nance data (^{13}C NMR) were obtained on a Varian CFT-20 instrument with Me_4Si as the internal standard. A Perkin-Elmer RMU-7 mass spectrometer was used to record mass spectral data at 70 eV. Melting points were determined by using a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or by M-H-W Laboratories, Phoenix, AZ.

General Procedure for the Preparation of 9-Arylfuro[3,4-*b*]quinolin-1(3*H*)-ones 3a-d. To a melt of the appropriate 2-aminobenzophenone was added an equimolar amount of 1 and a few milliliters of concentrated hydrochloric acid. The mixture usually solidifies quickly upon cooling. Recrystallization from ethanol afforded the pure products (if necessary the hot solution was decolorized with Norit A).

9-Phenylfuro[3,4-*b*]quinolin-1(3*H*)-one (3a): yield 51%; mp 204-205 °C (lit.[3] mp 204-205 °C); ^1H NMR (Me_2SO-d_6 and $CDCl_3$) δ 5.6 (s, 2 H, CH_2), 7.0-8.4 (m, 9 H, aromatic H); IR (KBr) 1770 (C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 261 (M^+, 100), 262 (M + 1, 19).

9-(2-Fluorophenyl)furo[3,4-*b*]quinolin-1(3*H*)-one (3b): yield 59.4%; mp 177-178 °C; ^1H NMR (Me_2SO-d_6) δ 5.6 (s, 2 H, CH_2), 7.08-8.48 (m, 8 H, aromatic H); IR (KBr) 1770 (C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 279 (M^+, 100), 250 (M - 29, 72). Anal. Calcd for $C_{17}H_{10}FNO_2$: C, 73.11; H, 3.61; N, 5.02. Found: C, 72.88; H, 3.65; N, 4.99.

7-Chloro-9-phenylfuro[3,4-*b*]quinolin-1(3*H*)-one (3c): yield 80.8%; mp 281-282 °C; ^1H NMR δ 5.6 (s, 2 H, CH_2), 7.83-9.1 (m, 8 H, aromatic H); IR (KBr) 1770 (C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 295 (M^+, 100), 297 (M + 2, 25). Anal. Calcd for $C_{17}H_{10}ClNO_2$: C, 69.04; H, 3.41; Cl, 11.99. Found: C, 68.81; H, 3.61; Cl, 12.33.

9-(4-Methylphenyl)furo[3,4-*b*]quinolin-1(3*H*)-one (3d): yield 64%; mp 226 °C; ^1H NMR (Me_2SO-d_6) δ 2.5 (s, 3 H, CH_3), 5.5 (s, 2 H, CH_2), 7.4-8.2 (m, 8 H, aromatic H); IR (KBr) 1780 (C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 275 (M^+, 100), 276 (M + 1, 20). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.60 H, 4.70; N, 4.89.

General Procedure for the Preparation of Furo[3,4-*b*]quinolin-1(3*H*)-ones 4a-c. Equivalent amounts of the appropriate 2-aminobenzaldehyde and 1 were dissolved in absolute ethanol and stirred at room temperature for several hours and monitored by TLC. (In the case of **4b** a few drops of conc. hydrochloric acid were added). The formed precipitate was filtered and recrystallized from acetonitrile (**4a**) or absolute ethanol (**4b**, **4c**).

Furo[3,4-*b*]quinolin-1(3*H*)-one (4a): yield 79%; mp 224-225 °C (lit.[3] mp 219-220 °C); ^1H NMR (Me_2SO-d_6) δ 5.60 (s, 2 H, CH_2), 7.60-8.53 (m, 4 H, aromatic H), 9.16 (s, 1 H, H at 9-position); IR (KBr) 1760 (C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 185 (M^+, 61), 156 (M - 29, 100). Anal. Calcd for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.56; H, 3.86; N, 7.54.

1,3-Dioxolo[4,5-*g*]furo[3,4-*b*]quinolin-8(6*H*)-one (4b): yield 75.1% (crude); mp 284-285 °C; ^1H NMR (Me_2SO-d_6) δ 5.52 (s, 2 H, CH_2), 6.37 (s, 2 H, OCH_2O), 7.55 (d, 1 H, $J \simeq 1$ Hz, H at 4-position), 7.67 (d, 1 H, $J \simeq 1$ Hz, H at 10-position), 8.85 (s, 1 H, H at 9-position); IR (KBr), 1765 (C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 229 (M^+, 88), 200 (M - 29, 100). Anal. Calcd for $C_{12}H_7NO_4$: C, 62.88; H, 3.08; N, 6.11. Found: C, 62.89; H, 2.88; N, 6.09.

Furo[3,4-*b*]naphthyridin-1(3*H*)-one (4c): yield 79%; mp 266-267 °C; ^1H NMR (Me_2SO-d_6) δ 5.65 (s, 2 H, CH_2), 7.73-9.32 (m, 4 H, aromatic H); IR (KBr) 1760 (C=O) cm^{-1}; mass spectrum, *m/e* 186 (M^+), 157 (M - 29). Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.51; H, 3.52; N, 15.05. Found: C, 64.42; H, 3.34; N, 14.93.

