An Alkali-labile Substituted Benzyloxycarbonyl Amino-protecting Group

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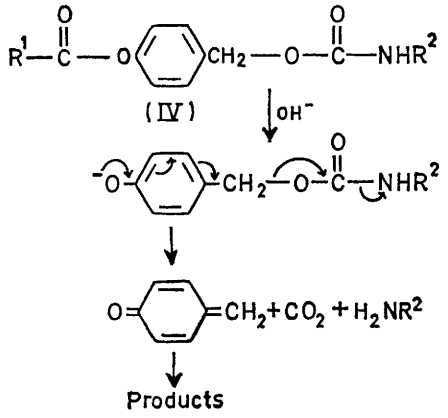
Summary 4-Isopropyloxycarbonyloxybenzyloxycarbonyl, Z(4-PriOCO), a new amino-protecting group stable under the conditions which cause cleavage of the t-butoxycarbonyl and 2-(*p*-biphenylyl)isopropyloxycarbonyl groups, can be removed in a slightly alkaline medium *via* a 1,6-elimination, by hydrogenolysis, or by HBr in acetic acid.

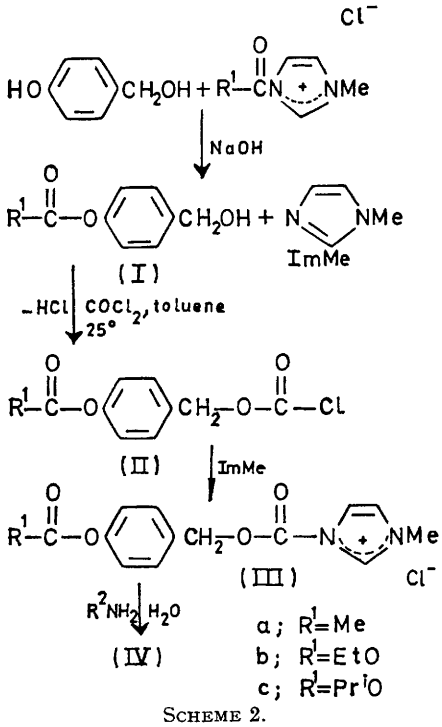
THE amino-protecting groups generally used in peptide synthesis are acid-labile. There has been a search for alkali-labile amino-protecting groups which can be removed selectively in the presence of the acid-labile groups. Carpino and Han[1] and Wünsch and Spangenberg[2] have used the 9-fluorenylmethoxycarbonyl and cyano-t-butoxycarbonyl groups which can be cleaved by base *via* a β-elimination reaction.



SCHEME 1.

We set out to synthesise a substituted benzyloxycarbonyl group from which the amine could be regenerated by alkali *via* a 1,6-elimination mechanism involving a quinone-methide[3] intermediate (Scheme 1). We prepared a series of crystalline glycine carbamates [(IVa; R^1 = Me) m.p. 91—92°, 50% yield; (IVb; R = EtO) m.p. 92—94, 75%; (IVc; R = Pr^iO) m.p. 109—110°, 95%] as shown in Scheme 2.[4] The chlorocarbonates (II) gave the stable crystalline *N*-methylimidazolium† derivatives (III)[4]‡ which react rapidly with amino-acids in water.

We studied the stability of (IVa—c), and found that free glycine is quantitatively released under the conditions which cause cleavage of the benzyloxycarbonyl group (40% HBr in AcOH or H_2, Pd/C). The isopropylcarbonate (IVc) is the most stable in acid; it does not decompose in CF_3CO_2H–CH_2Cl_2 which cleaves t-butoxycarbonyl-protected amines[5] (see Table). This substituted benzyloxycarbonyl



SCHEME 2.

group is easily cleaved in alkali. In 5% K_2CO_3 the reaction is slow but can be accelerated by the addition of 1 equiv. of hydrazine (98% cleavage after 2 h) and complete removal takes place rapidly in 0·1 N-NaOH.

By the same method, we have prepared other Z(4-Pr^iOCO)-amino-acids in good yields.

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TABLE

% Cleavage of Z(4-ROCO) *amino-protecting group of glycine (reaction followed by quantitative determination of free glycine*[6] *or by the change of absorbance at* 290 nm)

Conditions (22°)	(IVa)	(IVb)	(IVc)
CF_3CO_2H–CH_2Cl_2: 1–1, 1 h	10	2	<0·5
5% K_2CO_3, 1 h	100	80	35
0·1 N-NaOH, 10 min	100	100	100

† 4-Dimethylaminopyridine[7] also gives stable derivatives but without improvement of the yield.

‡ (Ic) m.p. 61—62°, 80%; (IIc) ν_{CO} (liquid) 1760—1770 cm^{-1}, δ ($CDCl_3$) 5·29 (CH_2); (IIIc) m.p. 93°, ν_{CO} (Nujol) 1755 and 1785 cm^{-1}, δ (D_2O) 5·68 (CH_2), 87% yield from (Ic); (IIIa) m.p. 62°; (IIIb) m.p. 51°.

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