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A mild and selective method for the *N*-Boc deprotection by sodium carbonate

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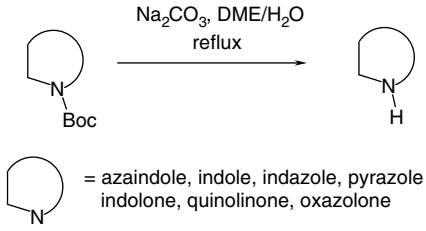
Abstract—A cleavage of *N-tert*-butyloxycarbonyl protection by Na_2CO_3 is reported. The N-free products are obtained in excellent yields. The compatibility of the method with the presence of acidic or basic groups is demonstrated. The reactions were performed on indole, azaindole, indazole, pyrazole, indolinone, quinolinone, and oxazolone.

1. Introduction

The *N-tert*-butyloxycarbonyl protection (Boc) is frequently used in peptide and nucleoside syntheses as well as in heterocyclic chemistry. For these reasons, several methods for *N*-Boc deprotection have been reported, in particular, under strong acidic conditions such as CF_3COOH, H_2SO_4, TsOH, and MsOH or Lewis acids.[1,2] The deprotection can also be achieved under thermal conditions (150 °C).[3] However, a very few methods for basic deprotection have been described.[2] In this case, Tom et al.[4] developed an interesting way for deprotecting primary Boc protected amines using excess of sodium *tert*-butoxide. Recently, the new deprotection methods of *N*-Boc have been reported using ceric ammonium nitrate (CAN),[5] $CeCl_3{\cdot}7H_2O$–NaI system[6] or SiO_2.[7] Interestingly, Routier and co-workers[8,9] described a mild method using TBAF.

2. Results and discussion

Herein, we describe a simple and very efficient method for the deprotecting secondary Boc protected amines using sodium carbonate (Na_2CO_3) in refluxing DME. The reaction provides the corresponding secondary amine in excellent yield (Scheme 1).



Scheme 1. General scheme for the Na_2CO_3 cleavage of *N*-Boc protective groups.

The *N*-Boc deprotection performed on 1-*N*-Boc-7-nitroindazole **1**, using 1.2 or 5 equiv of Na_2CO_3, at room temperature was not observed. However, in refluxing DME, 1.2 equiv of Na_2CO_3 afforded 7-nitroindazole **1a** in a 100% yield after only 15 min of stirring (Table 1, entry 1). The procedure is illustrated by a typical example. Na_2CO_3 (1.2 equiv) in H_2O was added to a solution of 1-*N*-Boc-7-nitroindazole (1.0 equiv) in DME and the reaction mixture was stirred at reflux for 15 min. After cooling, CH_2Cl_2 and water were added and the desired product was extracted (three extractions). The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed in vacuum to give 7-nitroindazole in a 100% yield (Table 1).

The scope and limitation of the method was investigated on various *N*-Boc protections (Table 1). In most cases, the treatment of *N*-Boc protected amines with 1.2 equiv of Na_2CO_3 in refluxing DME/H_2O, gave the

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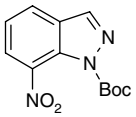
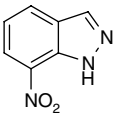
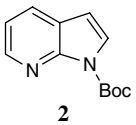
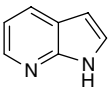
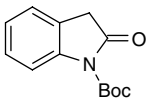
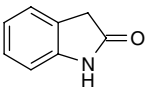
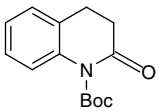
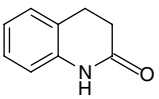
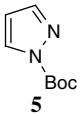
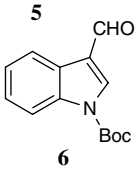
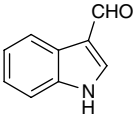
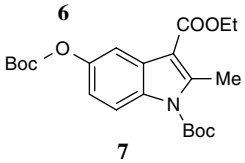
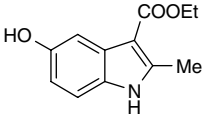
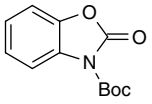
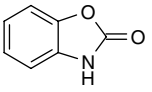
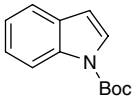
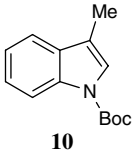
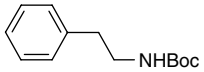
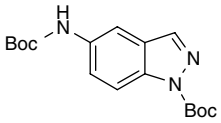
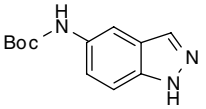
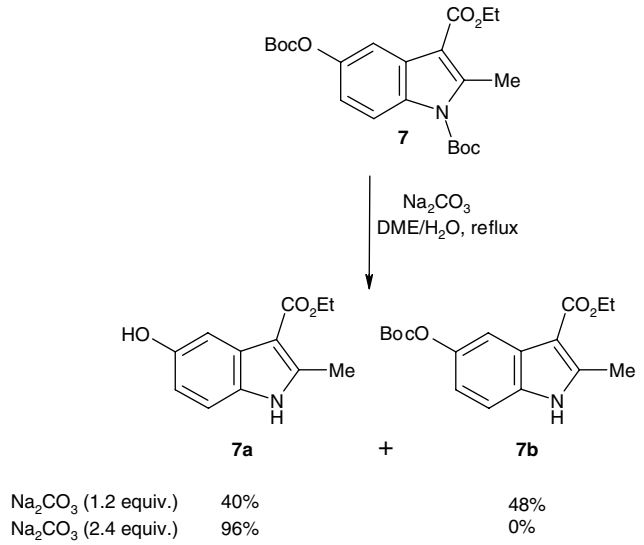
Table 1. Cleavage of *N*-Boc protected compounds with Na_2CO_3

