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# A mild and selective method for *N*-Boc deprotection

Sylvain Routier,* Laurence Saugé, Nathalie Ayerbe, Gérard Coudert and Jean-Yves Mérour

*Institut de Chimie Organique et Analytique, associé au CNRS, Université d'Orléans, BP 6759, 45067 Orléans Cedex 2, France*

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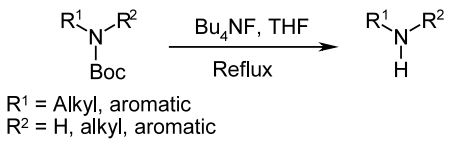
**Abstract**—A new mild method to remove *N*-*tert*-butyloxycarbonyl groups using TBAF in refluxing THF is reported. In all cases, the corresponding *N*-free products are obtained in good yields. The reactions are selective for acid- and base-sensitive groups, such as *tert*-butyl and alkyl esters, aldehydes. 

Acid labile *N*-Boc methodologies are widely used in organic synthesis to prepare various functionalized heterocycles as well as natural or non-natural amino acid derivatives to build scaffold or bioactive products.[1] Cleavage of the *tert*-butyloxycarbonyl protective group involves formic acid, trifluoroacetic acid, bromhydric acid or Lewis acids.[2] Isobutene, generated in these acidic conditions, was reported to give some electrophilic additions; in this case, the use of scavengers was recommended. In addition, several organic functions are incompatible with these methods. For *N*-Boc aromatic hererocycles, basic conditions (NaOMe and $NH_3$) were used[2] whereas formation of an alkoxide anion was reported to induce in specific cases the intramolecular cleavage of the carbamic moiety.[3] Recently, selective deprotection of *tert*-butyl ester was reported using a $CeCl_3 \cdot 7H_2O$–NaI system[4] or $SiO_2$ in refluxing toluene.[5] In contrast, *N*-Boc amino acid derivatives were selectively removed by $HNO_3$[6] in the presence of *tert*-butyl esters. $Bu_4NF$ has been used for the removal of some benzenesulphonyl groups[7] but never for the cleavage of acidic sensitive groups. In this regard, using this reagent, we have developed a new mild method to remove *N*-Boc protective groups in the presence of several sensitive organic functions (Scheme 1).




**Scheme 1.** General scheme for $Bu_4NF$ cleavage of *N*-Boc protective groups.

The deprotection reactions[7] were performed on different *N*-Boc derivatives using a 1 M $Bu_4NF$ solution in THF. The results are shown in Table 1. The free base compounds were obtained in high yields. The reaction was first optimized with the *N*-Boc-indole **1** (entry 1). No reaction was observed using $Bu_4NF$ hydrate, $Bu_4NF$ on silica gel and KF as reagents. Only partial cleavage was observed with 10 equiv. of $Bu_4NF$ at room teperature for 8 days. At reflux, 2 equiv. of $Bu_4NF$ afforded indole **1a** in 1 day in 81% yield. Reaction time was also modulated using 5 or 10 equiv. of fluorinated salt to afford **1a** in 91 and 93% yield, respectively, with complete disappearance of the starting material **1** and reaction time was reduced from 8 to 3 h.[8] THF as solvent gave better results than DMF.

Most assays described in Table 1 were carried out using 5 equiv. of $Bu_4NF$ in a reaction time limited to 8 h. Reactions performed with *N*-Boc-carbazole **2** (entry 2) and *N*-Boc-aniline **3** (entry 3) gave a quantitative cleavage of the Boc group. Interestingly, the *N*-Boc-indoline **4** (entry 4) affords only the starting material. In the same manner, *N*-Boc-*N*-methylaniline **5** does not react under these conditions. Acid sensitive groups like *tert*-butyl esters (entries 6 and 7), aldehyde (entry 8), and basic sensitive groups, like aromatic ester (entry 9), were not affected. All compounds **6a**–**9a** were isolated in good yields. Complete reaction was obtained with compound **6** using 10 equiv. of reagent. The reaction time was also reduced as described for indole **1**.

