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N_G-2,2,5,7,8-PENTAMETHYLCHROMAN-6-SULPHONYL-L-ARGININE: A NEW ACID LABILE DERIVATIVE FOR PEPTIDE SYNTHESIS

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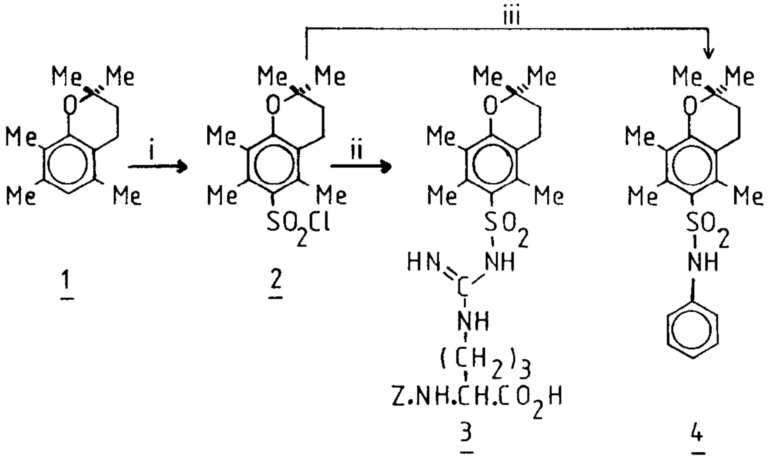
A new acid labile protecting group for the guanidino side chain functionality of arginine has been developed. N_G-(2,2,5,7,8-Pentamethylchroman-6-sulphonyl)-L-arginine, prepared from N_α-benzyloxycarbonyl-L-arginine and 2,2,5,7,8-pentamethylchroman-6-sulphonyl chloride, is cleaved rapidly in trifluoroacetic acid (TFA) or 50% TFA in dichloromethane at room temperature.

The search for acid labile side chain protecting groups for the highly basic guanidino function of arginine has led to the preparation of many derivatives based upon either urethane or arylsulphonyl groups, which offer orthogonal protection strategies to be pursued with regard to the masking of α-amino groups. However the urethane based derivatives have not received widespread application as a result of their steric bulk and (in some cases) unwieldy preparation, but perhaps the most serious disadvantage is the formation of considerable amounts of ornithine containing peptides *via* a deleterious side reaction arising from incomplete masking of the guanidino group.[1]

The introduction of the p-toluenesulphonyl group[2] for the protection of the guanidino function of arginine led to successful syntheses of many important peptides, but the major disadvantage has been the harsh conditions required for final deprotection.[2,3] The choice of arylsulphonyl compounds available for the protection of the guanidino function of arginine has been extended by the contributions of Fujino[4,5] and Yajima,[6] so that the most acid labile of these derivatives currently available, the 4-methoxy-2,3,6-trimethylbenzenesulphonyl (Mtr) group, can be cleaved by treatment with trifluoroacetic acid (TFA)-thioanisole (9:1) in *ca.* 1 hour. This group has been exploited, in association with the base labile fluorenylmethoxycarbonyl (Fmoc) N_α-protecting group, in the solid phase syntheses of synthetically challenging sequences,[7] yet long reaction times (5-6 hours in TFA-anisole-ethanedithiol at room temperature) were required for complete deprotection.

In an attempt to design a guanidino protecting group with enhanced acid lability over the Mtr group an examination of the report of Fujino *et al*[5] was carried out which suggested certain specific requirements based upon steric and electronic considerations. Substitution of the aromatic ring with electron donating substituents is an essential prerequisite for stabilisation of the arylsulphonyl cation formed by acidolysis, but the nature of the substituents must be carefully selected. Methyl groups in positions *ortho* to the sulphonyl group have been shown to induce greater acid lability than methoxy substituents in the same positions, presumably permitting greater interaction between the aromatic π-electrons with the vacant *d*-orbitals of sulphur. A methoxy group in the *para* position has been shown to increase acid lability, probably due to stablisation of the intermediate formed, however addition of two methyl groups in the *meta* positions does not provide the extra stabilisation that might be expected from consideration of inductive effects and the resulting 4-methoxy-2,3,5,6-tetramethylbenzene-sulphonyl arginine derivative is less acid labile than the Mtr derivative. Thus the steric interaction between the two methyl groups and the methoxy group causes the oxygen lone pairs to lie in a position such that their availability for delocalisation with the phenyl ring π-system is reduced. Thus it was necessary to control effectively the orientation of the alkoxy substituent and maintain maximum substitution of the ring. This has been achieved using 2,2,5,7,8-pentamethylchroman[8] (1) as the fundamental substituted aromatic unit which was chlorosulphonated by the method of Paleos *et al*[9] to give 2,2,5,7,8-pentamethylchroman-6-sulphonyl chloride[10] (Pmc-Cl) (2) and subsequently reacted with Z.Arg.OH,[11] according to the procedure described for the preparation of Z.Arg(Mtr).OH,[5] to give N_α-benzyloxycarbonyl-N_G-(2,2,5,7,8-pentamethylchroman-6-sulphonyl)-L-arginine (3) purified as cyclohexylamine salt (Z.Arg(Pmc).OH.CHA) as a white crystalline solid (m.p. 150-152°C).

X-Ray crystallographic analysis of the anilide (4) of Pmc-Cl has revealed the C-O-C bond angle to be 118°, close to the 120° required for maximum interaction of an oxygen lone pair with the aromatic ring, and the C-O bond to be at an angle of 4° out of the plane of the ring.



(i) $ClSO_3H$, $CHCl_3$ (53%); (ii) Z.Arg.OH, NaOH(aq), acetone (72%); (iii) $Ph.NH_2$, toluene reflux

Initial deprotection studies of the free amino acid, H.Arg(Pmc).OH (5), produced by hydrogenation of (3), under a variety of conditions revealed remarkable acid lability as the group was apparently cleaved by TFA-thioanisole, TFA, and HBr in acetic acid in under 2 hours at room temperature. Encouraged by these results a series of arginine-containing carboxyl terminal-fragments (6 to 9) of ubiquitin were synthesised using the Z group for α-amino protection (cleaved by hydrogenolysis over 10% palladium on charcoal) and diphenylphosphinic chloride for carboxyl activation.[12]

Z.Arg(Pmc).Gly.GlyOMe	(6)
Z.Leu.Arg(Pmc).Gly.GlyOMe	(7)
Z.Arg(Pmc).Leu.Arg(Pmc).Gly.GlyOMe	(8)
Z.Leu.Arg(Pmc).Leu.Arg(Pmc).Gly.GlyOMe	(9)

In each peptide the removal the Pmc group was complete in 20 minutes when treated with TFA at room temperature, whilst exposure to TFA for periods in excess of one hour caused partial cleavage of the Z group. Addition of 10% thioanisole to TFA offered only a small improvement in the rate of removal of the Pmc group, but the Z group was cleaved to a significant extent.[13] Deprotection of the free amino acid, (5), was accomplished in less than 5 minutes in a solution of 45% HBr in acetic acid.

The use of 50% TFA in dichloromethane offers a new dimension to the conditions available for the deprotection of N_G-arylsulphonyl groups. This reagent cleaved the Pmc group in all cases in one hour, without any detectable loss of the Z group and, moreover, these conditions are compatible with those employed for the removal of the t-butyl based side chain protecting groups used in association with N_α-Fmoc protection.

The byproduct of deprotection of the Pmc group has been shown to be 2,2,5,7,8-pentamethylchroman (1) by comparison with authentic material.

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