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α-Siloxyamides from a carbamoylsilane and carbonyl compounds

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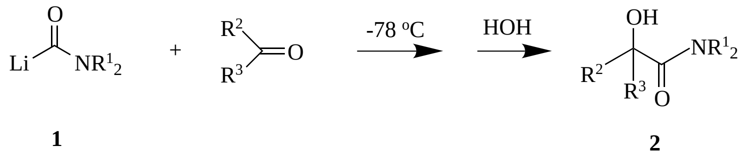
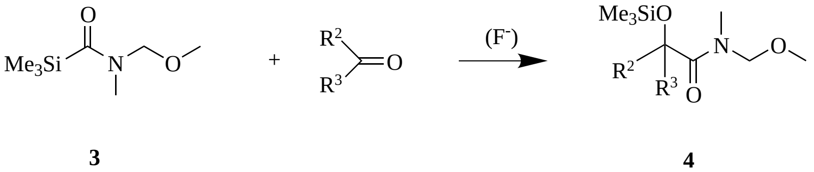
Abstract—The reaction of a carbamoylsilane with aldehydes or ketones affords α-siloxyamides. The addition reaction is catalyzed by fluoride ion (TBAT, 25–50°C), but proceeds in the absence of catalyst at higher temperatures (50–100°C). © 2002 Elsevier Science Ltd. All rights reserved.

α-Hydroxyamides (**2**) are both useful intermediates and synthetic targets in their own right.[1] One possible approach to these compounds is to establish the carbonyl to α-carbon bond by nucleophilic addition of an extant or masked amidoyl moiety to aldehydes or ketones. In addition to less direct methods,[2] carbamoyllithium reagents (**1**) have been employed for this purpose.[3,4] Unfortunately, the latter methodology is fraught with difficulties associated with thermal instability[3] and self-condensation,[4] as well as potential complications arising from the high basicity of these reagents. We now report that the reaction of cabamoylsilane **3**[5] with aldehydes or ketones directly affords the *O*-protected (silylated) adducts **4**. Our initial investigations were carried out employing fluoride ion sources as catalysts.[6] The use of cesium fluoride[7] in anhydrous acetonitrile was only effective with the most electrophilic co-reactant investigated, trichloroacetaldehyde, affording the corresponding **4d** in 67% yield after 6 h at 25°C. Other aldehydes were found to afford little or no adducts under these conditions, with the principal reaction being desilylation of **3** to the formamide via protonolysis of the Si–C bond.[8] However, using the soluble and non-hygroscopic tetrabutylammonium triphenyldifluorosilicate (TBAT)[9] as the fluoride ion source (2–4 mol%) in THF gave much improved results (Table 1).[10] Results obtained from aldehydes indicated that higher yields were obtained from substrates with no α-hydrogens, and that steric factors impeded the rate of the reaction, requiring a higher temperature for timely completion.[11] Although the ketones examined under these conditions proved to be reactive, a lower yield was again observed when α-hydrogens were present, with significant amounts of desilylated **3** again in evidence (cf. **4f**). These observations suggested that competitive protonolysis of **3** may be associated with the lability of α-hydrogens, and that conditions even less basic than those engendered by fluoride ion might be desirable. This led us to attempt reaction in the absence of any fluoride ion sources under strictly neutral conditions.





Keywords: α-siloxyamide; α-hydroxyamide; carbamoylsilane.

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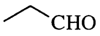
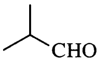
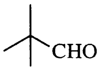
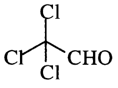
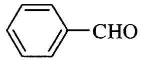
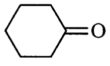
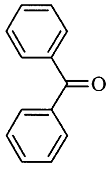
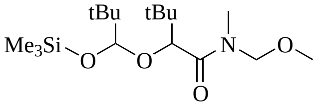
Table 1 also shows these results. In all instances, the addition reaction was not observed at 25°C, and elevated temperatures were required to achieve reasonable rates. At 50°C, all aldehydes except pivaldehyde had undergone complete or nearly complete addition within three hours to give yields equal to or in excess of those obtained with fluoride ion catalysis (chloral and pivaldehyde excepted). Presumably because of steric reasons, pivaldehyde was much less reactive, and small amounts of aldehyde and **3** were still present after 18 h at 70°C. Although the presence or absence of α-hydrogens no longer seemed to be a factor, minor amounts of a 2:1 (aldehyde: **3**) adduct were now in evidence. Small amounts of this adduct were isolated from the pivaldehyde reaction, and tentatively identified as **5** by spectral data.[12] Ketones were also found to undergo addition, but only at 100°C. However, useful yields of adducts **4f** and **4g** were then obtained, with better results than found in the fluoride ion-catalyzed runs.

