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Facile tert-Butoxycarbonylation of Alcohols, Phenols, and Amines using $BiCl_3$ as a Mild and Efficient Catalyst

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Facile *tert*-Butoxycarbonylation of Alcohols, Phenols, and Amines using $BiCl_3$ as a Mild and Efficient Catalyst

N. Suryakiran, P. Prabhakar, and Y. Venkateswarlu

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Abstract: Facile *tert*-butoxycarbonylation of alcohols, phenols, and amines is described by treatment of alcohols, phenols, and amines with di-*tert*-butyl dicarbonate in the presence of a catalytic amount of bismuth(III) chloride, a mild and efficient catalyst, at room temperature in excellent yields.

Keywords: alcohols, amine, $BiCl_3$, phenols, *tert*-butoxycarbonylation

1 INTRODUCTION

Organic reactions using reusable and water-tolerant catalysts have received much attention in recent years because they can be conveniently handled and removed from the reaction mixture, making the experimental procedure simple and ecofriendly.[1] On the other hand, organic reactions carried out in the absence of solvent also attract the attention of chemists because of ease of processing and environmental friendliness.

Among carbonic acid derivatives used as protecting groups, *tert*-butylcarbonates and *tert*-butylcarbamates are of great importance in organic chemistry[2] because they are stable to a wide range of nucleophiles in alkaline conditions and are very labile under moderately acidic conditions

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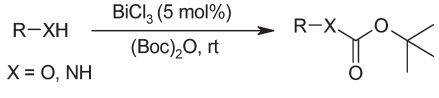
to give the parent alcohols and amines. *N-tert*-Boc derivatives are extensively used for protecting amino groups.[3–12] However, *O-tert*-Boc derivatives are less widely used for protection of alcohols, and they are restricted to aryl alcohols. Introduction of a *tert*-Boc group to alcohols is generally achieved by using di-*tert*-butyl dicarbonate in the presence of dimethyl amino pyridine (DMAP)[10] or *tert*-Boc transfer reactions using *tert*-Boc-imidazole[13] or *tert*-butoxycarbonyl-1,2-dihydroisoquinoline.[14] All these methods involve basic media or the presence of a Lewis base. However, Lewis acid–catalyzed *tert*-Boc protection of alcohols and amines is less thoroughly investigated.[15–20]

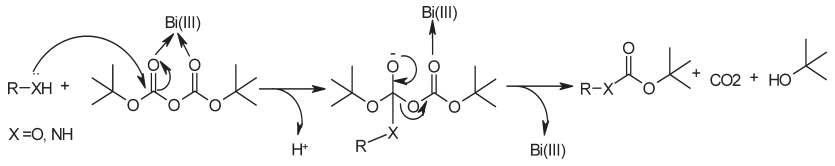
Recently, *N-tert*-Boc 3-amino pyrazoles and compounds of this class have proved to be efficient as ditipic proligands for metal salts.[21] However, the reported method involves long reaction times (16 h) at refluxing temperature in CH_3CN. Bismuth(III) chloride is relatively nontoxic, inexpensive, and insensitive to air, and no special care is required. It is used in various organic transformations as a mild and efficient Lewis acid catalyst.[22,23] Also, to the best of our knowledge, there is no report on the use of $BiCl_3$ for the *tert*-butoxycarbonylation of alcohols, phenols, or amines with di-*tert*-butyl dicarbonate. Recently we reported $BiCl_3$ as a mild and efficient Lewis acid catalyst for the synthesis of 2,3-unsaturated glycopyranosides,[24] chemoselective deprotection of acetonides,[25] and regioselective ring opening of aziridines with amines.[26] In continuation of our search for a chemoselective Lewis acid catalyst in the multistep synthesis of natural products, we observed that $BiCl_3$ can be utilized efficiently for the *tert*-butoxycarbonylation of alcohols and phenols with di-*tert*-butyl dicarbonate under solvent-free conditions.

2 RESULTS AND DISCUSSION

In this report (Scheme 1), we describe an efficient method for *tert*-butoxycarbonylation of alcohols, phenols, and amines. This method does not need expensive reagents or special care to exclude the moisture from the reaction medium. $BiCl_3$ is highly oxophilic, forms a labile bond with carbonyl oxygen of Boc anhydride, and initiates the formation of a C-X bond with alcohols, phenols, and amines (Scheme 2). During *O-tert*-butoxycarbonylation of phenols and alcohols using $BiCl_3$, the reaction conditions are very mild. Under the conditions of the reaction, labile protecting groups such as acetonides and Boc-protected amines are not affected, and Boc esters of alcohols formed neatly (e.g., entries 4, 11, and 16 in Table 1). We first examined the reaction of benzyl alcohol with di-*tert*-butyl dicarbonate in the presence of $BiCl_3$ (5 mol%) at room temperature, giving the corresponding *O-tert*-butylcarbonate



Scheme 1.



