55. An Easy and Fast Conversion of N^2-[(*tert*-Butoxy)carbonyl]-L-amino Acids to Corresponding Amino-aldehydes

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A new method for the preparation of N^2-[(*tert*-butoxy)carbonyl]-L-amino-aldehydes from N^2-[(*tert*-butoxy)carbonyl]-L-amino acids based on reduction of mixed anhydrides with LiAl(*t*-BuO)$_3$H is described.

1. Introduction. – *N*-Protected amino-aldehydes are important intermediates for the preparation of serine and cysteine proteinase inhibitors [1–3] or the formation of pseudopeptides [4]. Because we are interested in the development of new proteinase inhibitors and because the preparation of some peptide aldehydes was necessary, we developed a fast and straightforward method for the synthesis of N^2-Boc-amino-aldehydes (Boc = (*tert*-butoxy)carbonyl) as starting material for our subsequent work.

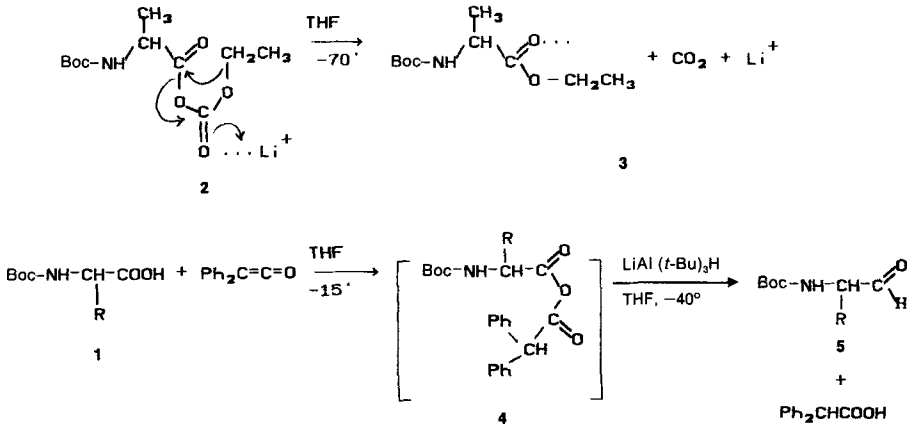
Ito et al. [5] described a synthesis of N^2-Z-amino-aldehydes (Z-benzyloxycarbonyl; 30–60% yield) *via* reduction of corresponding protected amino acid methyl esters by Al(i-Bu)$_2$H. The N^2-Z-amino aldehydes were purified as semicarbazones because of their high degree of racemisation (by keto-enol tautomerism) on silica gel [5]. These semicarbazones were stable enough during deprotection of common amino-protective groups [5] [10], and they were suitable for the incorporation into the peptide chain and the subsequent deprotection by formaldehyde in acidic medium to give the free aldehyde [5] [6].

Fehrentz and *Castro* [7] described the preparation of very pure N^2-Boc-amino-aldehydes *via* $LiAlH_4$ reduction of *N*-methoxy-*N*-methylamides of corresponding acids. The purity of the final products is, according to our experience, determined by the purity of the starting *N*-methoxy-*N*-methylamides which were purified by chromatography or by crystallisation.

Argininal and/or its derivatives occupy an exclusive position, and preparation of N^2-Boc-N^7-Z-argininal was commonly achieved *via* $LiAlH_4$ reduction of its δ-lactam [8] [9–11]. The reduction of N^2-Boc-N^7-nitroarginin methyl ester by Al(i-Bu)$_2$H was decribed [5] [12], as well as the $LiAlH_4$ reduction of *N*-methyl-*N*-methoxyamide [13].

2. Results and Discussion. – We investigated the reduction of mixed anhydrides of Boc-L-amino acids **1** used commonly in peptide chemistry as activating agents, with LiAl(*t*-Bu)$_3$H. The latter is known as a selective reducing agent for acyl halides [14] and *C*-acyl formiminium salts [15]. Reduction of N^2-Boc-L-alanine ethoxycarbonic anhydride (**2**) with LiAl(*t*-Bu$_3$)H yielded a mixture of the desired N^2-Boc-L-alaninal and ethyl Boc-L-alaninate (**3**). The formation of **3** is explained by a fast proceeding S_Ni substitution due to polarisation of C=O bond by the Li-cation (*Scheme 1*).

