Pergamon

Tetrahedron Letters 42 (2001) 3925–3927

TETRAHEDRON LETTERS

N-Protected amino acid bromides: efficient reagents for the incorporation into peptides of extremely hindered α,α-dialkyl- and α-fluoroalkyl-amino acids

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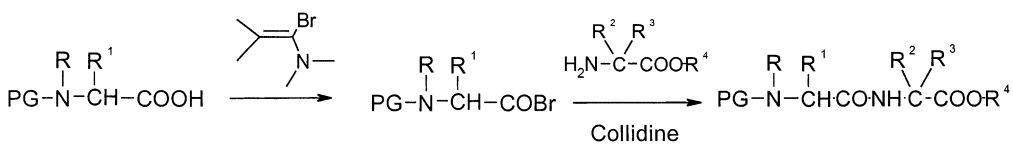
Received 8 March 2001; accepted 6 April 2001

Abstract—*N*-Protected amino acid bromides were found to be exceptionally well suited for the coupling of extremely hindered amino acids. Bromides were generated in situ under neutral conditions and used for coupling with a number of α,α-dialkyl- and *N*-Me-amino acids, affording configurationally pure peptides in very high yields. For the first time, peptide bond formation on the amino group of α-fluoroalkyl-amino acids is described with satisfactory yields. © 2001 Elsevier Science Ltd. All rights reserved.

The incorporation into peptides of unnatural amino acids containing a quaternary carbon atom at the 2-position is of common interest in the synthesis of peptidomimetics. However, standard peptide chemistry is mostly unsuccessful for this purpose, due to the reactivity of these molecules being rather different from that of proteinogenic amino acids.

In recent years, many difficult condensations have been improved using new potent carboxylic group activators, such as phosphonium and aminium/uronium salts, or *N*-protected amino acid fluorides in the presence of silylating agents.[1] These reagents proved to be very efficient for the coupling of well known, problematic, α,α-disubstututed and *N*-substituted amino acids. Nevertheless, none of the new reagents succeeded in the coupling of α-fluoroalkyl-amino acids. Peptides containing an α-trifluoromethyl residue (α-Tfm) at the N-terminal position have been obtained,[2–4] but the problem of chain elongation by derivatization of the amino group remains unresolved, except for the least bulky α-Tfm-alanine.[5] In fact, beside the steric hindrance, this amino function becomes unreactive (pK_a around 6), because of the polarizing effect of the fluoroalkyl group.[6] Activation of the nitrogen via the isocyanate gave only very poor yields in most cases.[7] On the other hand, the amino group of α-Tfm-AA was reported to react with *N*-protected amino acid chlorides in the presence of TEA, but this happens with total racemization of the non fluorinated amino acid. In fact, as we have demonstrated,† the substrate does not react with the chloride, but with a ketene formed through hydrogen halide elimination induced by TEA. This drastic reaction is limited to substrates where epimerization is not possible.[8,9]

Prompted by a need to synthesize peptides containing α-Tfm- or α-Dfm-amino acids (α-difluoromethyl) at different positions and considering that acyl bromides are known to be much more reactive than chlorides



Scheme 1.

Keywords: amino acid bromides; difficult couplings; α-fluoroalkyl-amino acids.

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† Unpublished results.

PII: S0040-4039(01)00584-6

Table 1. Synthesis of peptides with *N*-protected amino acid bromides (the numbers shown between brackets indicate the equivalents of bromide + equivalents of collidine employed)

