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Z-Gln(Trt)-Aib-Aib-Aib-OMe Synthesis Using UNCA and BOP/PyBroP Coupling Methods

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Abstract: The steric hindered Aib-Aib-Aib tripeptide was synthesized in mild conditions, using PyBroP for the coupling of two Aib and Fmoc-Aib-NCA for the generation of the tripeptide, which was obtained with an excellent yield in THF. The coupling of Gln was carried out in the presence of BOP.

Peptaibols are a class of antibiotic peptides which have a high content of α,α-dialkylated glycines (Aib, Iva) and are isolated from *Trichoderma* species . The total synthesis of such peptides, and particularly of those with sterically hindered homosequences such as Aib-Aib-Aib[1,2] represents a challenge, as coupling several Aib residues into a peptide remains difficult in mild conditions. We thus compared the efficiency of two modern coupling reactions involving BOP and PyBroP reagents and urethane-protected amino acids *N*-carboxyanhydrides (UNCAs)[3] derivatives for the generation of a key segment in the synthesis of trichorzianin[1a,b], trichotoxin[2c] and suzukacillin[2d] sequences, the tetrapeptide Z-Gln-Aib-Aib-Aib-OMe.

A recent investigation[4] showed that the activating agent PyBroP in the presence of DMAP gave excellent yields for the coupling of two Aib residues at room temperature. This method was applied to obtain Fmoc-Aib-Aib-Aib-OMe from Fmoc-Aib-OH and Tfa·H-Aib-Aib-OMe[5], but mediocre yields were obtained, especially when 1 equivalent of the carbonyl component was used. Results were more encouraging when reactions were carried out with 5 equivalents of Fmoc-Aib-OH and PyBroP, giving about 35% of the tripeptide (Table 1). Such procedures led to tripeptide yields which did not allow the total synthesis of a 19-residue peptaibol on a large scale, neither in solution nor in solid phase.

Recently, a broadly applicable stable class of protected and activated amino acids, the UNCAs, have been successfully used for the coupling of sterically hindered amino acids, such as *N*-methyl and α,α-dialkylated amino acids[6]. The UNCAs are highly reactive toward nucleophiles and form peptide bonds quickly and cleanly with carbon dioxide as the only coproduct. In order to improve the yield of coupling between one Aib and the Aib-Aib dipeptide, we tested the ability of Fmoc-Aib-NCA, 1, for the generation of the tripeptide.

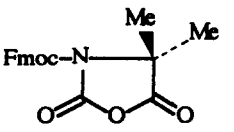
The reaction was run between the Tfa·H-Aib-Aib-OMe dipeptide salt and 1 (either 1 or 5 equivalents), in THF or DMF as solvent. In a general procedure[7], the Tfa·H-Aib-Aib-OMe dipeptide salt was placed under argon and the dry solvent was injected. The mixture was cooled to 0°C before adding DIEA. Then, a solution of 1, in the same solvent, was added through the septum and the mixture was stirred for 24 h at 22°C or at 50°C.

The release of carbon dioxide was controlled.

The best yield of tripeptide was obtained with 5 equivalents of 1 in THF, at room temperature. We noticed a large solvent effect comparing the reactions in THF and DMF. Heating at 50°C was required in DMF to obtain a yield higher than 80%. Reactions using the UNCA technique gave best results with an excess of the acylating agent.

Table 1: Synthesis of Fmoc-Aib-Aib-Aib-OMe

Coupling method	Solvent	Yield (%)[a]	
		1 eq.	5 eq.
Fmoc-Aib-OH + PyBroP/DMAP	THF	11	30
	DMF	13	33
Fmoc-Aib-NCA	THF[b]	68	95
Fmoc-Aib-NCA	DMF[b]	35	82[c]



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[a]Isolated products (purity was controlled by TLC and 300 MHz ^{1}H NMR).
[b]Dry solvents. [c]Heating at 50°C.

In the last step, the BOP methodology[4] was used for the chemical coupling between Aib-Aib-Aib-OMe and Z-Gln(Trt)-OH (1.1 equivalent), in 85% yield. The tetrapeptide Z-Gln(Trt)-Aib-Aib-Aib-OMe[8] was obtained in a global yield of 61%.

The results suggest that the combined use of BOP/PyBroP and UNCA coupling methods should be suitable for difficult peptide syntheses in solution.

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References and notes

Abbreviations: **Aib:** α-aminoisobutyric acid; **Iva:** isovaline; **PyBroP:** bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate; **DIEA:** diisopropylethylamine; **DMAP:** 4-dimethylaminopyridine; **BOP:** benzotriazol-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate; **Trt:** trityl; **Z:** benzyloxycarbonyl.

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5- Tfa-H-Aib-Aib-OMe was obtained from Boc-Aib-Aib-OMe. The dipeptide was deprotected in pure TFA.

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7- All reactions were carried out using Tfa-H-Aib-Aib-OMe (0.3 mmol), DIEA (0.6 mmol) and dry solvent (1ml) under argon.

8- ^{1}H NMR (300.13 MHz, CD_3OH, 296K): δ (ppm) 1.37 (6H, s, 2 CH_3 Aib), 1.41 (6H, s, 2 CH_3 Aib), 1.45 (6H, s, 2 CH_3 Aib), 1.83 (1H, m, Hβ Gln), 1.94 (1H, m, Hβ' Gln), 2.49 (2H, m, Hγγ' Gln), 3.60 (3H, s, OCH_3), 3.90 (1H, m, Hα Gln), 7.17-7.37 (15H, Ar Trt; 5H, Ar Z; 1H, NH Aib; 1H, NH Gln), 7.62 (1H, s, NH Aib), 8.35 (1H, s, NH Aib), 8.59 (1H, s, NHε Gln).

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