Scheme 1



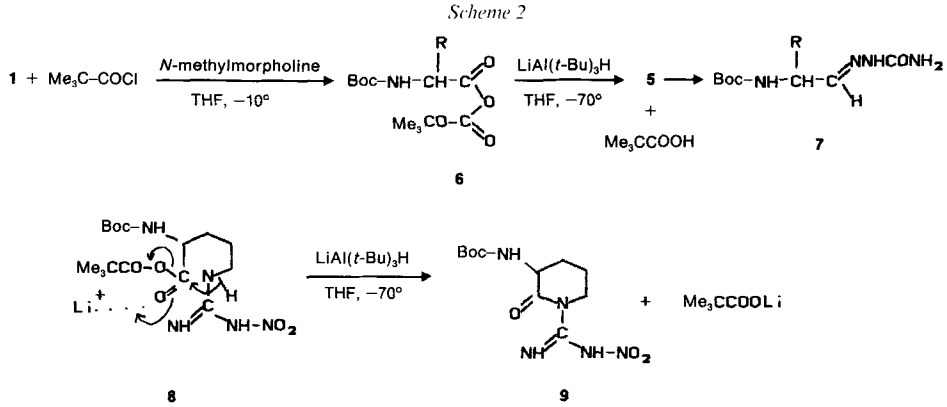
R = Me, i-Pr, Me_2CHCH_2, $MeSCH_2CH_2$, $PhCH_2$, (indol-3-yl)methyl

Reduction of mixed anhydrides unable to undergo a rearrangement of the type **2** → **3** should lead to the corresponding aldehydes: Thus, we prepared first the mixed anhydrides **4** derived from diphenylacetic acid because of their easy generation without by-products from *N*-Boc-L-amino acids and diphenylketene [16] (*Scheme 1*). The reduction of **4** led to aldehydes **5** contaminated by diphenylacetic acid which was hardly removable. After conversion of the aldehyde **5** to their semicarbazones, the mixtures could be separated by silica-gel chromatography.

Reduction of mixed anhydrides **6**, obtained from **1** and pivalic acid in THF with *N*-methylmorpholine as base, yielded the aldehydes **5** in *ca.* 90% chemical purity (impurities on TLC) with negligible racemisation (according to ^{1}H-NMR; *Scheme 2*).

The accompanying pivalic acid was removed by extraction with diluted Na_2CO_3 solution and by weakly basic resin, and the aldehydes were converted to the semicarbazones **7** [5].

Scheme 2



Reaction of N^2-Boc-N^7-nitro-L-arginine pivalic anhydride (**8**) with LiAl(*t*-BuO)$_3$H yielded cylic lactam **9**, known as a by-product in mixed-anhydride-method activation of N^2,N^7-diprotected arginines [8]. This observation is in good agreement with the report [17] on the formation of **9** in the reaction of N^2-Boc-N^7-nitroarginine isobutoxycarbonic anhydride and organolithium compounds. A fast cyclisation of mixed anhydride **8** due to polarisation of the carbonyl O-atom is proposed to explain the formation of **9**. The latter might be converted to the desired aldehyde *via* $LiAlH_4$ reduction [10].

Experimental Part

1. *General.* Boc-Amino acids were purchased from *Fluka*, others from *Merck*. TLC: *Silufol UV 254* (*CSFR*); detection by UV light or by spraying with 1% dinitrophenylhydrazine in 2N HCl; mobil phases (*v/v*): *A*, hexane/AcOEt 1:1; *B*, hexane/AcOEt 2:1; *C*, AcOEt/EtOH 8:1; *D* $CHCl_3$/EtOH 10:1. NMR Spectra: *Varian-200* spectrometer; in $CDCl_3$; δ in ppm tel. to Me_4Si as internal standard (= 0 ppm). Optical rotation: at 20° in MeOH (*c* = 1); *Polamat A*. Elemental analyses: *Carlo Erba 1106*.

2. *General Procedure for the Pivaloyl Chloride Method.* To a stirred soln. of N^2-Boc-L-amino acid (0.01 mol) and *N*-methylmorpholine (0.01 mol) cooled to −10° under dry N_2, pivaloyl chloride (0.01 mol) was added. After stirring at −10° for 20 min, the precipitated *N*-methylmorpholine hydrochloride was removed and the soln. of anhydride **6** filtered under dry N_2 into a pre-cooled flask (CO_2/EtOH bath) through a cooled frite. The soln. of **6** was cooled to −70° and LiAl(*t*-BuO)$_3$H (0.011 mol, 2.6 g) in THF (20 ml) added dropwise. After the addition the mixture was stirred for 10 min at −70°, poured into 20% citric acid (20 ml), and extracted with AcOEt (4×). The org. layer was washed with 10% Na_2CO_3 (2 × 20 ml), dried ($MgSO_4$), stirred 10 min with *Amberlite IRA-93* (10 g), and evaporated. Volatile by-products were removed at 0.6 Torr.

