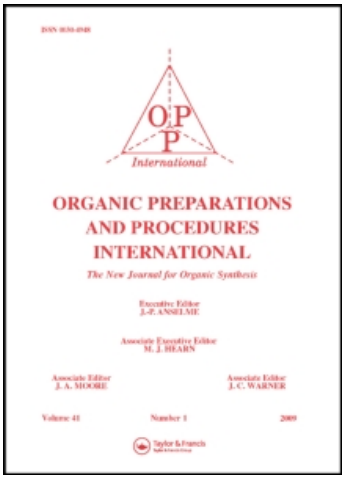


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# REDUCTIVE ALKYLATION OF α-AMINOAMIDES

Paolo Pevarello[a]; Raffaella Amici[a]; Vittorio Pinciroli[b]; Mario Varasi[a]
[a] Medicinal Chemistry Department, Pharmacia Pharmaceuticals Milan, R&D-CNS, Via per Pogliano, Nerviano(Ml), ITALY [b] R&D-Analytical Chemistry, ViaperPogliano, Nerviano(Ml), ITALY

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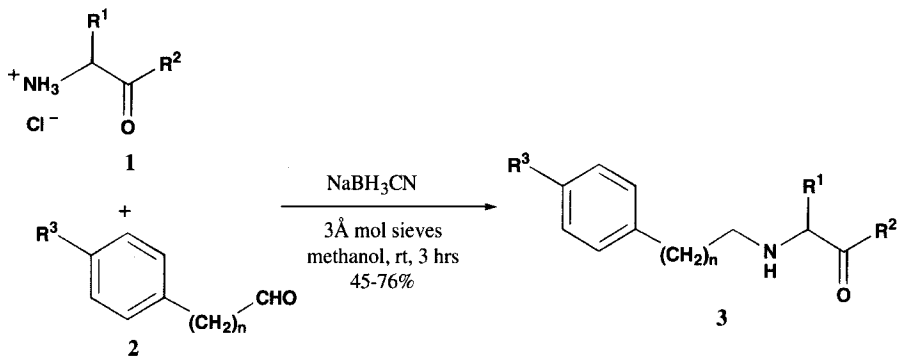
# REDUCTIVE ALKYLATION OF α-AMINOAMIDES

Paolo Pevarello*, Raffaella Amici, Vittorio Pinciroli† and Mario Varasi

*Pharmacia Pharmaceuticals Milan*
*R&D-CNS, Medicinal Chemistry Department*
*†R&D-Analytical Chemistry*
*Via per Pogliano, 20014 Nerviano(MI), ITALY*



In a program aimed at the synthesis of a new class of anticonvulsants containing an α-aminoamide moiety, we had to devise a general method for their N-monoalkylation. Because of the low nucleophilicity of the amino functionality in these molecules, the use of alkyl halides for the introduction of the alkyl residue[1] was excluded since preliminary results suggested that only activated halides (e. g. benzyl, allyl) were suitable for high-yield reactions and even then, products of double alkylation were always formed and became the major product in some cases. With regard to reductive amination, the presence of N-, O-, and S-benzyl groups in the products limited considerably the choice of reducing agents. We therefore chose the reductive amination procedure proposed by Ohfune[2] for the α-aminoacid monoalkylation.




a) (S) $R^1$ = Me, $R^2$ = $NH_2$, $R^3$ = H, n = 0 b) (S) $R^1$ = Me, $R^2$ = $NH_2$, $R^3$ = $PhCH_2N(CH_3)$- n = 0
c) (S) $R^1$ = Me, $R^2$ = $NH_2$, $R^3$ = 2-Thienyl-$CH_2O$-, n = 0 d) (S) $R^1$ = Me, $R^2$ = $NH_2$, $R^3$ = $PhCH_2S$-, n = 0
e) (S) $R^1$ = Me, $R^2$ = $NH_2$, $R^3$ = $Ph(CH_2)_3O$-, n = 0 f) (S) $R^1$ = $CH_2OH$, $R^2$ = $NH_2$, $R^3$ = H, n = 0
g) (S) $R^1$ = $CH_2OH$, $R^2$ = $NH_2$, $R^3$ = H, n = 1 h) (R) $R^1$ = $CH_2OH$, $R^2$ = OMe, $R^3$ = $PhCH_2O$-, n = 0
i) (S) $R^1$ = i-Pr, $R^2$ = $NHCH_3$, $R^3$ = $PhCH_2O$-, n = 0
l) (S),(R) $R^1$ = (R) $CH(OH)CH_3$, $R^2$ = $NHCH_3$, $R^3$ = $PhCH_2O$-, n = 0
m) (R) $R^1$ = Me, $R^2$ = $NH_2$, $R^3$ = $Ph(CH_2)_3O$-, n = 0

