Trifluoromethanesulphonic Acid, as a Deprotecting Reagent in Peptide Chemistry

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Summary Trifluoromethanesulphonic acid was found to cleave, in the presence of anisole, a number of protecting groups currently employed in peptide chemistry without significant side reactions.

TRIFLUOROMETHANESULPHONIC acid is a reagent acidic enough to cleave the benzyloxycarbonyl group within 15 min at room temperature (20°). We have found that this reagent also removes various protecting groups currently employed in peptide chemistry (Table).

Each amino-acid derivative was dissolved at 20° in methylene chloride or trifluoroacetic acid and 5—10 equiv. of the reagent were employed. In order to suppress the possible alkylation reaction,[1] anisole (1·5—3 equiv.) was used as a scavenger. Part of the solution was subjected to quantitative amino-acid analysis.

Acid labile amino-protecting groups, such as Boc, Z(OMe), and NPS, were cleaved quantitatively within 3—5 min. In addition to the t-butyl ester group, the benzyl group attached at the ω-carboxy-function of Glu and Asp and at the hydroxy-function of Ser and Thr was removed completely within 30 min. Treatment of Z-Trp-

Table. Removal of various protecting groups by trifluoromethanesulphonic acid

Treated amino-acid derivatives	Parent amino-acid regenerated (%) 3—5 min	15 min	30 min	60 min
NPS-Val-OH[a]	99·9			
Boc-Ser-OH[a]	99·2			
Z(OMe)-Gly-OH[a]	99·8			
Z-Trp-OH	85·6	94·6	100·9	
Z-Tyr-OH		92·4		
Z-Met-OH[b]		48·1	88·3	
Z-Glu-OH	91·7	100·1		
Z-Glu(OBu^{t})-OH		98·8		
H-Glu(OBzl)-OH	98·8	100·7		
H-Asp(OBzl)OH	95·8	97·2	100·4	
H-Ser(Bzl)-OH	76·3	96·3	100·4	
H-Thr(Bzl)-OH	91·7	96·5	99·0	
H-Tyr(Bzl)-OH		10·7	10·5	
H-Arg(Tos)-OH[c]	85·8	87·1	93·3	100·1
H-Arg(NO$_2$)-OH[c]		21·3	33·5	34·5
H-His(Tos)-OH	77·9	79·1	84·3	98·4
H-Cys(Bzl)-OH[c]		62·0	98·7	
H-Cys(MBzl)-OH	99·8	100·0		

[a] Methylene chloride was employed as a solvent. [b] Reaction in the presence of dithiothreitol. [c] Reaction at 40°.

OH and Z-Tyr-OH with this reagent for 30 min regenerated the parent amino-acids in nearly quantitative yields, indicating that addition of anisole is effective to prevent the alkylation during this deprotection. However, the recovery of Tyr, after similar treatment of H-Tyr(Bzl)-OH, was low, because of the predominant formation of the rearrangement product, 3-benzyltyrosine.[2] Under similar conditions, the recovery of Met, regenerated from Z-Met-OH, was also low. However, improvement was expected when the treatment was performed at 0° in the presence of anisole plus methyl ethyl sulphide or dithiothreitol.

Regeneration of Arg from H-Arg(Tos)-OH was achieved quantitatively after treatment with this reagent at 40° for 60 min, but only 35% was regenerated from H-Arg(NO$_2$)-OH under identical conditions. The *S-p*-methoxybenzyl ester group of Cys was found to be cleaved within 15 min, but removal of the *S*-benzyl group required somewhat elevated temperature (40°).

From the results so far obtained, trifluoromethanesulphonic acid seems to have a similar action to liquid hydrogen fluoride[3] or boron tris(trifluoroacetate).[4]

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