

Short communication

Rapid *N-tert*-butoxycarbonylation of amines using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ as a mild and highly efficient catalyst under solvent-free conditions[☆]

N. Suryakiran, P. Prabhakar, T. Srikanth Reddy, M. Srinivasulu,
N. Raghavendra Swamy, Y. Venkateswarlu^{*}

Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 5000 07, India

Received 26 July 2006; received in revised form 1 September 2006; accepted 4 September 2006

Available online 8 September 2006

Abstract

Rapid *N-tert*-butoxycarbonylation of amines by treatment with di-*tert*-butyl dicarbonate in the presence catalytic amount of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ as a mild and highly efficient catalyst under solvent-free conditions at room temperature in excellent yields is described.

© 2006 Elsevier B.V. All rights reserved.

Keywords: Bismuth(III) nitrate pentahydrate; Amines; *N-tert*-Butoxycarbonylation; Solvent-free conditions

The protection/deprotection of amines is one of the most fundamental and useful transformation in organic synthesis, especially in peptide synthesis [1]. Among the protecting groups for amines, *N-tert*-butoxycarbonylation [2] is used with high frequency, because *N-tert*-butylcarbamates are stable to wide range of nucleophiles in alkaline conditions and are very liable under mild acidic conditions to give the parent amine [1]. Although, various methods are available for the preparation of *N-tert*-butylcarbamates using di-*tert*-butyl dicarbonate [3–11], only few reports on acid mediated *N-tert*-butoxycarbonylation of amines, “Yttria–Zirconia” needs longer reaction times (3–48 h) [12] and very recently Lewis acids [13–16] such as ZrCl_4 , copper(II) tetrafluoroborate, InBr_3 , $\text{HClO}_4\text{--SiO}_2$ have been reported for this transformation.

A literature survey revealed that bismuth(III) nitrate pentahydrate is a relatively non-toxic, inexpensive, insensitive to air and no special care is required and used in various organic transformations [17a–h]. Also, there is no report on the use of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ for the *N-tert*-butoxycarbonylation of amines with di-*tert*-butyl dicarbonate. Here, we report rapid and an efficient method for *N-tert*-butoxycarbonylation of amines using di-*tert*-butyl dicarbonate in presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ under solvent-free conditions.

In continuation of our search for catalytic application of metal nitrate salts [18], in the multi-step synthesis of natural products and discovery of chemoselective reagents, we have observed that $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ can be utilized efficiently for the *N-tert*-butoxycarbonylation of amines with di-*tert*-butyl dicarbonate under solvent-free conditions. While *N-tert*-butoxycarbonylation of amines using $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$, the reaction conditions are compatible with the presence of other functionalities such as, acetyl, benzyl and some isopropylidene and no by-products were observed. We first examined the reaction of aniline with di-*tert*-butyl dicarbonate in the presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ at room temperature gave the corresponding *N-tert*-butylcarbamate 100% yield in very short time (Table 1, entry 1). This success has encouraged us to extend the generality of the reaction on various primary, secondary and aryl amines with di-*tert*-butyl dicarbonate in presence of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ to give the corresponding *N-tert*-butylcarbamates in good to excellent yields (Scheme 1, Table 1). Further, it is note worthy to observe that when the diamines were subjected to *N-tert*-butoxycarbonylation, major mono *N-tert*-butylcarbamate is formed with very good yields (Table 1, entries 10 and 13). The formation of the *N-tert*-Boc amine was recognized by the presence of nine-proton signal at $\delta \sim 1.40$ as singlet in ^1H NMR spectra of the products [19].

In conclusion, we have described mild and an efficient method for *N-tert*-butoxycarbonylation of amines using di-*tert*-butyl dicarbonate in the presence of catalytic amount of $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$. The method is having advantage of reduced

[☆] IICT Communication No. 060831.

^{*} Corresponding author. Tel.: +91 40 271 93167; fax: +91 40 271 60512.

E-mail address: luchem@iict.res.in (Y. Venkateswarlu).

Table 1

N-tert-Butoxycarbonylation of amines in the presence of bismuth(III) nitrate pentahydrate under solvent-free conditions

