Microwave-Assisted Deprotection of Boc-Protected Amines and Amino Acid Derivatives Using Solid Phase Supported Sulfonic Acids in a Catch-Release Manner

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Introduction

The *tert*-butyloxycarbonyl (Boc) group is a commonly used protecting group for amines in organic synthesis, particularly in peptide synthesis. It is removed using TFA, sulfonic acids or HCl. The possibility to use an acidic ion-exchanger as deprotecting agent and thus achieve a purification by a catch-release mechanism was pointed out by Liu et al.[1] They used Amberlyst 15 which gave a satisfying deprotection within 5 hours to 4 days, depending on the amine, at room temperature. In this work we show that silica supported sulfonic acids (*Table 1*) in conjunction with microwave heating are excellent Boc-deprotection agents. The time for deprotection is shortened to 10 minutes, the yields obtained are good to excellent and the products are of very high purity.

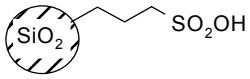
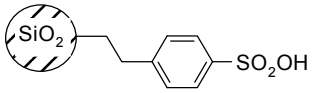
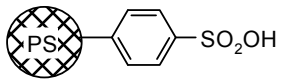
Deprotecting agent	Matrix material	Structure	Loading mmol/g
SCX-2[2]	Silica		0.6
SCX-3[2]	Silica		0.6
MP-TsOH[2] MP-TsOH(65)[2]	Macroporous polystyrene		3.43 4.45
Amberlyst 15[3]	Polystyrene		3.5

Table 1

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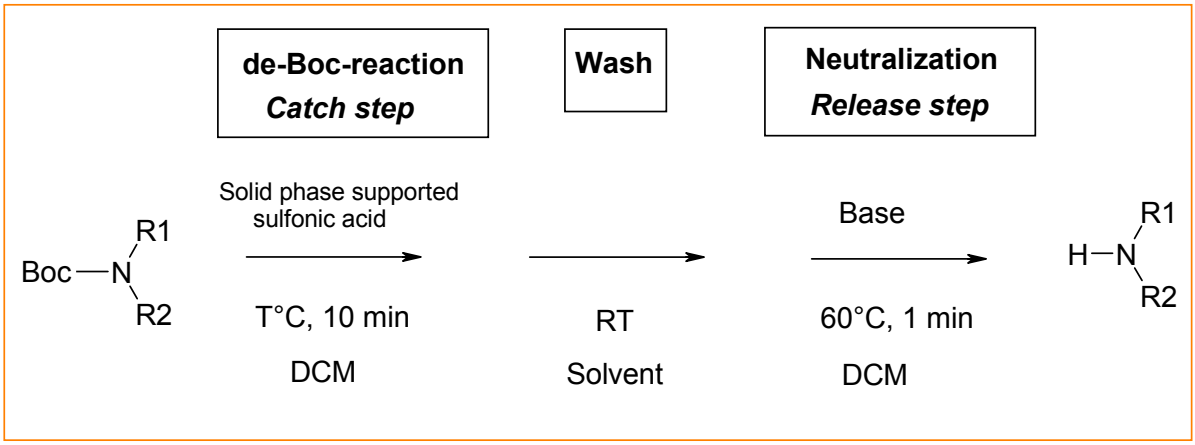
Results and discussion

Five solid phase supported sulfonic acids, two silica supported and three polystyrene supported (*Table 1*), were tried as Boc-deprotecting agents in conjunction with microwave heating. After the deprotection step, the amine was ionically bound to the solid matrix and impurities could be washed away. The amine was released from the solid matrix by neutralization with base under microwave heating at low temperature for 1 minute (*Scheme 1*).



