated without performing a deprotonation step. So far, bissilyl ketones **2** have very rarely been studied despite the fact that potentially the 1,2-Brook rearrangement can be exploited twice. Thus, ketones like **2** can be regarded as dianion equivalents based on formaldehyde.

Bis(triphenylsilyl) ketone and bis(trimethylsilyl) ketone have first been reported by Brook[3] and Ricci,[4] respectively. Later, Narasaka et al. described bis(dimethylphenylsilyl) ketone **7**.[5a] All these ketones show unusual spectroscopic properties which are already evident from their bright pink color.[5,6] For example, the carbon atom of **7** shows an extreme paramagnetic signal shift ($\delta = 318$ ppm). These data and density functional calculations (B3LYP, 6-31 G*) of bis(trimethylsilyl) ketone suggest that the energy difference (HOMO/LUMO) for the n,π* electron transfer ($\lambda_{max} = 513$ nm) is much smaller than for the carbon analogue (hexamethyl acetone)[7] for which a pronounced energy rise of the HOMO is expected to be responsible. The ^{17}O NMR and ^{13}C NMR chemical shifts, photon spectroscopy, and the pink color of bis(trimethylsilyl) ketone, further confirm this argument.[6] Due to the high energy of the n-orbital (HOMO) they are easily oxidized by oxygen.[3,4,6] Moreover, the density functional calculations provided an electrostatic charge at the carbonyl carbon of –0.005 (+0.122 for hexamethyl acetone) clearly indicating a low degree of carbonyl polarization for the bissilyl ketones. This is supported by an extended bond length (1.235 Å vs. 1.220 Å) and a reduced IR vibration frequency (1657 cm^{-1} vs. 1767 cm^{-1}).[7]

All these facts should have an impact on their chemical behaviour, for which only limited data are available. Thus, they have been subjected to the Peterson olefination using trimethylsilylmethyl-Grignard forming the addition product followed by elimination due to potassium hydride.[5a,b] *n*-Butyllithium adds to bissilyl ketones in a 1:1 mixture of addition and reduction product while treatment with alkyl Grignard reagents only affords the reduced carbinols.[5a,b] Addition of electron-deficient, 1,2-disubstituted alkynes in the presence of Pd(0) leads to the corresponding *Z*-configured 1,2-bissilyl alkenes.[5c] So far, additions of nucleophiles to bissilyl ketones followed by 1,2-Brook rearrangements have not been reported. Therefore, we planned to expand our ongoing research on cascade reactions based on Brook rearrangements as key steps[8] to bissilyl ketones, which is presented in this preliminary study.

We chose bis(dimethylphenylsilyl) ketone **7** as starting point for these studies which we prepared by a modified Narasaka protocol.[5a] We altered the preparation of dithioacetal **5** by conducting bissilylation in a sequential manner. Thus, monosilylated dithiane **4** was first isolated and then subjected to a second silylation step (Scheme 2). Although this procedure is lengthier it offers access to nonsymmetric bissilyl ketones. In the following the resulting bissilyldithioacetal **5** was subjected to transacetalization, which was necessary because bissilyl ketone **7** could only

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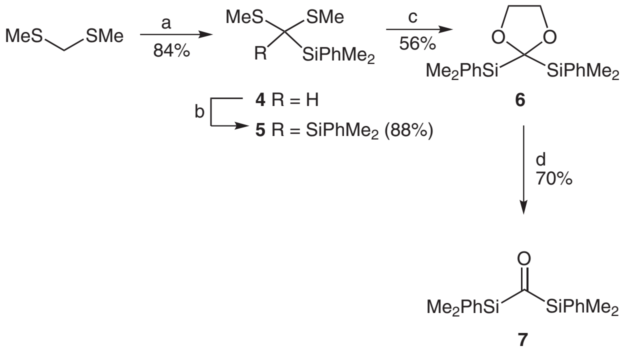
efficiently be accessed from acetal **6** and not directly from dithioacetal **5**. This is due to the fact that dithioacetal hydrolysis commonly proceeds under oxidative conditions.



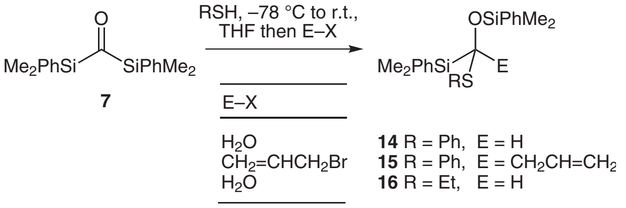
Scheme 2 Preparation of pink bis(dimethylphenylsilyl) ketone **7**. *Reagents and conditions*: a) *n*-BuLi, THF, $ClSiPhMe_2$; b) HMPA, *n*-BuLi, THF, $ClSiPhMe_2$; c) I_2, $HO(CH_2)_2OH$; THF d) $AcOH–H_2O$ (4:1).