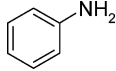
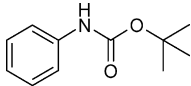
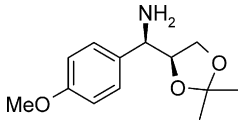
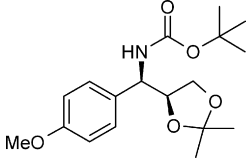
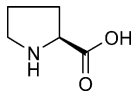
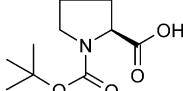
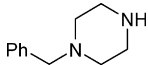
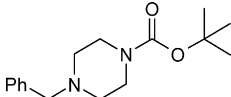
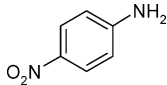
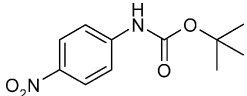
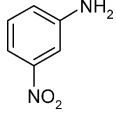
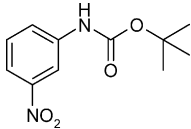
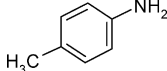
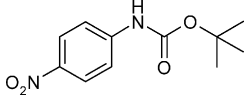
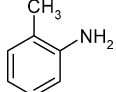
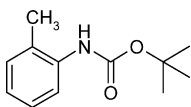
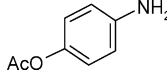
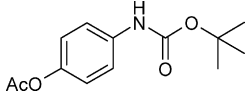
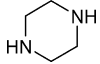
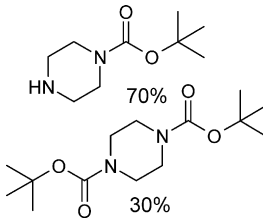
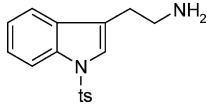
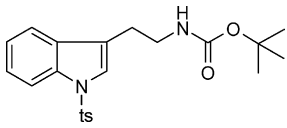
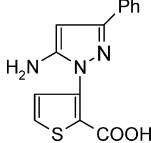
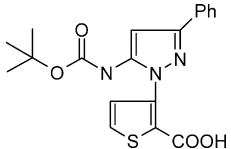
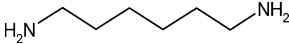
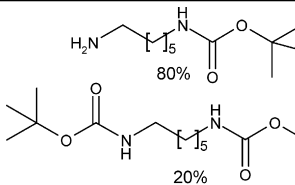
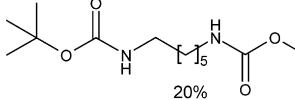
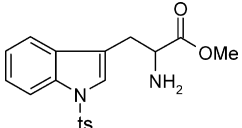
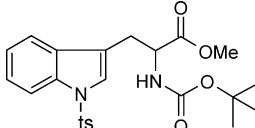

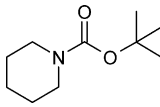

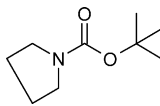
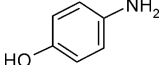
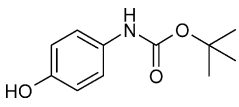
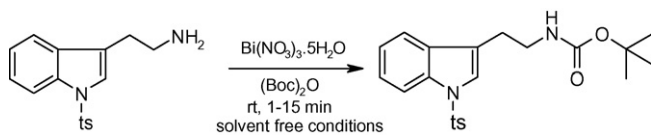
Entry	Substrate	Product ^a	Time (min)	Yield (%) ^b
1			1	100
2			2	98
3			3	95
4			2	100
5			4	98
6			2	98
7			1	99
8			2	100
9			3	98
10		 70% 30%	3	99
11			10	95
12			15	96

Table 1 (Continued)

Entry	Substrate	Product ^a	Time (min)	Yield (%) ^b
13		 80%  20%	2	98
14			10	95
15			2	98
16			1	99
17			2	98

^a The structures of the products were established from their spectral data (¹H NMR, EIMS).

^b Isolated yields obtained after column chromatography.



Scheme 1.

reaction time, simple experimental work-up procedure with high yields of products, which makes a useful addition to the present existing methodologies.

Typical experimental procedure. To a mixture of amine (1 mmol), di-*tert*-butyl dicarbonate (1.2 mmol) was added finely grinded $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ (5 mol%) and the reaction was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction as monitored by TLC, water (10 mL) was added to the reaction mixture and the product was extracted into ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine and concentrated in vacuum to give crude mass, which was purified over silica gel column chromatography to afford corresponding product.

Acknowledgements

The authors are thankful to CSIR, DOD, and DBT New Delhi for financial assistance and to Dr. J.S. Yadav, Director IICT for his constant encouragement.

