α-Alkyl-α-aminosilanes: Synthesis via Alkylation and Hydrosilylation

Scott McN. Sieburth,* Joseph J. Somers, Heather K. O'Hare and Gregory W. Hewitt
Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400, USA

The readily available aminomethylsilanes can be utilized to prepare the less available α-alkyl-α-aminosilanes. Versatile *t*-butoxycarbonyl (Boc) derivatives can be metalated between nitrogen and silicon, and then alkylated by an electrophile at this position. Two alternative procedures were also developed, including an aza-reverse-Brook rearrangement of metalated *N*-silylcarbamates and hydrosilylation of *N*-alkenylcarbamates.

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INTRODUCTION

Organosilanes are intrinsically non-natural; only silicon–oxygen and silicon–fluorine bonds are found in the natural environment. Biologically active organosilanes have therefore generated considerable interest, and this area has been extensively reviewed.[1,2] A few organosilanes have proved to be highly efficacious and the fungicidal flusilazole **1**[3] and insecticidal silafluofen **2**[4] (Fig. 1) are now sold commercially for crop protection.

Several significant α- and β-aminosilanes have been described, such as the aminomethyltrialkylsilanes **3**,[5,6] silaplatin **4**,[7] and sila-procyclidine **5** (Fig. 2).[8] The aminomethylsilanes **3**, including the simplest member **3a**, are

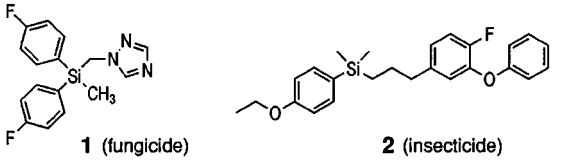

Figure 1 Commercial organosilanes flusilazole **1** and silafluofen **2**.

effective inhibitors of monoamine oxidase enzymes. In the case of **3b**, this molecule is selective for monoamine oxidase-B, making it a candidate for therapy of neurodegenerative disease.[6] The *cis*-platin analog **4** has demonstrated activity against a variety of tumors *in vivo*, including *cis*-platin-resistant strains.[7] Silanol **5** is a potent and selective muscarinic antagonist.[8]

α-Aminosilanes are also synthetic intermediates: they are precursors (via desilylation) of ammonium[9] and iminium ylids[10,11] leading to rearrangement and cycloaddition chemistry (Fig. 3).

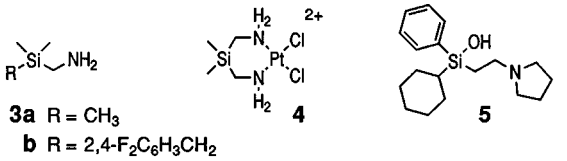

Figure 2 Biologically active α- and β-amino-organosilanes.

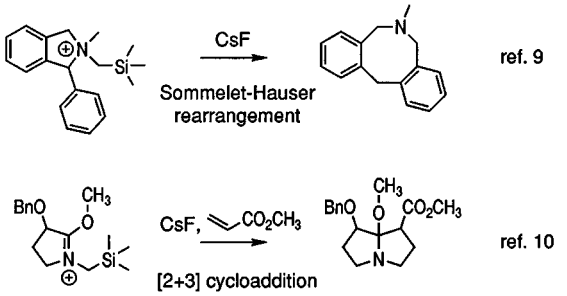

Figure 3 Rearrangement and cycloaddition reactions involving α-aminosilanes.

* Author to whom correspondence should be addressed.

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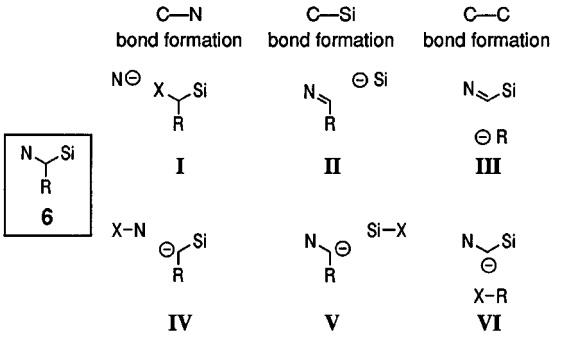

Figure 4 Possible ionic disconnections leading to α-alkyl-α-aminosilanes.

