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Deprotection of heteroaromatic carbamates via a base-catalyzed methanolysis

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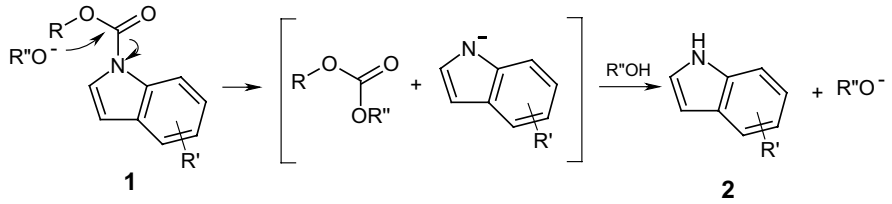
Abstract—A simple and mild method for the deprotection of heteroaromatic carbamates via methanolysis using a catalytic amount of base such as sodium methoxide, DBU, or Verkade's base (proazaphosphatranes) is presented. Carbamate protecting group of an aliphatic amine is not affected under these conditions.

Selective cleavage of a nitrogen protecting group for heteroaromatics containing multiple functionalities is a useful tool for the total synthesis of complex molecules. Recently, a mild method was reported for removing the Boc-group from indole compounds using tetrabutylammonium fluoride in refluxing THF without affecting the rest of acid-sensitive functionalities.[1] Heterogeneous conditions involving silica gel or silica gel-supported sodium hydrogen sulfate/HY-zeolite were also effective for the same purpose according to Wensbo and Apelqvist[2] and Das and co-workers,[3] respectively. Lipshutz et al. reported an elegant method for the selective cleavage of Cbz-protected heteroaromatic amines utilizing borane and a catalytic amount of Ni(0).[4] Reductive cleavage of tryptophan and histidine side-chain protecting groups utilizing controlled-potential electrolysis was demonstrated by Monteiro and co-workers.[5] Although these methods are effective, they employ either stoichiometric amounts of reagents or special equipment. Since developing greener chemistry is our constant goal, we explored a simpler method such as base-catalyzed solvolysis. We envisioned that the carbamate group on heteroaromatic nitrogens (such as indole **1**) is vulnerable to a base-catalyzed solvolysis since the resulting indolyl anion is stabilized by the delocalization of the negative charge (Scheme 1), especially when R′ is an electron-withdrawing group.

To test this hypothesis, we initially used DBU as the catalyst and Boc–Trp(Cbz)–OMe (**3**)[6] as the substrate in methanol (Scheme 2). The Cbz-group on the indole nitrogen was readily cleaved under these conditions (Table 1, entry 1). Employing triethylamine, we observed no reaction at all (entry 2). The use of Verkade's bases (proazaphosphatranes **6c**, Fig. 1) provided an equally interesting result affording the desired product Boc–Trp–OMe (**5**) in near 99% yield (entry 4, 22 h). Under these conditions, we observed by HPLC the formation of



Scheme 1. Nucleophilic catalysis.

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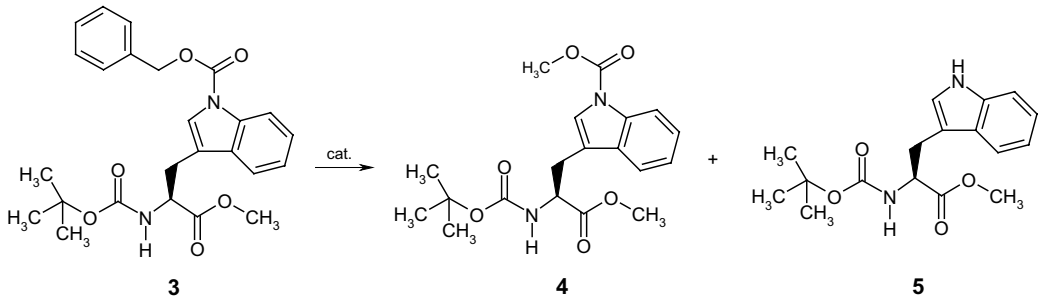


Scheme 2. Deprotection of Boc–Trp(Cbz)–OMe (**3**).

