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Studies of Selective Boc Removal in the Presence of Silyl Ethers

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Abstract : The selective removal of N-Boc protection can be obtained in the presence of either TBDMS or TBDPS ethers. On the basis of promising results from the literature, we first tried sonication, that failed, whereas the exclusive cleavage of the Boc group was successfully achieved by a saturated solution of HCl in ethyl acetate. Copyright © 1996 Published by Elsevier Science Ltd

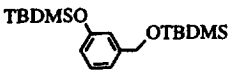
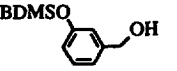
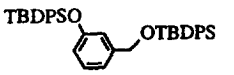
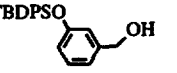
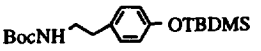
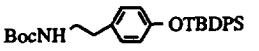
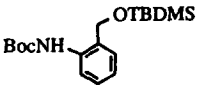
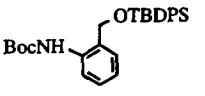
During our investigation on tentoxin analogues[1], the reactivity of the side-chain hydroxyl group of either serine or tyrosine which were part of a tetrapeptide sequence needed to be masked in a way that would resist to the N-terminal deprotection. That prompted us to examine in details the selectivity of *tert*-butyloxycarbonyl (Boc) group cleavage in the presence of silyl ethers. Indeed Boc protected amines have been used in combination with *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl (TBDPS) ethers but no specific reaction condition providing exclusive removal of the Boc group has been described so far in the literature. In many examples[2-5], standard solutions of trifluoroacetic acid in dichloromethane (30% v/v) were employed giving rise to unoptimized moderate yields of the desired silyl protected products. A slightly better result was obtained with a saturated solution of hydrochloric acid ethyl acetate[6] whereas on the contrary 1% HCl in methanol afforded nearly total silyl ethers deprotection without affecting the Boc group[7].

Recent results reported an interesting selectivity of TBDMS deprotection between benzylic and phenolic alcohols using sonication in solution of CH_3OH / CCl_4 (1:1)[8]. We thought that these conditions could be of assistance to solve our problem. In addition to amino phenol and amino benzyl alcohol, we tested two dipeptides: Boc-Leu-Ser-OMe and Boc-Leu-Tyr-OMe. Our results are summarized in Table 1. First of all the temperature of sonication was found to be of great importance as the published results were only reproduced when the sonicator bath reached 45°C (Table 1, Entry 1). According to the literature[8], a good selectivity (82%) of primary *versus* phenolic silyl protection cleavage was observed for the TBDMS group. We even improved the selectivity (92%) with the TBDPS group (Table 1, Entry 2). Unfortunately, such promising results could not be reproduced with the other substrates as some primary ethers were found to be stable (Table 1, Entries 5, 6 and 10) whereas phenolic alcohols were deprotected at the same time (Table 1, Entry 7). Such method seemed to be highly sequence dependant and thus could not be envisaged as a general deprotection method.

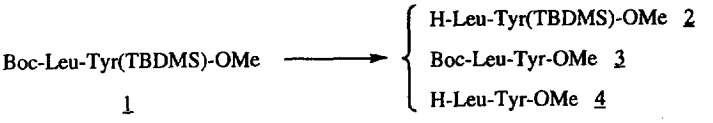
In order to find selective Boc removal conditions applicable to substrates bearing acid sensitive moieties such as the TBDMS group, we then explore a large variety of acidic conditions on Boc-Leu-Tyr(TBDMS)-OMe as a model (Scheme 1). In addition to the classical reagents such as TFA in dichloromethane at different

concentrations and temperatures or HCl in various solvents, other conditions were also employed including *p*-toluenesulfonic acid which was shown to provide selective Boc cleavage in the presence of the acid labile *p*-methoxybenzylic ester[9], acidic aqueous phases as well as *in situ* generation of HCl by the use of TBDMSCl in methanol. Such chlorosilane reagent was used instead of the usual TMSCl to prevent any exchange of the TBDMS ether.

Table 1: Stability of Boc, TBDMS and TBDPS groups under sonication in CH_3OH / CCl_4 (1:1)

Entry	Substrate	Reaction time (h)	Starting material (%)	Deprotected product (%)
1		2	0	82 % 
2		2	0	92 % 
3		8	100	
4		8	100	
5		6	100	
6		6	100	
7	Boc-Leu-Tyr(TBDMS)-OMe	6	0	50 %: H-Leu-Tyr(TBDMS)OMe 25 %: Boc-Leu-Tyr-OMe
8	Boc-Leu-Tyr(TBDPS)-OMe	6	100	
9	Boc-Leu-Ser(TBDMS)-OMe	6	58	42 %: H-Leu-Ser(TBDMS)OMe
10	Boc-Leu-Ser(TBDPS)-OMe	6	100	

The results are summarized in Table 2. The reaction mixture of entry 3 was chromatographied on silica gel to separate and characterize the expected product H-Leu-Tyr(TBDMS)-OMe (2) and the completely deprotected structure H-Leu-Tyr-OMe (4). The respective retention times being determined, reactions were then followed by reversed-phase HPLC on ODS C_{18} column at 214 nm (70% CH_3CN-30% H_2O) and the relative abundances of the various products were directly deduced from HPLC peak areas and confirmed by NMR signal integrations.



