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Chemoselective deprotection of *N*-Boc group in amino acids and peptides by bismuth(III) trichloride

Raghavendra S. Navath, Kumar B. Pabbisetty and Longqin Hu*

Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854-8020, USA

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Abstract—Selective deprotection of *N*-Boc group was achieved in excellent yields using bismuth(III) trichloride in a mixed solvent of acetonitrile and water (50:1, v/v) at 55 °C. Acid-labile groups such as Pmc and *tert*-butyl ester were not affected and no alkylation of tryptophan, methionine, and cysteine residues was observed under the deprotection conditions.

Chemoselective deprotection of *N*-Boc group is an important transformation in the synthesis of peptides and biologically active natural products.[1–3] A variety of reagents have been employed to effect this transformation including strong acids[4–9] (e.g., trifluoroacetic acid, HCl,[7] HBr,[8] H_2SO_4,[10] and HNO_3[11]), Lewis acids (e.g., $BF_3{\cdot}Et_2O$[12] and $ZnBr_2$[13]), and neutral conditions (e.g., In,[14] Zn,[14] and Bu_4NF[15]). However, many of these procedures suffer from disadvantages such as high acidity, strong oxidizing conditions, long reaction times, unsatisfactory yields, low chemo-selectivity and large amounts of reagent or catalyst needed. For instance, TFA, the most commonly used Boc deprotection reagent, is an extremely corrosive liquid; greater care must be taken when it is used. TFA deprotection of Boc group in amino acids and peptides also lacks selectivity and removes both *N*-Boc and *tert*-butyl esters at the same time. For peptides containing tryptophan, methionine, and cysteine residues, alkylation by the *tert*-butyl cation formed under the acidic cleavage conditions is a common side reaction resulting in modification of the product peptide.[16] With methionine, further reaction can occur giving rise to homoserine and fragmentation of the peptide chain. Scavengers like thioanisole, ethylmethyl sulfide (EMS), and ethanedithiol (EDT) are often added to minimize these side reactions. The addition of these scavengers brings its own problems such as added extraction steps during purification and environmental concerns. Lewis acids like $BF_3{\cdot}Et_2O$ and $ZnBr_2$ used for *N*-Boc deprotection were also reported to lack selectivity.[12] In addition, a large excess of these Lewis acids were needed to efficiently cleave the *N*-Boc group. Thus, there is still a need for the development of mild, selective deprotection conditions for the common Boc amino protecting group. Here, we report a mild method to selectively deprotect *N*-Boc group using $BiCl_3$ in a mixed solvent of acetonitrile and water in the presence of a variety of other functional groups and easily alkylated amino acids such as tryptophan, cysteine, and methionine.

Bismuth, a group 15 element, is the heaviest stable element and the least toxic of heavy metals. It has two 6s and three 6p electrons for bond formation. For the +3 oxidation state, only the three 6p electrons are used. When bound to strong electronegative ligands like chloride and triflate, bismuth (III) derivatives[17] exhibit significant Lewis acidity due to the availability of unoccupied d and Bi-X σ* orbitals.[18,19] Recently, the catalytic activity of bismuth(III) derivatives as Lewis acids has been utilized in the deprotection of ketoximes and acetonides,[20] the cleavage of epoxides[21] and aziridines,[22] the oxidation of alkenes, acyloins, epoxides, α-hydroxy acids, glycols and ketols, and the cyanation and allylation of carbonyl compounds.[18,23] Many other reactions such as Knoevenagel condensations, Friedel–Crafts acylation, sulfonylation, carbonyl and aza-Diels–Alder reactions, carbonyl-ene reactions, Mukaiyama-aldol reactions, Michael reactions, and Ferrier rearrangements[24] have been reported to be catalyzed by $BiCl_3$.[18]

* Corresponding author. Tel.: +1 732 445 5291; fax: +1 732 445 6312; e-mail: LongHu@rutgers.edu