Scheme 2. Plausible mechanism.

in 98% yield (Table 1, entry 1). To optimize reaction conditions, we compared other Lewis acid catalysts, but the $BiCl_3$ (5 mol%) was found to be most effective under autosolvent conditions (Table 2). This success has encouraged us to extend the generality of the reaction to various primary, secondary, and aryl alcohols and phenols (Scheme 1, Table 1). Further, we extended the methodology to *N*-Boc protection of 3-amino pyrazoles using 5 mol% bismuth(III) chloride; they are also efficiently and smoothly converted into the corresponding *N*-Boc derivatives in good to excellent yields (Scheme 1, Table 3). Further, it is noticed that the *tert*-butoxycarbonylation of alcohols, phenols, and amines, is not a reversible reaction under reaction conditions even after 6 h at room temperature. From the forgoing results (Tables 1 and 3), it is evident that the $BiCl_3$ is an excellent catalyst for *tert*-butoxycarbonylation of alcohols, phenols, and amines, especially 3-amino pyrazoles.

Further, we have studied the reusability of the catalyst without any modification of reaction conditions. After completion of the reaction, water was added, and the product was extracted into ethyl acetate. The catalyst was recovered from the aqueous layer by evaporation under reduced pressure and reused without loss of its activity for six runs. From the foregoing results (Tables 1 and 3), it is evident that $BiCl_3$ is an efficient catalyst for *tert*-butoxycarbonylation of alcohols, phenols, and amines.

3 CONCLUSION

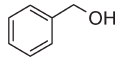
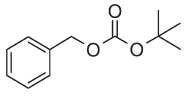
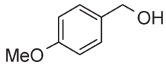
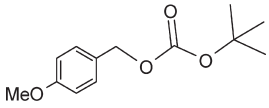
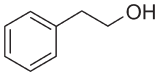
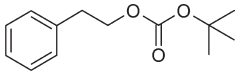
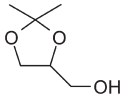
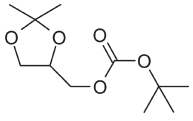
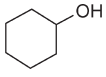
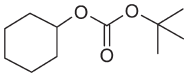
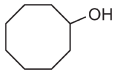
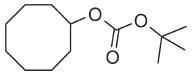
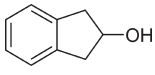
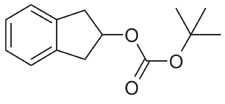
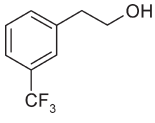
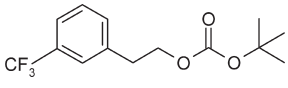
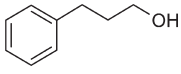
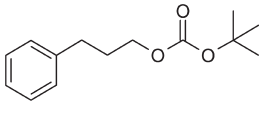
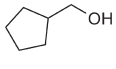
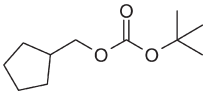
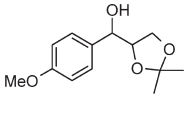
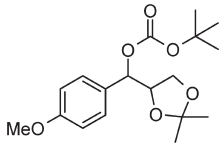
In conclusion, we have described a facile *tert*-butoxycarbonylation of alcohols, phenols, and amines using $BiCl_3$ as an efficient catalyst under autosolvent conditions. The present procedure has the advantage of short reaction times high yields of the products, no organic solvent, and simple workup procedure, which make it a useful and important addition to the existing methods.

4 EXPERIMENTAL

4.1 Typical Experimental Procedure

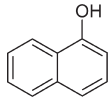
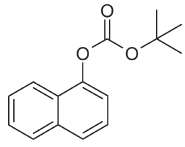
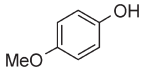
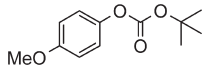
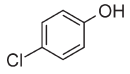
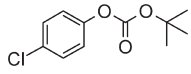
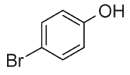
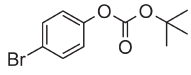
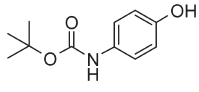
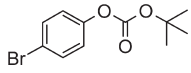
Di-*tert*-butyl dicarbonate (1.5 mmol) and finely powdered $BiCl_3$ (5 mol%) were added to a mixture of phenol/alcohol/amine (1 mmol), and the reaction was stirred under solvent-free conditions at room temperature for