We are exploring synthetic approaches to α-aminosilanes, with the objectives of achieving generality, particularly with regard to silicon and nitrogen substitution, and also substitution *between* nitrogen and silicon. Strategically, three different bond disconnections can be considered for the functional array **6**, and the ionic intermediates associated with these disconnections are shown in Fig. 4.[12] Among these, disconnection **I** is currently the most widely used method, and the displacement of a leaving group adjacent to silicon (chloride,[13, 14] triflate[9, 11]) has been used to prepare a variety of aminomethyltrialkylsilanes. Approach **V** has been exemplified in studies of the metalation chemistry of amine derivatives by Meyers[15] and by Beak.[16, 17] Methods related to disconnections **II**, **III**, **IV** and **VI** have seen little development.

Generally, the synthesis of α-aminosilanes has been limited to amino*methyl*silanes because chloromethylsilanes are commercially available, a typical example of this chemistry being the Gabriel synthesis of aminomethyltrimethylsilane[13] (Fig. 5, Eqn [1], a type **I** synthesis). Additional methods leading to α-aminosilanes are shown in Fig. 5, Eqns [2]–[5]. A type **V** approach employing metalation of a Boc-derivatized amine followed by reaction with a chlorosilane, largely restricted to secondary amine derivatives,[18] is shown in Eqn [2].[17] Tertiary amides, both aromatic and aliphatic, are reduced by trichlorosilane with formation of α-aminotrichlorosilane products (Eqn [3]).[19] Rearrangement of *N*-trialkylsilylammonium ylides leads to α-amino-α-cyanotrimethylsilanes.[20] The chemistry shown in Eqns [3] and [4] is limited to the preparation of tertiary amines. An interesting case is found in the chemistry of the symmetric 2,3-bis(trimethylsilyl)cyclopropanone (Eqn [5]), which undergoes a Schmidt reaction[21] with trimethylsilylazide to give a tris-silylated β-lactam.[22]

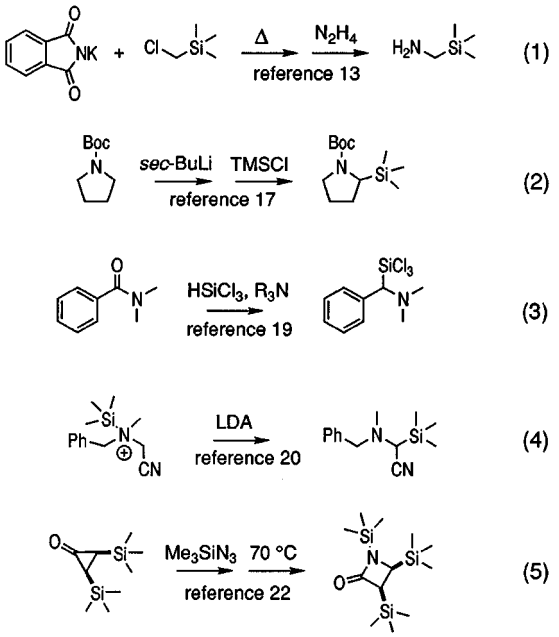

Figure 5 Preparative methods for α-aminosilanes.

RESULTS AND DISCUSSION

Metalation between nitrogen and silicon

The ready, often one-step, access to aminomethylsilanes via disconnection **I** (R = H) suggested the use of these compounds with disconnection **VI**, alkylation between nitrogen and silicon. This approach would take advantage of the anion-stabilizing effect of silicon[23] and the effectiveness of nitrogen derivatives as metalation directing groups.[24] We describe here our foray into type **VI** chemistry, using *t*-butoxycarbonyl (Boc) derivatives (**7**, Fig. 6) of aminomethyltrimethylsilane **3a**.

Based on the work of Greene and co-workers,[25] who demonstrated the use of the dianion of Boc-benzylamine **8**, we initially attempted to use

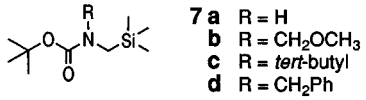

Figure 6 Metalation substrates.