In contrast to α-aminoacids, it was found that a full equivalent of hydrochloric acid per mole of α-aminoamide was necessary for reaction; this requirement calls for a role of the α-aminoamide as its hydrochloride in maintaining the appropriate pH (7-8) of the solution.[3] In the classical reductive amination procedure,[4] 0.3 equiv. of hydrochloric acid per mole of amine is sufficient to ensure the formation of the reactive intermediate iminium ion. The nature of both aldehyde and α-amino acid derivative also influenced the yields; as a general rule, steric features are important so that better results are obtained from the combination of serine or valine derivatives with 4-benzyloxybenzaldehydes. As expected, dilution favors mono- over dialkylation. The temperature is not a limiting factor; best results are obtained when the reaction mixture is allowed to reach 30-35° (which occurs spontaneously) and then stirred at room temperature for 3-6 hrs. Powdered 3Å molecular sieves enhance the yields as well as the rate of reaction. The procedure can be extended with similar results to α-aminoacid ester salt derivatives (e. g. **3h**). The yields, analytical and spectroscopic data of the compounds synthesized are collected in Tables 1-3.

**Table 1.** N-Alkylated α-aminoamides and Esters **3a-m**

| Prod. | Yield (%) | Salt | mp. (°C)[a] | $[\alpha]_D^{25}$ (c,AcOH) | MS(70eV); M/z (%) |
|---|---|---|---|---|---|
| **3a** | 63 | HCl | 225-227 | +14.1(1.1) | 134(53), 106(9), 91(100) |
| **3b** | 65 | $CH_3SO_3H$ | 139-141 | +15.4(1.1) | 298(100) |
| **3c** | 57 | free base | 111-113 | +19.2(1.1) | 246(10), 218(18), 203(8), 97(100) |
| **3d** | 45 | $CH_3SO_3H$ | 200(dec) | +17.3(1.2) | 300(2), 256(13), 228(31), 213(48), 91(100) |
| **3e** | 72 | $CH_3SO_3H$ | 182.5-185.5 | +12.3(1.1) | 268(17), 240(82), 225(100), 107(62), 91(49) |
| **3f** | 75 | free base | 90-91 | +20.1(1.2) | 163(5), 150(39), 106(12), 91(100) |
| **3g** | 67 | free base | 109-110 | +11.5(0.7) | 177(4), 164(71), 117(81), 105(100) |
| **3h** | 72 | HCl | 134.5-136 | +8.8(1.1) | 284(5), 256(11), 212(41), 197(83), 91(100) |
| **3i** | 76 | HCl | 161-163 | +21.3(1.2) | 268(19), 212(14), 197(39), 91(100) |
| **3l** | 70 | HCl | 190-191 | +12.6(1.1) | 270(11), 212(25), 197(38), 91(100) |
| **3m** | 71 | $CH_3SO_3H$ | 183-185 | -12.4(1.4) | 268(17), 240(82), 225(100), 107(62), 91(49) |

a)Uncorrected.

The one-pot reductive amination of α-aminoacid derivatives features an important advantage over imine isolation and subsequent reduction because some α-aminoacids (and even more so their derivatives) may be racemized rather easily.[5] All the compounds obtained showed optical rotation values (by comparison of the sign and the absolute value of enantiomer couples) and Differential Scanning Calorimetry (DSC) behavior consistent with retention of the optical purity of the starting material. These data were confirmed by chiral HPLC of selected couples of enantiomers.[6]