Table 1. *O-tert*-Butoxycarbonylation of alcohols and phenols in the presence of $BiCl_3$

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]
1			0.5	98
2			0.5	95
3			1.0	96
4			0.5	94
5			2.0	95
6			2.0	92
7			2.0	96
8			0.5	98
9			0.5	95
10			0.5	98
11			0.5	96

(*continued*)

Table 1. Continued

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]
12			1.0	96
13			1.0	98
14			1.0	93
15			1.5	95
16			1.0	95

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

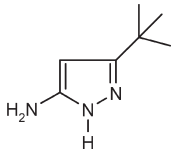
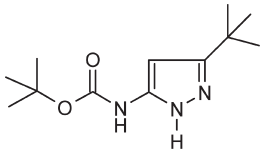
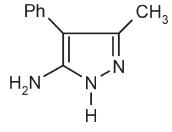
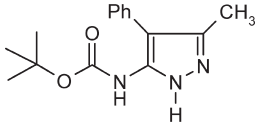
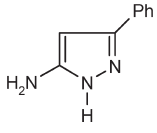
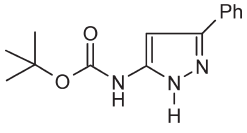
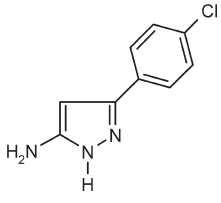
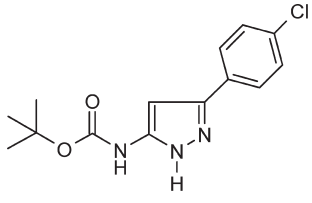
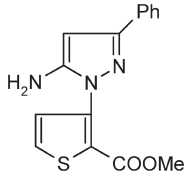
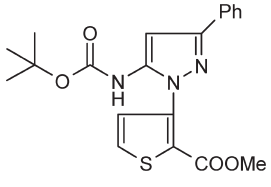
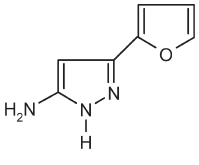
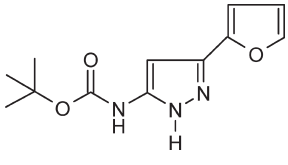
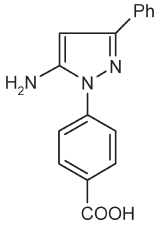
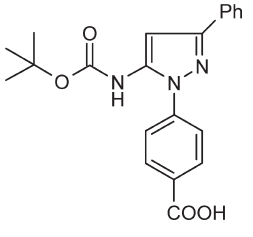
[b]Isolated yields obtained after column chromatography.

an appropriate time (Tables 1 and 3). After completion of the reaction as monitored by thin-layer chromatography (TLC), water (10 mL) was added, and the product was extracted into ethyl acetate (3×20 mL). The combined organic layer was washed with a brine solution and concentrated

Table 2. Comparison of the catalytic activity of bismuth(III) chloride with other catalysts on the *tert*-butoxycarbonylation of benzyl alcohol under different conditions at room temperature

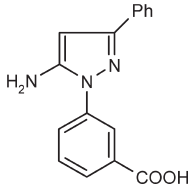
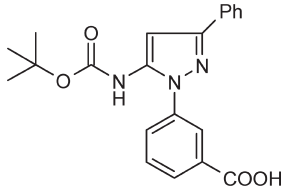
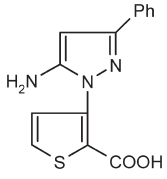
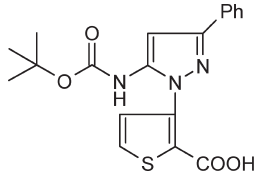
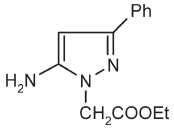
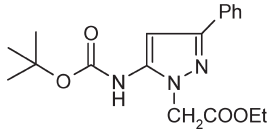
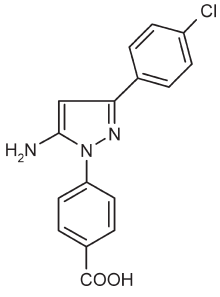
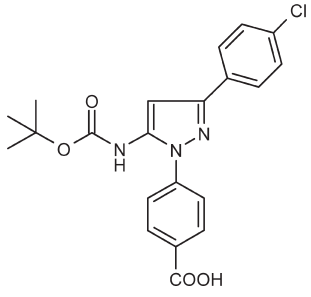
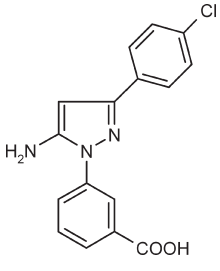
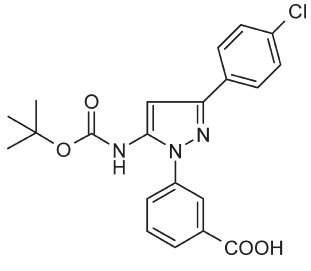
Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%)
1	None	No solvent	180	30
2	$Zn(OAc)_2$ (10)	DCM	360	98
3	$La(NO_3)_3 \cdot 6H_2O$ (5)	No solvent	30	60
4	I_2 (10)	No solvent	30	80
5	$LiClO_4$ (5)	No solvent	30	75
6	$ZrCl_4$ (5)	No solvent	180	90
7	$ZrOCl_2$ (5)	No solvent	60	90
8	$BiCl_3$ (5)	DCM	360	85
9	$BiCl_3$ (5)	$CHCl_3$	360	75
10	$BiCl_3$ (5)	No solvent	30	98