Scheme 1

As expected no complete selectivity of Boc removal was obtained using solutions of TFA in dichloromethane whatever the experimental concentration or the temperature, the best conditions giving 72% of the free N-terminal silyl derivatized peptide 2 (Table 2, Entry 3). Moreover *p*-toluenesulfonic acid was found to be too reactive and inadapted even in catalytic amount (Table 2, Entry 10) since the loss of the silyl protection occurs before the Boc cleavage leading to 3 as major product. The attempts made in aqueous media by lowering the pH with aqueous solutions of HCl or citric acid were not conclusive (Table 2, Entries 16 and 17). However very good results were obtained with saturated solutions[10] of HCl in either 1,4 dioxan (Table 2, Entry 6) or ethyl acetate (Table 2, Entry 7), the latter providing a 94% yield of the desired compound 2. Amazingly, switching the solvent to methanol erased the selectivity since the fully deprotected structure 4 was afforded in 93% yield (Table 2, Entry 8). In the same manner, *in situ* formation of HCl which took place in methanol caused simultaneous release of the Boc and TBDMS groups (Table 2, Entries 12,13,14 and 15).

Table 2: Deprotection of Boc and / or TBDMS groups under various acidic conditions

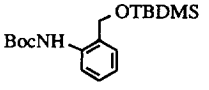
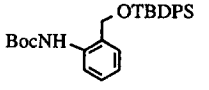
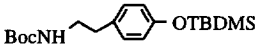
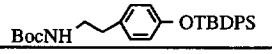
Entry	Reagent	T (°C)	RT (h)	Starting material 1 (%)	TBDMS protected product 2 (%)	Boc protected product 3 (%)	Fully deprotected product 4 (%)
1	20% TFA / CH_2Cl_2	0	24	100	-	-	-
2	20% TFA / CH_2Cl_2	25	24	30	47	-	23
3	30% TFA / CH_2Cl_2	0	7	-	72	-	28
4	30% TFA / CH_2Cl_2	25	3	-	52	-	48
5	HCl / CH_2Cl_2	25	24	18	-	75	8
6	HCl / 1,4 dioxan	25	48	14	75	-	11
7	HCl / EtOAc	25	8	4	94	-	2
8	HCl / MeOH	25	5	7	-	-	93
9	1 eq. *p*TsOH / CH_3OH	0	2	-	-	9	91
10	cat. *p*TsOH / CH_3OH	25	48	5	5	69	21
11	1eq. TBDMSCl / CH_3OH	25	24	100	-	-	-
12	1eq. TBDMSCl / CH_3OH	reflux	5	0	-	-	92
13	2eq. TBDMSCl / CH_3OH	25	5	4	-	21	75
14	Sonication / CCl_4-CH_3OH	35	2	55	8	8	29
15	Sonication / CCl_4-CH_3OH	45	2	-	-	2	98
16	HCl / H_2O / pH 3	25	-	50	28	22	-
17	HCl / H_2O / pH 2	25	-	14	-	-	86

According to this preliminary study, saturated HCl in ethyl acetate[10] stands for the best deprotection condition for Boc removal in the presence of an acid sensitive TBDMS ether. Subsequently, such reaction condition was applied to other Boc derivatized peptidic or non peptidic substrates bearing primary or phenolic alcohol protected by the TBDMS or TBDPS group.

The results are gathered in Table 3. In the case of the more acid sensitive TBDMS group, the selectivity was only achieved when the protected alcohol was phenolic. However, in the presence of a TBDPS ether, the

Boc protection was selectively removed by a solution of HCl in ethyl acetate whatever the nature of the substrate.

Table 3: Selectivity of Boc deprotection in the presence of TBDMS and TBDPS groups by a saturated solution of HCl in ethyl acetate[10] at room temperature

Substrate	Reaction time (h)	Starting material (%)	Free amino silylated product (%)	Fully deprotected product (%)
Boc-Leu-Tyr(TBDMS)-OMe	8	4	94	2
Boc-Leu-Tyr(TBDPS)-OMe	72	-	95	-
Boc-Leu-Ser(TBDMS)-OMe	72	-	-	100
Boc-Leu-Ser(TBDPS)-OMe	48	-	90	6
	48	-	-	100
	6	10	87	-
	15	2	96	-
	48	11	82	-

In summary, attempts using sonication to selectively remove Boc protection in the presence of either TBDMS or TBDPS groups failed. Nevertheless we were successful in the exclusive cleavage of the Boc group in the presence of TBDPS or phenolic TBDMS ethers by a saturated solution of HCl in ethyl acetate[10].

References and notes

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10. EtOAc was freshly distilled before use. Saturated solution of HCl in ethyl acetate has been titrated and found to be 7.5N.

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