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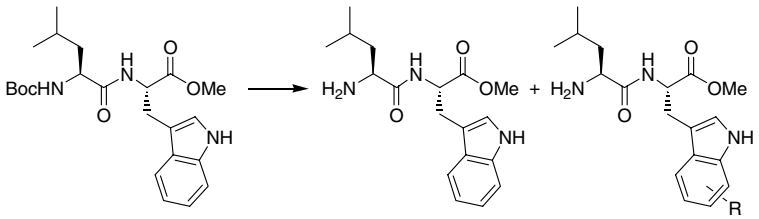
Table 1. Reaction conditions used to deprotect Boc-Leu-Trp-OMe (**1**)[a]



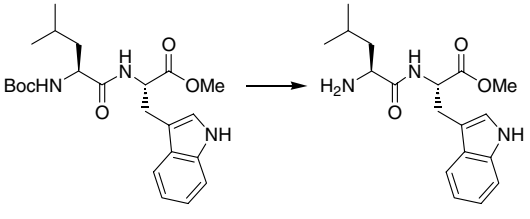
Entry	Reaction conditions	Isolated yield (%)	
		2	**3**
1	50% TFA/CH_2Cl_2, rt, 1 h	51	43
2	50% TFA/CH_2Cl_2 + 10 equiv thioanisole, rt, 1 h	58	35
3	$BiCl_3$ (20 mol %) in CH_3CN/H_2O (50:1), rt, 12 h	31	—[b]
4	$BiCl_3$ (2 × 20 mol %) in CH_3CN/H_2O (50:1), rt, 20 h	45	—[b]
5	$BiCl_3$ (2 × 20 mol %) in CH_3CN/H_2O (50:1), 55 °C, 2 h	95	—[b]

[a] Boc-Leu-Trp-OMe was deprotected at 1 mmol scale (0.2 M) under the conditions listed.
[b] No side product was detected and starting material was recovered.

In our research, we needed to deprotect *N*-Boc group from tryptophan containing peptides. When we used 50% TFA in dichloromethane for the deprotection, we found that 40–60% of the peptides were converted to the alkylated side products (e.g., Table 1, entry 1). The degree of side product formation varies from peptide to peptide and was dependent on the reaction time. The addition of 5–10 equiv of thioanisole as the scavenger, did not suppress the formation of the alkylated side product (Table 1, entry 2). When we treated Boc-Leu-Trp-OMe (**1**) with 20 mol % $BiCl_3$ in acetonitrile containing 2% water at room temperature for 12 h, we obtained 31% of the deprotected peptide **2** (Table 1, entry 3). More importantly, we did not observe the formation of any alkylated side product **3** as monitored by LCMS. The yield was improved to 45% when another aliquot of 20 mol % of $BiCl_3$ was added to the above reaction (Table 1, entry 4). When the reaction temperature was elevated to 55 °C, the deprotected dipeptide (H-Leu-Trp-OMe, **2**) was isolated in 95% yield (Table 1, entry 5). These results indicated the *N*-Boc group could be efficiently removed by $BiCl_3$ (2 × 20 mol %) in acetonitrile–water at 55 °C without the formation of any alkylated tryptophan side product.

We then studied the effect of organic solvent and water content on the $BiCl_3$-mediated deprotection of *N*-Boc using Boc-Leu-Trp-OMe (**1**) as the model substrate. Acetonitrile was found to be the preferred solvent for the deprotection reaction; the reaction rate would decrease if acetonitrile was replaced with other solvents (Table 2). In the latter cases, LCMS and TLC analysis of the reaction mixtures indicated significant quantities of unreacted starting material. The amount of water in the reaction medium also affected the reaction outcome. The use of neat organic solvent gave lower yields of

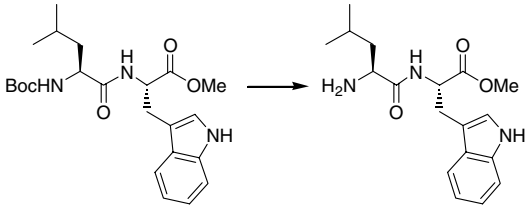
Table 2. Effect of solvent on the *N*-Boc deprotection reaction[a]



Entry	Solvent mixture (50:1)	Conversion yield (%)[b]
1	CH_2Cl_2/H_2O	65
2	CH_3CN/H_2O	95
3	THF/H_2O	75
4	DMF/H_2O	70
5	1,4-Dioxane/H_2O	78
6	$MeOH/H_2O$	72

[a] General conditions: Boc-Leu-Trp-OMe (1 mmol, 0.2 M), $BiCl_3$ (2 × 20 mol %), 55 °C, 2 h.
[b] Conversion yield to desired product as monitored by LC-MS.

