

Racemisation-free Esterification of 2-Nitrophenylsulphenyl-protected Amino-acids by Dicyclohexylcarbodi-imide-4-Dimethylaminopyridine

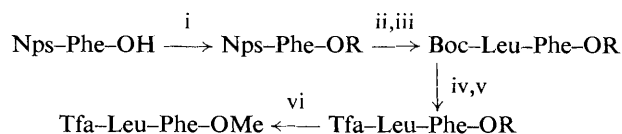
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Racemisation during esterification of *N*-protected amino-acids by dicyclohexylcarbodi-imide-4-dimethylaminopyridine (DCC-DMAP) can be avoided by use of the 2-nitrophenylsulphenyl (Nps) protecting group.

Recently, Atherton *et al.*¹ reported that esterification of urethane-protected amino-acids in the presence of 4-dimethylaminopyridine (DMAP) leads to a certain degree of racemisation, owing to the formation of 2-alkoxy-5(4*H*)-oxazolones.² Because ester formation from *N*-protected amino-acids is of significance in solid-phase peptide synthesis³ and depside synthesis,⁴ we tried to substitute the urethane group by another function less liable to racemisation.

We have now found that 2-nitrophenylsulphenyl(Nps)-protected amino-acids are well suited for this purpose, being esterified by the DCC-DMAP (DCC = dicyclohexylcarbodi-imide) procedure⁵ in high yield without any racemisation. This method was tested with the phenylalanine derivative, because this amino-acid is known for its tendency towards racemisation.⁶ In a first experiment, Nps-Phe-OH (2 mmol) was esterified with methanol (3 mmol) in the presence of DCC (2.1 mmol) and DMAP (0.2 mmol). After 5 min at 0 °C and 3 h at 25 °C, Nps-Phe-OMe⁷ was obtained in 94% yield. Cleavage of the Nps-group with HCl-Et₂O⁷ leads to phenylalanine methyl ester hydrochloride, which was transformed into *N*-trifluoroacetyl-leucylphenylalanine methyl ester by the steps shown in Scheme 1. G.l.c. analysis of this peptide derivative according to Weygand⁸ indicated only the presence of the



Scheme 1. Reagents and conditions: ROH, DCC, DMAP; ii, HCl-Et₂O; iii, Boc-Leu-OTDO, † NEt₃; iv, CF₃CO₂H, CH₂Cl₂; v, CF₃CO₂Me, NEt₃; vi, MeOH, Ti(OPrⁱ)₄ (ref. 9).

L,L-diastereoisomer. In a second test, Nps-Phe-OH was esterified with benzyl alcohol to give Nps-Phe-OBzl {m.p. 43–45 °C, [α]_D²³ –22.4° (*c* = 2 in AcOEt)} in 92% yield. This ester was converted into CF₃CO-Leu-Phe-OBzl (i–v), which yielded the corresponding methyl ester by titanate-mediated transesterification (vi). Again the gas-chromatogram showed the absence of any racemisation.

For application of the esterification method to solid-phase synthesis, Nps-Phe-OH was bound to the hydroxymethylated

† Boc-Leu-OTDO = *N*-*t*-butyloxycarbonyl-leucyloxy-2,3-dihydro-3-oxo-2,5-diphenylthiophen 1,1-dioxide: O. Hollitzer, A. Seewald, and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 444.

copolymer of styrene and 2% divinylbenzene in the presence of DCC–DMAP.³ The hydroxymethylated support was prepared from the chloromethylated resin (Merrifield resin) by exchange with acetate, followed by reflux (12 h) in isopropyl alcohol with a catalytic amount of Ti(OPrⁱ)₄.¹⁰ The latter procedure gives much better results than the usual alkaline hydrolysis.¹¹ The polymer-bound Nps–Phe–OH was transformed into Boc–Leu–Phe–resin in the usual way. Titanate-mediated transesterification with methanol yielded Boc–Leu–Phe–OMe, which after conversion into the trifluoroacetyl derivative showed only the peak of the L,L-compound on g.l.c. analysis.

Because the Nps residue is widely used as a protecting group in peptide chemistry,¹² our method offers a convenient way for the racemisation-free esterification of amino-acids under mild conditions. In accord with the literature,¹ esterification of Boc–Phe–OH by methanol–DCC–DMAP without special precautions leads to 36% racemate formation.

Received, 23rd March 1982; Com. 338

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