Table 3. *N-tert*-Butoxycarbonylation of 3-amino pyrazoles in the presence of $BiCl_3$

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]
1			0.5	98
2			0.5	97
3			0.5	98
4			0.5	95
5			0.5	96
6			0.5	95
7			1.0	99

(*continued*)

Table 3. Continued

Entry	Substrate	Product[a]	Time (h)	Yield (%)[b]
8			1.0	98
9			0.5	98
10			0.5	96
11			1.0	95
12			1.0	98

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

[b]Isolated yields obtained after column chromatography.

under reduced pressure to give the crude product, which was purified over a silica-gel column to afford the corresponding *tert*-Boc derivatives in excellent yields. The catalyst was recovered from the aqueous layer by removing water under reduced pressure and reused for six or more runs without loss of its activity.

4.2 Data from Table 1

Entry 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 4.40 (s, 2H, CH_2), 7.39 (m, 5H, Ar-H); EIMS: m/z 208.

Entry 2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 2.20 (s, 3H, ar-CH_3), 4.41 (s, 2H, CH_2), 7.39 (m, 5H, Ar-H); EIMS: m/z 222.

Entry 4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 1.35 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.56 (m, 1H, CH), 3.91 (d, 1H, CH^a), 4.12 (d, 1H, CH^b), 4.19 (d, 2H, CH_2); EIMS: m/z 232.

Entry 5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 1.35–1.5 (m, 6H, $3CH_2$) 1.90 (m, 4H, $2CH_2$), 4.22 (m, 1H, CH); EIMS: m/z 200.

Entry 7. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 2.90 (d, 2H, CH_2), 7.44–7.60 (m, 3H, Ar-H), 7.70 (s, 1H, Ar-H); EIMS: m/z 234.

Entry 8. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H, *t*-Bu), 2.90 (t, 1H, CH^a), 3.00 (t, 1H, CH^a), 3.50 (t, 1H, CH^b), 4.25 (t, 1H, CH^b), 7.40–7.44 (m, 4H, Ar-H); EIMS: m/z 290.

Entry 11. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 4.13 (d, 2H, CH_2), 4.50 (m, 1H, CH), 5.50 (d, 1H, CH), 7.40 (d, 2H, Ar-H), 7.64 (d, 2H, Ar-H); EIMS: m/z 338.

Entry 12. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, *t*-Bu), 7.32 (d, 1H, Ar-H), 7.43 (d, 1H, Ar-H), 7.66 (m, 2H, Ar-H), 8.01 (d, 1H, Ar-H), 8.10, (d, 1H, Ar-H), 8.37 (m, 1H); EIMS: m/z 244.

4.3 Data from Table 3

Entry 1. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 9H, *t*-Bu), 1.49 (s, 9H, *t*-Bu), 5.85 (s, 1H, Ar-H); EIMS: m/z 239.

Entry 2. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49 (s, 9H, *t*-Bu), 2.26 (s, 3H, CH_3), 7.40 (s, 5H, Ar-H); EIMS: m/z 273.

Entry 10. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, CH_3), 1.49 (s, 9H, *t*-Bu), 4.25 (q, 2H, CH_2), 4.92 (s, 2H, CH_2), 5.85 (s, 1H, Ar-H), 7.5 (m, 5H, Ar-H); EIMS: m/z 345.

Entry 11. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (s, 9H, *t*-Bu), 6.02 (s, 1H, Ar-H), 7.15 (d, 2H, $J = 8.15$, Ar-H), 7.35 (d, 2H, $J = 8.23$, Ar-H), 7.60 (d, 2H, $J = 8.15 <$ Ar-H), 8.10 (d, 2H, $J = 8.23$, Ar-H); EIMS: m/z 413, 415.

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