3,3'-[(4-Amino-5-pyrimidinyl)methylene]bis[4-hydroxy-2(5*H*)-furanone] (5). To 4-amino-5-formylpyrimidine (0.308 g, 2.5 mmol) dissolved in refluxing 2-propanol (10 mL) was added 1 (0.250 g, 2.5 mmol). A clear solution resulted; then, within a few minutes a precipitate began to form. After being refluxed for 1 h, the reaction mixture was cooled to room temperature. The precipitate was isolated by filtration and washed with hot 2-propanol and with hot acetonitrile to give the bis adduct: 0.351 g (92%); mp >300 °C (the substance slowly darkens and chars with heating); ^1H NMR (Me_2SO-d_6) δ 4.33 (s, 1 H, ≥C-CH-C≤, 4.52 (s, 4 H, CH_2), 8.06 (br s, 1 H, aromatic H), 8.73 (br s, 1 H, aromatic H), 9.1 (br s, 2 H, NH_2, D_2O exchangeable), 11.75 (br s, 2 H, C=COH, D_2O exchangeable); IR (KBr) 3365, (NH_2), 3165-3135 (enolic OH), 1730 (C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 205 (M - 100, 10), 187 (M - 118, 100). Anal. Calcd for $C_{13}H_{11}N_3O_6$: C, 51.15, H, 3.65; N, 13.77. Found: C, 51.24; H, 3.80; N, 13.49.

***tert*-Butyl 7-[(2,5-Dihydro-5-oxo-2-furanyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (7).** To a stirred solution of the *tert*-butyl ester of cephamic acid (0.2702 g, 10 mmol) in absolute ethanol was added 1 (1.00 g, 10 mmol). Initial crystal formation occured after 40 h, but stirring was continued for an additional 16 h. Filtration and recrystallization from methanol gave 7 as colorless crystals: 0.1127 g (32 %); mp 215-216 °C; ^1H NMR ($CDCl_3$ and Me_2SO-d_6) δ 1.5 (s, 9 H, $C(CH_3)_3$), 2.03 (s, 3 H, CH_3), 3.5 (d, 2 H, J = 6 Hz, OCH_2), 4.6-5.7 (m, 5 H), 8.2 (d, 1 H, $J \simeq 6$ Hz, NH, D_2O exchangeable); IR (KBr) 3225 (NH), 1740, 1730, 1710, (3 C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.53; H, 5.72; N, 7.95. Found: C, 54.17; H, 5.56; N, 7.89.

3-(1,3-Dihydro-1,3-dioxo-2*H*-inden-2-ylidene)-2,4-(3*H*,5*H*)-furandione Dihydrate (11). Combined with stirring in water were ninhydrin monohydrate (0.891 g, 5 mmol) and 1 (1.00 g, 10 mmol). Precipitation of product began quickly. After 15 min, TLC of the supernatant indicated complete reaction. The precipitate was isolated by filtration, washed generously with water, and dried at 80 °C in vacuo over P_4O_{10}. The yield of analytically pure product was 1.23 g (88.4%): mp 175-176 °C; ^1H NMR (Me_2SO-d_6) δ 4.76 (s, 2 H), 8.07 (s, 4 H), 8.78 (br s, 4 H, D_2O exchangeable); ^{13}C NMR (Me_2SO-d_6) δ 67.6 (CH_2, t), 74.8 (s), 95.7 (s), 123.5, (aromatic, d), 136.6 (aromatic, d), 140.1 (aromatic), 172.0, (s, C=O), 177.6 (s, C=O), 197.7 (s, C=O); IR (KBr) 3450 (H_2O), 1740, 1720 (2 C=O) cm^{-1}. Anal. Calcd for $C_{13}H_6O_5 \cdot 2H_2O$: C, 56.12; H, 3.62. Found: C, 55.88; H, 3.23.

5-(4,5-Dihydro-2,4-dioxo-3(2*H*)-furanylidene)-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione Monohydrate (12). Combined in anhydrous dimethoxyethane (DME, distilled from CaH_2, 10 mL) were alloxan monohydrate (1.60 g, 10 mmol) and 1 (2.00 g, 20 mmol). While the reaction mixture was stirred, a white precipitate formed. After 3 days at room temperature, the solid was removed by filtration, washed with DME, and dried at 80 °C in vacuo over P_4O_{10}: yield 1.97 g (81%); mp, foams at 204 °C then slowly deocmposes with increasing temperature; ^1H NMR (Me_2SO-d_6) δ 4.77 (s, 2 H, CH_2), 9.03 (br s, 2 H), 11.47 (s, 2 H, both D_2O exchangeable); ^{13}C NMR (Me_2SO-d_6) δ 67.3 (t, CH_2), 71.5 (s, C=C), 96.5 (s, C=C), 149.7 (s, C=O), 169.2 (s, C=O), 171.9 (s, C=O), 177.0 (s, C=O); IR (KBr) 3420, 3410, 3070, 2870 (H_2O, NH), 1705 (C=O), 1410 cm^{-1}. Anal. Calcd for $C_8H_4N_2O_6 \cdot H_2O$: C, 39.68; H, 2.50; N, 11.66. Found: C, 39.69; H, 2.51; N, 11.66.

