Tetrahedron Letters 50 (2009) 5094–5097

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient and selective cleavage of the *t*-butoxycarbonyl group from di-*t*-butylimidodicarbonate using catalytic bismuth(III) bromide in acetonitrile

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ARTICLE INFO

Article history:
Received 11 March 2009
Revised 12 June 2009
Accepted 19 June 2009
Available online 25 June 2009

ABSTRACT

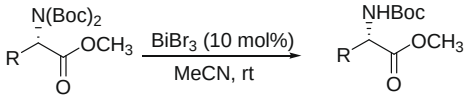
Di-*t*-butylimidodicarbonates can be chemoselectively and efficiently deprotected to the corresponding mono-BOC-protected amines in high yields using a catalytic amount of bismuth(III) bromide in acetonitrile at room temperature. This method is mild and compatible with the presence of a wide range of functional and other protecting groups in the substrates, such as TBDMS, MOM and mono-BOC or Cbz-protected amines, etc. The method has advantages of ease of operation and use of nontoxic and inexpensive catalyst.

The strategy to protection and deprotection of a functional group plays an important role in multi-step synthesis of many complex natural products and pharmaceutical intermediates. Among various amine-protecting groups, the *t*-butoxycarbonyl group is one of the most widely used amine-protecting groups during the synthesis of amino acids, peptides, and other biologically interesting molecules, due to its chemical stability over a pH range and its ease of removal under specific conditions.[1] Di-*t*-butylimidodicarbonates are very useful as phthalimide substitutes in Mitsunobu[2] and Gabriel-type processes[3] in the synthesis of several bioactive molecules and are found to be essential to the success of the reaction.[4] Typical conditions for acid-catalyzed removal of the *t*-BOC include conc. HCl[5a] or HBr,[5b] trifluoroacetic acid/DCM,[5c] $Mg(ClO_4)_2$,[5d,4f] indium, or zinc/refluxing methanol.[5e] However, many of these reaction conditions involve strong acids, corrosive reagents, or elevated temperatures which are difficult to handle especially on a large scale.

Recently, considerable effort has been focused on developing mild, selective methods for the removal of BOC group from di-*t*-butylimidodicarbonate. Several methods have been reported for cleaving BOC group from di-*t*-butylimidodicarbonate under nearly neutral conditions, wherein mild Lewis acids are often adopted instead of strong acids. For example, $CeCl_3{\cdot}7H_2O$–NaI in acetonitrile and Montmorillonite K-10 in CH_2Cl_2 can deprotect BOC group from di-*t*-butylimidodicarbonate efficiently.[6] Bismuth(III) reagents are specially attractive since they have suitable acidity, and are nontoxic, easy to handle, and are inexpensive, thereby making the process economically viable and environmentally benign.[7]

We report herein that bismuth(III) bromide in acetonitrile is a highly efficient catalytic system and practical method for selective deprotection of a *N*-Boc group in *N*-Boc-*N*-acyl-protected amines and α-amino acids, and leaves simple BOC-protected amines without any detectable racemization.[8] Since very few mild methods exist for the selective deprotection of BOC group from di-*t*-butylimidodicarbonate, we examined the use of this system on a variety of other functionalities. We found that the method was highly efficient and easy to apply. Furthermore, chemoselective deprotection of BOC group was achieved in the presence of other functional protecting groups, such as TBMDS, MOM, and mono-BOC and Cbz. The reaction proceeded very smoothly in acetonitrile with a catalytic amount of bismuth(III) bromide at room temperature (Scheme 1).[9]

As shown in Table 1, deprotection of the BOC group from di-*t*-butylimidodicarbonate was achieved in excellent yields, leaving simple BOC-protected amines unaffected (entries a–j) and affording the corresponding *N*-Boc amino derivatives. The procedure was found to be highly general. When another carbamoyl-based protecting group, such as Cbz, was used, the cleavage of the Boc group was accomplished cleanly and selectively, yielding the cor-



Scheme 1.