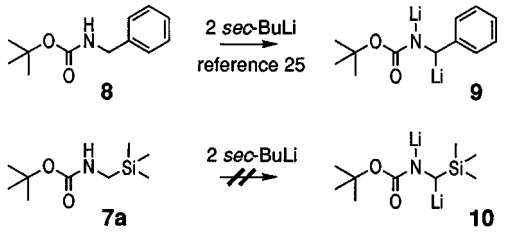

Figure 7 Dianion **10**, patterned after **9**,[25] proved elusive.

the dianion of **7a** (Fig. 7). Unfortunately, dianion **10** could not be formed, even under forcing conditions.[26]

The proximity of the two anions in **10**, in contrast to the delocalization of charge in **9**, is presumably responsible for the difficulty in forming this dianion. A protecting group for the amide nitrogen was therefore needed, and the readily removed methoxymethyl (MOM) group was selected. In this case, the diphenylmethylsilyl analog **11** was used (Fig. 8). The phenyl groups on silicon, more electronegative than methyl groups, would be expected to acidify the protons between nitrogen and silicon[27] (as well as the remaining methyl group on silicon). Metalation of the phenyl groups on silicon would not be expected.[28] Unfortunately, **12** also proved difficult to metalate. We attribute this lack of reactivity to a chelation of lithium by both the carbonyl and the MOM oxygen (**13**). Since the carbonyl oxygen is required to direct the metalation, a complex such as **13** would be unreactive.

In contrast to **7a** and **12**, use of *t*-butyl substitution on nitrogen gave a product (**7c**) (Fig. 9) that could be easily metalated and alkylated with allyl bromide.[26] The known amine **15**[29] was derivatized with di-*t*-butyldicarbonate and, on treatment with *s*-butyl-lithium, gave a bright yellow anion (**16**). After treatment with allyl bromide, product **17** was isolated in 66% yield.

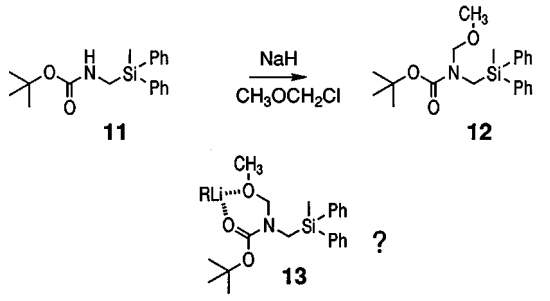

Figure 8 Preparation of MOM-protected carbamate **12**. Metalation remains elusive.

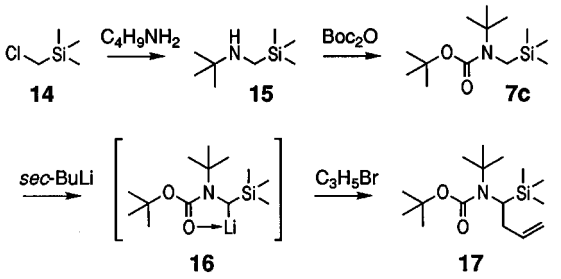

Figure 9 Metalation and alkylation of **7c** was very successful.

Removal of the Boc group of **17** was easily accomplished with trifluoroacetic acid; however removal of the *t*-butyl group from the amine could not be accomplished under a variety of acidic conditions.[26] Thus, a more readily removed *N*-substitution, such as a benzyl group, was clearly desirable.

Metalation substrate **7d**, with an *N*-benzyl group, was prepared in the same manner as **7c** (Fig. 10). As with **7c**, metalation and alkylation successfully led to the introduction of an electrophile between nitrogen and silicon, but another reaction pathway was found to limit the utility of this substrate; in addition to the desired product **19**, allylation adjacent to the phenyl group (**20**) was also observed. The metalation of **7d** kinetically favored the α-silyl anion (-78 °C, excess base), leading to the desired **19** by a small margin over **20**. Unfortunately, use of equilibrating conditions before introduction of the electrophile (0 °C, less than one equivalent of base) led to only the α-phenyl substitution product **20** due to the higher acidifying effect of phenyl relative to silicon.[30]

The aza-reverse-Brook rearrangement

t-Butyldimethylsilyl groups have been reported as stable protecting groups for the nitrogen of

