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Mild regeneration of the carboxylic group of amino acid alkyl esters by aqueous methanolic sodium hydrogen carbonate via 5-oxazolidinones

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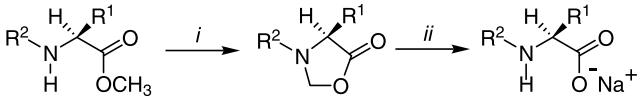
Abstract—A simple racemization-free procedure allows the regeneration of the carboxylic acid group of amino acid alkyl esters by way of an intermediate 5-oxazolidinone which is hydrolyzed by treatment with sodium hydrogen carbonate in aqueous methanol.

One of the key issues in peptide synthesis, both in solid phase and solution, is to have optically pure amino acids protected with acid–base stable protecting groups that are readily cleavable under non racemizing conditions.[1] This field has been extensively developed over the past few decades and some amino protecting groups have emerged as very satisfactory,[1–4] such as the benzyloxycarbonyl (Cbz),[5] the *tert*-butyloxycarbonyl (Boc),[6] the 9-fluorenylmethyloxycarbonyl (Fmoc),[7] and the recently introduced 1,1-dioxobenzo[*b*]thiophene-2-ylmethyloxycarbonyl (Bsmoc)[8a] and 2-(*tert*-butylsulfonyl)-2-propenoxycarbonyl (Bspoc)[8b,c] groups. On the other hand, protection of the carboxylic group, typically carried out with the easily formed methyl or ethyl esters, still suffers from problems associated with hydrolytic cleavage, which requires strongly basic conditions and may compromise the configuration of the regenerated amino acid or may damage other base labile groups present in the molecule. Thus, milder methods have been reported for the hydrolysis of methyl esters,[9] and other esters have been used,[1a] including *tert*-butyl esters[10] which are usually more difficult to obtain but can be cleaved under acidic conditions,[11] allyl esters[12] which can be removed with palladium complexes,[13,14] and benzyl esters which generally can be removed by catalytic hydrogenation.[14]

We report herein a successful protocol for a two-step cleavage of easily accessible methyl esters of Cbz-, Fmoc- and Boc-protected amino acids. This protocol consists of two simple reactions: the preparation of 5-oxazolidinones by acid-catalyzed condensation of protected amino esters, and their hydrolysis by treatment with sodium hydrogen carbonate in aqueous methanol (Scheme 1). Under these very mild conditions the regeneration of the amino acid carboxylic group occurs without racemization, and they are potentially compatible with many base-labile groups.

5-Oxazolidinones can be prepared by reaction of *N*-acylated amino acids with paraformaldehyde and catalytic amounts of a sulfonic acid, according to a procedure first described by Ben-Ishai.[15] The possibility of preparing them from the corresponding alkyl esters



R^2 = Cbz, Fmoc or Boc

Scheme 1. *Reagents and conditions*: (*i*) paraformaldehyde (5 equiv. of CH_2O when R^2 = Cbz; 50 equiv. of CH_2O when R^2 = Fmoc or Boc), *p*-TsOH (0.1 equiv.), toluene (0.01 M solution of **1**), 100°C, 0.5–2 h; (*ii*) $NaHCO_3$ (a saturated solution in MeOH–H_2O 1:1 v/v), 0.01 M for **3**, reflux, 5–10 min.

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Table 1.

Entry	Amino ester **1**		Yield[a] (%) of **2**	Final amino acid **3**		Yield[a] (%) of **3**
	R^1	R^2		R^1	R^2	
1	$(CH_2)_2SCH_3$	Cbz	85–90	$(CH_2)_2SCH_3$	Cbz	>95
2	$CH_2C_6H_5$	Cbz	85–90	$CH_2C_6H_5$	Cbz	>95
3	$CH_2(CH_3)_2$	Cbz	60–65	$CH_2(CH_3)_2$	Cbz	>95
4	$(CH_2)_3CO_2Me$	Cbz	80–85	$(CH_2)_3CO_2Me$	Cbz	>95
5	$(CH_2)_2SCH_3$	Fmoc	85–90	$(CH_2)_2SCH_3$	H	>95
6	$CH_2C_6H_5$	Fmoc	70–75	$CH_2C_6H_5$	H	>95
7	$CH_2(CH_3)_2$	Fmoc	80–85	$CH_2(CH_3)_2$	H	>95
8	$(CH_2)_2SCH_3$	Boc	35–40	$(CH_2)_2SCH_3$	Boc	75
9	$CH_2(CH_3)_2$	Boc	25–35	$CH_2(CH_3)_2$	Boc	80
10	$(CH_2)_3CO_2Me$	Boc	50–55	$(CH_2)_3CO_2Me$	Boc	5

[a] All starting esters were from commercial sources or obtained by esterification of commercial protected amino acids.

via a similar reaction was not reported. Our work has shown that α-substituted glycines can be similarly transformed into the corresponding 5-oxazolidinones, and that the 5-oxazolidinone ring can be hydrolyzed by treatment with aqueous sodium hydrogen carbonate. 5-Oxazolidinones have previously been cleaved by catalytic hydrogenolysis or by saponification with strong bases (i.e. 1 M NaOH).[16]

Our method was applied to various *N*-protected amino acid methyl esters (Scheme 1, Table 1).[17]

The protocol worked well with Cbz- and Fmoc-protected amino acids (entries 1–7) while unsatisfactory yields were obtained with Boc-protected amino acids (entries 8–10), due mainly to the low yields observed in the transformation of the Boc aminoesters to 5-oxazolidinones. Of particular interest is the possibility of selectively hydrolyzing the amino acid methyl ester of the dimethyl glutamate (entry 4).

In the case of Boc-protected amino acids the conversion was low and some by-products were formed before all the starting compound had reacted. However the yields were comparable to those observed in the preparation of the same 5-oxazolidinones from the free amino acids.[15] Hydrolysis of the 5-oxazolidinone rings was very satisfactory, in all but one case (entry 10).

Interestingly the opening of Fmoc-protected 5-oxazolidinones results in hydrolysis of the Fmoc group thereby regenerating the amine. The reaction involves a simple and unreported hydrolysis of the Fmoc group by means of aqueous hydrogen carbonate, instead of mild organic bases such as morpholine, which in some cases require repetitive treatment which can result in epimerization.[1b,19]

In conclusion, a two-step procedure for the regeneration of the carboxylic group of amino acid alkyl esters is reported. This work utilizes 5-oxazolidinones as intermediates in the deprotection of amino acid esters under mild conditions.

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17. All isolated and purified compounds gave satisfactory NMR (^1H and ^{13}C), mass spectrometry and infrared data, identical to those of commercial or authentic samples. The NMR spectra of 5-oxazolidinones were complicated by the presence of rotamers for Cbz protected derivatives. The optical purity of the final compounds was checked by chiral HPLC. After regeneration of the amino group (H_2, Pd/C, MeOH, room temp., 12 h for R^2 = Cbz or CF_3CO_2H: H_2O 95:5, v/v, room temp., 1 h for R^2 = Boc) the amino acids obtained were esterified with methanolic HCl (1 M; 0.2 mL; room temp.; 12 h) and then trifluoroacetylated [$(CF_3CO)_2O$:CF_3CO_2H; 1:1, v/v, room temp., 2 h)] and their behaviour on chiral GLC[3,18] [octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin (Lipodex E) capillary column] was examined and compared with that of the corresponding derivatives likewise prepared from natural commercial and racemic amino acids.
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