

9-FLUORENYLMETHYL ESTERS AS CARBOXYL PROTECTING GROUP

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Abstract: The use of 9-fluorenylmethyl esters for the protection of carboxyl groups is proposed. The advantage of this group is the selective deprotection under mild conditions using secondary amines without racemization.

Recently we got knowledge about the use of 9-fluorenylmethyl (Fm) esters for the protection of carboxyl groups¹. This leads us to publish our own results in this field² which differ in the preparation procedure of the Fm ester, whereas the cleavage conditions are similar to those reported by Bodanszky¹. The search for mild cleavage of the ester Boc-Pro-NBGly₂-OR (NBGly= o-Nitrobenzylglycyl) and Boc-NBGly₃-OR was the reason for the use of Fm esters (R= 9-fluorenylmethyl) because an alkaline hydrolysis of methyl esters (R= CH₃) under normal conditions yields no satisfying results whereas the Fm esters are cleaved in a clean manner as described below.

Fm esters of amino acids (Table) can be prepared by esterification of N-protected amino acids with 9-fluorenylmethanol³ using dicyclohexylcarbodiimid/p-dimethylaminopyridine⁴ whereas Bednarek and Bodanszky used the transesterification of active esters. The yields are not optimized but in each case sufficient for practical work. The Fm ester is stable under conditions of peptide synthesis (DCC coupling, Boc deprotection) and no transesterification could be observed by heating in alcohols. The cleavage is similar to the deprotection procedure

of Fmoc groups⁵ by treatment with diethylamine or piperidine in dichloromethane at room temperature for 2 hours. No racemization has been observed during formation and cleavage of N-protected amino acid Fm esters (Table). The Fm esters might offer some particular advantage in peptide synthesis, especially in designing orthogonal strategies.

Table I: Analytical Data of Amino Acid Fm Esters^{a)}

	yield	m.p. [°C]	IR [cm ⁻¹]	$[\alpha]_D^{20}$	$[\alpha]_D^{20}$ Boc-amino acid after cleavage
Boc-Pro-OFm	60%	oil	1750	-45.5°	-66.7°
Boc-Phe-OFm	50%	126-127	1730	-32.9° ^{b)}	+35.1° ^{c)}
Boc-Val-OFm	54%	65-66	1730	-37.2°	-24.6°
Z-Ala-OFm	66%	90-91	1720	-38.4°	- 4.0°
Boc-NBGly-OFm	89%	122-123	1740	---	---

a) Optical rotation in methanol (c=1). b) The value in chloroform (-7.0°, c=1) corresponds to ref.1). c) Measured as dicyclohexylamine salt.

Acknowledgement: We gratefully acknowledge discussions and getting the preprint from Prof. M. Bodanszky. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is also acknowledged.

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(Received in Germany 25 October 1982)