Registry No. 1, 4971-56-6; **3a**, 85422-43-1; **3b**, 85422-44-2; **3c**, 85422-45-3; **3d**, 85422-46-4; **4a**, 4945-38-4; **4b**, 6720-24-7; **4c**, 85422-47-5; **5**, 85422-48-6; **7**, 85422-49-7; **9**, 938-24-9; **10**, 50-71-5; **11**, 85422-50-0; **12**, 85422-51-1; *o*-aminobenzophenone, 2835-77-0; 2-amino-2'-fluorobenzophenone, 1581-13-1; 2-amino-5-chlorobenzophenone, 719-59-5; 2-amino-4'-methylbenzophenone, 36192-63-9; *o*-aminobenzaldehyde, 529-23-7; *o*-aminopiperonal, 23126-68-3; 2-amino-3-formylpyridine, 7521-41-7; 5-formyl-6-aminopyrimidine, 16357-83-8; *tert*-butyl cephamate, 33610-06-9.

Sodium-Liquid Ammonia Reduction of Carboxamides to Alcohols

István Schön,* Tamás Szirtes, Tamás Überhardt, and Attila Csehi

Chemical Works of Gedeon Richter, Ltd., H-1475 Budapest, Hungary

Received July 1, 1982

A partial reduction of amides of simple carboxylic acids to alcohols in liquid NH_3 by Na was first reported in 1912;[1,2] however, this reaction as a source of side reactions

0022-3263/83/1948-1916$01.50/0

Table I. Results of Na-Liquid NH_3 Reduction of Carboxamides

starting material	R_f	method	product	R_f	yield, %	mp, °C	$[\alpha]^{25}_D$, deg
1	0.20[a]	A	2[b,c]	0.40[a]	84.2	147-149	−3.85[d]
1	0.20[a]	B	2[b,c]	0.40[a]	77.5	147-149	−3.75[d]
3	0.20[a]	A	4[c]	0.40[a]	75.8	133-134	+8.40[e]
DL-3	0.20[a]	A	DL-4[c]	0.40[a]	78.3	147-150	
5	0.10[f]	B	6[g]	0.35[f]	79.3	135-136	+12.50[h]
7	0.50[f]	A	8[i]	0.55[f]	72.3	60-62	−20.90[j]
7	0.50[f]	B	8[i]	0.55[f]	77.0	58-59	−20.90[j]
9	0.40[a]	A	10[c]	0.55[a]	8.0	130-132	0[e]
11[k]	0.35[f]	A	12	0.40[f]	20[l]	not isolated	
			13	0.08[f]	22.0	131-136	
			17	0.70[m]	14.7	101-104	
14	0.60[a]	A[n]	15	0.65[a]	40.5	oil	
			16	0.40[a]	3.6	120-121	
14	0.60[a]	B[n]	15	0.65[a]	45.0	oil	
			16	0.40[a]	4.3	124-125	

[a] TLC in EtOAc/stock (4:1; see Experimental Section). [b] In ref 6: mp 149-150 °C; $[\alpha]^{25}_D$ −3.5° (c 2.0, DMF). In ref 3 and 4: mp 143-146 °C; $[\alpha]^{25}_D$ −3.25° (c 2.0; DMF). [c] Isolated as the DCHA salt. [d] c = 2.0 in DMF. [e] c = 1.0 in EtOH. [f] TLC in solvent system 4. [g] Isolated as the hemioxalate salt. [h] c = 2.0 in 80% EtOH. [i] See ref 11. [j] c = 1.2 in 1 N HCl; $[\alpha]^{25}_D$ −9.15° (c 5.0; EtOH). [k] Used as its hemioxalate salt. [l] Estimated conversion of 11 to 12 by TLC. [m] TLC in solvent system 1. [n] See Experimental Section.

in peptide chemistry has been only recently demonstrated.[3,4] As under the usual conditions of Na–liquid NH_3 reduction the reaction mechanism includes the simultaneous salt formation and partial reduction of the $CONH_2$ group to CH_2OH, so a complete reduction cannot be achieved, and the amount of the reduced product seems to be independent of the excess of Na used and of the duration of the treatment.[1-4]

Considering the competitiveness of salt formation and reduction of the $CONH_2$ group as well as the participation of other proton-donor functional groups in the mechanism,[3,4] we have developed two, theoretically identical methods for complete transformation of the $CONH_2$ group to CH_2OH. *N-tert*-(Butoxycarbonyl)-L-asparagine[5] (Boc-Asn-OH, 1) dissolved in liquid NH_3 was treated with 2 mol of Na/mol. When the Na was consumed, 1 mol of NH_4Cl/mol of 1 was added to the white suspension. The additions of 1 mol of Na/mol and subsequently 1 mol of NH_4Cl/mol were repeated 11 times, but for the final addition 2 mol of NH_4Cl/mol was added to the reaction mixture (method A). It is unnecessary to wait for the disappearence of the Na added in each cycle; it is sufficient to maintain the blue color of the reaction mixture for a period the same as that experimentally determined for complete comsumption of Na in the first cycle (10–15 min). Under these conditions the carboxamidate salt, formed simultaneously with *tert*-butoxycarbonyl-L-homoserine (2),[3,4,6,7] decomposes to 1 in the second step of each cycle, preparing it for the same competitive reactions of the next cycle. As the cycles follow each other, the amount of 1 gradually decreases, and its conversion to 2 proceeds. Deceleration of the Na consumption in the subsequent cycles is due to the increasing amount of 2, because OH group forms an alcoholate, but at a much slower rate as compared to the salt formation of the $CONH_2$ group. It should be mentioned that in this series of reactions the reduction of NH_4^+ ion, stemming from the salt formation of CO_2H group with NH_3, is the fastest one.[4]

