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Synthesis of α-alkyl-α-aminosilanes by rhodium-catalyzed hydrosilylation of Boc-protected vinyl amines

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Abstract

α-Aminosilanes can be readily prepared by rhodium-catalyzed hydrosilylation of Boc-substituted enamines, followed by acidic removal of the Boc group. This convergent approach allows for the rapid synthesis of new aminosilane structures, useful for their bioactivity and unique reactivity.

Few synthetic methods are available for the construction of α-substituted α-aminosilanes **1**, despite the bioactivity found for a number of α-aminosilanes[1,2] and their unique synthetic reactivity.[3] Our interest in these molecules stems from their central role in the structure of silanol-based peptide mimics, whose utility as protease inhibitors was recently described.[2] Many α-aminosilanes are known, however, the vast majority are aminomethyl silanes, lacking substitution between nitrogen and silicon, and derived from the commercially available chloromethyl silanes (Fig. 1, path **a**).[4] Few α-chloroalkylsilanes related to **3** are readily available. We have

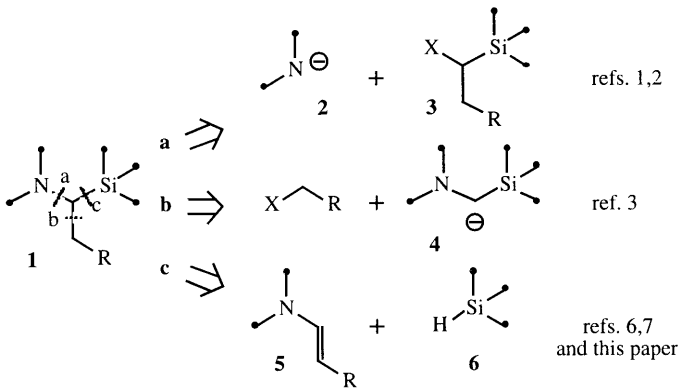

Figure 1. Three approaches to α-substituted-α-aminosilanes

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therefore studied the alternative synthesis paths **b** (alkylation)[5] and **c** (hydrosilylation). Path **c** is particularly attractive since it has the potential for catalytic asymmetric synthesis of the stereogenic center of **1**.

Hydrosilylation of enamines has not been widely studied, but pioneering efforts by Skoda–Földes[6] and by Murai and Kato[7] demonstrated the excellent potential of this approach (Fig. 2). A catalyst-dependent regioselectivity was found for *N*-vinyl pyrrolidinone **7**, favoring the α-amino silane **8** with Wilkinson's catalyst.[5] A broad and significant study by Murai and Kato[8] identified rhodium acetate as the preferred catalyst, and expanded the nitrogen substitution to include carbamoyl (*N*-alkenyl ureas). Nevertheless, the silicon substitution surveyed was largely limited to triethyl- and phenyldimethyl.

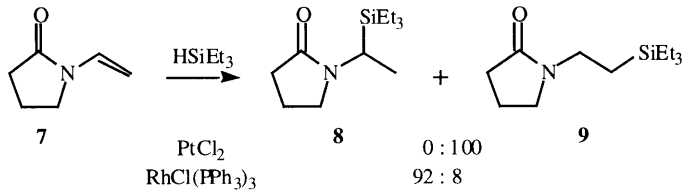
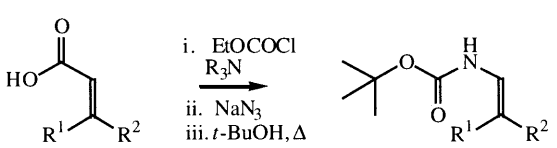


Figure 2. Regioselectivity of hydrosilylation is catalyst dependent

With an eye toward the application of this chemistry to construction of peptidomimetics, we have studied the hydrosilylation of *tert*-butyl *N*-alkenyl carbamates. These substrates would have the advantage of yielding Boc-protected α-amino silanes that could be easily deprotected and incorporated in polypeptide structures. The starting *tert*-butyl *N*-alkenyl carbamates **10–13** were readily prepared using Overman's Curtius rearrangement protocol in yields of 55–80% (Fig. 3).[9]

The *N*-pentenyl carbamate **10** was chosen as a representative substrate, and a selection of silanes were subjected to the standard conditions of Skoda–Földes, Murai and Kato: 0.05 equivalents of rhodium acetate and 1.3 equivalents of the silane in refluxing toluene for 24 h. As shown in Table 1, the isolated yields of hydrosilylation products were excellent for triethoxysilane, good to moderate for the dimethylphenylsilane and methyldiphenylsilane, and zero for triethylsilane and diphenylsilane. These results were consistent with a combination of steric and electronic effects for this transformation[10] and the remaining substrates (Fig. 3) were subjected to reaction with the three successful silanes **a–c**.

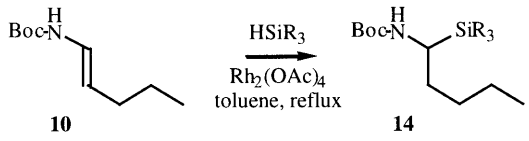
The results of this survey are shown in Table 2. For the 1,2-disubstituted alkenes **10–12**, the highest yields resulted from reactions with triethoxysilane and the lowest yields with methyldiphenylsilane. For the trisubstituted alkene **13**, no conversion to product was detected. In all cases, only the regioisomer **14** was produced, and the β-aminosilane isomer (cf. **9**) was not detected.