Table 1. Adducts (**4**) of carbonyl substrates and **3**

Substrate		Yields of Adducts **4** (Conditions)	
		With F$^-$	Without F$^-$
	**4a**	25 (25 °C, 2h)	72 (50 °C, 3h)
	**4b**	50 (25 °C, 2h)	66 (50 °C, 3h)
	**4c**	74 (50 °C, 1.5h)	38 (70 °C, 18h)[a]
	**4d**	65 (50 °C, 3h)[b]	56[c] (50 °C, 3h)
	**4e**	83 (50 °C, 2h)[b]	83 (50 °C, 3h)
	**4f**	27 (25 °C, 0.5h)	61 (100 °C, 18h)
	**4g**	60 (25 °C, 0.5h)	86 (100 °C, 31h)[d]

[a] Aldehyde bp 68 °C; no significant reaction at 50 °C, 3h. [b] Very slow conversion at 25 °C. [c] Isolated as the desilylated hydroxyamide after chromatography. [d] Little further change after 18h.



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To place these results in perspective, we note that several reports exist in which an *acyl*silane was added to aldehydes[13–15] or ketones[15] in the presence of fluoride ion to afford α-silyloxy- (or, as isolated, hydroxy-) ketones. However, similar *uncatalyzed* additions to carbonyl substrates are, to our knowledge, unknown. The synthetic advantage of being able to carry out condensation reactions as described herein under mildly basic (F$^-$ catalyzed) or strictly neutral conditions needs no elaboration.

Characterization data for adducts 4

4a: IR: 1657 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.87 and 4.84 (AB pattern, $J=10$ Hz, 2H), 4.35 (m, 1H), 3.34 (s, 3H), 3.00 (s, 3H), 1.75 (m, 2H), 0.97 (t, 3H) (major rotamer); 4.84 (s, 2H), 4.33 (m, 1H), 3.31 (s, 3H), 3.14 (s, 3H), 1.70 (m, 2H), 1.00 (t, 3H) (minor rotamer). ^{13}C NMR (126 MHz, CDCl$_3$): δ 174.0, 80.3, 75.1, 55.3, 33.7, 28.5, 10.2, −0.1 (major rotamer); 174.1, 78.4, 74.8, 55.9, 33.0, 27.6, 10.2, −0.1 (minor rotamer). Absorptions are believed to be coincident at δ 10.2 and −0.1. Anal. calcd for $C_{10}H_{23}NO_3Si$: C, 51.46; H, 9.93; N, 6.00. Found: C, 51.70; H, 10.25; N, 6.02.

4b: IR: 1655 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$): δ 4.68 and 4.52 (AB pattern, $J=9.5$ Hz, 2H), 4.28 (d, $J=8.5$ Hz, 1H), 3.01 (s, 3H), 2.95 (s, 3H), 2.11 (m, 1H), 1.12 or 1.05 (m, 3H), 0.29 (s, 9H) (major rotamer); 4.86 and 4.81 (AB pattern, $J=9.5$ Hz, 2H), 4.19 (d, $J=7.5$ Hz, 1H), 3.29 (s, 3H), 2.86 (s, 3H), 2.04 (m, 1H), 1.12 or 1.05 (m, 3H), 0.25 (s, 9H) (minor rotamer). ^{13}C NMR (126 MHz, CDCl$_3$): δ 173.6, 80.2, 78.6, 55.3, 33.6, 32.8, 19.0, 18.6, −0.23 (major rotamer); 173.8, 80.1, 79.5, 56.0, 33.1, 31.9, 18.8, 18.6, −0.17 (minor rotamer). Anal. calcd for $C_{11}H_{25}NO_3Si$: C, 53.40; H, 10.19; N, 5.66. Found: C, 53.37; H, 10.35; N, 5.25.