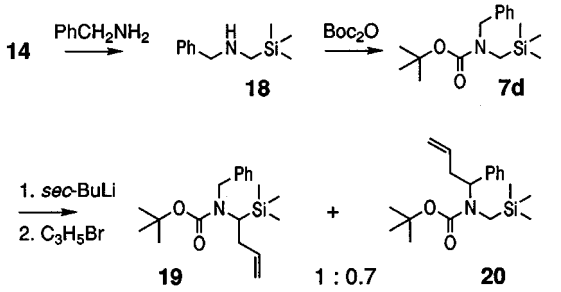

Figure 10 Preparation and metalation of *N*-benzyl **7d**.

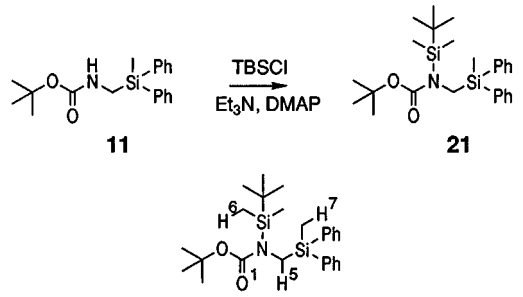

Figure 11 A *t*-butyldimethylsilyl protecting group for the amide nitrogen.

secondary amides.[31] Despite the rather hindered environment of the nitrogen in **11**, *N*-silylation to give **21** was straightforward (Fig. 11. This substrate presents an interesting case study of metalation adjacent to silicon. Counting from the carbamate oxygen, protons five, six and seven atoms away could potentially be removed by a base. A five-atom arrangement is expected to yield the kinetically labile proton, and this turned out to be the case.

Treatment of **21** with *s*-butyllithium gave a bright yellow anion, presumably **22** (Fig. 12). On warming to 0 °C this anion rearranges. Migration of the silicon from nitrogen to carbon is most likely driven by the relative stability of the resulting amide anion (**23a**). Silicon migration in structures such as **22** has the potential to be a general method for preparing α-aminosilanes.

The rearrangement of **22** to **23** has precedence in the work of Brook, Linderman and others.[32] Metal exchange with **24** results in the migration of silicon from oxygen to carbon to give, on workup, **26** (Fig. 13).

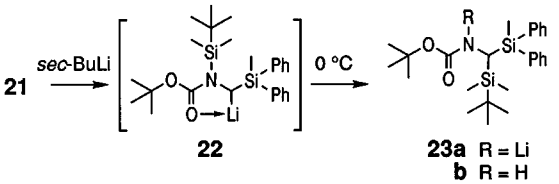

Figure 12 Aza-reverse-Brook rearrangement route to α-aminosilanes.

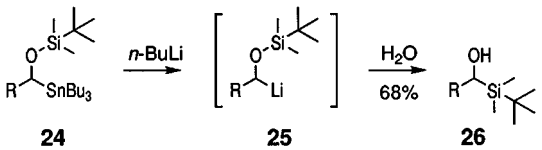

Figure 13 Reverse-Brook rearrangement.[32]

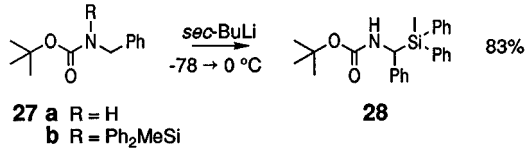

Figure 14 Aza-reverse-Brook rearrangement of Boc-derivatized benzylamine.

Phenyl and silyl groups are similar in the magnitude of their acidifying effect.[26, 30] Boc-protected benzylamine (**27a**) can be *N*-silylated and, upon metalation, rearranges smoothly to the corresponding α-amino–α-phenylsilane **28** (Fig. 14).

Hydrosilylation

We have also investigated an alternative approach to α-aminosilanes based on a hydrosilylation reaction reported by Murai and Kato,[33] who found that *N*-alkenyl amides and ureas will undergo rhodium acetate-catalyzed hydrosilylation with dimethylphenylsilane to give the α-aminosilane product **30** with high regiospecificity (Fig. 15).