Reagent	Substrate	Time	Product[a]	Yield (%)
Pht-Phe-Br (5+2)	α-Tfm-(*R*,*S*)-Phe-OEt	2 h	Pht-Phe-α-Tfm-(*R*,*S*)-Phe-OEt	94
Pht-Phe-Br (3+1)	α-Dfm-(*R*,*S*)-Phe-OEt	2 h	Pht-Phe-α-Dfm-(*R*,*S*)-Phe-OEt	90
Pht-Phe-Br (5+2)	α-Dfm(*R* or *S*)[b]-Phe-Ala-OMe	12 h	Pht-Phe-α-Dfm(*R* or *S*)[b]-Phe-Ala-OMe[c]	83
Pht-Val-Br (3+4)	*N*-Me-Val-OMe	10 min	Pht-Val-*N*-Me-Val-OMe[c]	89
Cbz-Pro-Br (3+4)	Aib-O*t*Bu	10 min	Cbz-Pro-Aib-O*t*Bu	91
Cbz-Pro-Br (3+4)	*N*-Me-Val-OMe	10 min	Cbz-Pro-*N*-Me-Val-OMe[c]	96
Cbz-Pro-Br (5+2)	α-Tfm-(*R*,*S*)-Phe-OEt	10 min	Cbz-Pro-α-Tfm-(*R*,*S*)-Phe-OEt	98
Fmoc-Pro-Br (3+4)	Aib-O*t*Bu	10 min	Fmoc-Pro-Aib-O*t*Bu	94

[a] Each peptide was isolated, purified by flash chomatography and characterized by ^{1}H NMR, ^{19}F NMR and FAB-mass spectroscopy. In all cases, the purity was >98%, as detected by RP–HPLC.
[b] The absolute configuration is unknown.
[c] For the products derived from the coupling of bromides with L-amino acids, it was possible to ascertain by HPLC the absence of racemization.

toward amines (up to two orders of magnitude), we sought a general method that could afford pure bromides from different amino acids.

Amino acid bromides have never been used in chemical practice, probably because they are unstable and difficult to obtain in a pure state. We were able to obtain pure amino acid bromides from *N*-protected carboxylic acids with 1-bromo-*N*,*N*-2-trimethyl-1-propenylamine under very mild and neutral conditions, following a method described in the literature[10,11] for simple acyl bromides (Scheme 1).

Other potential brominating agents have been proposed in the literature, such as BroP, PyBroP or TBFH, but, in our hands, none of them succeeded, yielding little if any peptide formation with Tfm-AA.‡

The generality of our method has been assessed using a variety of bromides with a variety of hindered substrates. In every case, very pure peptides were obtained in high yields by flash chromatography, after separation of the excess acids and reagents. All products were confirmed by ^{1}H NMR, ^{19}F NMR and FAB mass spectroscopy. When configurationally pure amino acid esters were employed as substrates, the optical purity of the final peptides was ascertained by HPLC.

It is worth pointing out that, unlike chlorides or fluorides, amino acid bromides, when protected with the Boc, Cbz or Fmoc groups, mostly undergo spontaneous decomposition to the corresponding oxazolones or Leuch's anhydrides. Whereas, for the other halides, the intramolecular cyclization cannot compete with the coupling reaction, the prerequisite for the overactivated bromides to survive their own preparation is to be *N*-protected as diacylamines.§

In conclusion, suitably *N*-protected amino acid bromides were shown to be very efficient reagents for the in situ acylation of building blocks bearing highly hindered amino groups.

However, their most impressive application is for the formation of the peptide bond at the N-terminal position of α-Tfm-amino acids, which failed to react in reasonable yields with all other known reagents.

In a *typical procedure*, to a solution of a suitably *N*-protected amino acid in dry DCM, bromoenamine was added (from 1 to 2 equiv. according to its purity) and the solution stirred under argon for 15 min; the total conversion of the acids to bromides was checked by TLC after quenching with MeOH. When the conversion was complete, a premixed solution of the amino acid esters and collidine was slowly added at 0°C. The ratio between bromides, amino acid esters and collidine were varied according to the substrates and are given in Table 1.

‡ It is interesting to note that, whereas Carpino's reagent TFFH (tetramethylfluoroformamidinium hexafluorophosphate)[12] can give pure and isolable fluorides, its bromo analogue led, within a few minutes, to the formation of the corresponding unreactive anhydrides under the same coupling conditions. This was demonstrated by HPLC and IR.

§ As shown in Table 1, only Cbz- and Fmoc-Pro-Br survived long enough to acylate the hindered AA esters, while Cbz- and Fmoc-*N*-Me-Val promptly gave Leuch's anhydrides. Evidently, the rigidity of the proline cyclic side-chain excludes certain transition states that are an integral part of the cyclization process.

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