4c: IR: 1672, 1647 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$): δ 4.86 and 4.83 (AB pattern, $J=10$ Hz, 2H), 4.55 and 4.47 (AB pattern, $J=9.5$ Hz, 2H), 4.43 (s, 1H), 4.29 (s, 1H), 3.31 (s, 3H), 2.99 (s, 3H), 2.96 (s, 3H), 2.89 (s, 3H), 1.18 (s, 9H), 1.17 (s, 9H), 0.27 (s, 9H), 0.21 (s, 9H) (1:1 mixture of rotamers). ^{13}C NMR (126 MHz, CDCl$_3$): δ 173.0, 79.3, 78.7, 56.3, 35.9, 34.1, 26.39, −0.2 (major rotamer); 172.7, 81.1, 79.3, 55.5, 35.6, 34.4, 26.37, −0.3 (minor rotamer). Absorptions are believed to be coincident at δ 79.3. Anal. calcd for $C_{12}H_{27}NO_3Si$: C, 55.13; H, 10.41; N, 5.36. Found: C, 55.01; H, 10.69; N, 5.33.

4d-OSi: IR: 1684 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$): δ 5.28 (s, 1H), 4.75 or 4.45 (AB pattern, $J=9.5$ Hz or 10.5 Hz, 2H), 2.90 (s, 3H), 2.86 (s, 3H), 0.29 (s, 9H) (major rotamer); 5.08 (s, 1H), 4.75 or 4.45 (AB pattern, $J=9.5$ Hz or 10.5 Hz, 2H), 3.24 (s, 3H), 2.79 (s, 3H), 0.22 (s, 9H) (minor rotamer). ^{13}C NMR (126 MHz, CDCl$_3$): δ167.2, 99.1, 81.6, 78.6, 55.9, 35.7, −0.2 (major rotamer); 167.4, 98.9, 79.3, 78.9, 56.3, 34.0, 0.0 (minor rotamer). Anal. calcd for $C_9H_{18}Cl_3NO_3Si$: C, 33.50; H, 5.62; N, 4.34. Found: C, 33.78; H, 5.53; N, 4.52.

4d-OH: IR: 3198, 1637 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6): δ 5.09 and 4.98 or 4.86 and 4.83 (AB pattern, J=10.6 or 10.6 Hz, 2H), 4.85 (d, J=10 Hz, 1H), 4.38 (d, J=10 Hz, 1H), 3.13 (s, 3H), 2.36 (s, 3H) (major rotamer); 5.09 and 4.98 or 4.86 and 4.83 (AB pattern, J=10.6 or 10.6 Hz, 2H), 4.61 (d, J=11.2 Hz, 1H), 3.92 (d, J=11.2 Hz, 1H), 2.77 (s, 3H), 2.71 (s, 3H) (minor rotamer). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.5, 99.9, 78.4, 76.7, 55.8, 33.2 (major rotamer); 168.0, 99.9, 80.8, 76.9, 54.6, 33.2 (minor rotamer). Absorptions are believed to be coincident at δ 99.9 and 33.2. Mp 129–130 (fine needles from hexane–ethyl acetate). Anal. calcd for $C_6H_{10}Cl_3NO_3$: C, 28.77; H, 4.02; N, 5.59. Found: C, 28.43; H, 3.80; N, 5.38.

4e: IR: 1655 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ 7.71 (m, 2H), 7.1–7.3 (m, 3H), 5.90 (s, 1H), 4.55 and 4.50 (AB pattern, J=10 Hz, 2H), 2.91 (s, 3H), 2.77 (s, 3H), 0.246 (s, 9H) (major rotamer); 7.71 (m, 2H), 7.1–7.3 (m, 3H), 5.78 (s, 1H), 4.78 and 4.9 (AB pattern, J=4 Hz, 2H), 3.25 (s, 3H), 2.72 (s, 3H), 0.252 (s, 9H) (minor rotamer). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.5, 139.0, 128.5, 127.8, 125.3, 79.4, 76.38, 54.5, 32.3, −0.3 (major rotamer); 172.7, 139.0, 128.2, 127.8, 125.6, 78.6, 76.44, 55.8, 32.8, −0.2 (minor rotamer). Absorptions are believed to be coincident at δ 128.5 and 127.8. Anal. calcd for $C_{14}H_{23}NO_3Si$: C, 59.75; H, 8.23; N, 4.98. Found: C, 59.55; H, 8.43; N, 4.95.

