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Simple and Selective Removal of the t-Butyloxycarbonyl (Boc) Protecting Group on Indoles, Pyrroles, Indazoles, and Carbolines

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Simple and Selective Removal of the *t*-Butyloxycarbonyl (Boc) Protecting Group on Indoles, Pyrroles, Indazoles, and Carbolines

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Abstract: A highly selective and efficient deprotection of the N-*t*-butoxy carbonyl (N-Boc) group on indoles, pyrroles, indazoles, and carbolines has been achieved in high yields using a catalytic amount of NaOMe as a base in dry MeOH, at ambient temperature.

Keywords: ±-butyloxycarbonyl (BOC), indoles, pyrroles, indazoles, carbolines, sodium methoxide

The *t*-butoxy carbonyl group is frequently used as a protecting group for 1° and 2° amines[1] and amino acids in peptide chemistry[2] because of its stability in mildly acidic as well as basic conditions. A number of reagents have been known to effect clean removal of this protecting group; most of them involve the use of strong acids such as CF_3COOH, HCl, H_2SO_4, TSOH, and MeOH or Lewis acids such as $BF_3 \cdot OEt_2$,TMSI, TMSOTf, $TiCl_4$, $SnCl_4$, $AlCl_3$, $Sn(OTf)_2$, and $ZnBr_2$.[3] The deprotection can also be effected with mildly acidic conditions such as montomorillonite K-10 clay catalyst[4] and silica gel at low pressure.[5] The N-Boc group can also be removed in the presence of other sensitive functionalities such as *t*-butyl esters and trityl

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groups with the acid catalysts such as 1M HCl in EtOAc,[6] H_2SO_4 in *t*-BuOAc, or $MeSO_3H$ in *t*-BuOAc/CH_2Cl_2.[7] It is also deprotected in thermolytic conditions.[8] Recently, selective deprotection of *t*-butyl ester was reported using a $CeCl_3 \cdot 7H_2O$-NaI system[9] or silica gel in refluxing toluene.[10]

During the synthesis of the natural product tiruchanduramine,[11] an intermediate **1** was prepared, and we have envisaged the deprotection of triflate[12] with NaOMe in methanol, while the Boc group is present on the β-carboline group (Scheme 1). As the reaction proceeds, we observed that Boc was deprotected and triflate was still retained. We extended this reaction on various substrates such as substituted pyrroles, β-carbolines, indazoles, and indoles (Table 1).

4-Bromo pyrrole-2-carboxylamide[13] was isolated from the sponge *Axinella carteri*, collected from Gulf of Mannar, Tamilnadu, India, which was protected with a Boc group using sodium hydride to give compound **2** (entry 2). Compound **2** was reacted with NaOMe in methanol to give **2a** with 92% yield.

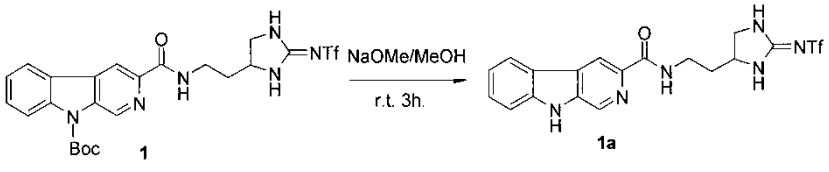
Most assays described in Table l were carried out using a catalytic amount of NaOMe in dry methanol, and the reaction time is limited to 3 h. In entry **8** (Table 1), the compound has two acid labile acetonide and Boc protecting groups. Using the present conditions, Boc group can be selectively deprotected, and under any acidic conditions both would have deprotected.

We have performed the same reaction on substituted indazoles where N-Boc is located on indazole and piperazine (entries 5 and 6) and found indazole N-Boc was selectively deprotected to give corresponding amines in excellent yields.

We also performed the reaction on substituted indole compounds (entries 9 and 10) as well as on Boc protected tryptophan (entry 3) and Boc protected tryptamine (entry 4). In entries 3 and 4, the Boc group on indole nitrogen was deprotected in excellent yields, retaining primary amine Boc.