We have found that this reaction can be extended to other carbonyl derivatives and to other silanes. For example, the Boc derivative **33** is available from the unsaturated acid **31** via a Curtius rearrangement using Overman's procedure[34] to give *N*-propenylcarbamate **33** in good yield (Fig. 16). Subjection of **33** to hydrosilylation with dimethylphenylsilane proceeds smoothly and cleanly to give **34** as the only

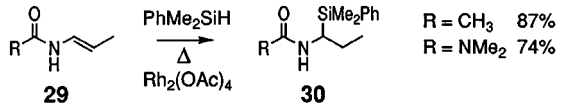

Figure 15 Hydrosilylation of *N*-alkenyl amides and ureas.[33]

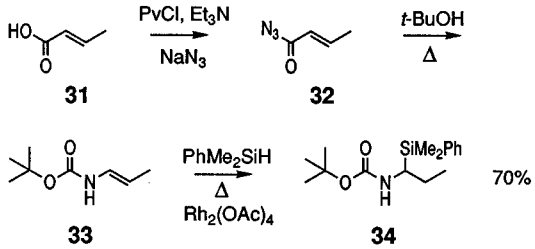

Figure 16 Hydrosilylation of **31** yields Boc derivative **32**. PvCl = pivaloyl chloride.

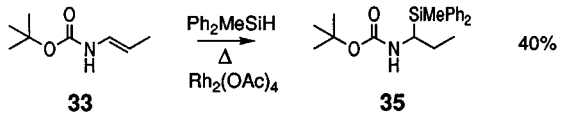

Figure 17 Methyldiphenylsilane also reacts with high selectivity, but more slowly.

isolable product.

Similarly, methyldiphenylsilane also gives a highly regioselective hydrosilylation; however, the reaction proceeds more slowly and the isolated yield is lower (Fig. 17).

With the goal of developing synthetic chemistry for the preparation of α-alkyl-α-aminosilanes, we have found three useful methods that utilize nitrogen conveniently derivatized with a Boc protecting group (Fig. 18). Deprotonation between silicon and nitrogen, followed by reaction with an electrophile, requires an additional (and unreactive group) on nitrogen to replace the acidic amide proton. Using *N*-alkylcarbamates, *N*-silylation followed by metalation of the alkyl group can lead to silyl migration. Finally, hydrosilylation of *N*-alkenylcarbamates with rhodium catalysis is very regioselective, and can proceed efficiently.

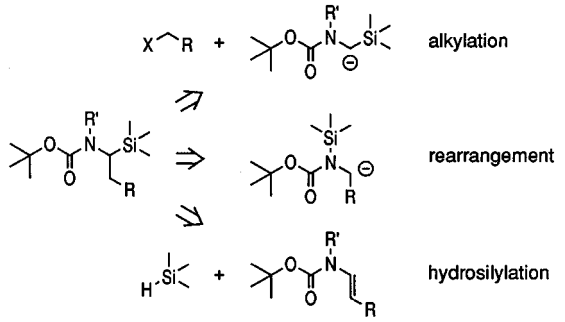

Figure 18 Three useful disconnections for Boc-derivatized α-amino silanes.

EXPERIMENTAL

t-Butyl (methyldiphenylsilyl)phenyl methylcarbamate (27b)

To a solution of *t*-butyl *N*-phenylmethylcarbamate **27a** (374 mg, 1.80 mmol) in methylene chloride (5 ml) at room temperature (rt) were added dropwise triethylamine (0.75 ml, 5.40 mmol) and chloromethyldiphenylsilane (0.45 ml, 2.16 mmol) and this mixture was then stirred for 20 h. After addition of water (30 ml), the aqueous phase was extracted with two 30 ml portions of ether. The combined organics were dried over $MgSO_4$ and concentrated to give a clear oil. Flash chromatography (ethyl acetate/hexane, 1:9) afforded **27b** (125 mg, 18%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 7.19 (m, 15H), 4.33 (s, 2H), 1.18 (s, 9H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 192.5, 156.0, 135.2, 134.9, 130.0, 129.3, 127.2, 126.6, 126.0, 67.0, 45.6, 30.2, 28.0. Exact mass (DCI) calcd for $C_{25}H_{30}NO_2Si$: 404.2046; found: 404.2028.