The maleimide moiety is also compatible with this reaction. Compounds **10** and **10a** were used to perform mono- or di-deprotection (Scheme 2).

With 5 equiv. of TBAF, the reaction using **10** was almost complete (5% recovery of **10**) and compounds

* Corresponding author. Tel.: (33) 2 38 49 48 53; fax: (33) 2 38 41 72 81; e-mail: sylvain.routier@univ-orleans.fr

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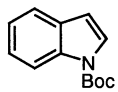
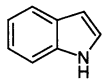
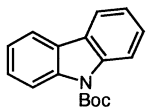
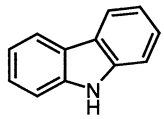
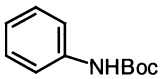
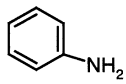
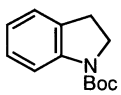
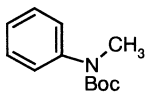
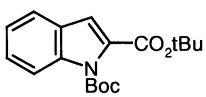
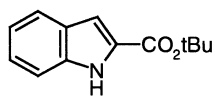
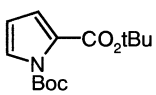
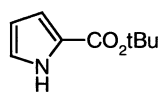
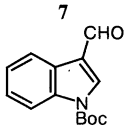
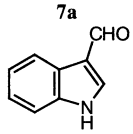
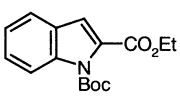
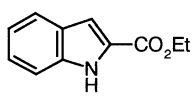
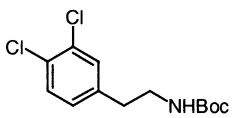
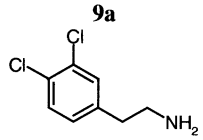
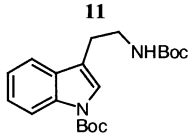
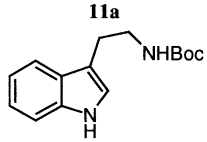
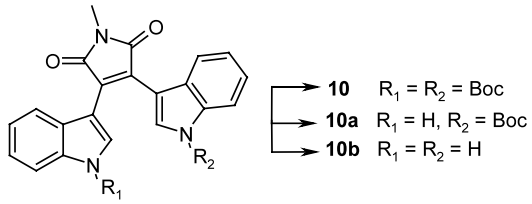
**Table 1.** Cleavage of *N*-Boc protected compounds with $Bu_4NF$

| Entry | Substrate | $Bu_4NF$ (eq.) | Time | Conditions | Product | Yield[a] (b) |
|---|---|---|---|---|---|---|
| 1 |  **1** | 5.0 | 24 h | THF, r.t. |  **1a** | (100 %) |
| | | 10.0 | 8 days | THF, r.t. | | 74 % (21 %) |
| | | 2.0 | 24 h | THF, reflux | | 81 % (7 %) |
| | | 5.0 | 8 h | THF, reflux | | 91 % |
| | | 10.0 | 3 h | THF, reflux | | 93 % |
| | | 5.0 | 8 h | DMF, 70 °C | | 78 % (12 %) |
| 2 |  **2** | 5.0 | 8h | THF, reflux |  **1a** | 90 % |
| 3 |  **3** | 5.0 | 8h | THF, reflux |  **3a** | 88 % |
| 4 |  **4** | 5.0 | 8h | THF, reflux | No reaction | (100 %) |
| 5 |  **5** | 5.0 | 8h | THF, reflux | No reaction | (100 %) |
| 6 |  **6** | 5.0 | 8h | THF, reflux |  **6a** | 81 % (11 %) |
| | | 10.0 | 5h | | | 95 % |
| 7 |  **7** | 5.0 | 8h | THF, reflux |  **7a** | 90 % |
| 8 |  **8** | 5.0 | 6h | THF, reflux |  **8a** | 93 % |
| 9 |  **9** | 5.0 | 6h | THF, reflux |  **9a** | 88 % |
| 10 |  **11** | 10.0 | 8h | THF, reflux |  **11a** | 54 % (44 %) |
| 11 |  **12** | 5.0 | | |  **12a** | 12 % (83 %) |
| | | 10.0 | 8h | THF, reflux | | 67 % (30 %) |
| | | 15.0 | | | | 83 % |