References

- [1] (a) T.W. Green, P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, John Wiley & Sons, New York, 1999; (b) N.S. Raghavendra, B.P. Kumar, H. Longquin, *Tetrahedron Lett.* 47 (2006) 389.
- [2] K. Ravinder, A. Vijender Reddy, P. Krishnaiah, P. Ramesh, S. Ramakrishna, H. Laatsch, Y. Venkateswarlu, *Tetrahedron Lett.* 46 (2005) 5475.
- [3] (a) L. Grehn, U. Ragnarsson, *Angew. Chem. Int. Ed. Engl.* 23 (1984) 296; (b) L. Grehn, U. Ragnarsson, *Angew. Chem. Int. Ed. Engl.* 24 (1985) 510; (c) M.J. Burk, J.G. Allen, *J. Org. Chem.* 62 (1997) 705.
- [4] J. Einhorn, C. Enhorn, J.-L. Luche, *Synlett* (1991) 37.
- [5] E. Guibe-Janpel, M. Wakselamann, *J. Chem. Soc., Chem. Commun.* (1971) 267.
- [6] E. Guibe-Janpel, M. Wakselamann, *Synthesis* (1977) 772.
- [7] M. Itoh, D. Hagiwara, T. Kamia, *Tetrahedron Lett.* 16 (1975) 4393.
- [8] S. Kim, J.I. Lee, *Chem. Lett.* (1984) 237.
- [9] G. Barcelo, J.-P. Senet, G. Sennyey, *Synthesis* (1986) 627.
- [10] (a) Y. Basel, A. Hassner, *J. Org. Chem.* 65 (2000) 6368; (b) S. Darnbrough, M. Mervic, S.M. Condon, C. Burns, *J. Synth. Commun.* 31 (2001) 3273.
- [11] K.A. Chakraborti, V. Sunay, *Org. Lett.* 8 (2006) 3259.
- [12] R.K. Pandey, S.P. Dagade, R.K. Upadhyaya, M.K. Dongare, K. Pradeep, *Arkivoc.* 7 (2002) 28.
- [13] (a) G.V.M. Sharma, J.J. Reddy, P.S. Lakshmi, P.R. Krishna, *Tetrahedron Lett.* 45 (2004) 6963; (b) S.V. Chankeshwara, A.K. Chakraborti, *Tetrahedron Lett.* 47 (2006) 1987.
- [14] G. Bortily, M. Bosco, E. Marcantoni, V.S. Massaccesi, J.J. Reddy, P.S. Lakshmi, P.R. Krishna, *Tetrahedron Lett.* 45 (2004) 6963.
- [15] A. Heydari, S.E. Hosseini, *Adv. Synth. Catal.* 347 (2005) 1929.

- [16] (a) K.A. Chakraborti, V. Sunay, *Synthesis* (2006) 2784;
(b) K.A. Chakraborti, V. Sunay, *Org. Biomol. Chem.* 4 (2006) 2769.
- [17] (a) S. Samajdar, F.F. Becker, B.K. Bnik, *Tetrahedron Lett.* 41 (2000) 8017;
(b) S. Samajdar, F.F. Becker, B.K. Banik, *Synth. Commun.* 31 (2001) 2691;
(c) B.A. Nattier, K.J. Eash, R.S. Mohan, *Synthesis* (2001) 1010;
(d) I.M. Baltork, M.M. Khodaei, K. Nikoofar, *Tetrahedron Lett.* 44 (2003) 591;
(e) V.M. Alexander, A.C. Khandekar, S.C. Samant, *Synlett* 12 (2003) 1895;
(f) N. Srivastava, B.K. Banik, *J. Org. Chem.* 68 (2003) 2109;
(g) M.M. Khodaei, A.R. Khosropour, M. Beygzadeh, *Synth. Commun.* 34 (2004) 1551;
(h) V.M. Alexander, R.P. Bhat, S.D. Samant, *Tetrahedron Lett.* 46 (2005) 6957.
- [18] (a) T. Srikanth Reddy, K. Ravinder, N. Suryakiran, M. Narasimhulu, K. Chinni Mahesh, Y. Venkateswarlu, *Tetrahedron Lett.* 47 (2006) 2341;
(b) S. Malla Reddy, Y. Venkat Reddy, Y. Venkateswarlu, *Tetrahedron Lett.* 46 (2005) 7439;
(c) M. Narasimhulu, K. Chinni Mahesh, T. Srikanth Reddy, K. Rajesh, Y. Venkateswarlu, *Tetrahedron Lett.* 47 (2006) 4381;
(d) T. Srikanth Reddy, M. Narasimhulu, N. Suryakiran, K. Chinni Mahesh, Y. Venkateswarlu, *Tetrahedron Lett.* 47 (2006) 6825;
(e) J.S. Jon Paul, V. Suresh, K. Rajesh, S. Ravinder Reddy, Y. Venkateswarlu, *Tetrahedron Lett.* 47 (2006) 2507.
- [19] Entry **2**: $^1\text{H NMR}$ (CDCl_3 , 200 MHz), δ = 1.31 (s, 3H), 1.40 (s, 9H), 1.48 (s, 3H), 3.7 (dd, 1H, J = 5.0 Hz), 3.78 (d, 3H), 3.91 (dd, 1H, J = 5.0 Hz), 4.28 (m, 1H), 5.17 (d, 1H), 6.81 (d, 2H, J = 8.0 Hz), 7.21 (d, 2H, J = 8.0 Hz). EIMS: 337 (M^+); Entry **14**: $^1\text{H NMR}$ (200 MHz, CDCl_3), δ = 1.42 (s, 9H), 2.50 (s, 3H), 2.88 (t, 2H, J = 6.4 Hz), 3.40 (m, 2H), 4.64 (br s, 1H), 6.8 (s, 1H), 7.04 (t, 1H, J = 7.0 Hz), 7.10 (t, 1H, J = 7.0 Hz), 7.24 (d, 1H, J = 7.4 Hz), 7.50 (d, 1H, J = 7.4 Hz), 7.60 (d, 2H, J = 8.5 Hz), 8.20 (d, 2H, J = 7.4 Hz). EIMS: 350 (M^+).