Na–liquid NH_3 reduction of the $CONH_2$ group to CH_2OH could be accomplished in the presence of proton-donating compounds. Preliminary experiments had shown that the application of MeOH is appropiate for this purpose.[8] The reduction of 1 was carried out in the presence of 30 mol of MeOH/mol by using 10–20 mol of Na/mol (method B).[9] Apparently, the procedure of method B is simpler, but in some cases the formation of a voluminous and gelatineous precipitate hinders the efficient stirring of the reaction mixture (e.g., during the reduction of Boc-Gln-OH, 3). Application of method A eliminates this problem, as addition of NH_4Cl in each cycle generally results in dissolution of precipitates of different character.

Besides 1 the reductions of 3, H-Ala-NH_2 (5), and H-Phe-NH_2 (7) to 2-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-L-valeric acid (4), L-alaninol (6), and 3-(1,4-cyclohexadienyl)-L-alaninol (8), respectively, have been accomplished in good yields. Reduction of Boc-Asp-NH_2 (9), Boc-Lys-NH_2 (11), and Boc-Lys(Boc)-NH_2 (14) to 3-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-L-butyric acid (10), N_α-Boc-L-lysinol (12), and N_α,N_ϵ-bis(*tert*-butoxycarbonyl)-L-lysinol (15), respectively, was accompanied by N–C_α cleavage, resulting in formation of succinamic acid, ϵ-aminocapronamide (13), and ϵ-[*tert*-butoxycarbonyl)-amino]capronamide (16), respectively, together with *tert*-butyl carbamate (17) (Table I).

As we indicated earlier,[4] the formation of 17 was observed exclusively when an α-$CONH_2$ group was treated

(1) Chabley, M. E. *C. R. Hebd. Seances Acad. Sci.* **1912**, *154*, 364.
(2) Chabley, M. E. *Ann. Chim. (Paris)* **1917**, *8*, 201.
(3) Schön, I.; Szirtes, T.; Überhardt, T. *J. Chem. Soc., Chem. Commun.* **1982**, 369.
(4) Schön, I.; Szirtes, T.; Überhardt, T.; Rill, A.; Csehi, A.; Hegedüs, B. *Int. J. Peptide Protein Res.*, in press.
(5) All amino acids are of L configuration unless it is otherwise stated. Amino acids and their derivatives are used in their abbreviated form as recommended by tentative rules of the IUPAC-IUB Commission on Biochemical Nomenclature: *Biochem. J.* **1972**, *126*, 773. Other uncommon abbreviations used: OPfp, pentafluorophenoxy; DCC, dicyclohexylcarbodiimide; DCU, dicyclohexylurea; DCHA, dicyclohexylamine; Boc, *tert*-butoxycarbonyl; Z, benzyloxycarbonyl; Boc_2O, di-*tert*-butyl dicarbonate.
(6) Turan, A.; Manning, M.; Haldar, J.; Sawyer, W. H. *J. Med. Chem.* **1977**, *20*, 1169.
(7) Manning, M.; Turan, A.; Haldar, J.; Sawyer, W. H. "Peptides, Proceedings 5th American Peptide Symposium"; Goodman, M., Meienhofer, J., Eds; Wiley: New York, 1977; p 201.
(8) No reduction of 3 to 4 occured in the presence of 30 mol of NH_4Cl/mol. A 20–25% conversion of 3 to 4 was observed in the presence of 30 mol of *i*-PrOH/mol.
(9) Reduction of disubstituted carboxamides to aldehydes generally in poor yields was reported earlier.[10,11] Birch et al. mentioned the further reduction of aldehydes and formation of nitrogen-free products without referring to the formation of alcohols.
(10) Clemo, G. R.; King, T. J. *J. Chem. Soc.* **1948**, 1661.
(11) Birch, A. J.; Cymerman-Craig, J.; Slaytor, M. *Aust. J. Chem.* **1955**, *8*, 512.

with Na in liquid NH_3 but not in the presence of an α-CO_2H group (1, 3, and Boc-Gly-OH). Unfortunately, the other product of N–C_α cleavage of **9** is undetectable with the usual visualization technique. However, besides **17**, 3-phenylpropanamide and 3-(4-hydroxyphenyl)propanamide as well could be isolated from the reaction mixtures of Na–liquid NH_3 reduction of Boc-Phe-NH_2 and Boc-Tyr-NH_2, respectively.[4] Similarly, the treatments of **11** and **14** resulted in the formation of **12**, **13**, and **17** and of **15**, **16**, and **17**, respectively, giving further proof that the N–C_α cleavage is related to the presence of the α-$CONH_2$ group. The extent of the cleavage seems to be dependent on the electronic effects of the side chain which is in situ ionized.