The removal of precipitated *N*-methylmorpholine hydrochloride could be omitted, when 2 equiv. of reducing agent were used.

Using N^2-Boc-N^8-nitro-L-arginine, lactam **9** was obtained and purified by flash chromatography.

3. *Data of Aldehydes* **5**. *Prepared According to* Exper. 2. N^2-*[(*tert-*Butoxy)carbonyl]*-L-*alaninal*: Yield 76%. TLC: R_f 0.55 (*A*), 0.36 (*B*). $[\alpha]_D = -25.52$. ^{1}H-NMR: 9.58 (*s*, 1 H); 5.5 (*s*, NH); 4.2 (*q*, 1 H); 3.7 (*q*, 1 H); 1.45 (*s*, 9 H); 1.25 (*s*, 3 H). ^{13}C-NMR: 199.7; 155.4; 79.8; 55.6; 28.6; 27.8.

N^2-*[(*tert-*Butoxy)carbonyl]*-L-*valinal*: Yield 79%. TLC: R_f 0.59 (*A*), 0.40 (*B*). $[\alpha]_D = -11.6$. ^{1}H-NMR: 9.6 (*s*, 1 H); 5.33 (*d*, NH); 4.23 (*dd*, 1 H); 2.29 (*m*, 1 H); 1.46 (*s*, 9 H); 0.95 (2*d*, 6 H). ^{13}C-NMR: 200.4; 172.2; 81.1; 56.5; 31.2; 24.3; 18.5; 17.9.

N^2-*[(*tert-*Butoxy)carbonyl]*-L-*leucinal*: Yield 85%. TLC: R_f 0.68 (*A*), 0.49 (*B*). $[\alpha]_D = -30.62$. ^{1}H-NMR: 9.55 (*s*, 1 H); 5.45 (*d*, NH); 4.2 (*m*, 1 H); 1.9–1.45 (*m*, 2 H); 1.45 (*m*, 9 H); 0.95 (*d*, 6 H). ^{13}C-NMR: 200.4; 184.2; 80.1; 41.3; 28.5; 24.6; 22.3; 22.1

N^2-*[(*tert-*Butoxy)carbonyl]*-L-*methioninal*: Yield 82%. TLC: R_f 0.77 (*A*), 0.56 (*B*). $[\alpha]_D = -21.30$. ^{1}H-NMR: 9.6 (*s*, 1 H); 5.78 (*d*, 1 H); 4.3 (*m*, 1 H); 3.2 (*m*, 2 H); 2.55 (*m*, 2 H); 2.1 (*s*, 3 H); 1.5 (*s*, 9 H). ^{13}C-NMR: 199.7; 175.3; 80.5; 49.4; 33.6; 30.9; 28.1; 20.3.

N^2-*[(*tert-*Butoxy)carbonyl]*-L-*phenylalaninal*: Yield 78%. TLC: R_f 0.86 (*A*), 0.76 (*B*), $[\alpha]_D = -36.03$. ^{1}H-NMR: 9.4 (*s*, 1 H); 7.25 (*m*, 5 H); 5.1 (*s*, NH); 4.2 (*m*, 1 H); 3.65 (*q*, 1 H); 3.6 (*d*, 2 H); 1.45 (*s*, 9 H). ^{13}C-NMR: 199.4; 161.5; 136.6; 129.4; 128.4; 126.6; 58.3; 36.2; 28.2.

N^2-*[(*tert-*Butoxy)carbonyl]*-L-*tryptophanal*: Yield 81%. TLC: R_f 0.90 (*A*), 0.76 (*B*). $[\alpha]_D = -8.50$. ^{1}H-NMR: 9.7 (*s*, 1 H); 7.5–7.6 (*d*, 1 H); 6.8–7.4 (*m*, 4 H); 8.3 (*s*, NH(ind)); 5.3 (*s*, 1 H); 3.6–3.8 (*m*, 1 H); 1.5–1.6 (*d*, 2 H); 1.3–1.45 (*s*, 9 H). ^{13}C-NMR: 200.6; 177.7; 135.5; 127.5; 124.1; 121.7; 120.5; 102.1; 79.3; 55.7; 31.0; 28.7.

N^2-*[(*tert-*Butoxy)carbonyl]*-N^7-*nitro*-L-*arginine 1,4-Lactam*: Yield 85%. TLC: R_f 0.50 (*C*), 0.79 (*D*). $[\alpha]_D = -2.20$. ^{1}H-NMR: 5.56 (*m*, 1 H); 4.30 (*m*, 2 H); 3.80 (*m*, 2 H); 1.35 (*s*, 9 H); 1.3 (*q*, 2 H). ^{13}C-NMR: 177.0; 159.7; 156.5; 80.3; 52.5; 42.8; 28.2; 24.9; 24.8.

