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Lithium Perchlorate-Catalyzed Boc Protection of Amines and Amine Derivatives

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Dedicated to Professor Abdoljalil Mostashari on the occasion of his 66th birthday.

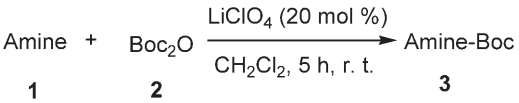
Abstract: A new mild and chemoselective method for mono-*N*-protection of amines and amine derivatives as *tert*-butoxycarbonyl derivatives is reported. The reaction proceeds with lithium perchlorate (20 mol %) and pyrocarbonates, and shows general applicability. The catalytic action of $LiClO_4$ is specific for the activation of Boc_2O, thus acid-sensitive functionalities of the starting materials remain unchanged in the protection process. This procedure works well for sterically hindered primary amine as well as electron-deficient primary arylamines, primary and secondary amino alcohols, α-amino acid esters, hydroxylamines, hydrazines and sulfonamides.

Keywords: amine protection; Boc derivatives; di-*tert*-butyl pyrocarbonate, lithium perchlorate

The development of mild and selective methods for the protection of amine groups is important for organic synthesis.[1]. Due to its stability towards catalytic hydrogenolysis and extreme resistance towards basic and nucleophilic reactions, the *tert*-butoxycarbonyl (abbreviated Boc or *t*-Boc) group is one of the most useful functions for the protection of amines.[2] Removal of the Boc protecting group is conveniently and easily carried out with CF_3COOH within 5–10 min at room temperature. Cheaper acids such as 3 M HCl in EtOAc or 10% H_2SO_4 in dioxane might be considered for large-scale deprotection. The stability of the Boc group makes it an ideal orthogonal partner for benzyl esters and carbamates which are used in peptide synthesis. The commercially available di-*tert*-butyl pyrocarbonate (Boc_2O) is an efficient reagent for the clean and rapid introduction of the Boc-protecting group at the amine functionality.[3] Although alkylamines are well known to give the mono-protected derivatives by the action of Boc_2O, without the assistance of any catalyst, the analogous reactions of some poorly reactive primary and secondary arylamines proceed sluggishly.[4] Moreover, when a primary arylamine is able to react, various side reactions such as biscarbamoylation or the formation of isocyanates as well as urea can also occur.[5] Due to the very attractive nature of the *N*-Boc group, there have been many attempts to find alternative methodologies for this reaction which do not suffer the severe drawbacks of the classical procedures, most of which are carried out in the presence of a base.[6] The use of Lewis acid catalysts to effect the above type of transformation is rare.[7] It is difficult to extend the Lewis acid-catalyzed Boc protection of amines, because the strong affinity of many Lewis acids for amino groups does not allow regeneration of the Lewis acids in the reaction.[8] Moreover, it should be noted that most Lewis acids cannot used in this reaction since they are decomposed or deactivated by the amines and amine derivatives. Even when the desired reactions proceed, because the acids are trapped by nitrogen, more than the stoichiometric amounts of Lewis acids are needed.[9]

In the past few years, lithium perchlorate has been widely exploited as a Lewis acid promoter in various organic transformations.[10] Furthermore, lithium perchlorate is found to retain its activity even in the presence of nitrogen-containing compounds.[11] This prompted us to use this catalyst for the synthesis of *N*-Boc protected amines. Herein we report that $LiClO_4$ serves as an excellent catalyst for the selective *tert*-butoxycarbonylation of amines.

The substrates examined in our studies and the results obtained are summarized in Scheme 1. Thus, the present procedure to introduce the *N*-Boc protecting group is quite general as a wide range of structurally varied amines such as open chain, cyclic, aromatic, heteroaromatic amines as well as α-amino alcohols and α-amino acid esters underwent reaction smoothly with Boc_2O. The method can be applied for the conversion of low reactive amine, such as 4-nitroaniline, as well as the sterically hindered *tert*-butylamine, to the corresponding *N*-Boc derivatives. Similarly, with 1,2-phenylenediamine the mono-*N*-Boc protected product was obtained in a



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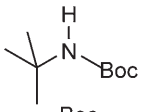
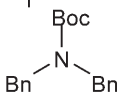
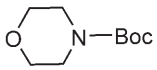
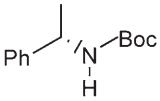
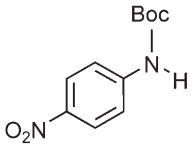
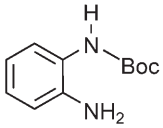
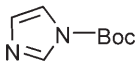
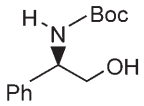
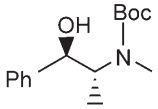
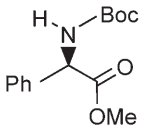
a		80
b		90
c		86
d		85
e		74
f		80
g		73
h		84
i		87
j		88

[a] Yields of pure products isolated by column chromatography.

