

Facile *N*-*tert*-butoxycarbonylation of amines using $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ as a mild and efficient catalyst under solvent-free conditions^{☆☆☆}

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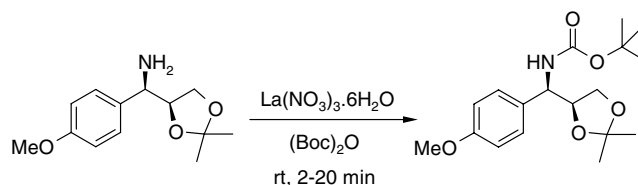
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Abstract—Facile *N*-*tert*-butoxycarbonylation of amines is described by the treatment of various primary, secondary, benzylic and aryl amines with di-*tert*-butyl dicarbonate in the presence of catalytic amounts of $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ under solvent-free conditions at room temperature to afford *N*-*tert*-butylcarbamates in excellent yields.

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Functional group protection/deprotection strategies are central to target molecule synthesis. The protection of amines is one of the most fundamental and useful transformations in organic synthesis, especially in peptide synthesis.¹ Among the protecting groups for amines, *N*-*tert*-butoxycarbonylation² is used frequently, because *N*-*tert*-butylcarbamates are stable in the presence of a wide range of nucleophiles under alkaline conditions and are very labile under mild acidic conditions liberating the parent amine.^{1a} Although, various base mediated methods are available for the preparation of *N*-*tert*-butylcarbamates using di-*tert*-butyl dicarbonate,^{3–11} there are only a few reports on the Lewis acid catalyzed reactions such as, ‘Yttria–Zirconia’ which needs long reaction times 3–48 h¹² and, very recently, ZrCl_4 , copper(II) tetrafluoroborate, InBr_3 and $\text{HClO}_4\text{–SiO}_2$ (Scheme 1).¹³

In the course of our on-going search for chemoselective reagents, our group has identified $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ as a mild and efficient catalyst for the chemoselective tetrahydropyranylation of primary alcohols,¹⁴ chemoselective deprotection of acetonides,¹⁵ synthesis of quinazolinones¹⁶ and the mild and efficient acetylation



Scheme 1.

of alcohols, phenols and amines with acetic anhydride.¹⁷ It has been observed that substrates containing other acid labile functional groups such as acetonides, TBDMS ethers, isopropylidene protected diols and *N*-*tert*-butylcarbamates were intact in the presence of $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$. Further, we report here that $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ is a mild and efficient catalyst for *N*-*tert*-butoxycarbonylation of amines using di-*tert*-butyl dicarbonate under solvent-free conditions.

The reaction of aniline (1 mmol) with di-*tert*-butyl dicarbonate (1.2 mmol) using $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (5 mol %) at room temperature rapidly gave the corresponding *N*-*tert*-butylcarbamate in a 100% yield (Table 1, entry 1). This success encouraged us to extend the generality of the reaction. In order to establish the scope of the catalytic activity of $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$, we carried out the reaction of various primary, secondary, benzylic and aryl amines (Table 1) with di-*tert*-butyl dicarbonate, which gave the corresponding *N*-*tert*-butylcarbamates in excellent yields. Furthermore, it was observed that when the

Keywords: $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$; Amines; *N*-*tert*-Butoxycarbonylation; Solvent-free conditions.

* Reactions using lanthanum(III) nitrate hexahydrate paper 5.

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Table 1. *N*-*tert*-Butoxycarbonylation of amines in the presence of La(NO₃)₃·6H₂O under solvent-free conditions

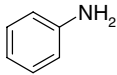
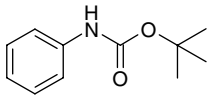
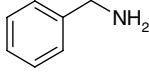
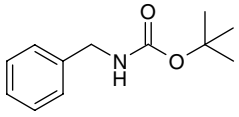
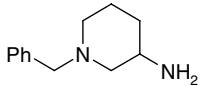
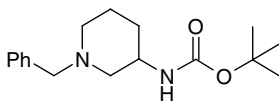

