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α-Aminoamides from a carbamoylsilane and aldehyde imines

Jianxin Chen† and Robert F. Cunico*

Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115, USA

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Abstract—The reaction of a carbamoylsilane with aldehyde imines in the presence of BF_3 etherate affords α-aminoamides.

As representatives of the smallest subunit of peptides and proteins, α-aminoamides are important synthetic targets.[1] Construction of such species by establishing the carbon-carbon bond alpha to the carbonyl group is often accomplished by the Ugi reaction, in which a multicomponent mixture of primary amine, carboxylic acid, aldehyde and isocyanide affords an α-(*N*-acyl-*N*-alkylamino)amide containing a new stereogenic center at the alpha-carbon atom.[2] Several limitations of this approach include (1) the difficulty of deacylating the protected amino function; (2) the restricted availability of isocyanides; (3) the ability to form only an *N*-monosubstituted amide function; (4) a low diastereoselectivity when employing chiral amines.[3] Although several of these limitations have been addressed to some extent,[2] we wish to report an approach which directly affords tertiary α-(*N*-alkyl)aminoamides from imines and may have potential for useful diastereoselectivity.

We have recently found that carbamoylsilanes[4] add to the C=N bond of iminium salts to afford α-aminoamides,[5] but the methodology was limited in generality of structure and ease of manipulation because of the hygroscopic nature of the iminium salts. We now find that BF_3 etherate promotes the addition of (*N*,*N*-dimethylcarbamoyl)trimethylsilane to many types of easily obtainable *N*-benzyl aldehyde imines to afford, after hydrolysis, the corresponding *N*-benzyl aminoamides (Eq. (1)). Results are summarized in Table 1.[6,7] Initial experiments were carried out utilizing equimolar amounts of imine, BF_3 etherate and carbamoylsilane. It was found that in those instances where the imines contained enolizable α-hydrogens (Table 1, entries 1 and 2), higher yields were obtained by using an excess of carbamoylsilane. This may reflect competitive protonolysis of the carbamoylsilane, a phenomenon which was previously observed to destroy the carbamoylsilane completely when iminium salts with enolizable α-hydrogens were used as substrates.[5] In contrast, the present chemistry produces synthetically useful amounts of adducts from a wide variety of aldehyde imines. Table 1 (entry 3) indicates that steric considerations are an important factor in the addition reaction, as no or little product was obtained from pivalaldehyde imine. Indeed, attempts to extend the reaction to (generally more hindered) ketone imines such as cyclohexanimine and diphenylcarbimines failed to afford any addition products. The use of benzene as solvent appeared to be a slightly better choice in a number of instances (Table 1, entries 4 and 7), although of limited value in other instances (Table 1, entries 3

Table 1. α-Aminoamides from imines and (*N*,*N*-dimethylcarbamoyl)trimethylsilane

Entry	Imine, R =	Aminoamide, % yield[a,b,c]
1	Et	31 (50)
2	*i*Pr	58 (92)
3	*t*Bu	0 [10]
4	CF_3	41 (46) [56]
5	(*E*)-PhCH=CH	76 (81)
6	TMS—≡	0
7	Ph	68 [85]
8	2-Furyl	73[d]
9	2-(Thiophene)yl	56 (82)
10	2-Pyridyl	62
11	CO_2Et[e]	57[e] [56]

[a] 1:1 mol ratio of imine and silane in THF.
[b] In parentheses: yield from, respectively, 1:1.5 mol ratio of imine and silane.
[c] In brackets: yield from 1:1 mol ratio in benzene.
[d] 1:1 mol ratio in CH_2Cl_2.
[e] The *N*-[(*S*)-α-phenylethyl]imine was employed.

* Corresponding author.
† Current address: Datong Medical College, Datong, China.

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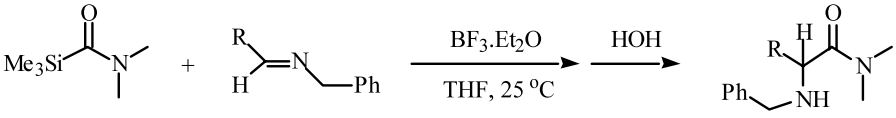
and 11). Alkyl, alkenyl, aryl and heteroaryl carbimines are all amenable to the transformation, but acetylenic substitution led to only high molecular weight material. The imine employed in entry 11, Table 1, was prepared from (*S*)-α-phenylethylamine instead of benzylamine, and was found (THF run) to afford the amide adduct in a stereoselective fashion (diastereomer ratio of 2:1). We are currently examining combinations of this and other chiral auxiliaries which may allow an increase in the stereoselectivity of the addition process.