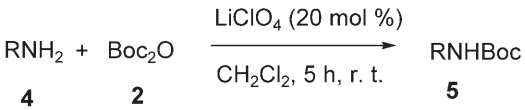
Scheme 1. $LiClO_4$ (20 mol %)-catalyzed protection of amines.

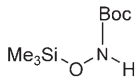
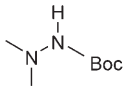
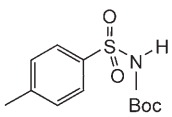
reasonably good yield. However, reaction of 2-aminoaniline with Boc_2O (1.5 equivs.) in MeCN at room temperature afforded the *N,N′*-di-Boc product in 95% yield after 24 h.[7a] The use of Boc_2O in the presence of 0.5 equivs. of 4-(dimethylamino)pyridine and 2-aminoaniline afforded 1,3-di-Boc-benzimidazolidinone in 50% yield and 50% of starting amine was recovered.[5a]

In a further study, an amino acid ester was converted to the corresponding *N*-Boc ester under similar reaction conditions. It is noteworthy that the reaction is chemoselective in the case of 2-phenylglycinol and ephedrine as the amine, where the *N*-Boc protected products were obtained as the sole products and neither *O*-Boc nor oxazolidinone derivatives were observed (by NMR). Although alcohols are known to react with Boc_2O in the presence of DMAP to give *O*-Boc derivatives together with symmetrical carbonates,[12] in the above cases no *O*-Boc or oxazolidinone derivatives were observed (by NMR). Another notable feature of the reaction is that even a secondary amine reacted smoothly to afford the product in high isolated yield.

To extend the synthetic potential this novel method of chemoselective protection of amines, we also examined its efficiency in reactions with hydroxylamines, hydrazines and sulfonamides. As shown in Scheme 2, the corresponding mono-*N*-Boc compounds were obtained in good isolated yields.

In summary, a new, simple and efficient method for the monoprotection of primary aliphatic and aromatic amines, secondary amines, 1, 2-diamines, as well as heteroaromatic amines, amino alcohols, α-amino acid esters, hydroxylamines, hydrazines and sulfonamides as *N*-Boc derivatives has been developed. The noteworthy feature of this methodology is that substrates with labile functionalities, such as esters, are compatible with the reaction conditions. The protection reaction is chemoselective: the amine is exclusively protected in the presence of an alcohol group. It is important to highlight that, in the case of primary amines or amine derivatives, any side reaction, such as formation of bis-Boc derivatives, isocyanates or ureas, were never observed, as verified by ^{1}H-NMR spectroscopy of the crude products.



	Product	Yield **5** [%][a]
a		76
b		78
c		88

[a] Yields of pure isolated products.

Scheme 2. $LiClO_4$ (20 mol %)-catalyzed protection of amine derivatives.

Moreover, this protocol appears to be competitive and in some cases superior to previously reported procedures that work under basic conditions. For example, in the case of *N*-Boc-4-nitroaniline (**3e**, Table 1) we obtained a good yield in 5 hours at room temperature, while other procedure failed or required long times or very harsh reaction condition (14 h, 50%).[7b]

Experimental Section

General Procedure for Preparation of *N*-Boc-Amines and Amine Derivatives

To a mixture of Boc_2O (437 mg, 2 mmol) and $LiClO_4$ (43 mg, 20 mol %) in 4 mL of CH_2Cl_2 was added 2 mmol of amine or amine derivative. After stirring for 5 h at room temperature, the resulting suspension was filtered and the filtrate concentrated on a rotary evaporatur to afford the crude product. The product was purified by flash chromatography (hexane-ethyl acetate). ^{1}H-NMR, ^{13}C-NMR, IR spectra were entirely consistent with the assigned structures. Spectroscopic data for selected examples are given below.

3a: IR (neat): $\nu = 3420$, 2950, 1799, 1762, 1680, 1451, 13671207, 1113, 1066 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta =$ 1.6 (s, 9H), 2.2 (s, 9H), 3.5 (bs, 1H); ^{13}C NMR (22.5 MHz): $\delta = 27.4$ (CH_3), 29.9 (CH_3), 50.1 (C), 85.1 (C), 147.1 (CO).

3b: IR (neat): $\nu = 2920$, 1685, 1445, 1403, 1230, 1161, 1112, 872 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.5$ (s, 9H), 4.5 (bs, 4H), 7.7–7.3 (m, 10H); ^{13}C NMR (22.5 MHz): $\delta = 28.1$ (CH_3), 48.9 (C), 80 (CH_2), 127.4 (CH), 127.9 (CH), 128.7 (CH), 138.2 (C), 156.3 (CO).