Reduction of the free derivative **5** to **6** proceeds smoothly; however, a partial saturation of the β-Ph group has been observed in the reduction of **7** to **8**.[12] Because of the tendency of **8** to undergo spontaneous aromatization, it was also characterized as the stable hemimaleate salt (see Experimental Section). In these cases no N–C_α cleavage has been observed, so contrary to the Boc-protected derivatives the unprotected ones can be reduced to the corresponding alcohols in good yields.

The Na–liquid NH_3 reduction of $CONH_2$ may be a valuable process for preparation of other alcohol derivatives too, as the reduction is not affected by the presence of NH_2, CO_2H, OH, and SH but is affected by α-Boc and presumably other acylamino groups.

Experimental Procedures

Melting points were determined by using a Tottoli (Büchi) apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. Ascending thin-layer chromatography (TLC) was performed on precoated silica gel 60 sheets (Merck). Solvent systems were made by mixing EtOAc and a stock solution of pyridine/HOAc/water (20:6:11) in the following proportions: (1) EtOAc/stock, 19:1; (2) EtOAc/stock 9:1; (3) EtOAc/stock, 3:2; (4) EtOAc/stock, 1:1; (5) $CHCl_3$/MeOH, 9:1. The plates were visualized by spraying them with ninhydrin and then with tolidine/KI after chlorination. Column chromatography was performed by using Kieselgel nach Stahl of 0.062–0.20 mm and the appropiate solvent system. UV spectra were taken on a Pye Unicam SP 1800 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 700 IR spectrophotometer. ^1H NMR spectra were obtained on Varian EM-360 and Varian XL-100 instruments with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on the latter. Mass spectra were taken on an MS-902 instrument (70 eV, direct adsorption, 160 °C).

Starting materials not mentioned here were synthesized as described in ref 4. A mixture of H-Ala-NH_2 and $^+H_2$-Ala-NH_2·^-O_2C-Ala-NH_2 was prepared according to ref 13,[13] and this mixture represents **5**.

Boc-Lys-NH_2 (11). to a solution of 10.8 g (19.8 mmol) of Boc-Lys(Z)-OPfp[14] in 60 mL of dioxane was added 10 mL of 25% NH_4OH. After 1 h the solvent was removed, and the residue was triturated with ether and recrystallized from EtOAc/petroleum ether to yield 6.81 g (90.5%) of Boc-Lys(Z)-NH_2 (**19**): mp 136–137 °C; TLC R_f^2 0.50. An analytical sample was recrystallized from MeOH/ether: mp 137 °C; $[\alpha]^{25}_D$ +1.9° (*c* 1.0, MeOH).

A suspension of 6.3 g (16.6 mmol) of **19** in 60 mL of MeOH was hydrogenated at ambient pressure and temperature in the presence of 0.6 g of 10% Pd on charcoal. After 1 h the catalyst was removed, and 2.1 g (16.6 mmol) of oxalic acid dihydrate dissolved in 10 mL of MeOH was added to the filtrate. The suspension was concentrated to a volume of 20 mL and then diluted with ether, resulting in 5.24 g (94.0 %) of the hemioxalate of **11**: TLC R_f^2 0, R_f^3 0.75. An analytical sample was recrystallized from EtOH/EtOAc: mp 123–125 °C; $[\alpha]^{25}_D$ +1.0° (*c* 1.0; MeOH).

Boc-Lys(Boc)-NH_2 (14). To an ice-cooled solution of 15.95 g (46 mmol) of Boc-Lys(Boc)-OH (prepared from its DCHA salt[15] in the usual way) and 8.5 g (46 mmol) of PfpOH in 100 mL of dry dioxane was added 9.5 g (46 mmol) of DCC. After 2 h DCU precipitated and was filtered off, the solvent was removed, and the residue was recrystallized from diisopropyl ether, resulting in 20.34 g (86.5 %) of Boc-Lys(Boc)-OPfp (**20**): mp 104–106 °C; TLC R_f^5 0.75. An analytical sample was recrystallized from EtOAc/*n*-hexane: mp 105–107 °C; $[\alpha]^{25}_D$ –18.7° (*c* 1.0; dioxane).

To a solution of 19.3 g (37.6 mmol) of **20** in 100 mL of MeOH was added 100 mL of MeOH saturated with NH_3. The reaction mixture was evaporated. The residual oil dissolved in EtOAc was washed with 1M HCl. The solvent was removed, and the residue was triturated with diisopropyl ether. The crude product was twice recrystallized from EtOAc/petroleum ether, resulting in 9.66 g (74.0 %) of **14**: mp 108–112 °C; TLC R_f^2 0.65; $[\alpha]^{25}_D$ 0 (*c* 1.0, MeOH); IR (KBr) 1730–1630 (br, CO), 3360 and 3220 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.0 and 1.43 (m + s, 24 H, 2 *t*-Bu and β-, γ-, δ-CH_2), 3.1 (q, 2 H, ϵ-CH_2), 4.1 (m, 1 H, α-CH), 5.03 (br, 1 H, ϵ-NH), 5.7 (d, 1 H, α-NH), 6.4 and 6.8 (2 br, 2 H, $CONH_2$).