**Table 2.** Spectroscopic Data of N-Alkylated α-aminoamides and Esters **3a-m**

| Cmpd | $^1$H NMR (DMSO-$d_6$/TMS); δ, J(Hz) |
|---|---|
| **3a** | 1.45 (d, 3 H, J = 7.0, $C\underline{H}_3CH$), 3.74 (q, 1 H, J = 7.0, $CH_3C\underline{H}$), 4.00 and 4.09 (2 d, 2 H, J = 13.0, $C\underline{H}_2NH$), 7.3-7.6 (m, 5 Harom), 7.61 and 8.04 (2 s, 2 H, $CONH_2$), 9.5 (bs, 2 H, $NH_2^+$) |
| **3b** | 1.38 (d, 3 H, J = 7.0, $C\underline{H}_3CH$), 2.29 (s, 3 H, $C\underline{H}_3SO_3H$), 3.03 (s, 3 H, $ArNCH_3$), 3.67 (q, 1 H, J = 7.0, $CH_3C\underline{H}$), 3.90 (m, 2 H, $C\underline{H}_2NH_2^+$), 4.59 (s, 2 H, $ArC\underline{H}_2NCH_3$), 6.72 (m, 2 Harom), 7.1-7.4 (m, 7 Harom), 7.60 and 7.87 (2 s, 2 H, $CONH_2$), 8.9 (bs, 2 H, $NH_2^+$) |
| **3c** | 1.31 (d, 3 H, J = 7.0, $C\underline{H}_3CH$), 3.22 (q, 1 H, J = 7.0, $CH_3C\underline{H}$), 3.64 and 3.73 (2 d, 2 H, J = 12.9, $C\underline{H}_2NH$), 5.19 (s, 2 H, $ArC\underline{H}_2O$), 5.60 and 7.05 (2bs, 2H, $CONH_2$), 6.70-7.05 (m, 3 Harom), 7.08 (dd, 1 Harom, J = 1.2, J = 3.5), 7.20 (m, 2 Harom), 7.30 (dd, 1 Harom, J = 1.2, J = 5.1) |
| **3d** | 1.40 (d, 3 H, J = 7.0, $C\underline{H}_3CH$), 2.30 (s, 3 H, $C\underline{H}_3SO_3H$), 3.71 (q, 1 H, J = 7.0, $CH_3C\underline{H}$), 4.03 (s, 2 H, $C\underline{H}_2NH_2^+$), 4.28 (s, 2 H, $ArC\underline{H}_2S$), 7.1-7.5 (m, 9 Harom), 7.64 and 7.90 (2 s, 2 H, $CONH_2$), 9.0 (bs, 2 H, $NH_2^+$) |
| **3e/m** | 1.39 (d, 3 H, J = 6.9, $C\underline{H}_3CH$), 2.00 (m, 2 H, $CH_2C\underline{H}_2CH_2O$), 2.30 (s, 3 H, $C\underline{H}_3SO_3H$), 2.72 (m, 2 H, $C\underline{H}_2CH_2CH_2O$), 3.69 (m, 1 H, $C\underline{H}CH_3$), 3.96 (m, 4 H, $C\underline{H}_2NH$ and $CH_2O$), 6.97 (m, 2 Harom), 7.1-7.3 (m, 5 Harom), 7.37 (m, 2 Harom), 7.62 and 7.88 (2 s, 2 H, $CONH_2$), 9.0 (bs, 2 H, $NH_2^+$) |