(1)

Acknowledgements

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6. **Typical procedure**. A Schlenk tube fitted with a Teflon vacuum stopcock was flame-heated under vacuum and refilled with Ar imine (0.3–0.8 mmol) and 1.6 mL of anhydrous THF (or other solvent) was added at ice bath temperature. After 20 min, an equivalent amount of BF_3 diethyl etherate was added and the mixture stirred for 30 min. One (or 1.5) equivalent(s) of (*N*,*N*-dimethylcarbamoyl)trimethylsilane was then added and the reaction held at 25°C. Generally 15–20 h were needed for complete consumption of the carbamoylsilane (1:1 mol ratio). Progress of the reaction was followed by monitoring the disappearance of the TMS peak of the carbamoylsilane in the ^{1}H NMR spectra of aliquots. The mixture was hydrolyzed in aqueous Na_2CO_3, extracted with CH_2Cl_2, and the dried ($MgSO_4$) extract subjected to flash chromatography on silica gel (hexane–acetone).
7. **Characterization data for α-aminoamides**. All NMR spectra were obtained at 11.75 T in $CDCl_3$. IR spectral data are from neat films. **R=Et**: IR: 3522, 1643, 1262 cm^{-1}. ^{1}H NMR: δ 7.2–7.4, m, 5H; 3.83 (d, J=13 Hz), 1H; 3.54 (d, J=13 Hz); 3.43 (t, J=6 Hz), 1H; 3.02 (s), 3H; 2.95 (s), 3H; 2.19 (br s), 1H; 1.5–1.7 (m), 2H; 0.98 (t, J=7.5 Hz), 3H. ^{13}C NMR: δ 175.0, 140.3, 128.6, 128.3, 126.9, 58.0, 52.1, 36.7, 35.6, 26.8, 10.4. Anal. calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72 Found: C, 71.15; H, 8.90; N, 12.50. **R=*i*Pr**: IR: 3317, 1642, 1264 cm^{-1}. ^{1}H NMR: δ 7.2–7.4 (m), 5H; 3.85 (d, J=13.5 Hz), 1H; 3.50 (d, J=13.5 Hz), 1H; 3.23 (d, J=6 Hz), 1H; 3.02 (s), 3H; 2.91 (s), 3H; 2.20 (br s), 1H; 1.82 (m), 1H; 1.00 (d, J=6.5 Hz), 3H; 0.95 (d, J=6.5 Hz), 3H. ^{13}C NMR: δ 175.1, 140.5, 128.5, 128.2, 126.8, 62.0, 52.3, 36.9, 35.6, 31.7, 19.8, 18.2. Anal. calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.77; H, 9.60; N, 11.75. **R=CF_3**: IR: 3321, 1656, 1264 cm^{-1}. ^{1}H NMR: δ 7.25–7.4 (m), 5H; 4.02 (q, J=7 Hz), 1H; 3.90 (d, J=13.5 Hz), 1H; 3.71 (d, J=13.5 Hz), 1H; 3.01 (s), 3H; 2.92 (s), 3H; 2.89 (br s), 1H. ^{13}C NMR: δ 166.5, 138.5, 128.5, 128.4, 127.5, 126.2 (q, J=282 Hz), 57.3 (q, J=28 Hz), 51.7, 37.1, 36.2. Anal. calcd for $C_{12}H_{15}F_3N_2O$: C, 55.38; H, 5.81; N, 10.76. Found: C, 55.66; H, 5.63; 10.58. **R=(*E*)-PhCH=CH**: IR: 3314, 1649 cm^{-1}. ^{1}H NMR: δ 7.25–7.45 (m), 10H; 6.54 (d, J=16 Hz), 1H; 6.19 (dd, J=16 Hz, J=7.5 Hz), 1H; 4.20 (d, J=7.5 Hz), 1H, 3.81 (AB pattern, J=14.5 Hz), 2H; 3.04 (s), 3H; 3.01 (s), 3H; 2.46 (br s), 1H. ^{13}C NMR: δ 172.0, 139.9, 136.3, 133.0, 128.6, 128.41, 128.37, 127.9, 127.0, 126.7, 