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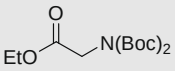
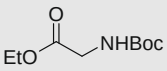
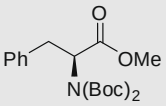
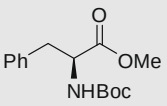
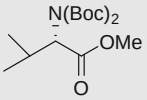
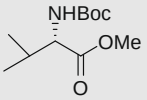
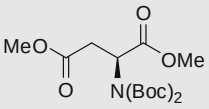
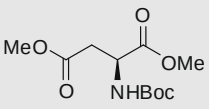
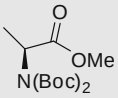
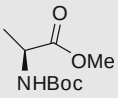
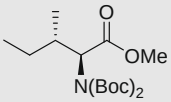
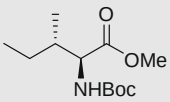
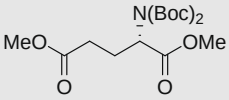
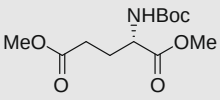
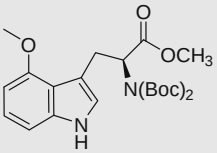
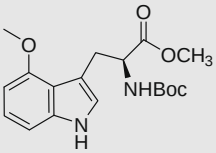
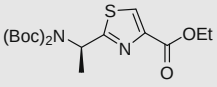
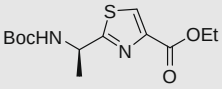
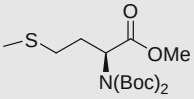
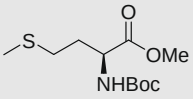
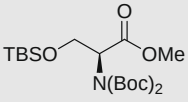
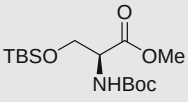
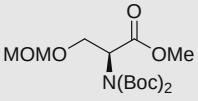
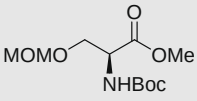
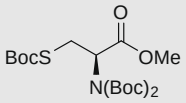
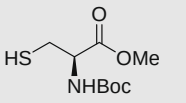
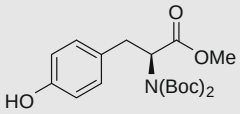
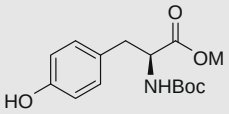
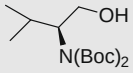
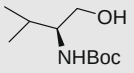
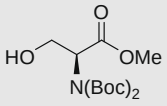
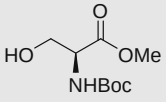
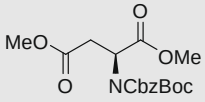
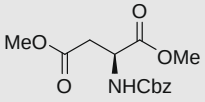
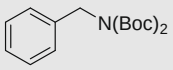
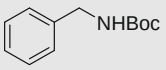
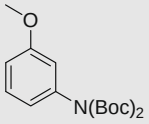
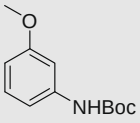
doi:10.1016/j.tetlet.2009.06.104

Table 1
Selective removal of BOC from BOC-protected amides using $BiBr_3$ in MeCN

Entry[a]	Substrate (**1**)	Time (h)	Conditions[b]	Product (**2**)	Yield[c] (%)
a		2	A		82
b		12	A		86
c		2	A		90
d		2	A		94
e		2	A		88
f		2	A		83
g		2	A		83
h		24	A		93
i		12	A		90
j		2	A		87
k		2	A		83
l		3	A		93

(*continued on next page*)

Table 1 (*continued*)

Entry[a]	Substrate (**1**)	Time (h)	Conditions[b]	Product (**2**)	Yield[c] (%)
m		2	A		81
n		12	B		82
o		12	B		89
p		12	B		70
q		12	B		78
r		2	A		93
s		1	A		96

[a] All substrates and products were fully characterized by spectroscopic methods.
[b] (A) CH_3CN, room temperature; (B) CH_3CN, 65 °C.
[c] Isolated yields.

responding *N*-Cbz amino derivative (entry q). TBDMS (entry k) and MOM (entry l) groups, which are highly acid sensitive groups, were also stable under this reaction conditions. However, the Boc group of Cys (entry m) was simultaneously cleaved using this protocol. When a hydroxyl group is present in the substrate, the reactions need to proceed with longer time and higher temperature (entries n–p), which was reasoned that this behavior is presumably related to the chelate complex of hydroxyl with bismuth(III) ion. In addition, the cleavage of the mono Boc group from *N*,*N*-di-Boc-protected benzylamine and aromatic amine was achieved with high selectivity and good yield (entries r and s). The reaction rate decreased when the preferred solvent (MeCN) was replaced with CH_2Cl_2. Significant quantities of unreacted starting materials were indicated by TLC monitoring. It is noteworthy that the reaction could be accelerated by a catalytic amount of H_2O, and could be reduced to 1 h or shorter. However, under these conditions the reaction system is weakly acidic. It should be emphasized that in most cases virtually pure samples were obtained after simple filtration and removal of solvents.

