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

By TSUNEHIKO FUKUDA, CHIEKO KITADA, and MASAHIKO FUJINO*

(*Chemical Research Laboratories, Central Research Division, Takeda Chemical Industries Ltd., Yodogawa-ku, Osaka, Japan*)

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.

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-chlorobenzyloxycarbonyl[2] and di-isopropylmethyloxycarbonyl[3] groups, are slowly cleaved by treatment with anhydrous hydrogen fluoride[4] 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*-$MeC_6H_4CH_2SO_2Cl$, was prepared by a procedure similar to that described for $PhCH_2SO_2Cl$,[5] and N^{ϵ}-Pms-lysine, m.p. 261 °C (decomp.), $[\alpha]_D^{20}$ + 15·5° (*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.

$$p\text{-}MeC_6H_4CH_2SO_2Cl + H_2NR \downarrow$$
$$p\text{-}MeC_6H_4CH_2SO_2NHR \xrightarrow[60\text{ min}]{HF,\ -20\ ^{\circ}C} H_2NR$$

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° (*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^t† was prepared by fragment assembly and treated with HF–anisole at −20 °C for 60 min. Pure neurotensin was obtained in

† Mbs = *p*-$MeOC_6H_4SO_2$ [O. Nishimura and M. Fujino, *Chem. and Pharm. Bull.* (*Japan*), 1976, **24**, 1968]; pGlu = 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-$NHNH_2$, 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.

We thank Drs. E. Ohmura and M. Nishikawa for their interest and helpful discussion.

(*Received*, 28*th November* 1977; *Com.* 1218.)

‡ $[\alpha]_D^{24}$ −65·6° (*c* 0·5 in H_2O); t.l.c. (cellulose), R_f (Bu^nOH–pyridine-AcOH–H_2O, 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° (*c* 0·45 in H_2O) (O.Nishimura, S. Shinagawa, and M. Fujino, unpublished data).

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