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α-(Dimethylamino)amides from a carbamoylsilane and iminium salts

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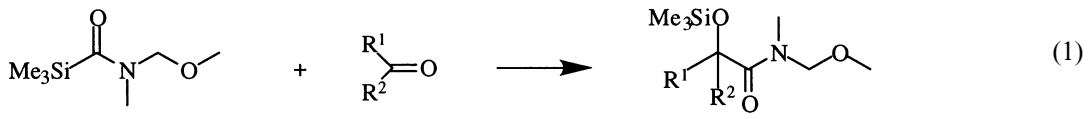
Abstract—The reaction of a carbamoylsilane with iminium salts derived from aldehydes lacking α-hydrogens affords the title compounds.

We have previously found that aldehydes or ketones may be directly converted to O-silyl α-hydroxyamides by reaction with a carbamoylsilane (Eq. (1)).[1] In an attempt to extend this chemistry to the formation of α-aminoamides,[2] we have begun an exploration of the reactivity of C=N-containing compounds with carbamoylsilanes, and report here on the first successful attempt in this regard by employing iminium salts (**2**) as the C=N substrate.[3] The readily obtained *N*,*N*-dimethylcarbamoylsilane (**1**)[4] was chosen as co-reactant for these studies. Equimolar amounts of **1** and **2** dissolved in benzene were, with a few exceptions, found to undergo complete reaction as indicated by Eq. (2) after 20 h at 25°C. Results are listed in the Table 1.[5]

The common feature of all successful runs is the absence of 'alpha' (HC–C=N) hydrogens in the iminium salt. Entry 2 indicates that no product was obtained when even one such hydrogen was present, despite the eventual addition of excess **1**. Instead, only desilylative protonolysis of **1** into DMF was observed.[6] In the absence of this feature, additions proceeded as expected, with representative iminium ions bearing aryl, heteroaryl and tertiary aliphatic substituents on the C=N function being accommodated. A comparison of the results obtained from **2a** and **2c** indicates that placing a large group on the C-terminus of the parent iminium structure causes no steric impediment to reaction. Entry 5 was investigated in order to determine whether 1,2- or 1,4-addition would occur in a conjugated system. Although much less reactive than other salts investigated, **2e** eventually afforded a good yield of exclusively 1,2-addition product. The use of **2g** in a 1:1 ratio with **1** failed to give any isolable product. However, when a 1:2 ratio was employed, the diamide **3g** was obtained. This behavior is easily understood, as the initial 1:1 adduct would be an α-chloroamine, whose resonance form as the corresponding iminium salt suggests it would thus be capable of adding a second equivalent of **1**. A selection of entries (1, 4, and 7) was also examined using an excess of **1** (see Table 1), and in two instances (1 and 4) resulted in much improved yields relative to the general range of equimolar ratio runs. We have not yet identified the source of the competing reaction leading to excessive consumption of **1**.

Although the scope of this chemistry is limited to iminium salts of carbonyl compounds lacking α-hydrogens, this protocol should be applicable to the synthesis of many other *N*,*N*-disubstituted α-aminoamides.



(1)

(2)

1 **2** **3**

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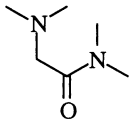
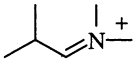
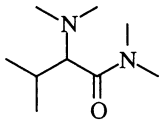
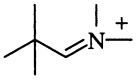
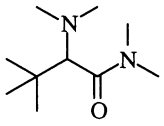
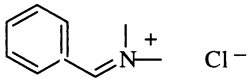
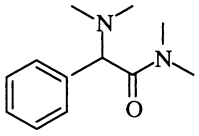
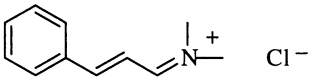
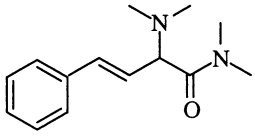
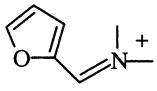
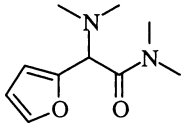
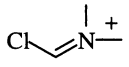
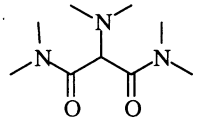
Table 1. α-Aminoamides **3** from iminium salts **2** and carbamoylsilane **1**

Entry	Iminium Salt	α-Aminoamide	Yield %[a]
1.	**2a** 	**3a** 	50 (89)[b]
2.	**2b** 	**3b** 	0
3.	**2c** 	**3c** 	57
4.	**2d** 	**3d** 	(92)[b]
5.	**2e** 	**3e** 	69[c]
6	**2f** 	**3f** 	64[d]
7	**2g** 	**3g** 	50 (55)[e]

[a] Isolated yield. Characterization data are given.[7] [b]1.5 equivalents of **1**. [c]60 °C, 4 d. [d]65 °C, 20 h. [e]2.5 equivalents of **1**.