| **3f** | 2.4 (bs, 1 H, $N\underline{H}CH$), 2.98 (dd, 1 H, J = 5.3, J = 6.0, $NHC\underline{H}$), 3.3-3.5 (m, 2 H, $C\underline{H}_2OH$), 3.56 and 3.73 (2 d, 2 H, J = 13.6, $C\underline{H}_2NH$), 4.74 (t, 1 H, J = 5.7, OH), 7.0 and 7.3 (2 bs, 2 H, $CONH_2$), 7.1-7.3 (m, 5 Harom) |
| **3g** | 2.0 (bs, 1 H, $N\underline{H}CH$), 2.6-2.8 (m, 4 H, $PhC\underline{H}_2C\underline{H}_2$), 2.97 (dd, 1 H, J = 5.2, J = 6.4, $C\underline{H}CH_2$), 3.2-3.6 (m, 2 H, $CHC\underline{H}_2OH$), 4.70 (t, 1 H, J = 5.5, OH), 7.0 and 7.2 (2 bs, 2 H, $CONH_2$), 7.1-7.4 (m, 5 Harom) |
| **3h** | 3.71 (s, 3 H, $COOCH_3$), 3.8-4.0 (m, 3 H, $C\underline{H}C\underline{H}_2OH$), 4.13 (2 d, 2 H, J = 12.9, $C\underline{H}_2NH_2^+$), 5.12 (s, 2 H, $ArC\underline{H}_2O$), 7.02 (m, 2 Harom), 7.3-7.5 (m, 7 Harom), 9.5 and 9.9 (2 bs, 2 H, $NH_2^+$) |
| **3i** | 0.88 (d, 3 H, J = 6.8, $C\underline{H}_3CH$), 0.93 (d, 3 H, J = 6.8, $C\underline{H}_3CH$), 2.20 (m, 1 H, $CH_3C\underline{H}$), 2.61 (d, 3 H, J = 4.5, $NHC\underline{H}_3$), 3.45 (m, 1 H, $COC\underline{H}NH_2^+$), 3.8-4.1 (m, 2H, $C\underline{H}_2NH_2^+$), 5.11 (s, 2 H, $ArC\underline{H}_2O$), 7.01 (m, 2 Harom), 7.2-7.5 (m, 7 Harom), 8.51 (q, 1 H, J = 4.5, $CON\underline{H}CH_3$), 9.0 and 9.5 (2 bs, 2 H, $NH_2^+$) |
| **3l** | 1.05 (d, 3 H, J = 6.4, $C\underline{H}_3CH$), 2.61 (d, 3 H, J = 4.6, $NHC\underline{H}_3$), 3.35 (d, 1H, J = 7.6, $C\underline{H}OH$), 3.8-4.1 (m, 3 H, $C\underline{H}_2NH_2^+$ and $NHC\underline{H}CO$), 5.10 (s, 2 H, $ArC\underline{H}_2O$), 5.7 (bs, 1 H, OH), 7.02 (m, 2 Harom), 7.2-7.5 (m, 7 Harom), 8.58 (q, 1 H, J = 4.6, $N\underline{H}CH_3$), 9.2 (bs, 2 H, $NH_2^+$) |

