The Mesitylene-2-sulphonyl Group, an Acidolytically Removable N^G-Protecting Group for Arginine

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Summary The mesitylene-2-sulphonyl (Mts) group attached at the guanidino function of arginine can be quantitatively cleaved by methanesulphonic acid, as well as trifluoromethanesulphonic acid and hydrogen fluoride; this new Arg(Mts) derivative was successfully applied to the synthesis of hypothalamic substance P.

WE report that the mesitylene-2-sulphonyl (Mts) group attached at the guanidino unit of arginine can be smoothly cleaved by methanesulphonic acid (MSA)[1] or trifluoromethanesulphonic acid (TFMSA).[2]

Z-Arg(Mts)-OH was prepared from Z-Arg-OH[3] and mesitylene-2-sulphonyl chloride,[4] by the procedure used for the preparation of Z-Arg(Tos)-OH,[5] and was characterized as its cyclohexylamine (CHA) salt. The corresponding t-butoxycarbonyl and *p*-methoxybenzyloxycarbonyl derivatives, Boc-Arg(Mts)-OH and Z(OMe)-Arg(Mts)-OH, were similarly prepared and characterized also as the respective CHA salts. H-Arg(Mts)-OH was obtained as a crystalline compound from water, by catalytic hydrogenation of the former or treatment of the latter two compounds with trifluoroacetic acid (TFA).

The Mts group survived intact under various conditions currently employed in peptide synthesis, such as treatment with TFA, 1 M sodium hydroxide, or hydrazine hydrate, and was removable by hydrogen fluoride, as for the Tos group.[6] However, in contrast to the Tos group, it could be quantitatively cleaved by TFMSA and MSA (within 60 min at 20 °C), while the Tos group was partially cleaved. It is noteworthy that the Mts group is rather resistant to the action of sodium in liquid ammonia, conditions under which the Tos group was quantitatively cleaved. Further, 25% hydrogen bromide in acetic acid partially removed the Mts group (> 70% within 60 min at 20 °C). Thus, the Mts group possesses properties comparable to those of the *p*-methoxybenzenesulphonyl group,[7] and as far as acid susceptibility is concerned, the Mts group is more labile than the latter, which is removable by MSA and TFMSA, but inert to hydrogen bromide.

In order to evaluate the usefulness of Arg(Mts) in peptide synthesis, a arginine-containing peptide, hypothalamic substance P,[8–10] was synthesized. Z-Arg(Mts)-OH was condensed with proline by the 2,4-dinitrophenyl ester procedure[11] and the resulting dipeptide, Z-Arg(Mts)-Pro-OH was then condensed, by the dicyclohexylcarbodiimide plus *N*-hydroxybenzotriazole procedure,[12] with a TFA-treated sample of Z(OMe)-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met(O)-NH_2 prepared by assembling three peptide fragments (Figure). The protected undecapeptide amide, Z-Arg(Mts)-Pro-Lys(Z)-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-(O)NH_2 thus obtained was treated with MSA–anisole in an

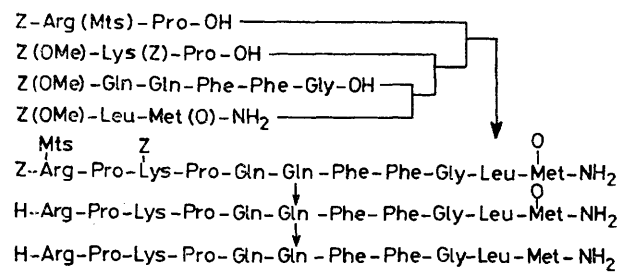

FIGURE. Application of Arg(Mts) to the synthesis of substance P.

icebath for 30 min and at room temperature for 30 min to remove the Z and the Mts groups, while the methionine sulphoxide remained intact preventing alkylation at the methionine sulphur atom.[13] The sulphoxide was removed with mercaptoethanol[14] and the reduced peptide was then purified by partition chromatography on Sephadex G-25.[15] The homogeneous peptide thus obtained (overall yield 74% in the deprotection and purification steps) possessed properties (R_f and rotation values) and biological activity (contractility on isolated guinea-pig ileum) identical with those of the peptide obtained in 36% yield by the hydrogen fluoride procedure.[10] The presence of the arginine residue was confirmed by its satisfactory recovery in an enzymatic (AP-M)[16] hydrolysate.

In a model experiment, when Z(OMe)-Ile-Tyr-Arg(Mts)OH was exposed to the MSA–anisole system, the phenolic group of tyrosine was partially mesitylenesulphonated. This side reaction could efficiently be suppressed by the use of an additional cation scavenger, such as *o*-cresol or phenol together with thioanisole.

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