ϵ-[(*tert*-Butoxycarbonyl)amino]capronamide (16). The ϵ-[(*tert*-butoxycarbonyl)amino]caproic acid·DCHA salt was prepared from ϵ-aminocaproic acid in the usual way by using Boc_2O:[16] yield 91.0%; mp 93–94 °C; TLC R_f^2 0.65.

Compound **16** was prepared from ϵ-[(*tert*-butoxycarbonyl)-amino]caproic acid via the mixed anhydride method[17–19] with isobutyl chloroformate and 25% NH_4OH: mp 121–122 °C (recrystallized from EtOH/diisopropyl ether); TLC R_f^2 0.45; IR (KBr) 1730–1630 (amide and urethane), 3360 and 3220 (NH) cm^{-1}; ^1H NMR (Polysol-*d*) δ 1.4 and 0.9–1.8 (s + m, 15 H, *t*-Bu and β-, γ-, δ-CH_2), 2.06 (t, 2 H, α-CH_2), 2.46 (br, 2 H, NH_2), 2.9 (q, 2 H, ϵ-CH_2), 7.1 (br, 1 H, NH).

Na–Liquid NH_2 Reductions (See Table I for Results). Method A. To a dry-ice-cooled solution of 10.0 mmol of carboxamide derivative in 200 mL of dry liquid NH_3 distilled from Na was added 0.23 g (10.0 mmol) of Na. An additional 1 equiv of Na was used for each of the other proton-donor groups in the starting material. When the Na was consumed (10–15 min), 0.535 g (10.0 mmol) of NH_4Cl was added to the reaction mixture. A cycle consisting of alternate additions of 0.23 g of Na and 0.535 g of NH_4Cl was repeated 10–15 times, but in the last cycle NH_4Cl, equivalent to the Na used in the first cycle, was added to the reaction mixture. In the subsequent cycles the consumption of Na gradually slowed down; however, the blue color of the reaction mixture was maintained for 10–15 min.

Method B. Into a dry-ice-cooled solution of 10 mmol of carboxamide derivative in 11.4 mL (0.3 mol) of MeOH was distilled from Na 250 mL of NH_3, and 3.79 g (163 mmol) of Na in about 10-mmol portions was added to the reaction mixture, waiting for the disappearance of metallic Na before addition of more Na. When the foaming of the reaction mixture stopped, 10.7 g (0.2 mol) of NH_4Cl was added.

Workup of Reduction Mixtures of Boc-Asn-OH (1) and Boc-Gln-OH (3). After evaporation of NH_3, a solution of the residue in water was adjusted to pH 3 by addition of 18% HCl and then extracted five times with EtOAc. After the extract was dried over Na_2SO_4, the organic solvent was removed, and to a solution of the residue in ether was added 1.96 mL (10.0 mmol) of DCHA.

Workup of Reaction Mixture of L-Alaninol (6). After evaporation of NH_3, the residue was washed thoroughly with ether. To the filtrate was added 1.26 g (10.0 mmol) of oxalic acid di-

(12) Also the formation of 3-(cyclohexen-1-yl)alaninol (**18**) originating from an alternative stabilization of anion participating in the Birch reduction, was proved by mass and NMR spectra (see Experimental Section). Reduction of L-phenylalanine to 1,4-cyclohexadienyl-L-alanine was reported earlier: Nagarajan, G. R.; Diamond, L.; Ressler, C. *J. Org. Chem.* **1973**, *38*, 621 and references cited herein.

(13) Schön, I.; Kisfaludy, L. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1978**, *33B*, 1196.

(14) Kisfaludy, L.; Löw, M.; Nyéki, O.; Szirtes, T.; Schön, I. *Justus Liebigs Ann. Chem.* **1973**, 1421.

(15) Schnabel, E. *Justus Liebigs Ann. Chem.* **1967**, *702*, 188.

(16) Moroder, L.; Hallett, A.; Wünsch, E.; Keller, O.; Wersin, G. *Z. Physiol. Chem.* **1976**, *357*, 1651.

(17) Wieland, T.; Bernhard, H. *Justus Liebigs Ann. Chem.* **1951**, *572*, 190.

(18) Boissonnas, R. A. *Helv. Chim. Acta* **1951**, *34*, 874.

(19) Vaughen, J. R. *J. Am. Chem. Soc.* **1951**, *73*, 3547.

hydrate in 10 mL of MeOH. The precipitate was filtered off and recrystallized from MeOH.

