New Amino-Protecting Groups with Special Application in Peptide Synthesis

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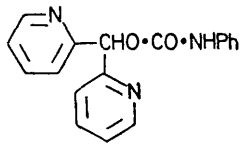
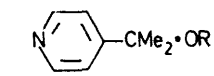
Summary The introduction of a tertiary amino substituent into urethane-type protecting groups [as in (**1**), (**4**), (**8**) and (**12**)] increases their acid-stability and provides a 'handle' for the facilitation of peptide synthesis; analogues of t-butoxycarbonyl and benzyloxycarbonyl groups having *NN*-dimethylcarbamoyl substituents [(**15**) and (**18**)], designed to increase the solubility of protected peptides in dimethylformamide, are also reported.

THE marked difference in properties between 4-picolyl[1] and benzyl esters (the former having greatly increased stability to acid and being cleaved by electrolytic reduction and by zinc and acetic acid) has led us to examine other protecting groups having tertiary amino substituents; such substituents also provide 'handles' for the facilitation of the isolation of the product during synthesis.[2] The effect of the replacement of phenyl by pyridyl substituents is well shown by di-2-pyridylmethyl *N*-phenylcarbamate (**1**), m.p. 153—155 °C, (prepared by the addition of di-2-pyridylmethanol[3] to phenyl isocyanate); whereas *N*-diphenylmethoxycarbonyl derivatives are cleaved within minutes by trifluoroacetic acid at 0 °C this analogue is stable to 45% hydrogen bromide in acetic acid for 48 h at room temp. Even the tertiary aralkyl derivative α,α-dimethyl-4-pyridylmethoxycarbonyl-L-phenylalanine (**4**), m.p. 161—163 °C [prepared *via* the alcohol (**2**)[4] and the mixed carbonate (**3**), m.p. 99—102 °C], is still stable to 2N-hydrogen bromide in acetic acid for 48 h at room temp., but it is readily cleaved by hydrogenolysis (Pd–C), by electrolytic reduction, and by zinc and acetic acid.

A tertiary aminoalkyl substituent has understandably less effect than that of the pyridyl residue in the above cases, and in benzyloxycarbonyl-L-valine *N*-(3-diethylamino-1,1-diphenylpropoxycarbonyl)hydrazide (**8**), m.p. 109—114 °C [prepared from the alcohol (**5**)[5] *via* the mixed carbonate (**6**),

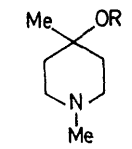


(1)



(2); R = H
(3); R = $CO_2 \cdot C_6H_2Cl_3$(2,4,5)
(4); R = CO-Phe

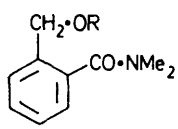
$Et_2N \cdot CH_2 \cdot CH_2 \cdot CPh_2 \cdot OR$



(5); R = H
(6); R = $CO_2 \cdot C_6H_4 \cdot NO_2$-*p*
(7); R = $CO \cdot NH \cdot NH_2$
(8); R = Z-Val-NH·NH·CO

(9); R = H
(10); R = $CO_2 \cdot C_6H_4 \cdot NO_2$-*p*
(11); R = $CO \cdot NH \cdot NH_2$
(12); R = Z-Val-NH·NH·CO

$Me_2N \cdot CO \cdot CH_2 \cdot CH_2 \cdot CMe_2 \cdot OR$



(13); R = H
(14); R = $CO_2 \cdot C_6H_4 \cdot NO_2$-*p*
(15); R = CO-Phe

(16); R = H
(17); R = $CO_2 \cdot C_6H_4 \cdot NO_2$-*p*
(18); R = CO-Phe

m.p. (hydrochloride) 84—86 °C and the hydrazide (**7**), m.p. (hydrochloride) 171—173 °C] the hydrazide-protecting group is cleaved by trifluoroacetic acid in 1 h at room temp. and by hydrogenolysis (Pd–C). The marked stabilisation caused even by an unconjugated basic site is shown by comparing the lability of the 1-methylcyclohexyloxycarbonyl group (cleaved within 1 min by trifluoroacetic acid at 25 °C) with the hydrazide-protecting group in benzyloxycarbonyl-L-valine *N*-(1,4-dimethylpiperidyl-4-oxycarbonyl)hydrazide (**12**), m.p. 80—85 °C [prepared from the alcohol (**9**)[6] *via* the mixed carbonate (**10**), m.p. 155 °C (decomp.) and hydrazide (**11**), m.p. (hydrochloride) 163—165 °C]. The 1,4-dimethylpiperidyl-1-oxycarbonyl group is stable to trifluoroacetic acid and to 2N-hydrogen chloride in tetrahydrofuran for 1 h at room temp. and to hydrogenolysis, but is cleaved by 45% hydrogen bromide in acetic acid in 1 h at room temp.; this could be a useful combination of properties.

The insolubility of fully protected peptide fragments can be a major difficulty during synthesis and we have started an investigation of protecting groups designed to increase the solubility of such intermediates in dimethylformamide, by the introduction of a dimethylcarbamoyl substituent. 4-Hydroxy-4-methylvaleric acid dimethylamide (**13**) (from the reaction of 3,3-dimethylbutyrolactone with dimethylamine) reacted with *p*-nitrophenyl chloroformate and 1-methylmorpholine giving the mixed carbonate (**14**), m.p. 56—58 °C, which with L-phenylalanine and tetramethylguanidine in dimethylformamide gave *NN*-dimethylcarbamoylethyldimethylmethoxycarbonyl-L-phenylalanine (**15**), m.p. 98—100 °C. The protecting group was removed by trifluoroacetic acid in 1 h at room temp. The dicyclohexylammonium salts of the glycine and L-isoleucine analogues have m.p. 119—121 °C and 120—122 °C respectively, and *N*-(α)-benzyloxycarbonyl-*N*(ε)-(*NN*-dimethylcarbamoylethyldimethylmethoxycarbonyl)-L-lysine dicyclohexylammonium salt has m.p. 106—108 °C. A similarly substituted benzyloxycarbonyl group was conveniently provided by the reaction of phthalide with dimethylamine; the *o*-substituted benzyl alcohol (**16**) was used directly to form the mixed carbonate (**17**), m.p. 81—83 °C, which as before with L-phenylalanine gave 2-(*NN*-dimethylcarbamoyl)benzyloxcarbonyl-L-phenylalanine (**18**) dicyclohexylammonium salt, m.p. 110—113 °C. The protecting group was stable to trifluoroacetic acid (3 h at room temp.) but was cleaved by 45% hydrogen bromide in acetic acid (3 h, room temp.) and by hydrogenolysis (Pd–C, 3 h). The dicyclohexylammonium salts of the glycine and L-isoleucine analogues have m.p. 150—152 °C and 155—157 °C respectively.

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