Table 1. Cleavage of Boc–Trp(Cbz)–OMe (**3**)[a]

Entry	Catalyst	2 h			22 h		
		3 Yield[b] (%)	**4** Yield[b] (%)	**5** Yield[b] (%)	**3** Yield[b] (%)	**4** Yield[b] (%)	**5** Yield[b] (%)
1	DBU	7.3	72.7	20.0	0	11.0	89.0
2	Et_3N	100	0	0	100	0	0
3	NaOMe	0.7	68.1	31.2	0	3.7	96.3
4	Verkade	0	55.9	44.1	0	1.3	98.7

[a] All reactions were performed using 1 N solution of **3** in methanol containing 20 mol % of catalyst at rt.
[b] HPLC yield.

methyl carbamate **4** as a common intermediate, implying that the methoxide ion generated in situ served as a catalyst. Based on this, we tried sodium methoxide as the catalyst and found that it was indeed sufficient to accomplish these deprotections (Table 1, entry 3) thus making this solvolysis method practical and economical. We also explored the generality of this method using Verkade's base,[7] and the results obtained are shown in Table 2.

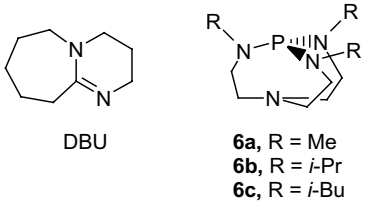


Figure 1.

In a typical experiment, deprotection of a particular substrate was performed in methanol at room temperature employing 20 mol % of a Verkade's base (**6b** or **6c**). The respective reaction was monitored by HPLC until none or a trace amount of starting material was

Table 2. Cleavage of carbamate protecting groups with proazaphosphatranes **6**

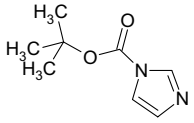
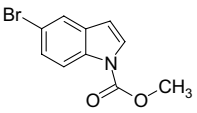
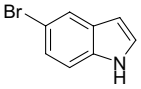
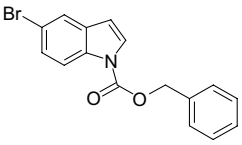
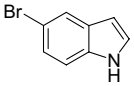
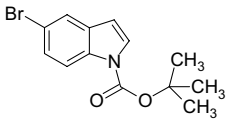
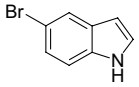
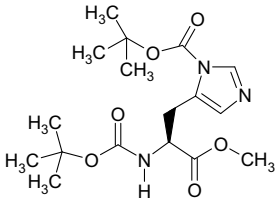
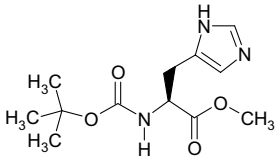
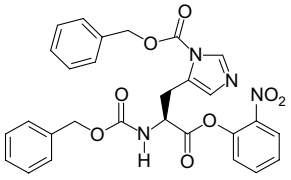
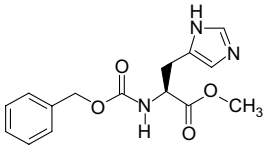
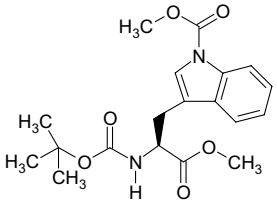
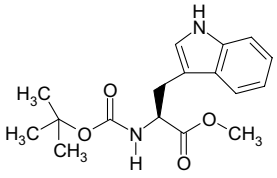
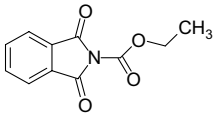
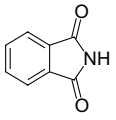
Entry	Substrate		Catalyst	Product	Time (h)	Yield[a] (%)
1		**7**	**6b**		0.5	99
2		**8**	**6c**		0.5	97
3		**9**	**6c**		0.75	99

Table 2 (*continued*)