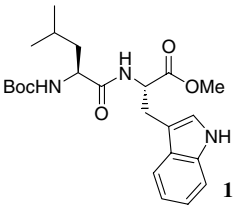
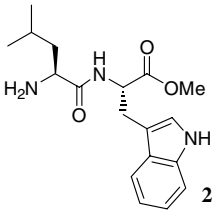
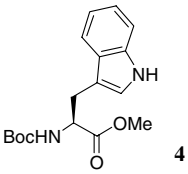
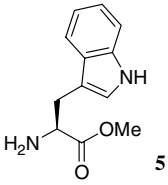
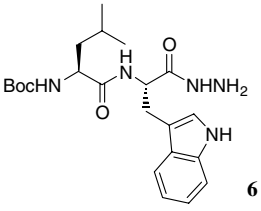
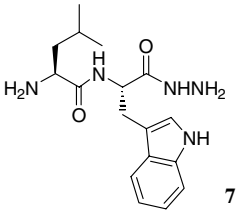
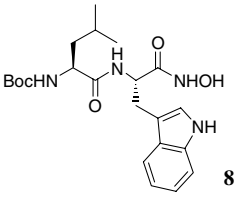
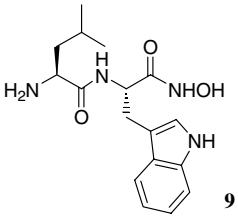
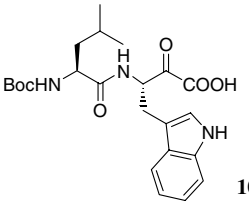
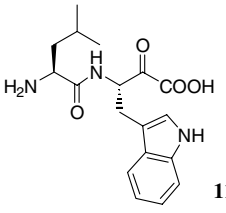
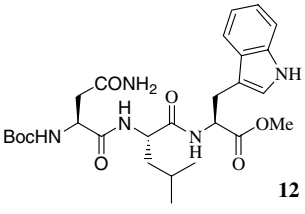
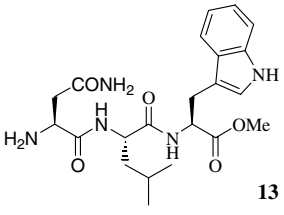
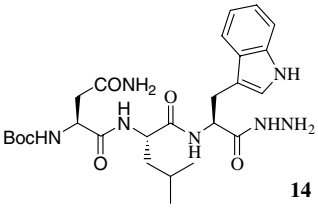
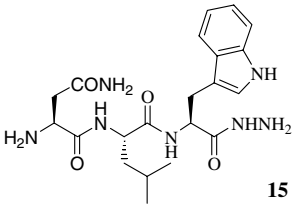
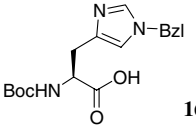
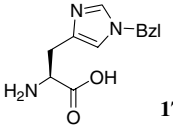
Table 3. Effect of water content on the *N*-Boc deprotection reaction[a]



Entry	CH_3CN:H_2O (v/v)	Conversion yield (%)[b]
1	10:1	80
2	20:1	85
3	25:1	87
4	50:1	95
5	100:1	85

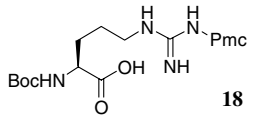
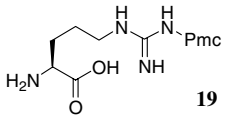
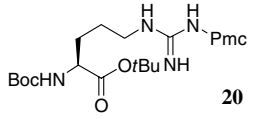
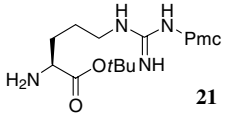
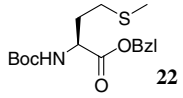
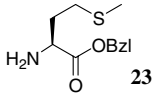
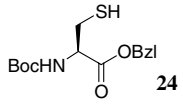
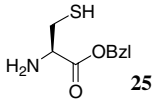
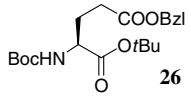
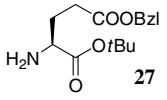
[a] General conditions: Boc-Leu-Trp-OMe (1 mmol, 0.2 M), $BiCl_3$ (2 × 20 mol %), 55 °C, 2 h.
[b] Conversion yield to the desired product as monitored by LC-MS.