Workup of Reaction Mixture of 3-(1,4-Cyclohexadienyl)-L-alaninol (8). After reduction of 9.80 g (40 mmol) of 7·HBr[20] according to method A, NH_3 was evaporated, and the residue dissolved in water was extracted with EtOAc. The organic solvent was removed, and the residue crystallized in ether was diluted with diisopropyl ether, resulting in 4.45 g (72.3%) of 8: IR (KBr) 3355 and 3270 (NH_2), 3150 (br) and 1056 (OH), 1593 (C=C), 1428, 962, 658 cm^{-1}, no peak characteristic to aromatic ring; ^1H NMR ($CDCl_3$) δ 1.75–2.25 (m, 5 H, NH_2 + OH + γ-CH_2), 2.65 (m, 4 H, 3',6'-CH_2) 3.0 (m, 1 H, β-CH), 3.3 and 3.6 (AB q, 2 H, α-CH_2), 5.5 (br, 1 H, 2'-CH), 5.7 (d, 2 H, 4',5'-CH); ^{13}C NMR ($CDCl_3$) δ 26.90 and 29.13 (3',6'-CH_2), 42.44 (γ-CH_2), 50.1 (β-CH), 66.55 (α-CH_2), 121.58 (2'-CH), 124.14 and 124.25 (4',5'-CH), 131.95 (1'-C). The structure of 8 is proved by these data and the UV spectra, where the conjugation of double bonds was excluded. 8 is not stable in the ambient atmosphere and slowly turns yellow.

To a solution of 4.0 g (26.0 mmol) of 8 in 50 mL of EtOAc was added 3.5 g (30.0 mmol) of maleic acid in EtOAc (50 mL)–EtOH (10 mL), resulting in 6.93 g of the hemimaleate salt of 8, mp 137–138 °C. An analytical sample was recrystallized from EtOH: mp 138–139 °C; $[\alpha]^{25}_D$ +5.95° (c 1.08; EtOH); ^1H NMR (Me_2SO-d_6/$CDCl_3$) δ 2.23 (d, 2 H, γ-CH_2), 2.63 (br, 4 H, 3',6'-CH_2), 2.9–3.3 (m, 1 H, β-CH), 3.56 (m, 2 H, α-CH), 5.56 (br, 1 H, 2'-CH), 5.68 (br s, 2 H, 4',5'-CH), 6.13 (s, 2 H, maleic CH=CH), 5.8–8.8 (br, 5 H, NH_3^+ + OH + CO_2H); mass spectrum, *m/e* (relative intensity) 152.107 (M – H, 0.8), 122 (4.3), 105 (4.5), 91 (6.5), 79 (5.5), 77 (4.3), 72 (6.2), 60.046 (100).

To the mother liquor of 4.45 g of 8 was added 1.20 g of maleic acid dissolved in EtOAc (20 mL)–EtOH (5 mL), resulting in a yellowish product: 2.15 g; mp 142–143 °C. Recrystallization from EtOH (15 mL) gave a mixture (about 1:1) of 8 (M_2) and 3-(cyclohexen-1-yl)alaninol (18, M_1) as hemimaleate salts: yield 0.73 g; mp 147–149 °C; $[\alpha]^{25}_D$ 0° (c 1.0, EtOH); IR (KBr) 3550–2200 (CO_2H), 1046 (OH), 1353, 1192, 957, 888, 864, 758, 703 cm^{-1}; ^1H NMR (KBr) δ 1.6 (br, 2 H) and 1.9 (br, 2 H) for 4'- and 5'-CH_2 in addition to the ^1H NMR spectrum of the hemimaleate salt of 8 with broader peaks; mass spectrum, *m/e* (relative intensity) 155 (M_1, 0.1), 152 (M_2 – H, 0.5), 124 (M_1 – 31, 10), 122 (M_2 – 31, 3.5), 81 (8), 79 (7), 60 (100).

Workup of Reduction Mixture of Boc-Lys-NH_2 (11). After reduction of 2.35 g (7.0 mmol) of 11 according to method A, NH_3 was evaporated, and the residue was washed with EtOH. The TLC picture of this solution was very heterogeneous. The presence of 17 (R_f^1 0.70), 12 (R_f^4 0.40), 11 (R_f^4 0.35), and 13 (R_f^4 0.08) was detected. The filtrate was evaporated, and ether was decanted from the residual oil. From this etheral solution was isolated 17: 0.12 g (14.6 %); mp 101–104 °C.

The residue of the original oil was chromatographed on a silica gel column by using solvent system 4. Because of poor resolution 13 was the only product isolated in a pure state: yield 0.20 g (22%); mp 131–136 °C; IR (KBr) 1650 (CO) cm^{-1}, no urethane; ^1H NMR (Me_2SO-d_6/$CDCl_3$) δ 1.5 (br, 6 H, β-, γ-, δ-CH_2), 2.1 (t, 2 H, α-CH_2), 2.65 (t, 2 H, ϵ-CH_2), 6.7 and 7.4 (br, 2 H, $CONH_2$), 7.7 (br, 2 H, NH_2). For confirmation of the structure, 13 was acylated with Boc_2O in the usual manner,[16] resulting in 16 which was identified by TLC, melting point, and IR and ^1H NMR spectra.

