

Easy Microwave Assisted Deprotection of N-Boc Derivatives

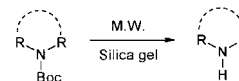
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Abstract. A simple and efficient method for the cleavage of *tert*-butoxycarbonyl amides and amines is described, which takes place on silica gel under microwave irradiation.



Scheme 1

The success of any protective group largely depends on how easily it can be installed and removed. The *tert*-butoxycarbonyl group is still now one of the most popular amino protecting groups.¹ The most standard method for its removal is trifluoroacetic acid (TFA) either neat or in CH_2Cl_2 solution,² although other mineral acids have been reported.³ In some instances Lewis acids have been also used such as $\text{BF}_3 \cdot \text{OEt}_2$.⁴ Less frequently, non-acidic conditions have been developed.⁵ In some cases, such as with electron rich substrates, thermolytic conditions have been also used.⁶ Recently Wensbo⁷ has described the selective removal of N-Boc protecting groups using silica gel at low pressure.

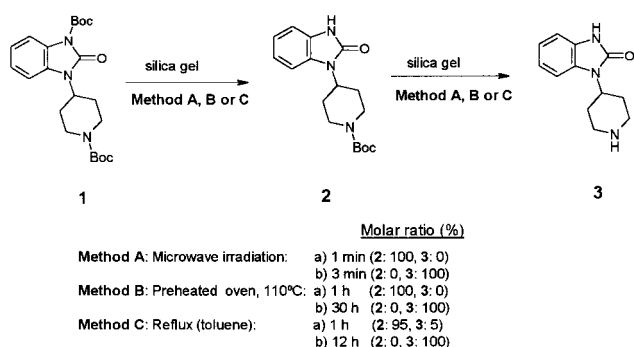
In the course of our investigations in connection with the synthetic uses of N-Boc protected alkyl pyroglutamates^{8a} or their modified derivatives^{8b} we have observed unexpected removal of this group when silica gel was present, so we decided to investigate this process. Our interest in the use of microwave energy as a way to accelerate organic reactions⁹ led us to apply this technique.

Herein we report our new findings concerning the microwave assisted silica gel deprotection of N-Boc derivatives (Scheme 1). When N-Boc pyroglutamic acid was irradiated in a microwave oven¹⁰ for 1 min at 650 watts a clean deprotection was observed and in this way

pyroglutamic acid was almost quantitatively obtained.¹¹ Control experiments were carried out in order to study the advantages of this method, so when the above mixture was placed in a preheated oven, 105–110°C, a clean deprotection could not be observed and even after 24 h a mixture of the starting compound, deprotected product and decomposition material was obtained. Similar results were observed when that reaction mixture was refluxed in toluene, 50 mL, for the same time. Other Boc protected amides, both primary and secondary, when irradiated produced similar results (see Table, entries 2–5). A new control experiment was done for the N-Boc pyrrolidin-2-one, obtaining for both preheated oven and high boiling point methods similar results (90% yield after 4 h of reaction time). However, N-Boc amines needed longer irradiation time (Table, entries 6–8) to produce efficient deprotection. This allowed good chemical differentiation of amino and amido protecting groups as in the time dependent selective deprotection of the di N-Boc protected 1-(4-piperidinyl)-2-benzimidazolone **1** (Scheme 2). One minute irradiation of **1** caused selective deprotection of the N-Boc amido group to give the piperidinyl protected derivative **2** (66%). Further irradiation (3 min) yielded the fully deprotected species

Table. Removal of Boc from different N-Boc derivatives

Entry	Substrate	React. Time (min.)	Yield (%)	Entry	Substrate	React. time (min.)	Yield (%)
1		1	91	6		3	91
2		1	96	7		3	86
3		1	95	8		3	56
4		1	95	9		1	95
5		1	96	10		2	98



Scheme 2

3 (77%). Control experiments shown, see Scheme 2, that conventional heating methods are less convenient, in particular for the removal of Boc protecting amino groups.

Chemoselective N-Boc amide removal was also observed in the presence of OTBDPS ether group, as in the 2-pyrrolidone derivative (see Table, entry 9). Finally, Boc groups attached to nitrogen atoms belonging to an aromatic system could only be eliminated in the case of an imidazole nucleus (see Table, entry 10). Decomposition products were obtained for other aromatic N-Boc protected heterocycles, such as pyrrole and indole.

In summary, a mild, simple, short, and efficient method for the *tert*-butoxycarbonyl deprotection of nitrogen atoms has been developed by coupling silica and microwave irradiation which it is of particular success for amino groups. The potential for chemoselective deprotection of different N-Boc groups has been demonstrated. The removal of other protecting groups using this procedure is currently under investigation.

References and notes

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10. A commercial microwave oven with 900 watts of power output was used. The power generated by the oven was measured before every experiment by the method described by Watkins, K.W. *J. Chem. Ed.* **1983**, *60*, 1043.
11. In a typical experiment, N-Boc derivative (1 mmol) was dissolved in CH₂Cl₂ (50 mL) and silica gel (230-400 mesh) (10 g) was added. The solvent was taken off *on vacuo* and the powdered solid obtained was irradiated in the microwave oven, in an open erlenmeyer flask for the time described (Table) at 450 watts. The resulting solid was thoroughly washed with acetone or methanol, and then isolated to afford pure products.