Environmentally Benign *N*-Boc Protection under Solvent- and Catalyst-Free Conditions

Xueshun Jia,* Qing Huang, Jian Li, Shaoyu Li, Qiushi Yang

Department of Chemistry, Shanghai University, Shanghai 200444, P. R. of China
Fax +86(21)66132797; E-mail: xsjia@mail.shu.edu.cn

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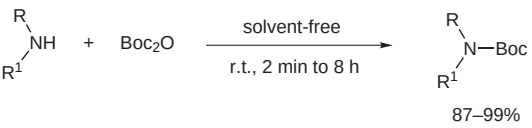
Abstract: A practical and highly efficient method for the protection of amines to their corresponding *N*-Boc derivatives is reported. In the absence of any solvent and catalyst, the present strategy works well for a series of electron-deficient and electron-rich aromatic amines as well as some sterically hindered substrates.

Key words: *N*-Boc protection, environmentally benign, solvent-free, catalyst-free

Functional group protection and deprotection strategies are important in target molecule synthesis. The protection of amines is one of the most fundamental and useful transformations in organic synthesis, especially in peptide synthesis.[1] Many mild and selective methods for the protection of amine groups have been developed for many different organic transformations.[2] Among them, the commercially available di-*tert*-butyl dicarbonate (Boc_2O) has become an efficient reagent for the clean and rapid introduction of the *tert*-butoxycarbonyl (Boc or *t*-Boc) protecting group at the amine functionality. Due to the stability of *N*-*tert*-butylcarbamates towards catalytic hydrogenolysis and extreme resistance to bases and nucleophiles, as well as easy conversion into the parent amines under mild acidic conditions,[1b] this protection of amines is used frequently.[3] Various base-mediated methods for the *N*-Boc protection of amines have been developed, for example DMAP, NaOH, K_2CO_3, Et_3N, $NaHCO_3$ and Me_4NOH.[4] However, these methodologies suffer from a variety of drawbacks such as long reaction times, high toxicity (DMAP), special syntheses of the *tert*-butyloxycarbonylation reagents, basic conditions and the use of solvents. Several Lewis acids such as yttria-zirconia, $Zn(ClO_4)_2$, $LiClO_4$, $Cu(BF_4)_2$, $La(NO_3)_3$ and $ZrCl_4$ have also been extensively investigated in order to achieve such transformations.[5] However, the Lewis acid catalyzed Boc-protection of amines is quite restricted as the strong affinity of many Lewis acids for amino groups does not allow regeneration of the Lewis acids.[6] Moreover, most Lewis acids are decomposed or deactivated by the amines and their amine derivatives.[7] Even when the desired reactions proceed, greater than stoichiometric amounts of Lewis acid are needed because the acids are trapped by nitrogen. Herein we wish to report a novel and highly practical strategy for *N*-Boc protection in the absence of solvent and catalyst (Scheme 1). To the best of our knowledge, this is the first example of the *N*-Boc protection of amines without the presence of any solvent or catalyst.

Our initial experiments were carried out using aniline as a model substrate. At room temperature, when one mmol of aniline was added to one mmol of Boc_2O under solvent- and catalyst-free conditions, there was an evolution of heat and quick bubbling. To our delight, this model reaction finished within 30 minutes and the corresponding mono *N*-Boc derivative was afforded in 95% yield. This is noteworthy as in the work of Adapa et al, the reaction between aniline and Boc_2O was quite sluggish and only 60% of the desired *N*-Boc product could be isolated after 48 hours.[8] Our results indicated that the transformation of aniline to the corresponding *N*-Boc derivative could be achieved in high efficiency without any catalyst or solvent.



Scheme 1

Encouraged by these experimental results, a series of structurally diverse aromatic and aliphatic amines were treated with Boc_2O under catalyst- and solvent-free conditions.[8] Various amines underwent smooth conversion into the corresponding mono *N*-Boc products in excellent yields (Table 1). No side-products were observed. Moreover, behavior of the present strategy is dependent on the type of substrate amine used. Generally, aliphatic amines reacted faster, while the aromatic analogues needed prolonged reaction times. Substituent groups on the aromatic rings dramatically affected the conversion rate of amines. Electron-donating groups such as methyl and methoxy groups add to the nucleophilicity of the aromatic amines and help with the conversion into the corresponding *N*-Boc products (Table 1, entries 10 and 11). In contrast, the presence of electron-withdrawing substituent groups, such as chloride and nitro, decreased the nucleophilicity of the aromatic amines and the corresponding conversion became quite sluggish (Table 1, entries 12 and 13). In particular, when a nitro group was present in the aromatic ring, the transformation to its *N*-Boc product did not occur at room temperature even with a prolonged reaction time. In this case, an elevated reaction temperature made a sig-

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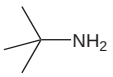
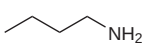
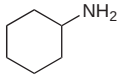
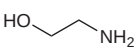
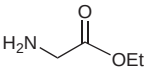
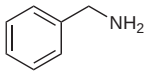
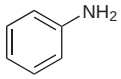
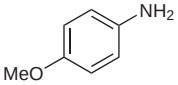
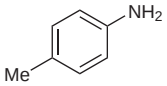
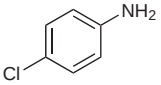
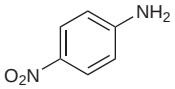
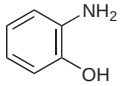
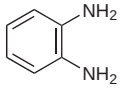
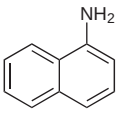
Table 1 *N*-Boc Protection of Amines Under Solvent- and Catalyst-Free Conditons[a]