4. *Semicarbazones* **7**. Semicarbazones were prepared according to [5] and purified by flash chromatography (silica gel (3 × 50 cm), Et_2O (500 ml), then Et_2O/EtOH 6:1 (700 ml)); product detection using a *Büchi* UV spectrometer (λ = 254 nm).

N^2-*[(*tert-*Butoxy)carbonyl]*-L-*alaninal Semicarbazone*: Yield 58%. TLC: R_f 0.34 (*C*), 0.28 (*D*). $[\alpha]_D = -23.82$. ^{13}C-NMR: 183.4; 158.5; 144.8; 79.9; 47.5; 38.5; 28.4; 18.8. Anal. calc. for $C_9H_{18}N_4O_3$ (250.17): C 46.95, H 7.87, N 24.34; found: C 46.84, H 7.75, N 24.19.

N^2-*[(*tert*-Butoxy)carbonyl]*-L-*valinal Semicarbazone*: Yield 63%. TLC: R_f 0.46 (*C*), 0.39 (*D*). $[\alpha]_D = -14.63$. ^{13}C-NMR: 176.4; 158.8; 144.2; 80.0; 56.7; 47.1; 31.3; 28.6; 18.4; 18.1. Anal. calc. for $C_{11}H_{21}N_4O_3$ (258.12): C 50.76, H 8.46, N 21.53; found: C 50.54, H 8.39, N 21.67.

N^2-*[(*tert*-Butoxy)carbonyl]*-L-*leucinal Semicarbazone*: Yield 67%. TLC: R_f 0.57 (*C*), 0.42 (*D*). $[\alpha]_D = -13.61$. ^{13}C-NMR: 177.2; 155.7; 139.8; 79.9; 40.6; 28.6; 24.7; 22.9; 14.4; 13.9. Anal. calc. for $C_{12}H_{24}N_4O_3$ (272.09): C 52.93, H 8.83, N 17.64; found: C 53.10, H 8.89, N 17.81.

N^2-*[(*tert*-Butoxy)carbonyl]*-L-*methioninal Semicarbazone*: Yield 62%. TLC: R_f 0.68 (*C*), 0.44 (*D*). $[\alpha]_D = -12.76$. ^{13}C-NMR: 176.3; 158.2; 143.5; 79.8; 51.5; 32.6; 30.0; 28.3; 15.5. Anal. calc. for $C_{11}H_{22}N_4O_3S$ (289.95): C 45.51, H 7.58, N 19.31; found: C 45.60, H 7.75, N 19.42.

N^2-*[(*tert*-Butoxy)carbonyl]*-L-*phenylalaninal Semicarbazone*: Yield 64%. TLC: R_f 0.72 (*C*), 0.51 (*D*). $[\alpha]_D = -5.10$. ^{13}C-NMR: 175.8; 158.6; 143.9; 136.6; 129.4; 128.7; 126.6; 80.5; 53.8; 39.9; 28.2. Anal. calc. for $C_{15}H_{21}N_4O_3$ (305.04): C 59.01, H 6.88, N 13.77; found: C 59.21, H 6.71, N 14.01.

N^2-*[(*tert*-Butoxy)carbonyl]*-L-*tryptophanal Semicarbazone*: Yield 62%. TLC: R_f 0.80 (*C*), 0.56 (*D*). $[\alpha]_D = -4.25$. ^{13}C-NMR: 175.4; 155.6; 138.5; 136.1; 127.8; 123.2; 121.9; 119.6; 118.7; 111.2; 109.8; 80.1; 54.3; 28.8; 17.6. Anal. calc. for $C_{17}H_{22}N_5O_3$ (344.11): C 59.30, H 6.39, N 20.34; found: C 59.78, H 6.23, N 20.67.

5. *General Procedure for the Diphenylketene Method.* Diphenylketene was prepared according to [18]. To a soln. of Boc-L-amino acid (0.01 mol) in dry THF (20 ml) Et_3N (20 µl) was added. The mixture was stirred under dry N_2 and cooled to −15.°. Then, diphenylketene (1.94 g, 0.01 mol) in THF (10 ml) was added dropwise and the temp. maintained at −15°. After 5 min stirring, the mixture was cooled to −40° and LiAl(*t*-BuO)$_3$H (2.25 g, 0.01 mol) in THF (20 ml) added dropwise at −40°. After the addition, stirring was continued for 10 min and the mixture processed as in *Exper. 2*. Yields of semicarbazone: 51–69%, after chromatography.

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