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ACETOL : A USEFUL NEW PROTECTING GROUP FOR PEPTIDE SYNTHESIS+

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ABSTRACT : Acetol can be conveniently used as a reagent for the protection of carboxylic acids in peptide synthesis. It has been found to be inert and stable to hydrogenolytic and acidolytic conditions normally used in peptide synthesis. Deblocking has been selectively achieved under mild conditions using $Bu_4NF.3H_2O$ in THF.

One of the essential requirements during peptide synthesis is to protect the carboxyl function of an amino acid with a suitable protecting group which in turn can be selectively removed without affecting other sensitive features of peptides[1]. There are a variety of esters reported in the literature which are envisaged for this purpose. However, the use of strong acid or bases necessary to affect ester cleavage often limit their scope. Use of readily hydrogenolysed substituted aromatic esters avoids the difficulty, however, problems often arise either due to their incompatibility with sulphur containing amino acid or due to undesired side reactions. This has necessiated a search for new carboxyl protecting groups both from the point of view of selectivity and stability.

In the present paper application of a new carboxyl protecting group : acetol (CH_3COCH_2OH) to peptide synthesis is described. In the first instance, several N-protected amino acid acetolyl esters have been synthesised. The N-protected amino acids were esterified with acetol using the DCC/DMAP procedure[2] in essentially quantitative yields. The acetolyl esters[3] were found to be stable to acidolytic[4] (HCl/dioxane, TFA/CH_2Cl_2) and hydrogenolytic[5] (H_2, Pd-C) conditions routinely used in the peptide synthesis for the removal of BOC and Z group respectively. This is in contrast to the analogous phenacyl ester which was found to be incompletely cleaved during hydrogenolysis due to partial reduction of the phenacyl carbonyl giving rise to ethylphenyl ester[6]. The deblocking of acetolyl ester can be carried

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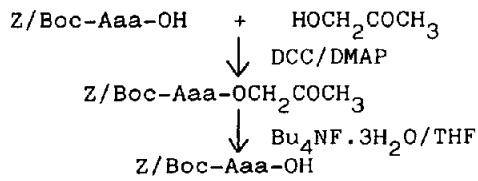

Aaa = Amino acid

out under very mild and nearly neutral conditions using $Bu_4NF.3H_2O$ in THF at room temperature in quantitative yields[7]. $Bu_4NF.3H_2O$ has been widely used as a good cleavage reagent both in solution and solid phase peptide synthesis[8]. In most cases deblocking was complete within 5-45 min and proceeded without any side reaction. The reaction generates acetol as a byproduct and hence the purification of the product was simple and convenient. Further, selective removal of the acetolyl group could be carried out even in the presence of Bzl and *t*-Bu groups generally used as side chain protection for COOH and OH functions.

The utility of acetolyl esters in peptide synthesis has been demonstrated by successful synthesis of a biologically active pentapeptide Leu-enkephalin[9]. The crude enkephalin obtained after Bu_4NF and acidolytic cleavage was analysed by reverse phase h.p.l.c. to check for the possibility of racemisation and no trace of D-Leu-enkephalin could be detected.

Compounds	Yield %	m.p. °C	$[\alpha]_D(CHCl_3)$	FABMS (M+H)
Z-Val-OAce	91	51	-24.9(c,1.8)	308.1
Boc-Val-OAce	85	59	-34.6(c,1.2)	274.1
Z-Gly-OAce	92	66		266.1
Boc-Thr(Bzl)-OAce	85	oil	-7.8(c,1.0)	366.1
Boc-Leu-OAce	83	oil	-26.5(c,1.1)	287.1
Boc-Asp(OBzl)-OAce	80	oil	+13.5(c,1.1)	380.1
Z-Asp(O-*t*-Bu)-OAce	84	85-87	+15.3(c,1.0)	380.1
Boc-Pro-OAce	89	oil	-39.3(c,1.0)	272.1
Boc-Phe-Leu-OAce	85*	97-99	-25.0(c,0.9)	435.2
Z-Gly-Phe-Leu-OAce	77*	91-92	-23.3(c,1.2)	526.3
Z-Gly-Gly-Phe-Leu-OAce	69*	80-82	-15.8(c,1.4)	583.3
BocTyr-Gly-Gly-Phe-Leu-OAce	68*	67-69	-29.2(c,1.1)	723.3

*Yields from peptide coupling reaction

These result show that acetol will be ideally suited for the masking of carboxyl functions in peptide synthesis and its fluoride ion final deprotection strategy based on two dimensional orthogonal protection scheme may make it a protecting group of better choice.

General procedure for esterification : To a solution of suitably protected amino acid (1 mmol), acetol (1.2 mmol) and catalytic amount of DMAP (5 mgs) in CH_2Cl_2 was added DCC (1.1 mmol) at 0°C. Reaction was stirred for 1 hr at 0°C and then left for overnight stirring at room temperature. DCU was filtered off and the filtrate was evaporated under reduced pressure. The residue was then taken up in EtOAc, washed successively with 5% aq. citric acid, water, 5% aq $NaHCO_3$ and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was either crystallised from EtOAc/Hexane or purified wherever necessary by silica gel column chromatography using EtOAc-Hexane (1:2) as an eluant.

General procedure for deblocking : A solution of peptide esters in THF was treated with Bu_4NF/THF (1.0 M, 2-4 equivalents) under stirring at room temperature. After completion of reaction as monitored by t.l.c., the reaction was quenched by adding cold water and concentrated under reduced pressure. The residue was then dissolved in EtOAc and washed with 5% aq $KHSO_4$ several times and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness to get required acid in excellent yield.

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References and Notes

1. Gross, E. and Meienhofer, J. in The Peptides, 3, p 102, Academic Press, New York (1981).

2. Dhaon, M.K., Olsen, R.K. and Ramasamy, K., J. Org. Chem., 47, 1962 (1982).

3. All N-protected amino acid acetolyl esters gave satisfactory ^1H-NMR.

4. Z-Val-OAce (100 mg) was treated separately with TFA/CH_2Cl_2 (1:1) and 4N HCl/dioxane for 1 hr at room temperature. After evaporation of the solvent, Z-Val-OAce was recovered in quantitative yield thereby suggesting stability of -OAce to acidolytic conditions.

5. Boc-Val-OAce (200 mg) was dissolved in MeOH (10 ml) and subjected to catalytic hydrogenation using 10% Pd-C for 20 hrs. After usual work up Boc-Val-OAce was recovered in quantitative yields suggesting stability of acetolyl carbonyl to hydrogenolysis.

6. Taylor-Papadimitriou, J., Yovanidis, C., Poganou, A. and Zervas, L. J. Chem. Soc. C 1830 (1967).

7. The N-protected amino acids obtained after removal of -OAce groups were characterised by comparing with authentic sample using optical rotation and ^{1}H NMR.

8. Namikoshi, M., Kundu, B. and Rinehart, K.L., J. Org. Chem., 56, 5464 (1991) and ref. therein.

9. Leu-enkephalin was synthesised in a stepwise manner using DCC/HOBt and mixed anhydride procedures. Boc-Tyr was coupled to the tetrapeptide by active ester (pentafluorophenyl) method.

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