	R^1	R^2
10	H	*n*-C_3H_7
11	H	CH_3
12	H	*i*-C_3H_7
13	CH_3	CH_3

Figure 3. *tert*-Butyl *N*-alkenyl carbamate synthesis

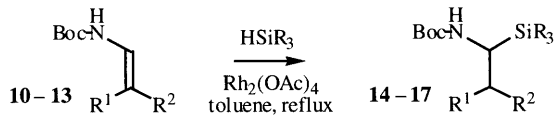
Table 1
Organosilane structure affects the yield but not the regioselectivity



10 14

	SiR_3	% Yield
a	$Si(OEt)_3$	86
b	$Si(CH_3)_2Ph$	61
c	$SiCH_3Ph_2$	46
d	$SiEt_3$	0
e	$SiPh_2H$	0

Table 2
Hydrosilylation yields are dependent on both the alkene and the organosilane[11,12]



10 – 13 14 – 17

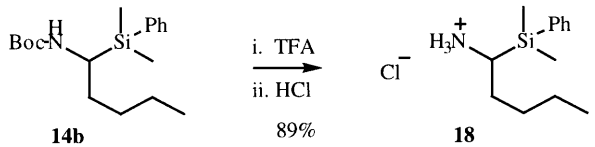
	R^1	R^2		SiR_3 = **a** $Si(OEt)_3$	**b** $Si(CH_3)_2Ph$	**c** $SiCH_3Ph_2$
10	H	n-C_3H_7	**14**	86%	61%	46%
11	H	CH_3	**15**	–	70%	40%
12	H	i-C_3H_7	**16**	71%	40%	39%
13	CH_3	CH_3	**17**	0%	0%	0%

In many hydrosilylation studies,[13] silanes carrying electron withdrawing groups such as chloride or alkoxide are the most reactive, and trialkylsilanes are the least reactive. The results in Table 1 are consistent with this reactivity. In addition, sterics may play a substantial role here, as the most hindered silane, methyldiphenylsilane (**c**) gave the lowest yields and the trisubstituted alkene **13** gave no reaction with any silane.

The reactions with triethoxysilane are notable. This reagent has been reported to fail in related transformations,[6,14] and it yields products that are at a silicon oxidation level close to that desired for the silanol protease inhibitors.[2]

Deprotection of product **14b** using trifluoroacetic acid proceeded smoothly and the product was characterized as the crystalline hydrochloride salt **18** (Fig. 4).

This preparative approach to α-alkyl-α-aminosilanes is a promising alternative approach to the synthesis of these molecules, and one of the few methods for preparing primary amines of this type. Applications to bioactive organosilanes are currently under study.



14b **18**

Figure 4. Removal of the Boc group

Acknowledgements

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11. Preparation of **14a** is representative. To the carbamate **10** (100 mg, 0.54 mmol) in toluene (2.7 ml) under a nitrogen atmosphere was added dirhodium tetraacetate (12 mg) and triethoxysilane (115 mg). The mixture was heated to reflux for 24 h, cooled to ambient temperature and filtered through a pad of silica gel. Flash chromatography (1:9 ethyl acetate/hexanes) gave **14a** as a colorless oil (162 mg, 86%).
12. Proton ^{1}H NMR (CDCl3) data: **14a**: δ 4.476 (d, $J=9.9$ Hz, 1H), 3.838 (q, $J=6.9$ Hz, 6H), 3.27–3.21 (m, 1H), 1.63–1.26 (m, 6H), 1.43 (s, 9H), 1.22 (t, $J=7.1$, 9H), 0.88 (t, $J=6.9$, 3H).
14b: δ 7.53–7.50 (m, 2H), 7.38–7.34 (m, 3H), 4.13 (bd, $J=10.3$ Hz, 1H), 3.37–3.29 (m, 1H), 1.62–1.18 (m, 7H), 1.41 (s, 9H), 0.83 (bt, $J=6.4$, 3H), 0.32 (s, 6H).
14c: δ 7.58–7.35 (m, 10H), 4.18 (bd, $J=10.4$, 1H), 3.82–3.77 (m, 1H), 1.58 (m, 1H), 1.41–1.18 (m, 6H), 1.39 (s, 9H), 0.82 (bt, $J=6.3$, 3H), 0.58 (s, 3H).
16a: δ 4.37 (bd, $J=9.9$ Hz, 1H), 3.82 (q, $J=7.1$, 14.0 Hz, 6H), 3.40–3.30 (m, 1H), 1.70–1.54 (m, 1H), 1.41 (s, 9H), 1.35–1.31 (m, 2H), 1.20 (t, $J=5.6$ Hz, 9H), 0.97–.0.87 (m, 6H).
16b: δ 7.54–7.26 (m, 5H), 4.09 (d, $J=0.2$ Hz, 1H), 3.81–3.41 (m, 1H), 1.69–1.59 (m, 1H), 1.40 (s, 9H), 1.31–1.08 (m, 2H), 0.86 (t, $J=6.3$ Hz, 6H), 0.321 (s, 3H), 0.233 (s, 3H).
16c: δ 7.60–7.25 (m, 10H), 4.15 (bd, $J=10.3$ Hz, 1H), 3.97–3.84 (m, 1H), 1.64 (m, 1H), 1.38 (s, 9H), 1.33–1.27 (m, 2H), 0.89 (dd, $J=6.5$ Hz, 20.4 Hz, 6H), 0.58 (s, 3H).
18: δ 7.87 (s, 3H), 7.57–7.38 (m, 5H), 2.68 (t, $J=7.0$ Hz, 1H), 1.49–1.10 (m, 6H), 0.72 (t, $J=6.9$ Hz, 3H), 0.42 (s, 3H), 0.41 (s, 3H).

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