A Lewis Acid-Mediated Protocol for the Protection of Aryl Amines as their Boc-Derivatives

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Abstract: A new protocol of protection of poorly reactive aryl amines and functionalized amines with Boc_2O in the presence of $Zn(ClO_4)_2 \cdot 6H_2O$ as the catalyst is reported. The catalytic action of $Zn(ClO_4)_2 \cdot 6H_2O$ is specific for the activation of the pyrocarbonates, thus acid sensitive functionalities and stereochemical configurations of the starting materials remain unaltered in the protection process.

Key words: protection, Lewis acid, zinc perchlorate, aryl amines, Boc-derivatives

The development of mild and selective methods for the protection and deprotection of functional groups continues to be an important tool in the synthetic chemistry of polyfunctional molecules.[1]

Protection of amino groups is often required during the synthesis of peptides, amino acids and other natural products. Among the various amine protecting groups, the *t*-butoxycarbonyl (Boc) is one of the most used, owing to its stability towards nucleophiles and strong basic conditions and because of its easy removal.[1]

Various reagents and methodologies have been developed over the years to introduce this group using Boc_2O. Most of them are carried out in the presence of a base (DMAP,[2] aq NaOH,[1,3] NaHMDS[4]). Although alkyl amines are known to give the mono-protected derivative by reaction with Boc_2O without the assistance of any catalyst, the analogous reaction of primary and secondary aryl amines proceeds sluggishly, owing to their reduced nucleophilicity.[4,5] Moreover, when an aryl amine is able to react, various side reactions, such as biscarbamoylation or the formation of isocyanates or ureas, can occur.[2a,4]

On the other hand, methods using a Lewis acid catalyst to perform this protection are still scarce. For example, a recently reported methodology employs an yttrium–zirconium based strong Lewis acid catalyst, whose preparation is, however, quite elaborate.[6]

We report here the first example of a protection methodology that employs a simple and mild Lewis acid as the catalyst, which is specific for the activation of Boc_2O.

In the last few years, we were interested in the use of anhydrous metallic perchlorates as Lewis acid promoters in various organic transformations.[7] $LiClO_4$ and $Mg(ClO_4)_2$ showed increased efficiency if hot-dried under vacuum before use. Owing to the potential hazards connected with the heating of such salts,[8] we focused our attention to more efficient perchlorates, active even in the presence of water. In fact, $Zn(ClO_4)_2 \cdot 6H_2O$ was recently found to behave as a powerful catalyst in the acylation of alcohols[9] and in the synthesis of N-substituted β-enamino esters.[10]

It has been recently reported that perchlorate salts activate bidentate compounds such as anhydrides by forming a cyclic complex.[11] It may be expected that an analogous activation can be exerted on pyrocarbonates, such as Boc_2O.

As a part of our research program devoted to the development of new Lewis acid systems, we report here that $Zn(ClO_4)_2 \cdot 6H_2O$ can act as a powerful catalyst for the protection of aryl amines as mono-Boc-derivatives. Moreover, $Zn(ClO_4)_2 \cdot 6H_2O$ showed to be able to promote the reaction of various functionalized alkyl amines with Boc_2O to give the *N*-Boc protected derivative.

Preliminary experiments were carried out on aniline **1a** in order to find the best reaction conditions. The reactions were carried out in various solvents with 1 equivalent of Boc_2O, and monitored by GC-MS. The results reported in Table 1 refer to the conversion after 4.5 hours. Although the differences are not remarkable, dichloromethane proved to be the best solvent. Moreover, an increased amount of the catalyst, from 2–10 mol%, does not improve conversion percentages.[12]

Afterwards, the methodology of protection was applied to various substrates, varying the catalyst amounts from 2–5% and using a slight excess of Boc_2O (1.3 equiv). The best-obtained results are reported in Table 2.[13] The choice of the solvent was determined by the peculiar solubility of the substrates. In some cases, if the products did not solidify during the course of the reaction and the mixture could be continuously stirred, the protection reaction was carried out under solvent free conditions.

