Selective Removal of Sulphur Protecting Groups of Cysteine Residues by Sulphenyl Halides

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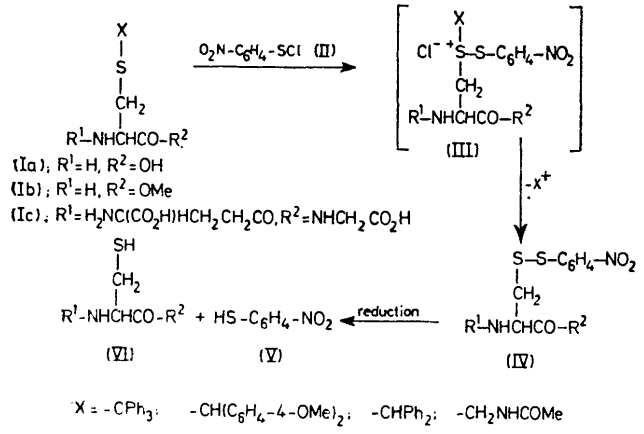
Summary Sulphur protecting groups of cysteine, such as triphenylmethyl, diphenylmethyl, 4,4′-dimethoxydiphenylmethyl and acetamidomethyl groups, are cleanly removed by the action of 2-nitrophenylsulphenyl chloride in acetic acid and subsequent reduction of the *S*-(2-nitrophenylsulphenyl)cysteine residues formed to regenerate the thiol function.

DEBLOCKING of thioether-type protecting groups of cysteine residues during peptide synthesis can be accomplished by means of strong acids, *via* reductive cleavage using sodium in liquid ammonia, with thiocyanogen, with iodine or with heavy metals like silver and mercury.[1] We have now demonstrated that 2-nitrophenylsulphenyl chloride can be used to cleave, in addition to the *S*-acetamidomethyl group,[2]

other common *S*-protecting groups. Cleavage is successfully effected if a stable cation can be ejected from the intermediate thiosulphonium salt (III) (Scheme).[3]



SCHEME

When the *S*-trityl, *S*-benzhydryl, *S*-(4,4′-dimethoxydiphenylmethyl) and *S*-acetamidomethyl derivatives of cysteine (Ia), cysteine methyl ester (Ib), or reduced glutathione (γ-glutamylcysteinylglycine) (Ic) were treated with 2—5 equivalents of 2-nitrophenylsulphenyl chloride (II) in acetic acid, the starting materials (I) smoothly reacted almost quantitatively to give the corresponding *S*-(2-nitrophenylsulphenyl) cysteinyl derivatives (IV). These mixed disulphides were isolated and shown to be identical with those prepared by treating cysteine and other cysteine derivatives with 2-nitrophenylsulphenyl chloride in acetic acid, as previously described.[4] Removal of the *S*-sulphenyl group was accomplished by reduction in aqueous methanol at room temperature with excess thiol such as β-mercaptoethanol or dithioerythritol or by $NaBH_4$, following the standard procedure for disulphide cleavage in peptides and proteins.[5]

The use of 2-nitrophenylsulphenyl chloride as the cleaving agent for *S*-protecting groups of cysteine appears to be a valuable alternative to the available methods and presents certain advantages since the reaction is both rapid and quantitative. The method is very selective, and amino acid side chains do not react with the reagent in acetic acid except the indole nucleus of tryptophan which is converted into a 2-substituted derivative.[6]

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