Entry	Substrate	Na_2CO_3 (equiv)	Time	Condition	Product	Yield[a] (%)
1	 **1**	1.2 1.2 5	15 min 3 days 3 days	DME/H_2O, reflux DME/H_2O, rt DME/H_2O, rt	 **1a**	100 0 0
2	 **2**	1.2 5	20 h 15 h	DME/H_2O, reflux DME/H_2O, reflux	 **2a**	100 100
3	 **3**	1.2	15 min	DME/H_2O, reflux	 **3a**	100
4	 **4**	1.2	1 h 15 min	DME/H_2O, reflux	 **4a**	95
5	 **5**	1.2	15 min	DME/H_2O, reflux	 **5a**	60[b]
6	 **6**	1.2	1.5 h	DME/H_2O, reflux	 **6a**	98
7	 **7**	1.2 2.4	24 h 15 h	DME/H_2O, reflux DME/H_2O, reflux	 **7a**	40 (52)[c] 96
8	 **8**	1.2	3 h	DME/H_2O, reflux	 **8a**	70
9	 **9**	1.2	20 h	DME/H_2O, reflux	No reaction	(100)[d]
10	 **10**	1.2	20 h	DME/H_2O, reflux	No reaction	(100)[d]
11	 **11**	1.2	24 h	DME/H_2O, reflux	No reaction	(100)[d]
12	 **12**	1.2	24 h	DMF/H_2O, 85 °C	 **12a**	95

[a] Yields are given in isolated products, all compounds were either compared with known data in the literature, or if new, fully characterized by IR, ^1H NMR, ^{13}C NMR, and MS.
[b] Yield given after filtration on Celite.
[c] Isolated yield of **7b** (see Scheme 2).
[d] Recovered starting material.



Scheme 2. Results of Na_2CO_3 cleavage of **7**.

corresponding deprotected amines in excellent yields (Table 1, entries 1–4), except for 1-*N*-Boc pyrazole **5**, which conducted to the corresponding pyrazole **5a** in a moderate yield of 60% (Table 1, entry 5).

Acid and/or basic sensitive groups (Table 1, entries 6–8) were not affected. Thus, the treatment of compounds **6**–**8** with Na_2CO_3 gave the desired products **6a**–**8a** in 70–98% yields. It is noticed that with 1.2 equiv of Na_2CO_3, the reaction using **7** was not complete and compounds **7a** and **7b**[10] were produced in 40% and 48% yields, respectively. However, when increasing the quantity of Na_2CO_3 (2.4 equiv), compound **7** was recovered to **7a** in a 100% conversion and in an excellent yield (Scheme 2, Table 1).

Surprisingly, 1-*N*-Boc indole **9**, 1-*N*-Boc-3-methylindole **10** and 1-*N*-Boc 2-phenylethylamine **11** afford only the starting material (Table 1, entries 9–11).

