Trimethylsilyl Iodide as a Peptide Deblocking Agent

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Summary Removal of urethane and benzyl ether blocking groups from peptides is readily accomplished by treatment with trimethylsilyl iodide which is particularly useful for the debenzylation of *O*-benzyltyrosine without the formation of rearrangement products.

EVEN though an earlier report by Rabinowitz[1] on alkyl phosphonate cleavage by trimethylsilyl chloride excited little interest, the development of the analogous trimethylsilyl iodide (TMSI) as a non-hydrolytic reagent for the cleavage of alkyl esters,[2] ethers,[2] acetals,[2b] phosphonates,[3] and carbamates[4] has burgeoned very recently. The properties of TMSI make it an extremely attractive reagent for use in peptide synthesis since ethers, esters, and carbamates are the most common blocking groups used and the reactions are carried out under neutral conditions at room temperature or slightly above and can be followed by n.m.r. spectroscopy. An important difference between TMSI deblocking and acid-catalysed deblocking procedures (CF_3CO_2H, HBr–AcOH, HF, *etc.*) commonly used in peptide synthesis is that in the case of the former, the key blocking group, *i.e.*, t-butyl, benzyl, or alkyl, is removed by S_N2 attack of iodide on the alkyl group without the formation of carbonium ions. It is well known that the formation of t-butyl and/or benzyl carbonium ions during acid-catalysed deblocking often leads to t-butylation and/or benzylation of the aromatic species in a peptide chain.[5] The absence of this side-reaction during TMSI deblocking of peptides should give purer products than those resulting from HF or trifluoroacetic acid treatment. This report gives a summary of our recent work on TMSI peptide deblocking.

To our knowledge, only the cleavage of benzyl carbamates by TMSI has been reported[4] in the literature. We therefore examined the reaction of several *N*-benzyloxy- (Z) and *N*-t-butoxy-carbonyl (Boc) peptide derivatives (Table) with TMSI in $CDCl_3$ or CD_3CN and followed the reaction course by n.m.r. spectroscopy.

Compounds (**1**)—(**8**) were treated with TMSI and the rate of ester and/or ether cleavage was monitored by n.m.r. spectroscopy. The silyl esters and/or ethers which were formed were then decomposed with methanol and the purity of the product was checked by t.l.c.† It is clear from the Table that the carbamate functions react rapidly while the methyl esters require treatment with an excess of TMSI at elevated temperatures for at least 1 h before any detectable amount of cleavage can be observed.‡ It was found that the tyrosine peptide (**1**) gave up only its Boc group when treated with 1·2 equiv. of TMSI for 6 min. However, t.l.c. indicated formation of a small amount of

† T.l.c. analyses were carried out on Whatman MK6F precoated silica gel plates in both Bu^tOH–AcOH–H_2O (4:1:1) and $CHCl_3$–MeOH–AcOH (17:2:1). Visualization was effected by ninhydrin.

‡ In the case of tyrosine peptide the methyl ester did not begin to react until 1 h had elapsed at 50 °C with 3·6 equiv. of TMSI.

TABLE

Peptide		Solvent	Equiv. TMSI	Temp./°C	Time for removal[a]/h Z/Boc	Benzyl/NO_2
Boc-Val-Tyr(Bzl)·OMe	(1)	CD_3CN	1·2	25	0·1	—
Boc-Val-Tyr(Bzl)·OMe	(1)	CD_3CN	3·6	50	0·1	2[b]
Z-Pro-Phe·OH	(2)	$CDCl_3$	2·4[c]	25	0·1	—
Boc-Pro-Phe·OMe	(3)	$CDCl_3$	1·2	25	0·1	—
Z-Pro-ΔPhe·OMe[d]	(4)	$CDCl_3$	1·2	25	0·1	—
Boc-Leu-ΔLeu·OMe[d]	(5)	$CDCl_3$	1·2	25	0·1	—
Z-Cys(Bzl)·OH	(6)	DMF[e]	3·6[c]	50	0·1	f
Z-Arg(NO_2)·OH	(7)	CD_3CN	3·6[c]	50	0·1	f
Boc-His(Bzl)·OH	(8)	$CDCl_3$	3·6[c]	50	0·1	f

[a] Complete deblocking was determined by integration of pertinent peaks in the n.m.r. spectrum. [b] The benzyl ether is *ca.* 50% removed when the methyl ester begins to react, but removal of the benzyl ether is quantitative. [c] Carboxy group reacts with TMSI requiring an extra equivalent. [d] ΔPhe = αβ-dehydroPhe; ΔLeu = αβ-dehydroleucine. [e] DMF (dimethylformamide) was used to prevent precipitation of the amino acid when TMSI was added. [f] No reaction over a period of 24 h.

another product, possibly the debenzylated compound. The benzyl ether of the tyrosine peptide can be completely removed upon treatment with an excess of TMSI at 50 °C with no evidence for formation of a 3-benzyltyrosine peptide. We found also that none of the side-chain protecting groups (6—8) were removed by TMSI under the conditions used. Although we have not examined the use of TMSI in solid phase peptide synthesis, it should be possible to remove either a Boc or Z group from the growing *N*-terminus of a peptide chain attached to a resin by brief TMSI–CH_2Cl_2 treatment without significant loss of side-chain blocking groups or loss of peptide chains from the resin.

The following general procedure was used. To 0·1 mmol of protected peptide dissolved in 1 ml of $CDCl_3$ (or CD_3CN) in a 5 mm n.m.r. tube under N_2 was added 1·2 equiv. of TMSI *via* a dry syringe. The progress of the reaction was monitored by n.m.r. spectroscopy (Varian T-60): Boc-t-butyl (δ *ca.* 1·49) to t-butyl iodide (δ 1·95), Z-benzyl (δ *ca.* 5·13) to benzyl iodide (δ 4·49), tyrosine-OBzl (δ 5·11, CH_2Ph). Upon completion the reaction was quenched with 3—4 equiv. of MeOH per equiv. of TMSI. The tube was agitated for 5 min and the reaction mixture was poured into a 5 ml round-bottomed flask and the volatile components were evaporated *in vacuo*. The residue was dissolved in a mixture of 2 ml of ether and 2 ml of 30% HOAc. The aqueous layer was separated and extracted again with 2 ml of ether. Evaporation of the aqueous phase gave the pure peptide.

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