In summary, we have demonstrated that the use of catalytic (10 mol %) amount of bismuth(III) bromide in acetonitrile at room temperature provides a mild and effective protocol for selective cleavage of a Boc group in *N*-Boc-*N*-acyl-diprotected amines in high yield. This reagent system operates under neutral conditions thereby leaving acid- and base-labile protecting groups intact. Advantages of this method include the simplicity of the procedure and the use of inexpensive, nontoxic catalyst.

Acknowledgments

This project was supported by the National Natural Science Foundation (Grant No. 20802078), National Basic Research Program of China (973 Program, Grant No. 2009CB940900), the Guangdong Natural Science Foundation (Grant No. 8151066 302000008), and NN-CAS Research Foundation (Grant No. NNCAS-2008-8).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.104.

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8. Comparative analysis of *N*-Boc-protected α-amino acids and similar materials obtained by the di-*t*-butylimidodicarbonate and further *N*-Boc cleavage sequence using the present methodology provided compounds with identical specific rotations.
9. *Experimental procedure*: A mixture of di-BOC derivative (3.3 mmol) and bismuth(III) bromide (0.33 mmol) in acetonitrile (10 mL) was stirred at room temperature for 0.5 h. Then water (0.36 mmol) was added, the reaction mixture was stirred at room temperature until all starting material had disappeared, and was then quenched by adding 1 ml of saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford pure mono-BOC-protected amine. Spectroscopic data of **1b**: $[\alpha]_D^{25}$ −89.3 (*c* 0.7, $CHCl_3$); (lit.,[5e] $[\alpha]_D^{25}$ −90.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.16 (m, 5H), 5.13 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.73 (s, 3H), 3.41 (dd, *J* = 14.0, 4.9 Hz, 1H), 3.19 (dd, *J* = 14.0, 10.4 Hz, 1H), 1.37 (s, 18H) ppm. **2b**: $[\alpha]_D^{25}$ +60.0 (*c* 0.8, $CHCl_3$); (lit.,[5e] $[\alpha]_D^{25}$ +44.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.13 (m, 5H), 4.98 (d, *J* = 5.3 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 1H), 3.71 (s, 3H), 3.08 (m, 2H), 1.42 (s, 9H) ppm. **1g**: $[\alpha]_D^{25}$ −36.5 (*c* 2.2, $CHCl_3$); (lit.,[5e] $[\alpha]_D^{25}$ −37.2 (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$):δ 4.93 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 2.49–2.39 (m, 3H), 2.18 (m, 1H), 1.49 (s, 18H) ppm. **2g**: $[\alpha]_D^{25}$ +12.8 (*c* 2.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (br s, 1H), 4.31 (br s, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 2.39 (m, 2H), 2.14 (m, 1H), 1.92 (m, 1H), 1.41 (s, 9H) ppm. Compound **1i**: $[\alpha]_D^{25}$ +3.6 (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 5.73 (q, *J* = 7.0 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 1.85 (d, *J* = 6.8 Hz, 3H), 1.46 (s, 18H), 1.26 (t, *J* = 7.0 Hz, 3H) ppm. Compound **2i**: $[\alpha]_D^{25}$ +40.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 5.20 (br s, 1H), 5.10 (br s, 1H), 4.41 (q, *J* = 7.0 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.38 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm. Compound **1j**: $[\alpha]_D^{25}$ −39.0 (*c* 2.8, $CHCl_3$); (lit.,[5e] $[\alpha]_D^{25}$ −35.57 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (dd, *J* = 8.6, 5.3 Hz, 1H), 3.70 (s, 3H), 2.54 (m, 2H), 2.45 (m, 1H), 2.13 (m, 1H), 2.10 (s, 3H), 1.48 (s, 18H) ppm. Compound **2j**: $[\alpha]_D^{25}$ +23.1 (*c* 0.8, $CHCl_3$); (lit.,[5e] $[\alpha]_D^{25}$ +24.3 (*c* 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.11 (br s, 1H), 4.41 (br s, 1H), 3.8 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.14 (m, 1H), 2.10 (s, 3H), 1.93 (m, 1H), 1.44 (s, 9H) ppm.