t-Butyl α-(methyldiphenylsilyl)phenylmethylcarbamate (28)

To a -78 °C solution of **27b** (33.7 mg, 0.08 mmol) and tetramethylethylenediamine (TMEDA) (0.02 ml, 0.13 mmol) in ether (5 ml) was added dropwise *s*-butyllithium (0.10 ml of a 1.2 M solution in cyclohexane, 0.13 mmol). The resulting yellow solution was allowed to stir for 15 min and then warmed to 0 °C over the course of 1 h, after which time most of the yellow color had disappeared. After addition of 10 ml of saturated NH_4Cl solution and extraction with two 20 ml portions of ether, the combined organics were dried over $MgSO_4$ and concentrated. Flash chromatography gave 28 mg (83%) of **28** as a colorless oil. ^{1}H NMR (C_6D_6) δ 7.06 (m, 15H), 5.24 (m, 1H), 5.09 (m, 1H), 1.35 (s, 9H), 0.31 (s, 3H). ^{13}C NMR (C_6D_6) δ 193.5, 156.2, 135.7, 135.5, 130.1, 130.0, 127.7, 126.8, 126.0, 79.7, 46.2, 30.1, 28.4. Exact mass (DCI) calcd for $C_{25}H_{30}NO_2Si$: 404.2046; found: 404.2028.

t-Butyl α-(dimethylphenylsilyl)-n-propylcarbamate (34)

A solution of *t*-butyl (1-propenyl)carbamate[35] **33** (77 mg, 0.49 mmol), dimethylphenylsilane (0.10 ml, 0.64 mmol) and rhodium acetate (4.3 mg, 0.01 mmol) in degassed toluene (5 ml) was heated to reflux under nitrogen for 3.5 h. After cooling to rt, the solution was concentrated and purified by flash chromatography (ethyl acetate/hexane, 1:9) to give 102 mg of **34** as a colorless oil (70%). ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 2H), 7.35 (m, 3H), 4.1 (bd, 1H, J=10.4 Hz), 3.24 (dt, 1H, J=3.8, 10.4 Hz), 1.54 (m, 1H), 1.41 (s, 9H), 1.25 (m, 1H), 0.89 (t, 3H, J=7.3 Hz), 0.32 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 156.4, 136.6, 134.0, 129.3, 127.9, 79.0, 42.2, 28.4, 24.7, 12.0,

−4.5, −5.2. MS (FAB) 294 (MH^+, 18), 236 (18), 222 (24), 192 (39), 160 (100). Exact mass (FAB) calcd for $C_{16}H_{28}NO_2Si$: 294.1889; found: 294.1890.

t-Butyl α-(methyldiphenylsilyl)-n-propylcarbamate (35)

A solution of *t*-butyl (1-propenyl)carbamate[35] **33** (165 mg, 1.05 mmol), methyldiphenylsilane (0.26 g, 1.3 mmol) and rhodium acetate (9 mg, 0.02 mmol) in degassed toluene (5 ml) was heated to reflux for 18 h. The resulting mixture was passed through a pad of silica gel with ethyl acetate/hexane (1:9) and the volatiles were removed *in vacuo*. Flash chromatography (ethyl acetate/hexane, 1:9) gave 140 mg of **35** as a colorless oil (40%). ^{1}H NMR ($CDCl_3$) δ 7.6–7.4 (m, 10H), 4.26 (bd, 1H, J=10.0 Hz), 3.76 (dt, 1H, J=2.5, 10.0 Hz), 1.69 (m, 1H), 1.43 (s, 9H), 0.96 (t, 3H, J=7.5 Hz), 0.62 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 156.4, 135.0, 134.9, 134.7, 134.1, 129.64, 129.59, 128.0, 78.9, 40.7, 28.4, 25.3, 12.0. IR (neat) 3432, 3354, 1694 cm^{-1}. MS (FAB) 356 (MH^+, 2.5), 298 (9), 284 (10), 254 (30), 222 (100), 197 (47). Exact mass (FAB) calcd for $C_{21}H_{30}NO_2Si$: 356.2046; found: 356.2039.

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