In the cases of low reactive substrates, such as nitroaniline and 3-aminobenzoic acid (Table 2, entries 4 and 9), the best results were obtained increasing the reaction temperature, which, in any case, cannot get over 50 °C to avoid the Boc_2O decomposition.

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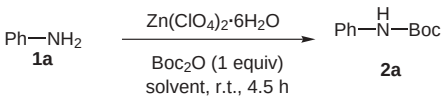
Table 1 Protection of Aniline as the Boc-Derivative under Various Conditions



Entry	Cat. (mol%)	Solvent[a]	Yields (%)[b]
1	–	THF	50
2	2	THF	65
3	2	Et_2O	70
4	2	*t*-BuOH	72
5	2	CH_2Cl_2	75
6	5	CH_2Cl_2	78
7	10	CH_2Cl_2	78

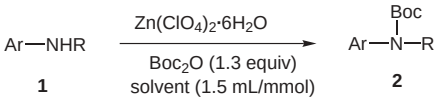
[a] The amount of the solvent was 1.5 mL/mmol of substrate.
[b] Conversion determined by GC-MS analysis after 4.5 h.

Although an excess of Boc_2O is often used to complete the protection reaction, we generally obtained high yields with a slight excess of di-*t*-butyl dicarbonate (1.3 equiv). Moreover, it is important to highlight that any side reaction, such as biscarbamoylation or the formation of isocyanates or ureas, was never observed, as verified by GC-MS and ^1H NMR analysis of the crude of the reactions.

Reaction rates and yields are governed by the nucleophilicity of the amines. In particular, activated anilines give the Boc-derivatives in very good yields (Table 2, entry 2, 3, and 5). On the other hand, deactivated substrates give the protected derivative with acceptable results considering their low reactivity (Table 2, entries 4, 9). Also secondary aryl amines, such as *N*-methyl aniline, can be protected in high yields (Table 2, entry 13).

The protection reaction is chemoselective: the amine is exclusively protected in the presence of amide, acid, indole and thiol groups.

Table 2 Protection of Aryl Amines as Boc-Derivatives[a]



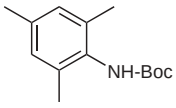
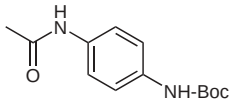
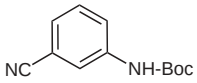
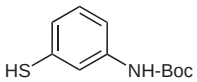
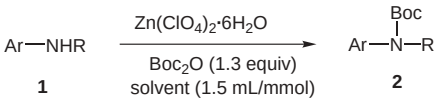
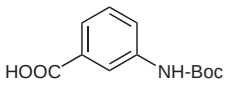
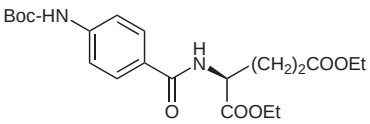
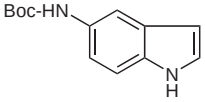
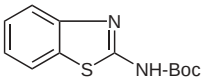
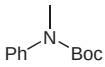
Entry	Product	Cat. (mol%)	Solvent	Time (h)	Yields (%)[b]
1	Ph-NH-Boc **2a**	5	CH_2Cl_2	12	92
2	*p*-MeO-Ph-NH-Boc **2b**	5	*t*-BuOH	6	99
3	*m*-MeO-Ph-NH-Boc **2c**	5	*t*-BuOH	10	99
4	*p*-NO_2-Ph-NH-Boc **2d**	5	CH_2Cl_2	14	50[c,d]
5	 **2e**	5	CH_2Cl_2	48	94
6	 **2f**	5	*t*-BuOH	72	95
7	 **2g**	2	–	89	86
8	 **2h**	2	–	9	90

Table 2 Protection of Aryl Amines as Boc-Derivatives[a] (continued)



Entry	Product	Cat. (mol%)	Solvent	Time (h)	Yields (%)[b]
9	 **2i**	5	*t*-BuOH	41	68[e,f]
10	 **2l**	5	CH_2Cl_2	164	94
11	 **2m**	5	*t*-BuOH	21	90
12	 **2n**	5	CH_2Cl_2	168	83
13	 **2p**	2	–	30	89

[a] Unless otherwise mentioned, reactions were carried out with Boc_2O (1.3 equiv) in the presence of $Zn(ClO_4)_2·6H_2O$ (2–5 mol%) in the appropriate solvent (1.5 mL/mmol of substrate) at r.t.
[b] Yields of pure products isolated by column chromatography.
[c] Reaction carried out at reflux.
[d] Starting material was also recovered (42%).
[e] Reaction was carried out at 50 °C.
[f] Starting material was also recovered (23%).

