Solvolysis of Carboxamide Protected Asparagine and Glutamine Derivatives with Boron Tris(Trifluoroacetate) in Trifluoroacetic Acid and in Acetic Acid Solutions

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Asparagine and glutamine derivatives with their carboxamide side-chain protected with 2,5-dimethyl-4-mehtoxybenzyl (I); 1-(3,4-dimethylphenyl)ethyl (II) ; 2-methoxyl-1-naphthalenemethyl (III); 1-(4-methoxyphenyl)ethyl (IV); 2,4,6-trimethylbenzyl (V); diphenylmethyl (VI) and 4-methoxy-1-napthalenemethyl (VII) groups were each cleaved in boron tris(trifluoroacetate) (BTFA) in trifluoracenate acid (TFA) and in acetic acid solutions. Groups II, III, IV and V on asparagine derivatives were completely removed by BTFA in TFA while other groups were only partially removed. Only groups II and IV on glutamine derivatives were completely removed by BTFA in TFA in each case a very small amount of ammonia were detected along with gree asparagine and glutamine. A solution of Boron tris(trifluorocetate) in acetic acid cleaved group VII and free asparagine or glutamine was obtained without being formation of ammonia.

INTRODUCTION

Boron tris(trifluoroacetate) (BTFA) in either trifluoroacetic acid or acetic acid is used as deprotecting reagent in peptide chemistry [1]. The ability of BTFA reagent in removing various protecting groups used in peptide synthesis is supposed to be similar to that of liquid hydrogen fluoride [2,3,4,5] or hydrogen bromide in acetic acid [6]. It has been demonstrated that liquid HF removes carboxamide protecting groups on a free amino acid such as on N^{CA} diphenlymethylglutamine [7] or on an amino acid residue within a peptide chain such as *tert*-butyloxycarbonyl-S-p-methoxybenzylcysteinylphenylalanylisoleucylleucyl-N^{CA}-diphenylmenthylasparaginyl-S-p-methoxybenzylcysteinylprolylleucylglycinamideResin [8] . The protected carboxamide group is converted to free carboxamide group and no side products involving carboxamide side chain are formed in the course of the HF cleavage. As BTFA is an easier reagent to handle and to work with than liquid HF this research work will shed some light as to whether the BTFA is equally a good carboxamide deprotecting reagent as liquid HF. Thus it may be used inplace of liquid HF to remove these groups.

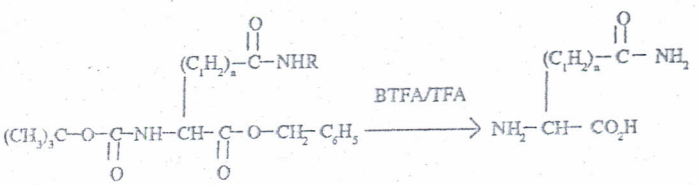
EXPERIMENTAL

Boron tris(trifluoroacetate): A solution of 125.3g (0.5 mol) of boron tribromide (BBr_3) in 60 ml of dichloromethane (CH_2Cl_2) was cooled to -10°C. To this solution was added dropwise a solution of 161.0g (1.5 mol) of TFA in 60 ml of CH_2Cl_2 for a period of 30 min. The mixture was allowed to stand for 40 min. The solvent was evaporated to dryness in vacuo: wt. 142.9g (81.7%): m.p. 87-89 (Lit. 88°C decomposed) [9].

BTFA-TFA Cleavage: A sample of 25μ mole of carboxamide-protected asparagine of glutamine derivative was dissolved in 0.2 ml of TFA and 0.5 ml of 1.0 M BFTA in TFA was added. The mixture was shaken for 90 min. and evaporated to dryness in vacuo. The residue was dissolved in 25 ml of methanol and evaporated to dryness. This was repeated three times. The final residue was dissolved in 25 ml of methanol and evaporated to dryness. This was repeated three times. The final residue was dissolved in 25ml of pH 3.10 citrate (Na^+) buffer, the undissolved material was filtered off and the filtrate was applied directly for the quantitative determination of the extent of deprotection of carboxamide protecting group on amino acid analyzer, Beckman Model 120 C at 55°C using pH 3.10, 4.25 and 5.26 citrate (Na^+) buffers at a flow rate of 70 ml/hr. and ninydrin reagent at a flow rate of 35 ml/hr. A standard sample of asparagine/N^{CA}-R-asparagine or glutamine/N^{CA}-R- glutamine was used to determine the extent of the cleavage of the carboxamide protecting group.

RESULTS AND DISCUSSIONS

Fully protected α-Benzyl *tert*-butyloxycarbonyl-N^{CA}-R-asparaginate or α-benzyl *tert*-butyloxycarbonyl-N^{CA}-R-glutaminate derivative, where R is the carboxamide protecting group, was subjected to a solution of BTFA in TFA or in acetic acid and the product composition analysed for free asparagine or glutamine. The general reaction expected is as follows:



n=1, asparaginyl derivative

n=2, glutaminyl derivative

R= carboxamide group.