With a sufficient amount (gram scale) of **7** in hand, we investigated the reactivity towards nucleophiles. We initially examined the addition of methyllithium reckoning that the steric bulk around the carbonyl group and the electronic properties exerted by the two dimethylphenylsilyl groups could promote the silicon shift,[9] which would be in analogy to simple acylsilanes.[10]

Thus treatment of **7** with methyllithium at –78 °C and gradually warming to room temperature overnight gave a 2:1 mixture of silyl ether **8** and the simple addition product **9** in 40% yield (Scheme 3). Importantly, the desired 1,2-Brook rearrangement had taken place in the aftermath of the nucleophilic attack. Taking into consideration that the Brook rearrangement could be facilitated by the presence of a negative-charge-stabilizing group,[11] we investigated the reaction of **7** with phenyllithium. Indeed, after one hour at –78 °C, we observed the formation of silyl ether **10** along with the addition product **13** in 85% yield (ratio **10**/**13** = 2:1). In order to further demonstrate that the newly formed carbanion α to the siloxy group had formed, we added methyl iodide to the reaction which gave a 1:1 mixture of silyl ether **11** and byproduct **13** in 20% yield.

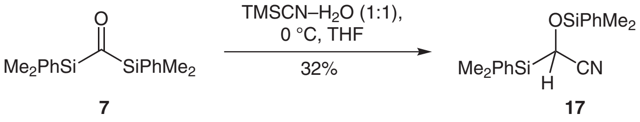
When allyl bromide was added instead of methyl iodide the pure product **12** was obtained in 22% yield.

Thiols like thioethanol and thiophenol turned out to be equally well suited as nucleophiles (Scheme 4). Using thiophenol under standard conditions a 2:1 mixture of the rearranged product **14** and the corresponding addition product was obtained in 80% yield whilst the pure product **15** could be isolated in 40% yield when the intermediate carbanion was trapped with allyl bromide. Employing thioethanol under standard conditions silyl ether **16** was formed in 88% yield.



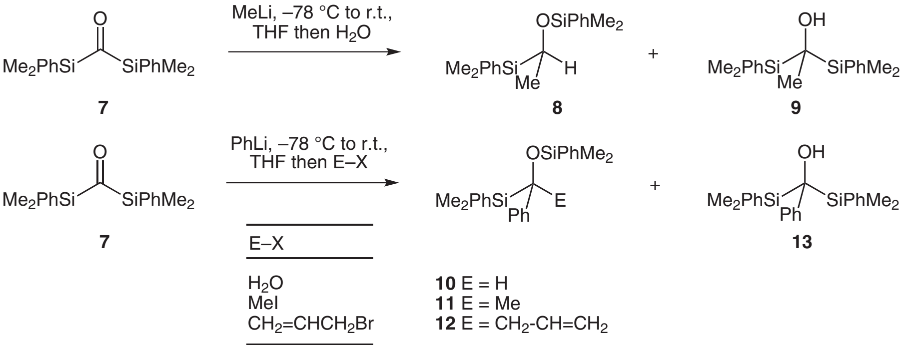
Scheme 4 Reaction of bissilyl ketone **7** with S-nucleophiles

Additionally, we tested cyanide as nucleophile, which could only successfully be used when TMSCN was chosen (Scheme 5). Within 30 minutes at 0 °C the pink color disappeared and rearranged product **17** was formed and finally isolated in 32% yield. Surprisingly, the reaction only proceeded when equimolar amounts of water were added.

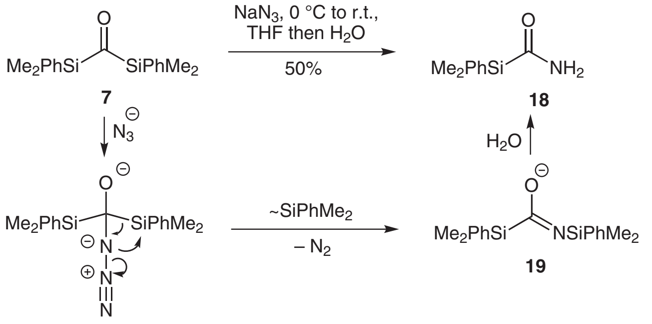


Scheme 5 Reaction of bissilyl ketone **7** with cyanide as nucleophile

Finally, the unexpected dimethylphenylsilyl formamide **18** was isolated when NaN_3 was employed as nucleophile. A possible mechanism of its formation is depicted in Scheme 6. After nucleophilic azide attack, an aza-Brook rearrangement[12] occured which is driven by expulsion of nitrogen. Subsequent hydrolysis of labile intermediate **19** yielded amide **18**.



Scheme 3 Reaction of bissilyl ketone **7** with organolithium agents



Scheme 6 Reaction of bissilyl ketone **7** with azide as nucleophile

Importantly, other nucleophiles like phosphines, amines, isonitriles or alkoxides did not react or led to complete decomposition of **7** under the optimized conditions. Also other C-nucleophiles like organoalkynes or exchange of lithium by Na, K, Cu(I) did not give improved results. This is a clear indication that the carbonyl group in bissilyl ketones shows an altered polarity with reduced reactivity towards nucleophiles.

Finally, it must be noted, that yields refer to isolated yields. These were reduced as purification was hampered by the presence of byproducts such as the hydrolysis product of **7**[13] and 1,2-addition products like **9** that both showed similar polarity to the Brook rearrangement products.

