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

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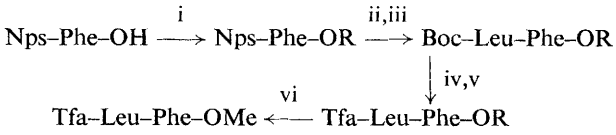
Racemisation during esterification of *N*-protected amino-acids by dicyclohexylcarbodi-imide–4-dimethylaminopyridine (DCC–DMAP) can be avoided by use of the 2-nitrophenylsulphenyl (Nps) protecting group.

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 synthesis[3] 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) procedure[5] 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–OMe[7] was obtained in 94% yield. Cleavage of the Nps-group with HCl–Et_2O[7] 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 Weygand[8] indicated only the presence of the



Scheme 1. *Reagents and conditions*: ROH, DCC, DMAP; ii, HCl–Et_2O; iii, Boc–Leu–OTDO,† NEt_3; iv, CF_3CO_2H, CH_2Cl_2; v, CF_3CO_2Me, NEt_3; vi, MeOH, $Ti(OPr^i)_4$ (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, $[\alpha]_D^{23}$ −22.4° (*c* = 2 in AcOEt)} in 92% yield. This ester was converted into CF_3CO–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 $Ti(OPr^i)_4$.[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.

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