Entry	Amine	Time	Yield (%)[b]
1		2 min	97
2		4 min	95
3		2 min	94
4		7 min	98
5		15 min	92
6		4 min	92
7		5 min	99
8		8 min	94
9		30 min	95
10		40 min	96
11		50 min	95
12		6 h	96
13		8 h	87[c]
14		5 h	91
15		5 h	97[d]
16		7 h	94

[a] Unless otherwise stated, all reactions were carried out using amine (1 mmol) and Boc_2O (1 mmol) at room temperature.[9]
[b] Isolated yields.
[c] The mixture was heated to 110 °C with five equivalents of Boc_2O.
[d] Both amino groups were protected.

nificant improvement (Table 1, entry 13). Following literature precedent,[9] we also tried adding a catalytic amount of iodine in the protection of 4-nitroaniline, but only trace amounts of the protected product were formed (10%) after 48 hours. In view of the importance of peptide synthesis, we also tried to protect ethyl 2-aminoacetate using our conditions and the result was quite satisfactory (Table 1, entry 7).

It is of note that this method also shows good chemoselectivity. In the presence of a hydroxy group, only the mono *N*-Boc products were isolated and no *O*-Boc protection could be observed from the ^1H NMR (Table 1, entries 5 and 14). However, when *o*-phenylenediamine was used as the substrate with one equivalent of Boc_2O, the mono *N*-Boc protected product was isolated as the major product in 70% yield and the corresponding *N*,*N*′-di-Boc derivative was also afforded as a side-product (30%). The *N*,*N*′-di-Boc derivative was formed exclusively when the amount of the Boc_2O was increased to two equivalents.

We have developed a practical and highly efficient method for the protection of amines with Boc_2O. This new protocol allows for the efficient conversion of both aliphatic and aromatic amines into their corresponding mono *N*-Boc protected derivatives without the occurance of bis-Boc protection. The advantages including solvent- and catalyst-free conditions, operation at room temperature, excellent chemoselectivity, high yields and environmentally benign conditions make this present method superior to existing methods. We believe that our method will find its use in organic synthesis, especially in large-scale industrial preparation.

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References and Notes

(1) (a) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, **2000**. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, **1999**. (c) Brar, A.; Vankar, Y. *Tetrahedron Lett.* **2006**, *47*, 9035. (d) Navath, R. S.; Pabbisetty, K. B.; Hu, L. *Tetrahedron Lett.* **2006**, *47*, 389.
(2) Xiao, X.; Ngu, K.; Choa, C.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 6968.
(3) (a) Ravinder, K.; Reddy, A. V.; Krishnaiah, P.; Ramesh, P.; Ramakrishna, S.; Laatsch, H.; Venkateswarlu, Y. *Tetrahedron Lett.* **2005**, *46*, 5475. (b) Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701.
(4) (a) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296. (b) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 510. (c) Basel, Y.; Hassner, A. *J. Org. Soc.* **2000**, *65*, 6368. (d) Handy, S. T.; Sabatini, J. J.; Zhang, Y.; Vulfova, I. *Tetrahedron Lett.* **2004**, *45*, 5057. (e) Lutz, C.; Lutz, V.; Knochel, P. *Tetrahedron* **1998**, *54*, 6385. (f) Khalil, E. M.; Subasinghe, N. L.; Johnson, R. L. *Tetrahedron Lett.* **1996**, *37*, 3441. (g) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, 4393. (h) Einhorn,

J.; Einhorn, C.; Luche, J. L. *Synlett* **1991**, 37. (i) Guibe-Jampel, E.; Wakselman, M. *Chem. Commun.* **1971**, 267. (j) Sikchi, S. A.; Hultin, P. G. *J. Org. Chem.* **2006**, *71*, 5888.

(5) (a) Reddy, M. S.; Narender, M.; Nageswar, Y. V. D.; Rama Rao, K. *Synlett* **2006**, 1110. (b) Bartoli, G.; Basco, M.; Locatelli, M.; Marcantoni, E.; Massaccesi, M. *Synlett* **2004**, 1794. (c) Heydari, A.; Hosseini, S. E. *Adv. Synth. Catal.* **2005**, *347*, 1929. (d) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Radha Krishna, P. *Tetrahedron Lett.* **2004**, *45*, 6963. (e) Pandey, R. K.; Ragade, S. P.; Upadhyay, R. K.; Dongare, M. K.; Kumar, P. *ARKIVOC* **2002**, *(vii)*, 28. (f) Chankeshwara, S. V.; Chakraborti, A. K. *Tetrahedron Lett.* **2006**, *47*, 1087. (g) Suryakiran, N.; Prabhakar, P.; Reddy, S. T.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 8039.

(6) Niimi, L.; Serita, K. J.; Hiraoka, S.; Yokozawa, T. *Tetrahedron Lett.* **2000**, *41*, 7075.

(7) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.

(8) General Procedure: To Boc_2O (1 mmol) that was being magnetically stirred in oven-dried glassware at r.t. was added the amine (1 mmol). Rapid heat evolution and bubbling was then observed. The mixture was stirred until completion of the reaction. The product was purified using silica gel column chromatography eluting with hexane–EtOAc (5:1) to afford the corresponding *N*-Boc protected product. All of the products are known and were characterized by comparison of their spectral data with those of authentic samples.

(9) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283.