Scheme 1

Initiator 60

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Entry	Boc-compound	Scale (mmol)	Deprotecting Agent	T (°C)	Equiv. DIEA[a]	Yield (%)	Purity (%)*
1	Boc-Phe-OMe	0.25	SCX-2	120	2.5	78	>99
2	- „ -	- „ -	- „ -	100	- „ -	78	>99
3	- „ -	- „ -	SCX-3	120	- „ -	87	>99
4	- „ -	- „ -	- „ -	100	- „ -	87	>99
5	- „ -	- „ -	SCX-2	120	3.8	83	>99
6	- „ -	1.25	- „ -	100	3.8	83	>99
7	- „ -	- „ -	SCX-3	- „ -	2.5	92	>99
8	- „ -	- „ -	MP-TsOH(65)	- „ -	- „ -	74	>99
9	- „ -	- „ -	MP-TsOH	- „ -	- „ -	27	93
10	Boc-Phe-OBzl	0.25	SCX-2	- „ -	4.0	85	>98
11	- „ -	- „ -	SCX-3	- „ -	2.5	88	>98
12	- „ -	- „ -	- „ -	- „ -	2.5**	91	>99
13	- „ -	- „ -	MP-TsOH(65)	- „ -	4.0	61	>98
14	- „ -	- „ -	Amberlyst 15	- „ -	2.5	20	>99
15	- „ -	- „ -	- „ - **3.5 eq.**	- „ -	4.5	38	>99
16	Boc-Bzl-piperazine	0.25	SCX-3 **3.0 eq.**	- „ -	5.0	32	>99
17	- „ -	- „ -	- „ -	- „ -	5.0**	80	>99
18	Boc-phenylendiamine	0.25	SCX-3	- „ -	2.5	93	95
19	Boc-4-Abz	0.25	SCX-3	- „ -	5.0	83	88
20	Boc-N-Me-Val-OBzl	0.25	SCX-3	- „ -	2.5	89	>99
21	Boc-Pro-OBzl	0.4	SCX-3	- „ -	2.5	80	>99
22	Boc-Tic-OBzl	0.35	SCX-3	- „ -	2.5	92	>99
23	Z-Lys(Boc)-OBzl	0.3	SCX-3	- „ -	2.5	38	95[b]
24	- „ -	1.0	SCX-3	- „ -	4.0	42	72[c]
25	- „ -	1.0	SCX-3	- „ -	4.0**	79	>99

Table 2 *[a] DIEA= Diisopropylethylamine, [b] 5 % dimer, [c] 28 % dimer, * By LC-MS, ** DEA= Diethylamine*

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It appears from *Table 2* (entries **1-9**) that the silica supported sulfonic acids were more efficien as Boc-deprotecting agents than the polystyrene supported ones. It was also evident that reaction temperature of 100°C and only a small excess of reagent (1.5 equiv.) were sufficient SCX-3 appeared to be slightly more efficient than SCX-2. The strongly acidic ion-exchange Amberlyst 15 used by Liu et al.[1] was shown to be less efficient than MP-TsOH even when th amount of acid was increased to 3 equiv. (entries **14 & 15**). Both Boc-protected aliphatic amine (primary & secondary) and anilines (entries **18 & 19**) were tested. In case of an additional amin function in the Boc-compound (entries **16 & 17**), double the amount of acid and neutralizing ba (entry **19**) is used. **DIEA** was generally used as base at neutralization, but in some cases (entrie **17 & 25**) diethylamine (**DEA**) proved to be superior.