In agreement with the proposed mechanism for $NaBH_3CN$-mediated reductive amination, it is likely that the hydrochloride of the α-aminoamide is required for the generation of the reactive iminium ion intermediate which is known to react faster than a carbonyl group with $NaBH_3CN$ in neutral medium.[4] In the case of the corresponding α-aminoacid reduction, the same function would be played by the carboxy group. It is interesting to note that, in the light of our results, the free carboxy group of the parent α-aminoacid does not seem to play an important role for N-monoalkylation; in fact, in contrast with the α-aminoacids, it is not possible for α-aminoamides and α-aminoesters to produce a zwitterion intermediate in the N-monoalkylated product,[2] and still selectivity for monoalkylation is roughly the same for all α-aminoacid derivatives.

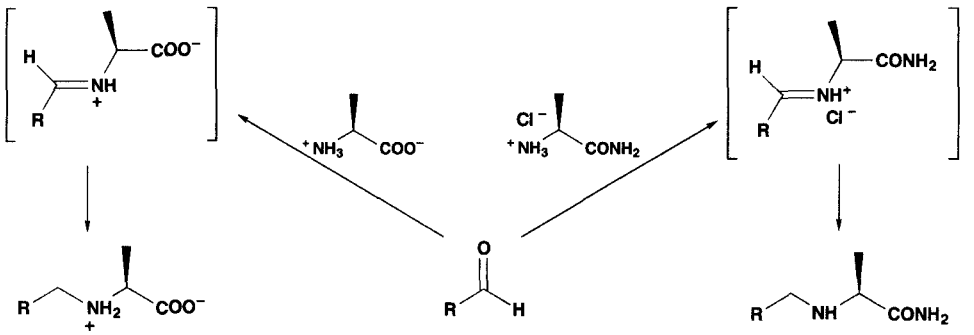


**Table 3.** Elemental Analyses for Compounds **3** (Found)

| Cmpd. | | C | H | N |
|---|---|---|---|---|
| **3a** | ($C_{10}H_{14}N_2O$•HCl) | 55.94 (55.83) | 7.04 (7.06) | 13.05 (13.04) |
| **3b** | ($C_{18}H_{23}N_3O$•$CH_3SO_3H$) | 57.99 (57.86) | 6.92 (6.78) | 10.68 (10.68) |
| **3c** | ($C_{15}H_{18}N_2O_2S$) | 62.01 (62.18) | 6.24 (6.24) | 9.64 (9.42) |
| **3d** | ($C_{17}H_{20}N_2OS$•$CH_3SO_3H$) | 54.52 (54.44) | 6.10 (6.15) | 7.06 (6.98) |
| **3e** | ($C_{19}H_{24}N_2O_2$•$CH_3SO_3H$) | 58.80 (58.89) | 6.91 (6.97) | 6.86 (6.76) |
| **3f** | ($C_{10}H_{14}N_2O_2$) | 61.84 (61.81) | 7.26 (7.32) | 14.42 (14.39) |
| **3g** | ($C_{11}H_{16}N_2O_2$) | 63.44 (63.38) | 7.74 (7.78) | 13.45 (13.39) |
| **3h** | ($C_{18}H_{21}NO_4$•HCl) | 61.45 (61.42) | 6.30 (6.32) | 3.98 (3.92) |
| **3i** | ($C_{20}H_{26}N_2O_2$•HCl) | 66.19 (65.90) | 7.50 (7.30) | 7.72 (7.54) |
| **3l** | ($C_{19}H_{24}N_2O_3$•HCl) | 62.54 (62.29) | 6.91 (6.80) | 7.68 (7.60) |
| **3m** | ($C_{19}H_{24}N_2O_2$•$CH_3SO_3H$) | 58.80 (58.60) | 6.91 (6.84) | 6.86 (6.95) |



In summary, a series of α-aminoacid derived homochiral N-monoalkylated α-aminoamides and esters were synthesized in moderate to good yields, following a general reductive amination protocol. The need of employing starting α-aminoacid derivatives as their salts (e. g. hydrochloride) was rationalized on the basis of the generally accepted mechanism for $NaBH_3CN$ mediated reductive amination, as well as on the ability of α-aminoamide hydrochlorides to buffer the solution. The experimental factors influencing the reaction were outlined.

## EXPERIMENTAL SECTION

Most of α-aminoamides and esters **1** and aldehydes **2** were commerciallly available (Aldrich, Bachem-Ca, Bader, Maybridge, Serva and K&K). Compounds **1i**,[7] **2b**,[8] **2e**[9] and **2d**[10] were prepared as described in the literature. $^1H$ NMR spectra were acquired on a Varian VXR 400 or Varian VXR 200, respectively at 400 and 200 MHz. Chemical shift are reported in ppm (δ) relative to the solvent signal (DMSO-$d_5$, 2.49 ppm). EI-MS spectra were recorded on a Varian MAT CH-7 mass. Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

**N-Alkyl-α-amino Esters and Amides (3). General Procedure**.- To a suspension of starting α-aminoamide hydrochloride **1** (11 mmol) and powdered 3Å molecular sieves (2.5 g) in dry methanol (70 mL) kept under nitrogen, $NaBH_3CN$ (8 mmol) was added and the mixture was stirred at room temperature for 15 min. Then the appropriate aldehyde **2** (10 mmol) was added in a single portion. (CAUTION: sodium cyanide is produced). The reaction mixture was allowed to reach 30-35 and then stirred at room temperature for 3 hrs. After filtration, the solvent was evaporated to give a residue which was flash-chromatographed using $CH_2Cl_2$-$CH_3OH$-30%$NH_4OH$ (99:1:0.1 to 95:5:0.5 depending on the type of α-aminoacid derivative and aldehyde used) to give the N-alkylated compound **3** (if necessary characterised as its methanesulfonate or hydrochloride salt) (Tables 1-3).

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6. The enantiomeric couple **3e-3m** for instance was checked for purity (Chiralpak WH 25x4.6; Daicel column thermostated at 50C; mobile phase: 0.25 mM $CuSO_4$; flux: 1.0 ml/min; detector: UV-227 nm) giving an enantio- meric purity >99.0% for the S-enantiomer (**3e**) and >98.7% for the R-enantiomer (**3m**).

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