3c: IR (neat): $\nu = 2995$, 1683, 1448, 1413, 1360, 1277, 1246, 1166, 1123, 1083, 860 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta =$ 1.5 (s, 9H), 3.37 (t, 4H), 3.52 (t, 4H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 28.1$ (CH_3), 43.7 (C), 66.6 (CH_2), 79.9 (CH_2), 155 (CO).

3d: IR (neat): $\nu = 3385$, 3030, 1679, 1507, 1441, 1390, 1365, 1307, 1244, 1167, 1070, 749, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.42$ (s, 9H), 1.41 (d, 3H), 4.8 (bs, 2H , NH and CH), 7.22–7.34 (m, 5H); ^{13}C NMR (122 MHz, $CDCl_3$): $\delta =$ 22.6 (CH_3), 28.1 (CH_3), 50.2 (C), 79.4 (CH), 125.8 (CH), 12.7 (CH), 128.5 (CH), 144.0 (C), 155.1 (CO).

3e: IR (neat): $\nu = 3380$, 2990, 2965, 1718, 1588, 1522, 1492, 1461, 1365, 1305, 1281, 1220, 1106, 840 cm^{-1}; ^{1}H NMR (90 MHZ, $CDCl_3$): $\delta = 1.5$ (s, 9H), 4.5 (bs, 1H), 6.7 (d, 2H), 8.1 (d, 2H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 29.1$ (CH_3), 51.5 (C), 113.0 (CH), 125.3 (CH), 126.3 (C), 137.6 (C), 152.7 (CO).

3f: IR (neat): $\nu = 3445$, 3350, 3300, 3120, 2975, 1677, 1622, 1587, 1513, 1484, 1444, 1365, 1294, 1248, 1159, 1049, 740 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$); $\delta = 1.5$ (s, 9H), 3.8 (bs, 2H), 6.4 (bs, 1H), 6.7–7.4 (m, 4H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta =$ 28 (CH_3), 80.4 (C), 117.8 (CH), 119.8 (CH), 124.9 (CH), 125.0 (CH), 126.0 (C), 139.7 (C), 154.2 (CO).

3g: IR (neat): $\nu = 3125$, 2975, 1747, 1464, 1379, 1315, 1291, 1241, 1150, 1089, 995, 833, 765, 644 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$): $\delta = 1.5$ (s, 9H), 7.2 (s, 1H), 7.37 (s, 1H), 8.1 (s, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 27.6$ (CH_3), 85.6 (C), 117.2 (CH), 130.3 (CH), 137.2 (CH), 147.4 (CO).

3h: IR (neat): $\nu = 3345$, 3305, 2895, 1663, 1541, 1363, 1285, 1176, 1049, 1023, 753, 694 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.35$ (bs, 1H, NH), 1.47 (bs, 1H, OH), 1.5 (s, 9H), 3.8 (d, 2H), 4.7 (t, 1H), 7.2–7.6 (m, 5H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 27.9$ (CH_3), 56.8 (C), 66.6 (CH), 79.9 (CH_2), 126.7 (CH), 127.8 (CH), 128.8 (CH), 139.8 (C), 156.5 (CO).

3i: IR (neat): $\nu = 3430$, 3060, 2945, 2925, 1798, 1741, 1660, 1469, 1437, 1398, 1368, 1331, 1249, 1148, 1044, 754, 693 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.3$ (d, 3H), 1.7 (s, 9H), 2.6 (s, 3H), 3.2 (bs, 1H), 4.1 (q, 1H), 4.7 (d, 1H, CH), 7.1–7.5 (m, 5H); ^{13}C NMR (22.5 MHz): $\delta = 12.7$ (CH_3), 27.1 (CH_3), 28.0 (CH_3), 30.8 (CH), 57.4 (CH), 79.6 (C), 126.5 (CH), 127.6 (CH), 128.2 (CH), 142.5 (C), 156.5 (CO).

5a: IR (neat): $\nu = 3305$, 2970, 1700, 1451, 1398, 1366, 1277, 1247 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 0.13$ (s, 9H), 1.5 (s, 9H), 7.1 (bs, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 3.25$ (CH_3), 29.6 (CH_3), 83.4 (C), 160 (CO).

5b: IR (neat): $\nu = 3245$, 2970, 2850,1706, 1505, 1441, 1364, 1242, 1180, 1094 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.5$ (s, 9H), 2.7 (s, 6H), 5.5 (bs, 1H); ^{13}C-NMR (22.5 MHz, $CDCl_3$): $\delta = 28.0$ (CH_3), 47.5 (CH_3), 80.2 (C), 154.7 (CO).