[a]Yield are given in isolated products; all compounds were either compared with known data in the literature, or if new, fully characterized by IR, $^1$H NMR, $^{13}$C NMR and MS; [b] recovered starting material.



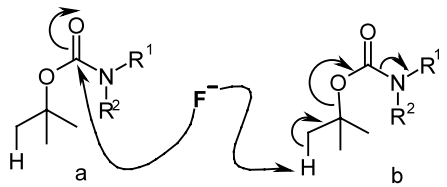

**Scheme 2.** Reaction performed with a bis-*N*-Boc indolic compound containing a maleimide group.

**10a** and **10b** were isolated in 82 and 10% yield, respectively. When increasing the quantity of $Bu_4NF$ (10 equiv.), compound **10** was converted to **10a** and **10b** in 22 and 74% yield, respectively. A further reaction could be performed with the isolated compound **10a** to afford **10b** in 94% yield. All reactions were performed in 8 h.

Silyl derivatives are often utilized to protect hydroxy groups or free indolic nitrogen atoms. A common mode of deprotection consists of the use of a fluorinated agent. For 2-OTBDMS-*N*-Boc-aniline, a selective deprotection of oxygen atoms was realized using 1.1 equiv. of reagent at room temperature. The 2 hydroxy-*N*-Boc aniline was obtained in 91% yield.

In the case of aminoalkyl compounds, deprotection was not so easy; 10 equiv. of reagent were needed to afford the free amine **11a** in only 54% yield with recovery of the starting material **11** (44% yield). Selectivity between indole and amino alkyl deprotection was studied using compound **12** which bears both aliphatic and indolic *N*-Boc protection. Only the indolic deprotection was observed in all cases. 5 equiv. of reagent afforded only 12% of mono indolic deprotected product **12a** whereas 10 equiv. of reagent afforded 67% of **12a**. This reaction was achieved in 8 h with 15 equiv. of TBAF. Compound **12a** was directly extracted and could be used without further purification.

Several proposals could explain the mechanism of this reaction (Scheme 3). First, fluorine may be assimilated as a nucleophile[9,10] (a) which directly added to the carbonyl group. The aminated residue could be considered as a leaving group and Boc-F was produced.[11]




**Scheme 3.** Postulated mechanism.

After hydrolysis, *tert*-butanol, $CO_2$ and HF are effectively produced. Another possibility was β-elimination[12] (b), which gives the amide, isobutene, $CO_2$ and HF under the acidic cleavage conditions. In both cases, HF was neutralised by the released amide.

At first sight, mechamism (a) seems more appropriate to explain the inertness of *tert*-butyl ester derivatives.

Several *N*-Boc protected aromatic compounds are easily deprotected by $Bu_4NF$. This method is compatible with several acidic and basic sensitive groups, like esters, aldehydes or maleimides. Selective deprotection could be achieved with substrates containing both aromatic and aliphatic *N*-Boc groups. Studies are in progress to trap the intermediates with electrophiles and to provide more insight into this reaction.

## References

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8. Standard procedure: *N*-Boc-indole **1** (200 mg, 0.92 mmol) was dissolved under argon in 6 mL of dry THF. A 1 M solution of $Bu_4NF$ (4.6 mL, 4.6 mmol) in THF was then added and the reaction mixture was refluxed for 8 h. After cooling to room temperature, water (20 mL) was added. After extraction with AcOEt (2×20 mL), the organic layers were washed with brine (10 mL), dried with $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/AcOEt 98/2) to afford indole **1a** (98 mg, 91%).
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