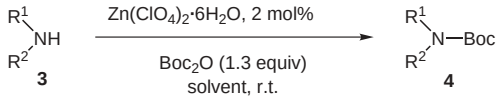
The methodology has been extended to benzylic and functionalized alkyl amines.

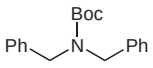
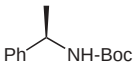
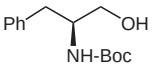
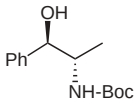
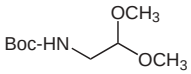
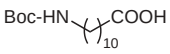
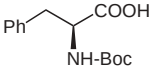
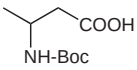
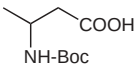
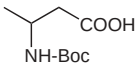
The reaction works well with primary and secondary benzyl amines (Table 3, entries 1–4). Also in these cases a complete chemoselectivity towards the amino group was observed: alcohols, acetals and acids remain unaffected during the reaction. Moreover, some general considerations can be outlined. Stereogenic centers do not undergo racemization or epimerization, (Table 2, entry 8 and Table 3, entries 3–6) as confirmed by the comparison of the experimental $[\alpha]_D$ with literature data. The methodology works also with amino acids which give the N-protected derivatives in good yields, provided that the aminic and the carboxylic function are distant each other (Table 2, entry 7, Table 3, entry 8). With α- and β-amino acids, in fact, a maximum of 43% yields is attained (Table 3, entry 9). Very likely, under these reaction conditions, the amino acid exists almost completely in the zwitterionic form, so that the aminic group is unreactive towards Boc_2O. Even the addition of a relatively weak base such as Et_3N or pyridine does not increase the yields (Table 3, entries 10, 11).

In conclusion, $Zn(ClO_4)_2·6H_2O$ shows a powerful catalytic activity in promoting the protection of aryl amines as Boc-derivatives. The present method is the first example employing a cheap and easy available Lewis acid as catalyst to perform such protection. Our methodology works with various aromatic amines under mild conditions and the protecting agent is used only in a small excess.

Moreover, this protocol appears to be competitive and in some cases superior to previously reported procedures that work under basic conditions. In particular, with activated *m*-methoxy aniline **2c** (Table 2, entry3) our results are superior to those obtained with NaHDMS procedure[4] (99% vs. 88% yields). In the case of *N*-Boc-2,4,6-trimethylaniline (**2e**, Table 2, entry 5) we obtained excellent yields in 10 hours at room temperature, while other procedures failed[4] or required long times[2a] or very hard reaction conditions (60 h at 82%).[2c]

Table 3 Protection of Amines as Boc-Derivatives[a]



Entry	Product	Solvent	Time (h)	Yields (%)[b]
1	$PhCH_2$-NH-Boc **4a**	–	5.5	92
2	 **4b**	–	5.5	93
3	 **4c**	–	2.5	97
4	 **4d**	CH_2Cl_2	43	87[c]
5	 **4e**	CH_2Cl_2	6	94[c]
6	 **4f**	–	16	90
7	 **4g**	*t*-BuOH	26	68[c,d]
8	 **4h**	*t*-BuOH	50	43[c,d]
9	 **4i**	*t*-BuOH	20	41[c,d]
10	 **4i**	*t*-BuOH	20	33[c,d,e]
11	 **4i**	*t*-BuOH	20	7[c,d,f]

[a] Unless otherwise mentioned, reactions were carried out with Boc_2O (1.3 equiv) in the presence of $Zn(ClO_4)_2·6H_2O$ (2 mol%) in the appropriate solvent (1.5 mL/mmol of substrate) at r.t.
[b] Yields of pure products isolated by column chromatography.
[c] Reaction was carried out with 5 mol% of catalyst.
[d] Reaction was carried out at 50 °C.
[e] In the presence of 1 equiv of Et_3N.
[f] In the presence of 1 equiv of pyridine.