In conclusion, we report the first 1,2-Brook rearrangements with bissilyl ketones like **7**, which is initiated after addition of different C- and S-nucleophiles. The resulting, newly formed carbanion can be trapped with electrophiles. Despite the fact that the carbonyl group in **7** showed reduced reactivity compared to acyl silanes, these studies can pave the way for utilizing bissilyl ketones as formyl dianion equivalents in the future.

Preparation of Dimethylphenylsilylbis(methylthio)methane (4)
To a solution of bis(methylthio)methane **3** (5 g, 46.30 mmol) in dry THF (115 mL), *n*-BuLi (2.5 M in hexane, 18.5 mL, 46.30 mmol) was added at –50 °C, and the solution was stirred at this temperature for 1 h under argon. Then it was warmed up to –25 °C and stirred for additional 2 h. Chlorodimethylphenylsilane (7 g, 42.0 mmol) was added at –78 °C, and then the mixture was stirred again for 2 h at –25 °C and at 0 °C overnight. The mixture was hydrolyzed with sat. aq NH_4Cl and the aqueous layer was extracted (3×) with Et_2O. The combined organic extracts were washed with sat. aq NaCl and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude material was purified by bulb-to-bulb distillation under vacuum ($1.9\cdot10^{-2}$ bar, bp 145 °C) to afford product **4** as a deep violet liquid (9.4 g, 38.80 mmol; 84%).

Preparation of bis(dimethylphenylsilyl)bis(methylthio) mehane (5)
To a solution of dimethylphenylsilyl-bis(methylthio)methane **4** (9.4 g, 38.80 mmol) and freshly distilled HMPA (8.1 mL, 46.70 mmol) in dry THF (122 mL), *n*-BuLi (2.5 M in hexane, 15.8 mL, 39.60 mmol) was added at –50 °C, and the solution was stirred at this temperature for 1 h under argon. Then it was warmed to 0 °C and stirred for 1 h. Chlorodimethylphenylsilane (6.5 mL, 38.80 mmol) in dry THF (19.5 mL) was added at 0 °C. After stirring for 1 h at 0 °C and then at r.t. for 1 h, it was hydrolyzed with sat. aq NH_4Cl and the aqueous layer was extracted (3×) with Et_2O. The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude material was purified by bulb-to-bulb distillation under vacuum ($9.3\cdot10^{-3}$ bar, bp 145 °C) to afford product **5** as a dark orange liquid (12.9 g, 34.3 mmol; 88%).

Preparation of 2,2-bis(dimethylphenylsilyl)-1,3-dioxolane (6)
Iodine (8.3 g, 32.80 mmol) was dissolved in a mixture of THF (50 mL) and ethylene glycol (23 mL) at r.t. To this mixture, a solution of bis(dimethylphenylsilyl)bis(methylthio)methane **5** (3.4 g, 9.00 mmol) in THF (15 mL) was added at r.t. under argon. After 1 h, excess of I_2 was reduced by adding sat. aq $Na_2S_2O_3$ (50 mL) and borax (0.025 M $Na_2B_4O_7$, 50 mL). The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine and dried (K_2CO_3). The solvent was evaporated under reduced pressure, and the crude material was purified by chromatography on SiO_2 (PE–EtOAc, 99:1) to give product **6** as pale yellow crystals (1.7 g, 4.97 mmol; 56%).

Preparation of bis(dimethylphenylsilyl) ketone (7)
To a solution of 2,2-bis(dimethylphenylsilyl)-1,3-dioxolane **6** (1.2 g, 3.39 mmol) in degassed AcOH (12 mL), degassed H_2O (3 mL) was added dropwise at 50 °C under argon. After stirring at 70 °C for 1 h, degassed H_2O (12 mL) was added. Pink crystals were formed after cooling to 0 °C overnight. The precipitate was filtered under argon in vacuum in a Schlenk apparatus and washed with degassed H_2O. Pure crystals of bis(dimethylphenylsilyl) ketone **7** (707 mg, 2.37 mmol; 70%) were obtained after drying under high vacuum for 5–6 h at r.t. The material was stored at 0 °C in a glove box.

General Procedure for the Reaction of Bissilyl Ketone 7 with Nucleophiles Followed by Addition of Electrophiles
Bis(dimethylphenylsilyl) ketone **7** (55 mg, 0.18 mmol) was introduced in a dry flask under argon and vacuum working in the glove box. Degassed dry THF (1.3 mL) was added, and the resulting solution was cooled to –78 °C. Then, the nucleophile (0.18 mmol) was added dropwise, and the pink solution gradually turned to yellow. After stirring at –78 °C for 1 h, the mixture was allowed to warm to 0 °C, and stirring was continued for 1 h. Then, the electrophile (0.36 mmol) was added and, after 1 h at 0 °C, the mixture was stirred overnight at r.t. It was diluted with hexane and passed through a pad of SiO_2 in order to remove inorganic salts. The solvent was evaporated under reduced pressure and the crude mixture was purified by chromatography on SiO_2 (PE–EtOAc, 99:1).

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