

## ***N*<sup>1m</sup>-*p*-Methoxyphenylsulphonylhistidine, a New Derivative for Peptide Synthesis**

By KOUKI KITAGAWA, KUNIAKI KITADE, YOSHIAKI KISO, TADASHI AKITA, SUSUMU FUNAKOSHI,  
NOBUTAKA FUJII, and HARUAKI YAJIMA\*

(Faculty of Pharmaceutical Sciences, Tokushima University, Tokushima, 577 and Faculty of Pharmaceutical Sciences,  
Kyoto University, Kyoto, 606, Japan)

**Summary** The *p*-methoxyphenylsulphonyl group attached at the *N*<sup>1m</sup> function of histidine can be quantitatively cleaved by trifluoroacetic acid in the presence of dimethyl sulphide at room temperature within 1 h; the *N*<sup>1m</sup>-tosyl group was also cleaved under similar conditions, but at a slower rate.

We report that the *p*-methoxyphenylsulphonyl (MPS) group attached at the *N*<sup>1m</sup> atom of histidine can be smoothly cleaved by trifluoroacetic acid (TFA) in the presence of dimethyl sulphide at room temperature within 40–60 min. Boc-His(MPS)-OH (Boc = *t*-butoxycarbonyl) (m.p. 128–131 °C) was prepared from Boc-His-OH<sup>1</sup> and *p*-methoxybenzenesulphonyl chloride by the procedure used for the preparation of Boc-His(Tos)-OH<sup>2</sup> (Tos = tosyl), and was obtained, through its dicyclohexylamine salt, as a crystalline compound. The corresponding benzyloxy-carbonyl and *p*-methoxybenzyloxycarbonyl derivatives,

Z-His(MPS)-OH (m.p. 64–65 °C) and Z(OMe)-His(MPS)-OH (m.p. 79–81 °C), respectively, were similarly obtained as crystalline compounds.

As for the tosyl group, the *N*<sup>1m</sup>-MPS group could be removed either by *N*-hydroxybenzotriazole (HOBT)<sup>2,3</sup> or under basic conditions, *e.g.*, completely in 1 *N* NaOH within 1 h and partially in 80% hydrazine hydrate after 24 h. The *N*<sup>1m</sup>-MPS group was not removed under the acidic conditions which are required for *N*<sup>2</sup>-deprotection of the Boc and Z(OMe) groups, *e.g.*, the use of TFA-anisole or 25% HBr-acetic acid. H-His(MPS)-OH (m.p. 155–158 °C) was obtained as a crystalline compound by TFA-anisole treatment of Z(OMe)-His(MPS)-OH. Acidolytical removal of the *N*<sup>1m</sup>-MPS group was, however, possible when hydrogen fluoride<sup>4</sup> in the presence of anisole was used, but it was not completely removed by the methanesulphonic acid-anisole system.<sup>5</sup> Thus, the MPS group attached at the *N*<sup>1m</sup> atom of histidine behaved quite

differently from the same group attached at the guanidino function of arginine,<sup>6</sup> as the *N*<sup>ε</sup>-MPS group is known to be smoothly cleaved under the latter conditions. Therefore the *N*<sup>1m</sup>-MPS group is more stable in acid solutions than the *N*<sup>ε</sup>-MPS group.

Despite the stability of the *N*<sup>1m</sup>-MPS group to acids, we have found that it can be cleaved by TFA in the presence of various sulphur compounds, such as thioanisole, dimethyl sulphide, ethanedithiol, or mercaptoethanol, of which dimethyl sulphide was judged the most effective. When H-His(MPS)-OH was exposed to TFA in the presence of dimethyl sulphide (5 equiv.) at room temperature, histidine

was regenerated quantitatively within 40—60 min. When Z(OMe)-His(MPS)-Gly-OBzl, prepared by the *p*-nitrophenyl ester procedure,<sup>7</sup> was used as a model compound, removal of the *N*<sup>1m</sup>-MPS group by TFA-dimethyl sulphide, as well as by HOBT, was further demonstrated.

It is noteworthy that the tosyl group could also be removed completely from Boc-His(Tos)-OH by TFA-dimethyl sulphide within 90 min, while Arg(Tos)<sup>8</sup> and Arg(MPS)<sup>6</sup> remained intact.

(Received, 23rd July 1979; Com. 790.)

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