Entry	Substrate		Catalyst	Product	Time (h)	Yield[a] (%)
4		**10**	**6c**		19	97
5		**11**	**6c**		2	99
6		**12**	**6c**		16	99
7		**13**[8]	**6b** **6c**		40 48	97 96
8		**14**	**6b**		0.25	99

[a] HPLC yield.

detected. *N*-Boc–imidazole **7**, although containing a bulky protecting group, was cleaved with high efficiency (99%) and speed (0.5 h, entry 1). For three different alkyl carbamates of 5-bromoindole utilizing **6c** as the catalyst, cleavage was fast for carbomethoxy- or carbobenzyloxyindole (0.5–0.75 h, entries 2 and 3), but slower for *N*-Boc-5-bromoindole (19 h, entry 4). Applying similar conditions to a fully protected histidine or tryptophan, the protecting groups on heteroaromatic nitrogens (Boc, Cbz, and methyl carbamate) were selectively deprotected without affecting those on the aliphatic amines (entries 5–7). This protocol is practical and requires no special equipment as opposed to the electrolysis methods developed by Monteiro and coworkers.[5] It is noteworthy that a transesterification reaction also took place for substrate **12**, where the *o*-nitrophenol group was replaced with methanol leading exclusively to the methyl ester as the major product. This is a predictable reaction, since **6b**-catalyzed transesterification of dipeptides has been reported.[9] For substrate **13** containing methyl carbamate, the deprotection rate was slow (>40 h), and no significant kinetic difference was observed utilizing either **6b** or **6c** (entry 7). Our protocol also worked efficiently for a non-heteroaromatic compound, *N*-carbethoxyphthalimide (**14**) employing **6b** (entry 8, 0.25 h).

In conclusion, we have demonstrated an efficient process for the cleavage of carbamate groups on heteroaromatic nitrogens via methanolysis using catalytic amounts of bases such as NaOMe, DBU or Verkade's base, thus providing additional options in the armamentarium for selective carbamate deprotection. This protocol can also selectively cleave the carbamates on the heteroaromatic nitrogens of histidine or tryptophan without affecting those on the aliphatic amines.

References and notes

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6. Boc–Trp–(Cbz)–OMe (**3**) was prepared from commercially available Boc–L-Trp–OMe and dibenzyl dicarbonate employing catalytic amount of DMAP. Compound **3**: mp 114–116 °C (lit. 118–120 °C, Kiso, Y.; Inai, M.; Kitagawa, K.; Akita, T. *Chem. Lett*. **1983**, 739–742); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br, 1H), 7.53–7.26 (m, 10H), 5.46 (s, 2H), 5.12 (d, $J = 7.9$ Hz, 1H), 4.67 (dd, $J = 13.3$, 5.7 Hz, 1H), 3.69 (s, 3H), 3.28 (dd, $J = 14.5$, 5.4 Hz, 1H), 3.20 (dd, $J = 14.5$, 5.4 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 155.1, 150.1, 135.1, 128.8, 128.5, 124.9, 123.7, 123.0, 119.0, 116.1, 115.3, 80.0, 68.7, 53.6, 52.4, 28.3, 27.8; LC/MS 475 (M^++Na), 353 (M^++1–Boc).
7. For a review on 'Recent Applications of Proazaphosphatranes in Organic Synthesis', see: Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3–14.
8. Boc–Trp–(COOMe)–OMe (**13**) was prepared from commercially available Boc–L–Trp–OMe and dimethyl dicarbonate employing catalytic amount of DMAP. Compound **13**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (br, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.44 (s, 1H), 7.36 (t, $J = 7.6$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 5.15 (d, $J = 7.9$ Hz, 1H), 4.69 (m, 1H), 4.05 (s, 3H), 3.72 (s, 3H), 3.29 (dd, $J = 14.8$, 5.3 Hz, 1H), 3.20 (dd, $J = 14.8$, 5.3 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 155.1, 151.3, 135.4, 130.5, 124.9, 123.6, 122.9, 119.0, 116.1, 115.2, 80.1, 60.4, 54.4, 52.4, 28.3, 27.9; LC/MS 277 (M^++1–Boc), 377 (M^++1), 399 (M^++Na).
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