5c: IR (neat): $\nu = 3360$, 3340, 3125, 2990, 2980, 1799, 1755, 1452, 1371, 1302, 1208, 1151, 1116, 1066, 767, 661 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.5$ (s, 9H), 2.2 (s, 3H), 5.2 (bs, 1H), 7.3 (d, 2H), 7.8 (d, 2H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 21.5$ (CH_3), 27.4 (CH_3), 85.1 (C), 126.4 (CH), 129.4 (CH), 139.2 (C), 143.5 (C), 146.7 (CO).

Acknowledgements

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References and Notes

[1] a) P. J. Kociensky, in: *Protecting Groups*; Georg Thieme Verlag, Stuttgart, New York, **2000**; b) T. W. Greene, P. G. M. Wuts, in: *Protective Group in Organic Synthesis*, 3rd edn., John Wiley and Son, New York, **1999**; c) J. Podlech, in: *Houben-Weyl, Methods of Organic Chemistry*, 4th edn., Vol. E22, (Eds.: M. Goodman, A. Felix, L. Moroder, C. Toniolo), Georg Thieme Verlag, Stuttgart, **2001**, pp. 86–100.

[2] a) E. Wuensch, in: *Houben-Weyl, Methods of Organic Chemistry*, 4th edn., Vol. 15/1, (Eds.: E. Müller, O. Bayer, H. Meerwein, K. Ziegler), Georg Thieme Verlag, Stuttgart, **1974**, p. 46; b) X. Yi. Xiuo, K. Ngu, C. Choa, D. V. Patel, *J. Org. Chem.* **1997**, *62*, 6968.

[3] a) L. Moroder, A.Hallett, E. Wuensch, O. Keller, G. Wersin, *Hoppe Seyler's Z. Physiol. Chem*. **1976**, *357*, 1651; b) B. M. Pope, X. Yamamoto, D. S. Tarbell, *Org. Synth. Coll. Vol. VI*, **1988**, 418.

[4] a) S. Darnbrough, M. Mervic, S. M. Condon, C. J. Burns, *Synth. Commun*. **2001**, *31*, 3273; b) T. A. Kelly, D. W. McNeil, *Tetrahedron Lett.* **1994**, *35*, 9003.

[5] a) Y. Basel, A. Hassner, *J. Org. Chem*. **2000**, *65*, 6368; b) H.-J. Knoelker, T. Braxmeier, G. Schlechtingen, *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2497; c) H.-J. Knoelker, T. Braxmeier, G. Schlechtingen, *Synlett* **1996**, 502.

[6] For examples, see: a) L. Grehn, U. Gagnarsson, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 510; b) H. J. Knoelker, T. Braxmeier, *Tetrahedron Lett*. **1996**, *37*, 5861; c) C. Lutz, V. Lutz, P. Knochel, *Tetrahedron* **1998**, *54*, 6385; d) S. W. Bailey, R. Y. Chandrasekaran, J. E. Ayling, *J. Org. Chem*. **1992**, *57*, 4470; for highly sterically hindered substrates as well as electron deficient arylamines these methods often give poor yields and are generally not satisfactory.
[7] a) F. Porta, S. Cenini, M. Pizzotti, C. Crotti, *Gazz. Chim. Ital*. **1985**, *115*, 275; b) G. Bartoli, M. Bosco, M. Locatelli, E. Marcantoni, M. Massaccesi, *Synlett* **2004**, *10*, 1794; c) R. K. Pandey, S. P. Ragade, R. K. Upadhyay, M. K. Dongare, P. Kumar, *Arkivoc* **2002**, 28.
[8] L. Niimi, K.-J. Serita, S. Hiraoka, T. Yokozawa, *Tetrahedron Lett*. **2000**, *41*, 7075.
[9] a) S. Kobayashi, M. Araki, M. Yasuda, *Tetrahedron Lett*. **1995**, *36*, 5773; b) S. Kobayashi, R. Akiyama, M. Kawamura, H. Ashitani, *Chem. Lett*. **1997**, 1039.
[10] For a review, see: A. Heydari, *Tetrahedron*, **2002**, *58*, 6777, and references cited therein.
[11] a) J. S. Yadav, B. V. S. Reddy, Ch. V. S. R. Murthy, J. M. Kumar, Ch. Madan, *Synthesis* **2001**, 783; b) J. S. Yadav, B. V. S. Reddy, R. Srinivas, Ch. Madhuri, T. Ramalingam, *Synlett* **2001**, 240.
[12] V. F. Pozdnev, *Int. J. Pept Protein Res.* **1992**, *40*, 407.