126.5, 59.7, 51.1, 36.7, 35.9. Anal. calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.50; H, 7.29; N, 9.50. **R=Ph**: IR: 3329, 1648, 1263 cm^{-1}. ^{1}H NMR: δ 7.2–7.4 (m), 10H; 4.52 (s), 1H; 3.73 (AB pattern, J=13 Hz), 2H; 3.01 (s), 3H; 2.84 (s), 3H; 2.77 (br s), 1H. ^{13}C NMR: δ 172.1, 139.9, 138.6, 128.8, 128.4, 128.3, 127.8, 126.9 (one aromatic C believed coincident), 61.6, 51.3, 36.7, 35.9. Anal. calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.96; H, 7.84; N, 10.34. **R=2-furyl**: IR: 3328, 1649, 1263 cm^{-1}. ^{1}H NMR: δ 7.25–7.4 (m), 6H; 6.33 (dd, J=3 Hz, J=2 Hz), 1H; 6.25 (d, J=3 Hz), 1H; 4.56 (s), 1H; 3.72 (AB pattern, J=14.5 Hz), 2H; 2.99 (s), 3H; 2.88 (s), 3H; 2.79 (br s), 1H. ^{13}C NMR: δ 171.7, 153.7, 141.9, 138.3, 128.9, 128.4, 127.9, 110.1, 107.2, 61.6, 44.1, 36.7, 35.9. Anal. calcd for $C_{15}H_{18}N_2O_2$: C, 69.75; H, 7.02; N, 10.84. Found: C, 69.75; H, 7.05; N, 10.64. **R=2-(thiophene)yl**: IR: 3319, 1649, 1258 cm^{-1}. ^{1}H NMR: δ 7.25–7.45 (m), 6H; 6.97 (m), 1H; 6.92 (d, J=3.5 Hz), 1H; 4.78 (s), 1H; 3.77 (AB pattern, J=13 Hz), 2H; 3.03 (s), 3H; 2.93 (s), 3H; 2.71 (br s), 1H. ^{13}C NMR: δ 171.5, 142.2, 139.6, 128.4 (intensity and bandwidth suggests coincident absorptions), 127.0, 126.6, 125.6, 125.3, 56.5, 51.1, 36.9, 35.9. Anal. calcd for $C_{15}H_{18}N_2OS$: C, 65.66; H, 6.61; N, 10.21. Found: C, 65.29; H, 6.56; N, 10.24. **R=2-pyridyl**: IR: 3312, 1649, 1261 cm^{-1}. ^{1}H NMR: δ 8.50 (d, J=4.5 Hz), 1H; 7.70 (t, J=8 Hz), 1H; 7.48 (d, J=8 Hz), 1H; 4.82 (s), 1H; 3.78 (AB pattern, J=13 Hz), 2H; 3.01 (s), 3H; 3.00 (s), 3H; 2.96 (br s), 1H. ^{13}C NMR: δ 171.7, 159.2, 149.0, 139.8, 137.0, 128.4, 128.3, 127.0, 122.5, 121.8, 63.7, 51.8, 37.0, 35.9. Anal. calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.10; H, 7.34; N, 15.70. **R=CO_2Et (*N*-[(*S*)-α-phenylethyl])**: IR: 3327, 1746, 1656, 1266 cm^{-1}. ^{1}H NMR (major diastereomer):δ 7.2–7.4 (m), 5H; 4.23 (q, J=5 Hz), 2H; 4.04 (s), 1H; 3.81 (q, J=7 Hz), 1H, 2.90 (s), 3H; 2.79 (s), 3H; 2.68 (br s), 1H; 1.38 (d, J=7 Hz), 3H; 1.23 (t, J=5 Hz), 3H. ^{13}C NMR (major diastereomer): δ 170.0, 168.0,

144.2, 128.4, 127.4, 127.2, 61.4, 60.0, 56.5, 37.2, 35.8, 24.4, 14.2. ^{1}H NMR (minor diastereomer): δ 7.2–7.4 (m), 5H; 4.17 (m), 2H; 4.16 (s), 1H; 3.69 (q, $J=6$ Hz), 1H; 3.00 (s), 3H, 2.83 (s), 3H; 2.68 (br s), 1H; 1.30 (d, $J=7$ Hz), 3H; 1.24 (t, $J=6$ Hz), 3H. ^{13}C NMR (minor diastereomer): δ 168.3, 168.7, 144.3, 128.5, 127.3, 127.0, 61.5, 59.8, 56.0, 37.0, 36.1, 24.6, 14.0. Anal. calcd for $C_{15}H_{22}N_2O_3$ (mixture of diastereomers): C, 64.73; H, 7.97; N, 10.06. Found: C, 64.65; H, 7.92; N, 10.08.