Acknowledgements

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References

1. Cunico, R. F. *Tetrahedron Lett.* **2002**, *43*, 355–358.
2. For other approaches and leading references to applications, see: Lin, Y.-S.; Alper, H. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 779–781.
3. Iminium salts were purchased from Aldrich Chemical Co. (**2g**), or prepared from aldehydes by known methods and purity ascertained by ^{1}H NMR. **2b**, **2c**, **2e**, **2f**: (a) Ulrich, J.; Schroth, W. *Tetrahedron Lett.* **1993**, *34*, 5863–5866; (b) Schroth, W.; Jahn, U.; Ströhl, D. *Chem. Ber.* **1994**, *127*, 2013–2022. **2d**: Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999–2007. **2a**: Böhme, H.; Hartke, K. *Chem. Ber.* **1960**, *93*, 1305–1309.
4. Prepared from DMF by the procedure of Cunico, R. *Tetrahedron Lett.* **2001**, *42*, 1423–1425. At this scale, an addition period of 8 h, achieved by motorized syringe introduction of LDA, was critical to obtaining a syntheti-

cally useful yield (70%) of **1**, bp 37–41°C (0.9 mmHg). **1** showed appropriate spectral and combustion data. We have also been able to prepare other *N*,*N*-dialkylcarbamoylsilanes by this method.

5. **Typical procedure**. A Schlenk tube fitted with a Teflon vacuum stopcock and a micro stirbar was flame-heated under vacuum and refilled with Ar. Iminium salt (0.5–1.5 mmol) was introduced in a dry box and the tube then attached to an Ar line. An equivalent amount of **1** was then added together with 2 mL of anhydrous benzene (Aldrich). Except for entries 5 and 6 (see Table 1), reactions were complete within 20 h at 25°C. The progress of the reaction could be monitored by following the TMS absorption of **1** in the ^{1}H NMR spectrum of aliquots. For all but runs 3 and 7, volatiles were removed under vacuum and the residue evaporatively distilled. For runs 3 and 7, the reaction mixture was washed with aqueous $NaHCO_3$, dried, and distilled (**3c**) or directly recrystallized (**3g**).
6. The heightened acidity of N=C–CH protons in iminium salts has long been known. See Böhme, H.; Haake, M. In *Iminium Salts in Organic Chemistry*; Böhme, H.; Viehe, H. G., Eds.; J. Wiley & Sons: New York, 1976; pp. 157–161.
7. All NMR spectra were obtained in $CDCl_3$ at 11.75T unless otherwise indicated. **3a**: Kugelrohr distillation (Kd): 50°C/0.1 mmHg. IR: 1648 cm^{-1}. ^{1}H NMR: δ 3.11 (s, 2H), 3.08 (s, 3H), 2.95 (s, 3H), 2.31 (s, 6H). ^{13}C NMR: δ 169.9, 62.0, 45.6, 36.9, 35.4. Anal. calcd for $C_6H_{14}N_2O$: C, 55.36; H, 10.84; N, 21.52. Found: C, 55.39; H, 10.94; N, 21.68%. **3c**: Kd: 100°C/1.2 mmHg. IR: 1640 cm^{-1}. ^{1}H NMR: δ 3.39 (s, 1H), 3.12 (s, 3H), 3.00 (s, 3H), 2.51 (s, 6H), 1.07 (s, 9H). ^{13}C NMR: δ 170.8, 68.9, 44.7, 38.5, 35.9, 35.3, 27.7. Anal. calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.37; H, 11.71; N, 15.38%. **3d**: Kd: 130°C/0.05 mmHg, mp 59.0–60.5°C. IR: 1652 cm^{-1}. ^{1}H NMR: δ 7.3–7.5 (m, 5H), 4.15 (s, 1H), 3.0 (s, 3H), 2.98 (s, 3H), 2.29 (s, 6H). ^{13}C NMR: δ 171.0, 163.2, 129.2, 128.6, 128.1, 71.7, 43.4, 37.0, 36.1. Anal. calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found: C, 69.53; H, 8.84; N, 13.49%. **3e**: Kd: 180°C/0.1 mmHg, mp 77–78°C. IR: 1648 cm^{-1}. ^{1}H NMR: δ 7.25–7.45 (m, 5H), 6.58 (d, J=15 Hz), 6.46 (dd, J=15 Hz, 9 Hz), 3.83 (d, J=9 Hz), 3.21 (s, 3H), 3.00 (s, 3H), 2.34 (s, 6H). ^{13}C NMR: δ 170.8, 136.4, 134.6, 128.6, 127.9, 124.4, 70.2, 42.5, 37.0, 36.0. Anal. calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.40; H, 8.95; N, 11.91%. **3f**: Kd: 100°C/0.05 mmHg, mp 47.5–48.5°C (hexane). IR: 1649 cm^{-1}. ^{1}H NMR (4.7T): δ 7.44 (br s, 1H), 6.41 (m, 2H), 4.53 (s, 1H), 3.07 (3H), 3.01 (s, 3H), 2.36 (s, 6H). ^{13}C NMR (4.7T): δ 169.4, 150.2, 142.7, 110.8, 110.4, 64.7, 42.9, 37.6, 36.4. Anal. calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; 14.27. Found: C, 61.03; H, 8.30; N, 14.37%. **3g**: mp 91.5–92.5°C (hexane). IR: 1639 cm^{-1}. ^{1}H NMR (4.7T): δ 4.17 (s, 1H), 3.15 (s, 6H), 2.98 (s, 6H), 2.44 (s, 6H). ^{13}C NMR (4.7T): δ 167.9, 71.5, 42.8, 37.5, 36.4. Anal. calcd for $C_9H_{19}N_3O_2$: C, 53.71; H, 9.51; 20.88. Found: C, 53.61; H; 9.63; N, 20.60%.