Table 4. Bismuth(III) trichloride-mediated *N*-Boc deprotection[a]

Substrate	Product	Time (h)	Yield (%)[b]
 **1**	 **2**	2	95
 **4**	 **5**	2	96
 **6**	 **7**	2	94
 **8**	 **9**	2	91
 **10**	 **11**	2.5	90
 **12**	 **13**	2	92
 **14**	 **15**	2	91
 **16**	 **17**	2	96

(*continued on next page*)

Table 4 (*continued*)

Substrate	Product	Time (h)	Yield (%)[b]
 **18**	 **19**	2	95
 **20**	 **21**	1.5	81
 **22**	 **23**	2	91
 **24**	 **25**	2	90
 **26**	 **27**	1.5	82

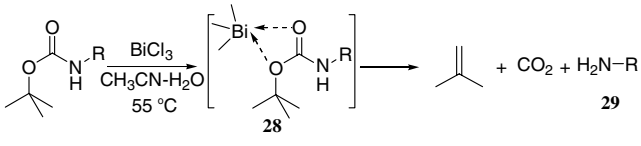
[a] 1 mmol scale (0.2 M), $BiCl_3$ (2×20 mol %), CH_3CN/H_2O (50:1), 55 °C.
[b] Isolated yield.

deprotected product. As shown in Table 3, the preferred composition for our binary solvent system was found to be 50:1 (acetonitrile to water, v/v).

After optimization of our reaction conditions, we examined the general applicability of the method to other substrates using the following representative procedure for the deprotection of *N*-Boc group from amino acids and peptides. A solution of the *N*-Boc protected peptides (1 mmol) in acetonitrile/water (5 mL/100 μL) was treated with $BiCl_3$ (20 mol %) and stirred at 55 °C. After 1 h, an additional 20 mol % aliquot of $BiCl_3$ was added and the reaction was allowed to continue at 55 °C until TLC or LC-MS showed disappearance of the starting material. Upon completion of the reaction, solid $NaHCO_3$ was added and the reaction mixture was filtered through Celite. The solvent was then removed under reduced pressure to give pure desired compound in high yields usually without the need for further chromatographic purification.

As shown in Table 4, methyl esters (compounds **1**, **4**, and **12**), hydrazides (compounds **6** and **14**) and hydroxamic acids (compound **8**) were stable under these reaction conditions. Amino acid protecting groups such as Pmc (compounds **18** and **20**) and *tert*-butyl esters (compounds **20** and **26**) were also stable under these conditions. In all cases, deprotected peptides were isolated in excellent yields. It should be noted that the *tert*-butyl esters (compounds **20** and **26**) could be cleaved if the reaction time was prolonged beyond 1.5–2 h. As with tryptophan (compound **4**), deprotection of *N*-Boc group in both methionine and cysteine (compounds **22** and **24**) proceeded without the formation of any alkylated side product as monitored by LC-MS.

It is clear that our reaction conditions favor the deprotection of *N*-Boc group in the presence of *tert*-butyl ester. Although this selectivity is not completely understood, we would expect, as confirmed by our calculations using PC Spartan, that electron densities on the carbamate oxygens are relatively higher and would associate more readily with the limited amounts of Bi(III) species present as compared to those on the ester oxygens. This might help explain why the *tert*-butyl carbamate was more susceptible to $BiCl_3$-mediated deprotection than *tert*-butyl esters. A generalized mechanism is proposed here for the Boc deprotection and is shown in Scheme 1. The Lewis acid Bi(III) coordinates with both the carbamate oxygen atoms to form complex **28**, which then breaks down to form isobutene, carbon dioxide, and the desired deprotected amine **29**. However, this scheme does not explain the role of water in the $BiCl_3$-mediated deprotection of *N*-Boc and the need to add $BiCl_3$ in two portions for better yields. $BiCl_3$ is