It is noteworthy that the selectivity of the *N*-Boc deprotection by Na_2CO_3 was also studied using compound **12**, which bears both aromatic and indazolic *N*-Boc protection[11] (Table 1, entry 12). The reaction was performed with 1.2 equiv of Na_2CO_3 in DMF/H_2O at 85 °C (the starting material was not very soluble in DME/H_2O). In these conditions, only the indazolic deprotection was observed. The structure of **12a** was established by the comparison between ^1H NMR, ^{13}C NMR, mass spectroscopy data of **12** and **12a** (see analytical data of **12** and **12a**).[11,12] We observed, in particular, in ^1H NMR spectra of **12a**, recorded in DMSO-d_6, the appearance of NH signal of 1-NH at 12.90 ppm. The ^1H NMR spectra of **12** and **12a** also showed a singlet at δ 9.56 (5-NH) for **12** and a singlet at δ 9.26 (5-NH) for **12a**. These results serve to confirm the structure of **12a**.

In conclusion, we found a simple and efficient method for the cleavage of Boc protected amines using Na_2CO_3. The reaction conditions are mild and compatible with acidic and basic sensitive groups. The method is used for deprotecting various *N*-Boc protected compounds and offers a good selectivity for amine deprotection.

References and notes

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10. Compound **7b** is prepared from **7** as described for **1a**. Analytical data for **7b** is described as follows. 5-*tert*-Butoxycarbonyloxy-2-methyl-1*H*-indole-3-carboxylic acid ethyl ester. Yield 48%; ^1H NMR (250 MHz, DMSO-d_6): δ 11.92 (1H, s, 1-N*H*), 7.61 (1H, d, $J = 2.2$ Hz, Ar*H*), 7.35 (1H, d, $J = 8.8$ Hz, Ar*H*), 6.92 (1H, dd, $J = 2.2$, 8.8 Hz, Ar*H*), 4.26 (2H, q, $J = 7.2$ Hz, OCH_2), 2.64 (3H, s, CH_3), 1.48 (9H, s, –C(CH_3)$_3$), 1.32 (3H, t, $J = 7.2$ Hz, OCH$_2$CH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 164.8 (CO), 152.1 (CO), 146.0 (C), 145.5 (C), 132.5 (C), 127.1 (CH), 115.6 (C), 112.3 (CH), 111.6 (CH), 103.0 (C), 82.7 (C), 58.9 (CH_2), 27.3 ((CH_3)$_3$), 14.4 (CH_3), 13.8 (CH_3). MS (IS) 320 $(M+1)^+$.
11. Compound **12** is prepared from 5-aminoindazole as described in the literature: Bouissane, L.; El Kazzouli, S.; Léonce, S.; Pfeiffer, B.; Rakib, E. M.; Khouili, M.; Guillaumet, G. *Bioorg. Med. Chem.* **2006**, *14*, 1078. Analytical data for **12** is as follows. 5-*tert*-Butoxycarbonylamino-indazole-1-carboxylic acid *tert*-butyl ester. Yield 85%; ^1H NMR (250 MHz, DMSO-d_6): δ 9.56 (1H, s, 5-N*H*Ar), 8.34 (1H, s, Ar*H*), 8.04 (1H, Ar*H*), 7.94 (1H, d, $J = 9.10$ Hz, Ar*H*), 7.57 (1H, d, $J = 9.10$ Hz, Ar*H*), 1.63 (9H, s, –C(CH_3)$_3$), 1.49 (9H, s, –C(CH_3)$_3$); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 153.3 (CO), 148.8 (CO), 140.1 (CH), 136.1 (C), 135.2 (C), 126.3 (C), 121.6 (CH), 114.4 (CH), 109.2 (CH), 84.6 (C), 79.6 (C), 28.5 ((CH_3)$_3$), 28.0 ((CH_3)$_3$). MS (IS) 334 $(M+1)^+$.
12. Compound **12a** is obtained from **12** as described for **1a**. Analytical data for **12a** is described as follows. (1*H*-Indazol-5-yl)-carbamic acid *tert*-butyl ester. Yield 95%; ^1H NMR (250 MHz, DMSO-d_6): δ 12.90 (1H, s, 1-N*H*), 9.26 (1H, s, 5-N*H*Ar), 7.97 (1H, s, Ar*H*), 7.88 (1H, Ar*H*), 7.33–7.45 (2H, m, Ar*H*), 1.49 (9H, s, –C(CH_3)$_3$); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 153.8 (CO), 137.2 (C), 133.6 (CH), 133.1 (C), 123.5 (C), 120.5 (CH), 110.7 (CH), 108.8 (CH), 79.4 (C), 28.9 ((CH_3)$_3$). MS (IS) 234 $(M+1)^+$.