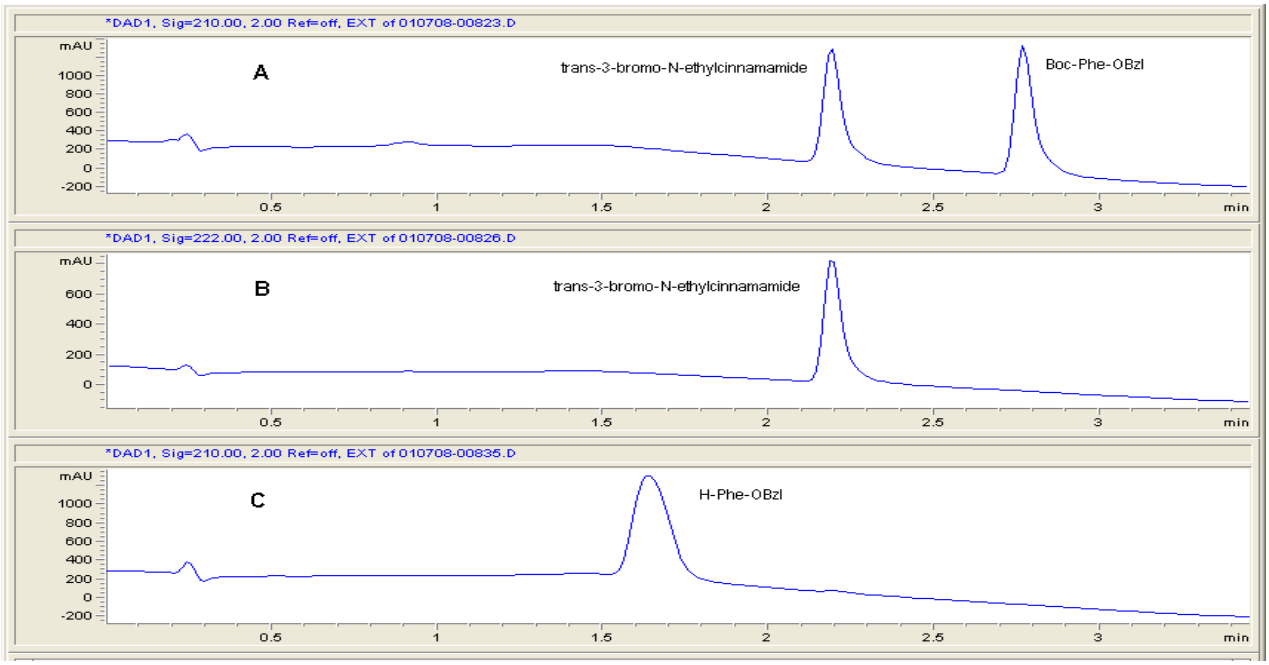

Fig.1

In order to demonstrate the purification effect excercised by the catch-release mechanism, a non-charged compound (trans-3-bromo-*N*-ethylcinnamamide) was mixed with the Boc-compound (*Entry 10*). The LC-MS trace of the starting solution is shown in *Fig.1**A***. In *Fig.1**B***, the LC-MS trace of the solution after the deprotection is shown. After washing of the matrix and subsequent neutralization, the trace shows only released deprotected amine in the solution (*Fig.1**C***).

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General experimental procedure

De-Boc-reaction: In a 2-5 ml microwave reaction vial, 0.25 mmol Boc-compound was dissolved in 2.5 ml DCM, and 1.5 equiv. solid supported sulfonic acid was added. The vial was capped and heated with stirring at 100°C in an Initiator™ Sixty for 10 minutes. **Neutralization**: After cooling, the solid support was filtered off, washed with an appropriate solvent, suspended in 2.5 ml DCM in a 2-5 ml microwave reaction vial and 2.5-5.0 equiv. base was added. The vial was capped and heated with stirring at 60°C in an Initiator™ Sixty for 1 minute. **Work-up**: After cooling, the solid support was filtered off and washed several times with DCM. The solvent was removed and the residue was dried, weighed and analyzed by LC-MS at an appropriate wavelength.

Conclusion

Silica supported ethyl benzene sulfonic acid, SCX-3,[2] is shown to be an excellent agent for deprotection of Boc-protected amines in combination with microwave heating. Boc-protected primary and secondary aliphatic amines as well as Boc-protected anilines are fully deprotected within 10 minutes, and the catch-release mechanism results in a simultaneous purification of the amine.

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References & notes:

1. Liu, Y.-S.; Zhao, C.; Bergbreiter, D. E.; Romo, D. J. Org. Chem., **1998**, 63, 3471
2. Biotage GB Ltd, UK
3. Merck KGaA, Darmstadt, Germany

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