A New Carboxy-protecting Group for Peptide Synthesis and Its Direct Conversion into an Activated Ester Suitable for Peptide Formation: 4-(Methylthio)phenyl and 4-(Methylsulphonyl)phenyl Esters

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WE have found a new carboxy-protecting group, 4-(methylthio)phenyl ester (MTP), which can be oxidized to the sulphoxide, 4-(methylsulphinyl)-phenyl ester, and further oxidized to the sulphone, 4-(methylsulphonyl)phenyl ester, in order to activate it toward aminolysis. This direct conversion of a protective ester to an activated ester should be of great utility in peptide synthesis, particularly in the synthesis of polypeptides of known repeating sequence of amino-acids or other large peptides. In any sequence where a variety of protecting groups must be used, a protective ester which does not have to be removed but which can be converted under mild conditions and in good yield to an activated ester suitable for peptide formation could effect a large saving of time and valuable material.

The MTP esters,† compounds (I), (II), (III), (IV), (VI), and (VII) (see Table), were easily prepared in high yield by the condensation of an *N*-protected amino-acid and 4-(methylthio)phenol with dicyclohexylcarbodi-imide.[1] The *N*-t-butyloxycarbonyl group was easily removed in the presence of the MTP ester; *N*-t-butyloxy-carbonylglycine 4-(methylthio)phenyl ester (IV) was treated with hydrogen chloride in methylene chloride or chloroform to yield glycine 4-(methyl-thio)phenyl ester hydrochloride (V). The MTP ester is also stable to the acid conditions used to remove the benzyloxycarbonyl protecting group:

† All new compounds gave satisfactory analyses.

crude L-valine 4-(methylthio)phenyl ester hydrobromide (VIII) was prepared from the ester (VII) by the use of hydrogen bromide in glacial acetic acid in the presence of methylethyl sulphide.[2] The hydrobromide (VIII) was characterized by condensation with *N*-benzyloxycarbonyl-L-valine and DCCI in the presence of triethylamine to yield *N*-benzyloxycarbonyl-L-valyl-L-valine 4-(methylthio)phenyl ester (IX).

(XI), leucine methyl ester hydrochloride, and triethylamine in methylene chloride after a week at room temperature gave the tripeptide *N*-benzyloxycarbonyl-L-alanylglycyl-L-leucine methyl ester (XV).

Oxidation of the MTP ester (II) or the sulphoxide (X) with excess hydrogen peroxide in glacial acetic acid for 12 hr. at room temperature gave the sulphone (XII).[4] In addition, the t-butyl ester

TABLE

$R^1NH{\cdot}CHR^2{\cdot}CO_2{\cdot}C_6H_4{\cdot}SMe$

	R^1	R^2	m.p. (°c)
(I)	$PhCH_2{\cdot}O{\cdot}CO$	H	110°
(II)	$PhCH_2{\cdot}O{\cdot}CO$	Me	114°
(III)	$PhCH_2{\cdot}O{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CO$	H	141—142°
(IV)	$Me_3CO{\cdot}CO$	H	79°
(V)	HCl, H	H	223° (decomp.)
(VI)	$PhCH_2{\cdot}O{\cdot}CO$	$CH_2{\cdot}CH_2{\cdot}CO_2{\cdot}CMe_3$	80—81°
(VII)	$PhCH_2{\cdot}O{\cdot}CO$	$CHMe_2$	77°
(VIII)	HBr, H	$CHMe_2$	226° (decomp.)
(IX)	$PhCH_2{\cdot}O{\cdot}CO{\cdot}NH{\cdot}CH(CHMe_2){\cdot}CO$	$CHMe_2$	184—185°

$R^1NH{\cdot}CHR^2{\cdot}CO_2{\cdot}C_6H_4{\cdot}SOMe$

(X)	$PhCH_2{\cdot}O{\cdot}CO-$	Me	95°
(XI)	$PhCH_2{\cdot}O{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CO-$	H	149°

$R^1NH{\cdot}CHR^2{\cdot}CO_2{\cdot}C_6H_4{\cdot}SO_2Me$

(XII)	$PhCH_2{\cdot}O{\cdot}CO$	Me	106°
(XIII)	$PhCH_2{\cdot}O{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CO$	H	145—146°
(XIV)	$PhCH_2{\cdot}O{\cdot}CO$	$CH_2{\cdot}CH_2{\cdot}CO_2{\cdot}CMe_3$	104°
(XV)	$PhCH_2{\cdot}O{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH(CH_2{\cdot}CHMe_2){\cdot}CO_2Me$		134°

Controlled oxidation of the ester (II) at room temperature with hydrogen peroxide in glacial acetic acid gave the corresponding sulphoxide, *N*-benzyloxycarbonyl-L-alanine (4-methylsulphinyl)phenyl ester (X), m.p. 95°, in good yield. The amide bond was also found to be stable under these conditions:[3] oxidation of (III) gave, cleanly and in good yield, the ester (XI). Investigation of these sulphoxides as possible active esters showed them to be only mildly activated toward aminolysis; a solution of *N*-benzyloxycarbonyl-L-alanine 4-(methylsulphinyl)-phenyl ester (X), glycine 4-(methylthio)phenyl ester hydrochloride (V), and triethylamine in methylene chloride gave the dipeptide (III) in poor yield. Simiarly, a solution of the dipeptide

was also found to be stable under these conditions: the oxidation of (VI) yielded the ester (XIV). The utility of converting a protecting group to an activated ester was shown by the oxidation, without rupture of the peptide linkage, of the dipeptide MTP ester (III) to give the ester (XIII). A solution of this dipeptide in methylene chloride was readily coupled to L-leucine methyl ester hydrochloride at room temperature in the presence of one equivalent of triethylamine to give in good yield the tripeptide ester (XV).

These preliminary results indicate that the sulphoxides are not sufficiently activated to warrant further investigation as activated esters; however the sulphones would appear to have an activity useful for peptide formation.

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[4] R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, 1958, **41**, 2190. These authors have reported a few 4-(methylsulphonyl)phenyl esters prepared from 4-(methylsulphonyl)phenol through the diaryl sulphite method.