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(9) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Sambri, L. *Eur. J. Org. Chem.* **2003**, 4611.
(10) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 239.
(11) Chakraborti, A. K.; Sharma, L.; Gulhane, R.; Shivani, *Tetrahedron* **2003**, *59*, 7661.
(12) The reaction was also carried out by changing the Zn(II) counterion of the potentially explosive $Zn(ClO_4)_2·6H_2O$ using $Zn(OAc)_2$. We obtained worse results, only a 60% conversion after 4.5 h in CH_2Cl_2 at r.t. was detected.
(13) **Representative Experimental Procedure. Synthesis of *tert*-Butyl *N*-Phenylcarbamate (2a):** To a round-bottom flask were added $Zn(ClO_4)_2·6H_2O$ (28 mg, 0.075 mmol), CH_2Cl_2 (2.25 mL), aniline (0.14 g, 1.50 mmol) and Boc_2O (0.43 g, 1.95 mmol, 1.3 equiv). The reaction mixture was stirred at r.t. for 12 h. After addition of 5 mL of CH_2Cl_2, the solution was washed with H_2O. The organic layer was dried over $MgSO_4$ and concentrated at reduced pressure. The crude product was purified by column chromatography on silica gel. Compounds **2a**, **2b**, **2i**, **2m**, **4a**, **4d** and **4i** are commercial products; **2c**,[4] **2d**[14], **2e**,[4] **2p**[15], **4c**[16], **4e**[17], **4g**[18] and **4h**[19] are known compounds. Spectroscopic data for selected examples follow. ***tert*-Butyl *N*-[4-(Acetylamino)phenyl] Carbamate (2f)**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, *t*-Bu), 2.15 (s, 3 H, CH_3), 6.50 (br s, 1 H, NH), 7.20 (br s, 1 H, NH), 7.26–7.35 (m, 2 H, Ph), 7.40–7.45 (m, 2 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7 (CH_3), 26.9 (CH_3), 79.8 (C), 116.3 (CH), 118.8 (CH), 133.3 (C), 134.3 (C), 152.7 (C), 168.4 (C). ***tert*-Butyl *N*-(3-Sulfanylphenyl) Carbamate (2h)**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51

(s, 9 H, *t*-Bu), 3.46 (s, 1 H, SH), 6.60 (br s, 1 H, NH), 6.90–6.95 (m, 1 H, Ph), 7.00–7.05 (m, 1 H, Ph), 7.05–7.10 (m, 1 H, Ph), 7.40 (br s, 1 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (CH_3), 80.7 (C), 115.5 (CH), 118.7 (CH), 123.6 (CH), 129.4 (CH), 131.8 (C), 138.9 (C), 152.5 (C). **Diethyl (2*S*)-2-(4-[(*tert*-Butoxycarbonyl)amino] Benzoylamino) Pentanedioate (2l)**: $[\alpha]_D$ = 13 (*c* 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, 3 H, J_{HH} = 7.1 Hz, CH_3), 1.30 (t, 3 H, J_{HH} = 7.2 Hz, CH_3), 1.52 (s, 9 H, *t*-Bu), 2.05–2.60 (m, 4 H, 2 CH_2), 4.10–4.20 (m, 2 H, CH_2), 4.20–4.30 (m, 2 H, CH_2), 4.75–4.80 (m, 1 H, CH), 6.80 (br s, 1 H, NH), 7.0 (br d, 1 H, J_{HH} = 7.2 Hz, NH), 7.40–7.45 (m, 2 H, Ph), 7.75–7.80 (m, 2 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 14.1 (CH_3), 27.1 (CH_2), 28.2 (CH_3), 30.5 (CH_2), 52.3 (CH), 60.7 (CH_2), 61.6 (CH_2), 80.9 (C), 117.2 (CH), 127.6 (C), 128.2 (CH), 141.8 (C), 152.3 (C), 166.5 (C), 172.0 (C), 173.2 (C).

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