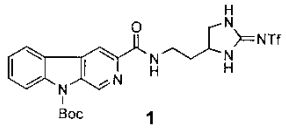
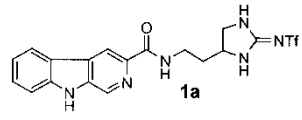
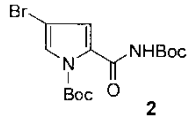
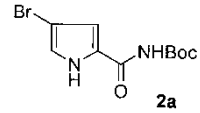
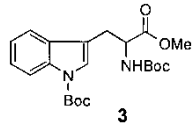
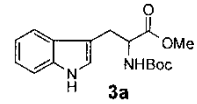
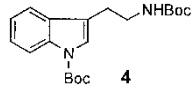
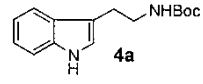
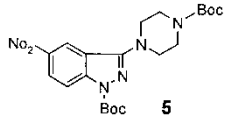
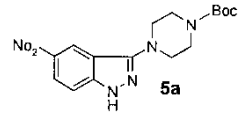
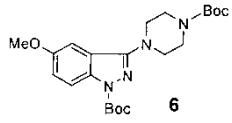
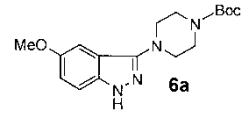
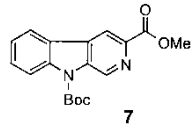
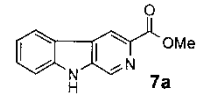
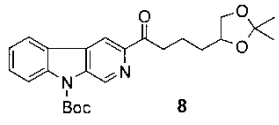
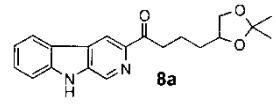
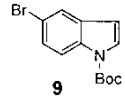
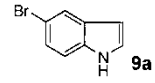
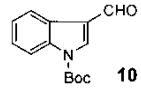
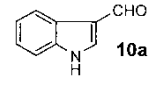
EXPERIMENTAL PROCEDURE

To a solution of Boc derivative (0.5 mmol) in dry methanol, a catalytic amount of NaOMe (20 mmol%) was added and stirred at ambient temperature for an appropriate time (Table l). After complete conversion as indicated by



Scheme 1.

Table 1. Deprotection of Boc with NaOMe in dry MeOH

Entry	Substrate	Time	Product[a]	Yield (%)[b]
1	 **1**	3 h	 **1a**	92
2	 **2**	30 min	 **2a**	92
3	 **3**	3 h	 **3a**	90
4	 **4**	3 h	 **4a**	94
5	 **5**	10 min	 **5a**	86
6	 **6**	30 min	 **6a**	90
7	 **7**	1 h	 **7a**	96
8	 **8**	2 h	 **8a**	98
9	 **9**	30 min	 **9a**	92
10	 **10**	1 h	 **10a**	96

[a]All products were characterized by ^{1}H NMR, IR, and mass spectra.
[b]Isolated and unoptimized yields.

thin-layer chromatography (TLC), the reaction mixture was diluted with water (10 ml) and extracted into ethyl acetate (2 × 20 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel to afford the pure Boc deprotected product with 85–98% yield.

SPECTROSCOPIC DATA

Compound (1)

IR (KBr) ν_{max}: 3417, 1625, 1618, 1353, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (9H, s), 1.96 (2H, m), 3.42 (1H, dd, $J = 7.6$, 1.6 Hz), 3.50 (1H, m), 3.84 (2H, m), 4.10 (1H, m), 6.96 (1H, bs, NH), 7.38 (1H, t, $J = 7.0$ Hz), 7.48 (1H, t, $J = 7.0$ Hz), 7.74 (bs, NH), 8.04 (1H, d, $J = 8.0$ Hz), 8.28 (1H, d, $J = 8.0$ Hz), 8.40 (bt, NH), 8.70 (1H, s), 9.40 (1H, s); FABMS: 555 ($M^+ + l$).

Compound (1a)

IR (KBr) ν_{max}: 3415, 1637, 1527, 1350, 1220 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.86 (2H, m), 3.54 (2H, m), 3.68 (2H, m), 7.20 (1H, t, $J = 7.0$ Hz), 7.48 (2H, m), 7.80 (bs, NH), 8.10 (1H, d, $J = 8.2$ Hz), 8.22 (bs, NH), 8.60 (bt, NH), 8.76 (1H, s), 8.78 (1H, s), 11.38 (1H, bs); FABMS: 455 ($M^+ + l$).

Compound (2)

IR (KBr) ν_{max}: 3270, 2965, 1672, 1650, 1460, 1365, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.42 (9H, s), 1.58 (9H, s), 6.58 (1H, d, $J = 1.2$ Hz), 7.26 (1H, $J = 1.2$ Hz), 8.30 (bs, NH). LCMSD: 411 ($M^+ + Na$).

Compound (2a)

IR (KBr) ν_{max}: 3412, 2985, 1670, 1642, 1442, 1365, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.56 (9H, s), 6.84 (d, $J = 1.2$ Hz), 7.04 (d, $J = 1.2$ Hz), 8.06 (bs, NH); LCMSD: 311 ($M^+ + Na$).

Compound (4)

IR (KBr) ν_{max}: 3385, 2927, 2360, 1735, 1700, 1457, 1372, 1224, 1166 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.42 (9H, s), 1.65 (9H, s), 2.88 (2H, t,

$J = 6.4$ Hz), 3.42 (2H, m), 4.68 (1H, bt), 7.22 (2H, m), 7.34 (1H, s), 7.48 (1H, d, $J = 7.2$ Hz), 8.09 (1H, d, $J = 7.2$ Hz); LCMSD: 359 ($M^+ - 1$).