4f: IR: 1655 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 75°C): δ 4.91 (s, 2H), 3.21 (s, 3H), 3.10 (s, 3H), 2.21 (m, 2H), 1.90 (m, 2H), 1.73 (m, 4H), 1.46 (m, 1H), 1.40, (m, 1H). ^{13}C NMR (126 MHz, C_6D_6, 70°C): δ 174.4, 80.6, 79.0, 55.2, 37.0, 34.2, 25.6, 22.6, 1.5. Anal. calcd for $C_{13}H_{27}NO_3Si$: C, 57.10; H, 9.95; N, 5.12. Found: C, 57.15; H, 10.16;, 4.85.

4g: IR: 1655 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ 7.70 (s, 4H), 7.1–7.3 (m, 6H), 4.88 (s, 2H), 3.29 (s, 3H), 2.79 (s, 3H), 0.15 (s, 9H) (major rotamer); 7.70 (s, 4H), 7.1–7.3 (m, 6H), 4.81 (s, 2H), 3.03 (s, 3H), 2.57 (s, 3H), 0.07 (s, 9H) (minor rotamer). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 142.8, 128.2, 127.8, 127.7 86.0, 79.9, 56.0, 34.8, 1.6 (major rotamer); 173.8, 143.2, 128.2, 127.8, 127.7 85.9, 80.1, 54.0, 32.5, 1.4 (minor rotamer). Absorptions are believed to be coincident at δ 128.2, 127.8 and 127.7. Anal. calcd for $C_{20}H_{27}NO_3Si$: C, 67.19; H, 7.61; N, 3.92. Found: C, 66.92; H, 7.72; N, 3.94.

5: IR: 1643 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ 5.44 (d, J=19 Hz, 1H), 4.51 (d, J=19 Hz, 1H), 4.46 (s, 1H), 4.02 (s, 1H), 3.33 (s, 3H), 3.24 (s, 3H), 1.20 (s, 9H), 1.06 (s, 9H), 0.28 (s, 9H) (major rotamer); 5.42 (d, J=18 Hz, 2H), 4.57 (d, J=18 Hz, 2H), 4.48 (s, 1H), 4.12 (s, 1H), 3.12 (s, 3H), 3.08 (s, 3H), 1.22 (s, 9H), 1.08 (s, 9H), 0.33 (s, 9H) (minor rotamer). ^{13}C NMR (126 MHz, 1:3 C_6D_6–CCl_4): δ 170.5, 106.6, 90.5, 78.8, 55.5, 37.2, 34.2, 31.8, 27.7, 25.6, 0.76 (major rotamer); 169.6, 106.5, 90.6, 80.3, 54.5, 35.9, 35.3, 32.7, 27.2, 25.6, 0.82 (minor rotamer). Absorptions are believed to be coincident at δ 25.6.

Acknowledgements

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7. 'Anhydrous' CsF was flame heated under vacuum before use. The heterogeneous mixture from 13 mol% CsF in 4 mL acetonitrile for a 1 mmol run was agitated by vibration.
8. Similar results were obtained using THF as the solvent.
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10. Runs were carried out on a 0.75 mmol scale (10% excess of **3**) in flame-dried (under vacuum) and argon purged Teflon-screw sealed tubes. Catalyzed reactions employed 10 mg of TBAT in 0.5 mL of anhydrous THF and were homogeneous. Uncatalyzed reactions were run neat.

Adducts **4** were obtained directly from Kugelrohr distillation or radial chromatography (hexane–EtOAc, silica gel).

11. More electrophilic aldehydes such as chloral or benzaldehyde may slow the formation of adduct by equilibrium sequestering of fluoride ion through carbonyl addition.
12. This constituted 18% of the total product mass in this run. Inspection of the crude reaction products obtained from propionaldehyde and isobutyraldehyde by NMR spectroscopy indicated lesser amounts of what seemed to be analogous 2:1 adducts in these runs as well. A mixture of pivaldehyde and pure **4c** afforded no **5** after 23 h at 70 °C, suggesting that **5** results from a route mechanistically associated with that resulting in adducts **4**.
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