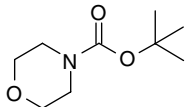
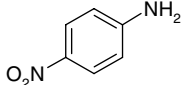
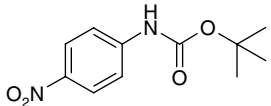
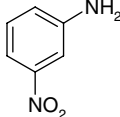
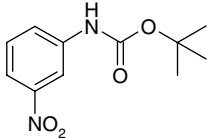
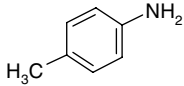
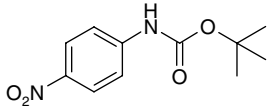
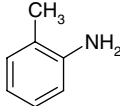
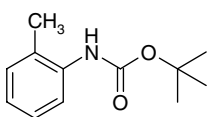
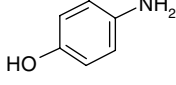
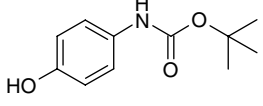
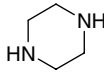
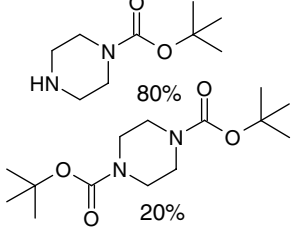
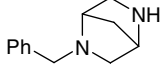
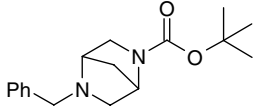
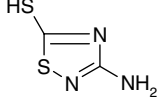
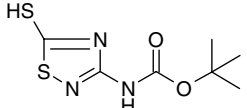
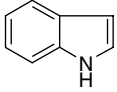
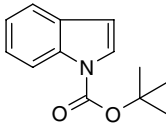
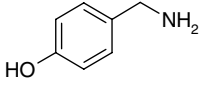
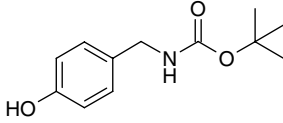
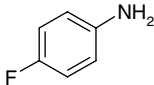
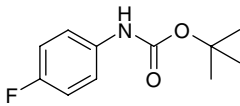
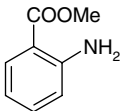
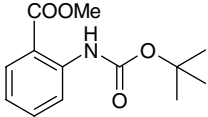
Entry	Substrate	Product ^a	Time (min)	Yield ^b (%)
1			2	100
2			2	98
3			3	95
4			2	100
5			3	95
6			3	98
7			3	98
8			2	100
9			3	98
10		 80% 20%	3	98
11			3	98
12				

Table 1 (continued)

Entry	Substrate	Product ^a	Time (min)	Yield ^b (%)
13			3	99
14		 	2	98
15			10	98
16			11	95
17			5	99
18			20	95
19			20	96
20			15	98
21			15	99

(continued on next page)

Table 1 (continued)

Entry	Substrate	Product ^a	Time (min)	Yield ^b (%)
22			10	99
23			05	98
24			05	99
25			05	99

^a All compounds were characterized by ¹H NMR and EIMS spectral data.

^b Isolated yields after column chromatography.

diamines were subjected to *N-tert*-butoxycarbonylation, a mono-*N-tert*-butylcarbamate was formed in a very good yield (entries 10 and 14). The *N-tert*-butylcarbamate is stable under the reaction conditions for 3–6 h at room temperature. From these results (Table 1) it is evident that La(NO₃)₃·6H₂O is an excellent catalyst for *N-tert*-butoxycarbonylation of amines under solvent-free conditions.

Typical experimental procedure: To a mixture of amine (1 mmol) and di-*tert*-butyl dicarbonate (1.2 mmol) was added finely powdered La(NO₃)₃·6H₂O (5 mol %) and the reaction mixture was stirred under solvent-free conditions at room temperature for an appropriate time (Table 1). After completion of the reaction as monitored by TLC, water 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, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography to afford the corresponding *N-tert*-butylcarbamate.

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