Compound (4a)

IR (KBr) ν_{max}: 3413, 2976, 2927, 2360, 1691, 1604, 1510, 1456, 1393, 1366, 1336, 1253, 1221, 1169 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.42 (9H, s), 2.88 (2H, t, $J = 6.4$ Hz), 3.40 (2H, m), 4.64 (1H, bs), 6.8 (1H, s), 7.04 (1H, t, $J = 7.0$ Hz), 7.10 (1H, t, $J = 7.0$ Hz), 7.24 (1H, d, $J = 7.4$ Hz), 7.50 (1H, d, $J = 7.4$ Hz), 8.50 (1H, bs, NH); LCMSD: 283 ($M^+ + Na$), 261, 127, 205, 161, 144.

Compound (5)

IR (KBr) ν_{max}: 2981, 1694, 1522, 1338, 1249, 1155, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.70 (9H, s), 3.56 (4H, m), 3.64 (4H, m), 8.24 (1H, d, $J = 7.8$ Hz), 8.18 (1H, d, $J = 7.8$ Hz), 8.60 (1H, bs); LCMSD: 447 (M^+), 391, 335, 126.

Compound (5a)

IR (KBr) ν_{max}: 3412, 2926, 2345, 1692, 1518, 1393, 1253, 1169, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 1.40 (9H, s), 3.36 (4H, m), 3.58 (4H, m), 7.26 (1H, d, $J = 8.2$ Hz), 8.02 (1H, dd, $J = 8.2$, 1.2 Hz), 12.19 (s, NH); LCMSD: 348 ($M^+ + 1$).

Compound (6)

IR (KBr) ν_{max}: 2978, 2932, 2361, 1697, 1536, 1483, 1340, 1368, 1250, 1156, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.48 (9H, s), 1.67 (9H, s), 3.45 (4H, m), 3.62 (4H, m), 3.82 (3H, s), 6.96 (1H, d, $J = 2.4$ Hz), 7.08 (1H, dd, $J = 8.8$, 2.4 Hz), 7.94 (1H, d, $J = 8.8$ Hz); LCMSD: 455 ($M^+ + Na$), 433, 377, 321, 192.

Compound (6a)

IR (KBr) ν_{max}: 3412, 2986, 2928, 2312, 1686, 1527, 1468, 1328, 1210 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.50 (9H, s), 3.34 (4H, m), 3.65 (4H, m), 3.88 (3H, s), 6.92 (1H, d, $J = 1.7$ Hz), 6.98 (1H, dd, $J = 8.6$, 1.7 Hz), 7.22 (1H, d, $J = 8.6$ Hz); LCMSD: 333 ($M^+ + 1$).

Compound (7)

IR (KBr) ν_{max}: 2934, 2354, 1665, 1456, 1347, 1245 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.78 (9H, s), 4.02 (3H, s), 7.40 (1H, t, $J = 6.0$ Hz), 7.60 (1H, t, $J = 6.0$ Hz), 8.06 (1H, d, $J = 7.8$ Hz), 8.40 (1H, d, $J = 7.8$ Hz), 8.90 (1H, s), 9.58 (1H, s); EIMS: m/z 326 (08) [M^+], 270 (22), 226 (100), 168 (96).

Compound (7a)

IR (KBr) ν_{max}: 3412, 2364, 1656, 1459, 1337, 1253 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.02 (3H, s), 7.30 (1H, t, $J = 7.0$ Hz), 7.58 (1H, t, $J = 7.0$ Hz), 7.62 (1H, d, $J = 7.8$ Hz), 8.10 (1H, d, $J = 7.8$ Hz), 8.84 (1H, s), 9.18 (1H, s), 10.70 (1H, bs); EIMS: m/z 226 (100) [M^+].

Compound (8)

IR (KBr) ν_{max}: 3182, 1938, 1736, 1652, 1440, 1344, 1263, 1171, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, s), 1.42 (3H, s), 1.80 (9H, s), 1.96 (2H, m), 3.60 (3H, m), 4.06 (1H, dd, $J = 7.0$, 6.0 Hz), 4.22 (1H, m), 7.42 (1H, t, $J = 8.0$ Hz), 7.62 (1H, t, $J = 8.0$ Hz), 8.12 (1H, d, $J = 8.0$ Hz), 8.36 (1H, d, $J = 8.0$ dHz), 8.40 (bt, $J = 6.5$ Hz, NH), 8.78 (1H, s), 9.42 (1H, s); FABMS: 440 (M^+)

Compound (8a)

IR (KBr) ν_{max}: 4315, 1637, 1527, 1350, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, s), 1.46 (3H, s), 1.96 (2H, m), 3.65 (3H, m), 4.12 (1H, dd. $J = 7.0$, 6.0 Hz), 4.28 (1H, m), 7.32–7.46 (1H, m), 7.60 (1H, m), 7.82 (bt, NH), 8.20 (1H, d, $J = 8.0$ Hz), 8.50 (bt, NH), 8.82 (1H, s), 8.90 (1H, s), 9.54 (1H, bs); FABMS: 340 ($M^+ + l$).

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