Scheme 1.

known to be hygroscopic and undergoes hydrolysis to form water-insoluble bismuth oxychloride (BiOCl) and HCl.[19] This instability and reactivity of $BiCl_3$ in the presence of water might partially explain the need to add fresh $BiCl_3$ a second time after 1 h to improve the conversion yield. But, attempts to mimic the result of such hydrolysis by reducing the amount of $BiCl_3$ used and adding the expected amount of HCl failed to effect the desired deprotection. Additional experiments are necessary to fully understand the mechanistic aspects of the reaction.

In summary, we developed a new procedure for the deprotection of *N*-Boc that offers mild reaction conditions, excellent yield, and high chemo-selectivity. The deprotection procedure uses inexpensive catalyst ($BiCl_3$) and a simple experimental work-up procedure. In addition, no alkylated side reactions of tryptophan, methionine, and cysteine residues were observed. This $BiCl_3$-mediated *N*-Boc deprotection should find general application in the synthesis of amino acids and peptides.

Acknowledgements

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References and notes

1. Jarowinski, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2109–2135.
2. Green, T. W.; Wuts, P. G. M. In *Protecting Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp 65–67, and 404–408.
3. Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, 2nd ed.; Springer: Berlin, Germany, 1994.
4. Connell, R. D.; Rein, T.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845–3849.
5. Brosse, N.; Pinto, M.-F.; Gregoire, B. J. *Tetrahedron Lett.* **2000**, *41*, 205–207.
6. Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873–7876.
7. Carpino, L. A. *J. Org. Chem.* **1964**, *29*, 2820–2824.
8. Allan, R. D.; Johnston, G. A.; Kazlauskas, R.; Tran, H. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2983–2985.
9. Degerbeck, F.; Fransson, B.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 1* **1992**, 245–253.
10. Lin, L. S.; Lanza, T.; Laszlo, S. E. d.; Truoung, Q.; Kamenecka, T.; Hagmann, W. K. *Tetrahedron Lett.* **2000**, *41*, 7013–7016.
11. Strazzolini, P.; Melloni, T.; Glumanini, A. G. *Tetrahedron* **2001**, *57*, 9033–9043.
12. Green, T. W.; Wuts, P. G. M. In *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 518–525, and 617–618.
13. Ramesh, K.; Yann, B.; Zohreh, S.; Karl, A. H.; William, D. L. *J. Org. Chem.* **2004**, *69*, 6131–6133.
14. Yadav, J. S.; Reddy, B. V. S.; Reddy, K. S.; Reddy, K. B. *Tetrahedron Lett.* **2002**, *43*, 1549–1551.
15. Routier, S.; Sauge, L.; Ayerbe, N.; Coudert, G.; Merour, J. Y. *Tetrahedron Lett.* **2002**, *43*, 589–591.
16. Atherton, E.; Sheppard, R. C. *Solid Phase Peptide Synthesis: A Practical Approach*; IRL Press: Oxford, 1989.
17. Like other group 15 elements, bismuth has +3 and +5 oxidation states. In the +3 state, the two 6s electrons are increasingly less available as one goes down from N to Bi. Thus, Bi(III) derivatives are much less basic than other E(III) derivatives in the same group.
18. Le Roux, C.; Dubac, J. *Synlett* **2002**, 181–200, and references cited therein.
19. Briand, G. G.; Burford, N. *Chem. Rev.* **1999**, *99*, 2601–2657.
20. Swamy, N. R.; Venkateswarlu, Y. *Tetrahedron Lett.* **2002**, *43*, 7549–7552.
21. Swamy, N. R.; Gondaji, G.; Nagaiah, K. *Synth. Commun.* **2002**, *32*, 2307–2312.
22. Swamy, N. R.; Venkateswarlu, Y. *Synth. Commun.* **2003**, *33*, 547–554.
23. Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215–7218.
24. Swamy, N. R.; Venkateswarlu, Y. *Synthesis* **2002**, 598–600.