2-Bromoamides as Synthons for Pseudopeptides containing Aminodicarboxy Units

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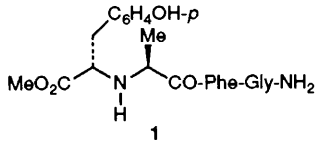
The monoalkylating and enantioselective behaviour of a chiral 2-bromoamide allows the synthesis of pseudopeptides in which a dipeptide component is changed into an aminodicarboxy moiety, with overall retention of configuration.

The well known role of peptides in biology has prompted a wealth of synthetic and structure–activity studies of partially altered structures, *e.g.* pseudopeptides where the CONH link is replaced by NHCO, CH_2NH, CH_2S, CH_2CO, CSNH, *etc.*[1] We considered it interesting to provide a simple access to pseudopeptides where the NH_2 group of an amino acid or peptide provides the NH link of a built-in aminodicarboxy unit. Accordingly, we looked again at the early Fisher peptide synthesis where a 2-bromoacyl amino acid was allowed to react with ammonia,[2a] as well as the early synthesis of 'imino acids.'[2b] Aminodicarboxylic acids (imino acids, opines, alines, *etc.*), extensively studied in connection with some sea organisms, are obtained by nucleophilic substitution (with inversion of configuration);[2b,3a,b] related compounds have been obtained upon amination–reduction (as racemates).[4,5] Following our recent demonstration that a 2-bromopropanamide reacts slowly with inversion of configuration with representative amines, but faster, and with retention of configuration, with the same amines in the presence of silver oxide,[6] we have now found that the free amino group of an amino acid ester substitutes the bromine of a chiral 2-bromoacylamino acid ester in the presence of Ag_2O, with relevant retention of configuration.

We believe that, under the present conditions, Ag_2O behaves as a 'coupling agent' and promotes a neighbouring group mechanism, with the observed reaction rates and stereochemistry. The mechanism operating in the homogeneous phase[7a] as well as the role of Ag_2O are under active investigation.[7b] We report as examples, the synthesis of: (*a*) two pseudopeptides **1** and **2**† where the original Tyr[1]-D-Ala[2] moiety of the opioid tetrapeptide dermorphin[8] and heptapeptide deltorphin-C[9] have been changed into a related aminodicarboxy unit; and (*b*) a modified peptide **5** carrying a substituted *N*-terminal allylamino group.



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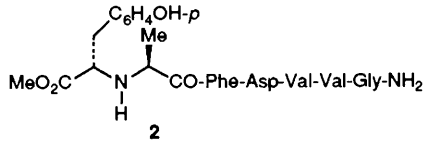

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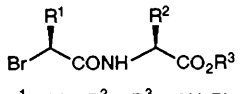
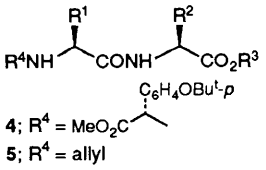


3; R^1 = Me, R^2 = R^3 = CH_2Ph (Bzl)



4; R^4 = MeO_2C

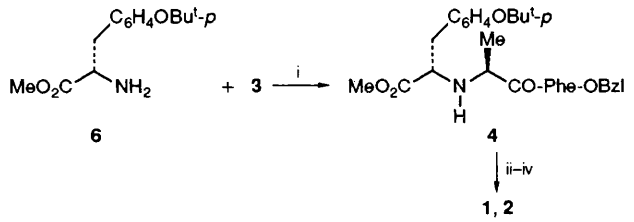
5; R^4 = allyl

† All new compounds gave satisfactory analytical and spectral data. Selected data for **1**: m.p. 179–181 °C; $[\alpha]_D^{20}$ + 7.6 (*c* 1, DMF); *K'* 5.54 (capacity factor) was determined using Vydac C_{18} with a gradient consisting of two mobile phases: B = 60% acetonitrile in 0.1% CF_3CO_2H; A = 10% acetonitrile in 0.1% CF_3CO_2H. A 25 min linear gradient was run from 0% B to 50% B in 25 min, flow rate 1.0 ml min^{-1}, λ = 220 nm; FAB-MS (MH^+) *m/z* 471; amino acid analysis: Phe 0.97, Gly 1.0 [PITC methodology; peptides (50–1000 pmol) were hydrolysed in 200 μl 6 mol l^{-1} HCl containing 1% phenol for 1 h at 150 °C].

