

p-Tolylmethylsulphonyl: a New Amino-protecting Group in Peptide Synthesis

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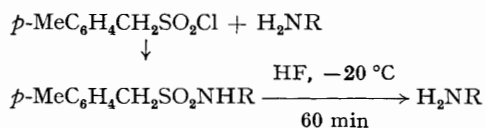
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Summary The *p*-tolylmethylsulphonyl group for the protection of the ϵ -amino group of lysine, which is readily removed with anhydrous hydrogen fluoride but is strongly resistant to trifluoroacetic acid or dilute hydrogen chloride, can be applied to both solid-phase and solution synthesis of peptides.

N^ϵ -Pms-lysine, m.p. 261 °C (decomp.), $[\alpha]_D^{20} + 15.5^\circ$ (*c* 0.5 in AcOH), was prepared from the copper-lysine complex and Pms chloride. In spite of complete stability of the Pms group to TFA at 20 °C for 24 h, the group could be cleanly removed by treatment with HF in the presence of anisole at -20 °C for 60 min.

Two different types of amino-protecting group are required for the synthesis of a peptide containing lysine residues. When the *t*-butoxycarbonyl (Boc) group is used as an N^ϵ -protecting group, the N^α -protecting group must be one which is left intact on repeated removal of the Boc group with a weak acid, since partial removal of the N^ϵ -protecting group results in the formation of branched peptides during the coupling process.¹ However, N^ϵ -protecting groups which are stable to weak acids, such as the 2-chlorobenzylloxycarbonyl² and di-isopropylmethyloxycarbonyl³ groups, are slowly cleaved by treatment with anhydrous hydrogen fluoride⁴ used widely in peptide chemistry.

We now report the use of the *p*-tolylmethylsulphonyl (Pms) group as a new N^ϵ -protecting group which has excellent stability against trifluoroacetic acid (TFA) or dilute hydrogen chloride. The reagent for the introduction of this group, *p*-MeC₆H₄CH₂SO₂Cl, was prepared by a procedure similar to that described for PhCH₂SO₂Cl,⁵ and



Z-Gly-Lys(Pms)-Gly-OBzl, prepared by the conventional solution procedure using Boc-Lys(Pms)-OH, m.p. 94–95 °C, $[\alpha]_D^{20} - 1.5^\circ$ (*c* 0.5 in MeOH), as the starting material, was treated with HF at -20 °C for 60 min to give H-Gly-Lys-Gly-OH in quantitative yield. Moreover, the protected tripeptide was hydrogenolysed to H-Gly-Lys(Pms)-Gly-OH in the presence of palladium black as a catalyst.

A biologically active peptide, neurotensin,⁶ has been synthesised in solution to demonstrate the applicability of this method. Z-*p*Glu-Leu-Tyr-Glu(OBzl)-Asn-Lys(Pms)-Pro-Arg(Mbs)-Arg(Mbs)-Pro-Tyr-Ile-Leu-OBu[†] was prepared by fragment assembly and treated with HF-anisole at -20 °C for 60 min. Pure neurotensin was obtained in

[†] Mbs = *p*-MeOC₆H₄SO₂ [O. Nishimura and M. Fujino, *Chem. and Pharm. Bull. (Japan)*, 1976, **24**, 1968]; *p*Glu = pyroglutamic acid residue.

good yield. To determine the usefulness of this protecting group in a solid-phase procedure,⁷ a protected *N*-terminal heptapeptide hydrazide of FTS (facteur thymique serique),⁸ *p*Glu-Ala-Lys(Pms)-Ser(Bzl)-Gln-Gly-Gly-NHNH₂, was prepared by the solid-phase method. The hydrazide was effectively coupled with the *C*-terminal dipeptide ester, H-Ser-Asn-OBu^t. The resulting protected nonapeptide was

deblocked by HF-anisole to give FTS. The synthetic product[‡] was identical with a reference sample prepared by the conventional solution method.

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‡ $[\alpha]_D^{24} -65.6^\circ$ (*c* 0.5 in H₂O); t.l.c. (cellulose), *R_f* (BuⁿOH-pyridine-AcOH-H₂O, 30:20:6:24) 0.19; paper electrophoresis, pH 1.9, 0.34 × arginine, pH 6.5, 0.17 × arginine; amino-acid analysis (acid hydrolysate): Lys 1.01, Asp 1.03, Ser 1.86, Glu 2.05, Gly 2.00, Ala 1.00 (average recovery, 71.3%); reference sample: $[\alpha]_D^{24} -66.5^\circ$ (*c* 0.45 in H₂O) (O.Nishimura, S. Shinagawa, and M. Fujino, unpublished data).

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