Workup of Reduction Mixture of Boc-Lys(Boc)-NH_2 (14). After evaporation of NH_3 the residue was extracted with EtOAc. Column chromatography on silica gel, by using EtOAc and solvent system 3, resolved 40.5% of 15 as an oil [TLC R_f^2 0.65; IR (film) 1685 (urethane), 1065 (OH), no amide; ^1H NMR ($CDCl_3$) δ 1.43 and 1.2–1.9 (s + m, 24 H, 2 *t*-Bu and γ-, δ-, ϵ-CH_2), 3.05 (m, 2 H, ζ-CH_2), 3.5 (m, 3 H, α-CH_2 + β-CH), 3.8 (br, 1 H, OH), 5.2 (m, 2 H, 2 NH)] and 3.6% of 16. The other products of the reductions with methods A and B could not be completely resolved.

Acknowledgment. We are grateful to B. Hegedüs for IR spectra, to Mrs. M. Rényei for UV spectra, to L. Radics for ^{13}C NMR spectra, to J. Tamás for mass spectra, and to Mrs. Z. Muck for her skillful technical assistance.

Registry No. 1, 7536-55-2; 2·DCHA, 63491-82-7; L-3, 13726-85-7; DL-3, 85535-45-1; L-4·DCHA, 85535-46-2; DL-4·DCHA, 85535-48-4; 5, 7324-05-2; 6·hemioxalate, 85535-49-5; 7, 5241-58-7; 7·HBr, 24730-33-4; 8, 85535-50-8; 8·hemimaleate, 85535-51-9; 9, 74244-17-0; 10·DCHA, 85535-52-0; 11·hemioxalate, 85535-53-1; 12, 85535-54-2; 13, 373-04-6; 14, 55592-82-0; 15, 85535-55-3; 16, 85535-56-4; 17, 4248-19-5; 18·hemimaleate, 85535-58-6; 19, 55592-81-9; 20, 85535-59-7; Boc-Lys(Z)-OPfp, 50903-59-8; Boc-Lys(Boc)-OH, 2483-46-7; ϵ-[(*tert*-butoxycarbonyl)amino]caproic acid·DCHA salt, 85535-60-0; ϵ-aminocaproic acid, 60-32-2; sodium, 7440-23-5; ammonia, 7664-41-7.

(20) Kisfaludy, L.; Schön, I.; Náfrádi, J.; Varga, L.; Varró, V. *Z. Physiol. Chem.* **1978**, *359*, 887.

Sunlamp-Irradiated Phase-Transfer Catalysis. 2.[1] Cobalt Carbonyl Catalyzed Carbonylation of Benzyltriethylammonium or Allyltriethylammonium Halides under 1 atm of Carbon Monoxide

Jean-Jacques Brunet, Christian Sidot, and Paul Caubere*

Laboratoire de Chimie Organique I, ERA CNRS No. 476, Université de Nancy I, BP 239, 54506 Vandoeuvre les Nancy Cédex, France

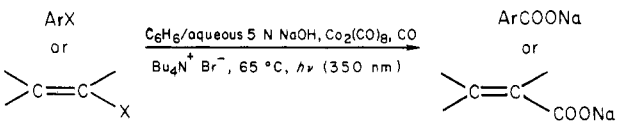
Received July 16, 1982

In a previous publication,[2] we have shown for the first time that cobalt-catalyzed carbonylation (1 atm of CO) of aryl and vinyl halides can be easily achieved provided that the reaction medium is irradiated. These reactions were performed under photostimulated (350 nm in a Rayonet device) phase-transfer-catalysis (PTC) conditions (C_6H_6/aqueous NaOH) in the presence of catalytic amounts of both $Co_2(CO)_8$ and $Bu_4N^+Br^-$ (Scheme I). The corresponding acids were obtained in high yields.

Since these first results, we have been able to show that simple irradiation through Pyrex flasks with an inexpensive commercial sun lamp is sufficient to perform these reactions.[1,3] Moreover, we also showed that a number of these reactions might be performed in aqueous sodium hydroxide, i.e., without an organic solvent.[1]

Numerous arguments support a $S_{RN}1$ type mechanism (Scheme II)[1] between the aryl (or vinyl) halide and $Co(CO)_4^-$ generated in situ from $Co_2(CO)_8$.[5]

Scheme I



Of course, most of these carbonylations necessitated the use of an ammonium salt as phase-transfer catalyst. During the preliminary study of the influence of the structure of the ammonium salt on the course of the carbonylation, we observed that under the above conditions, benzyltriethylammonium chloride was easily carbonylated

(1) For part 1, see: J. J. Brunet, C. Sidot, and P. Caubère, *J. Org. Chem.*, in press.
(2) J. J. Brunet, C. Sidot, and P. Caubère, *Tetrahedron Lett.*, **22**, 1013 (1981).
(3) We have also proposed the alternative use of $Co(NO_3)_2$ for the in situ generation of $Co(CO)_4^-$ according to ref 4.
(4) A. A. Blanchard and P. Gilmont, *J. Am. Chem. Soc.*, **62**, 1192 (1940).
(5) H. Alper, H. des Abbayes, and D. des Roches, *J. Organomet. Chem.*, **121**, C31 (1976). See also H. Alper, *Adv. Organomet. Chem.*, **19**, 183 (1981).

0022-3263/83/1948-1919$01.50/0