Selected data for **2**: m.p. 151–153 °C; $[\alpha]_D^{20}$ + 10.8 (*c* 1, DMF); *K'* 8.28; FAB-MS (MH^+) *m/z* 784; amino acid analysis: Phe 1.02, Asp 0.97, Val 1.89, Gly 1.0.

Intermediate **4**. ^1H NMR (200 MHz, $CDCl_3$): δ 1.12 (d, 3H), 1.32 (s, 9H), 2.69 (d, 2H), 2.81–3.16 (m, 3H), 3.34–3.49 (m, 1H), 3.6 (s, 3H), 4.69–4.8 (m, 1H), 5.17–5.22 (m, 2H) and 6.8–7.37 (m, 15H); yield 80%, R_f 0.43 (n-hexane–AcOEt, 4 : 1 v/v).

N-Allylamine **5**. ^1H NMR: δ 1.19 (d, 3H), 1.25 (br s, 1H), 2.98–3.22 (m, 5H), 4.86–5.2 (m, 4H), 5.6–5.85 (m, 1H), 7.02–7.36 (m, 10H) and 7.66 (d, 1H); yield 89%, R_f 0.2 (n-hexane–AcOEt, 1 : 1 v/v).



Scheme 1 *Reagents and conditions*: i, **6** : **3** : Ag_2O (molar ratio 2 : 1 : 1), room temp., 3 h, toluene, 75%; ii, H_2, Pd/C, EtOH, room temp., 1 h, 95%; iii, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC), Et_3N, hydroxybenzotriazole (HOBt), dimethylformamide (DMF), H-Gly-NH_2·HBr or H-Asp(OBu^t)-Val-Val-Gly-NH_2,[13] −5 °C to room temp., 16 h, 71%; iv, CF_3CO_2H (95%), 0 °C, 1 h, 100%. Compounds indicated in the text as **1'**, **2'** *etc.* bear the opposite configuration of the alanine unit.

(*S,S*)-2-Bromopropanoyl-Phe-OBzl **3** was prepared by acylating Phe–OBzl with (*S*)-2-bromopropanoyl chloride. The latter was obtained, in turn, from L-alanine, *via* the diazonium salt and the 2-bromoacid, with overall retention of configuration.[10] The diastereoisomeric mixture of **3** and (*R*)-2-bromopropanoyl-Phe-OBzl **3'** was obtained, in turn, starting from commercial (*R,S*)-2-bromopropanoyl bromide (Fluka).

The monoalkylating and enantioselective behaviour of a chiral non-racemic 2-bromoamide synthon becomes apparent when the mixture **3**, **3'**, or pure **3** is independently allowed to react with Tyr(Bu^t)-OMe **6**, in the presence of Ag_2O (Scheme 1). Whereas two diastereoisomeric products, *i.e.* (*S,S,S*)-**4** and (*S,R,S*)-**4'** were obtained starting from the diastereoisomeric mixture **3**, **3'**, only one diastereoisomer was obtained starting from diastereoisomerically pure **3**, as confirmed by careful HPLC screening. We assign the (*S,S,S*)-configuration to the diastereoisomer **4** arising from **3**, by assuming that the Ag_2O-promoted substitution of bromine occurs with retention of configuration. We believe that traces of the undesired diastereoisomer are due to impurities in the reagent rather than to a leak in the mechanism of the substitution at the C^{α}–Br bond.[6,7a,b]

Intermediate **4**, including an aminodicarboxylic unit, was debenzylated at the *C*-terminal benzyl ester function and condensed with the *C*-terminal part of dermorphin tetrapeptide or deltorphin-C, with no protection of the novel secondary amino group. The resulting **1** and **2** have the final (*S,S*)-configuration of the new moieties, as shown. The diastereoisomeric **1'**, **2'** with the related (*S,R*)-configurations were also obtained, starting from the diastereoisomeric mixture **4**, **4'**; preparative HPLC allowed the separation of the final products.

The *N*-allylamine **5** was obtained upon reaction of allylamine with **3** or **3**, **3'**; no HPLC separation could be achieved, in this case, for the diastereoisomeric mixture.

The four compounds **1**, **2**; **1'**, **2'** were tested in quantitative opioid binding assays: **1'** and **2'** proved better[11] than compounds containing the D-Tyr^1-D-Ala^2 unit.[12]

In conclusion, in pseudopeptides such as **1** and **2**, the secondary amino function results from the amino acid reacting as a nucleophile with the bromoamide, whereas the peptide linkages result from routine peptide synthesis. The scope and limitations of our findings are under investigation.

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