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A novel *tert*-butoxycarbonylation reagent: 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI)

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Abstract—The use of 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) as a *tert*-butoxycarbonylation reagent for acidic proton-containing substrates such as phenols, aromatic and aliphatic amines hydrochlorides, and aromatic carboxylic acids in the absence of a base is described. The reactions proceed chemoselectively in high yield under mild conditions.

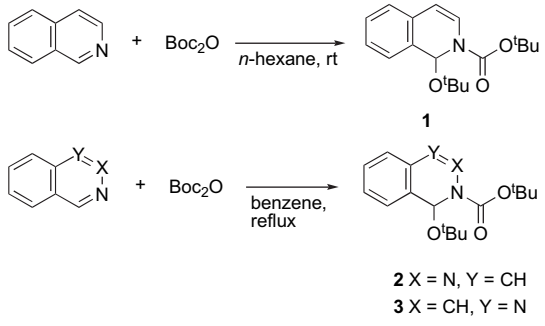
1. Introduction

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 functional molecules.[1] Among the various protection groups available, the *tert*-butoxycarbonyl (Boc) group is resistant to nucleophilic reagents, because of the electron donating and sterically bulky *tert*-butyl group.[1] It is noteworthy that the Boc group for protecting amino functionalities is most frequently used in organic synthesis due to its chemical stability to nucleophiles and strong basic conditions and its ease of removal under specific conditions.[2] In addition, the Boc group can also act as a useful protecting group for alcohols and phenols, since it is more stable than the corresponding ester under basic conditions.[3] Various reagents and methods for introducing this group using Boc_2O have been developed. Most reactions are carried out in the presence of a base such as DMAP[4] or organic/inorganic bases.[3a,5] In addition, the *tert*-butoxycarbonylation of acidic substrates such as phenol and thiophenol also require a base.[6] On the other hand, the use of a Lewis acid catalyst to perform this protection has not been extensively studied.[7] In these contexts, we discovered that the Reissert like reaction of Boc_2O with isoquinoline afforded 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) **1**, which appears to be a promising *tert*-butoxycarbonylating agent.[8] Our efforts toward the use of BBDI **1** as a de novo *tert*-butoxycarbonylation reagent for acidic proton-containing substrates such as amine hydrochlorides, phenols, and carboxylic acids have been described in detail.[9]

2. Results and discussion

2.1. The reaction of Boc_2O with nitrogen-containing aromatic compounds

We, first, found that the exposure of isoquinoline to Boc_2O in *n*-hexane at room temperature resulted in the loss of carbon dioxide to give **1** in 86% yield, which is stable and can be stored at room temperature for periods of over 1 year without any decomposition. Similarly, when a solution of phthalazine and quinazoline is refluxed with Boc_2O in benzene, the adducts **2** and **3** are produced, in 86% and 68% yields, respectively (Scheme 1). Surprisingly, the addition of Boc_2O to pyridine, pyrimidine, quinoline, and quinoxaline gave no adducts, resulting in the recovery of starting materials. Only heterocycles bearing a nitrogen at the β-position in the naphthalene ring such as isoquinoline, phthalazine, and quinazoline were amenable to reaction with Boc_2O to give the corresponding adducts **1**–**3**, although the reasons for this remain unclear.



Scheme 1. Synthesis of **1**–**3**.

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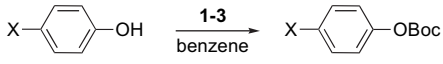
2.2. *tert*-Butoxycarbonylation of phenols with BBDI

A variety of natural polyphenols that have attracted the interest of scientists and synthetic research into this class of compounds has been vigorously carried out in recent years.[10] The phenolic hydroxyl group(s) on those compounds often play an important role in their biological activities.[11] The protection of the hydroxyl group(s) is necessary in order to maintain these activities and to avoid expected side reactions. A variety of protecting groups for phenols have been developed and have been utilized in synthetic studies.[1] Recent studies have highlighted the utility of the *tert*-butoxycarbonyl (Boc) group for phenols.[4] Based on these properties, we embarked on an investigation of the *tert*-butoxycarbonylation of phenol (**4a**) using **1**. A solution of **4a** and **1** in benzene was heated under reflux for 1 h to give phenyl *tert*-butyl carbonate (**5a**) in quantitative yield. The *tert*-butoxycarbonylation of **4a** using **2** and **3**, however, resulted in low yields (Table 1, entries 2 and 3). The reaction of *p*-methoxy- and *p*-nitorophenol (**4b** and **4c**), respectively, with **1** afforded the corresponding carbonates **5b** and **5c** in high yields, respectively (Table 1, entries 4 and 5). In the case of **4c**, however, the reaction proceeded easily at room temperature. Unfortunately, the exposure of **2** and **3** to **4c** also resulted in low yields (Table 1, entries 6 and 7). It is noteworthy that the *tert*-butoxycarbonylation of *p*-hydroxymethylphenol (**4d**) took place chemoselectively to give **5d** without any substitution of the hydroxymethyl group. Surprisingly, although the *tert*-butoxycarbonylation of phenols in alkaline media has been reported,[4,6] this is the first example of such a reaction in the absence of base.

2.3. *tert*-Butoxycarbonylation of amine hydrochlorides with BBDI

The Boc group is extensively used for amino protection because of its chemical inertness to nucleophilic reagents including base and deprotection using acid reagents.[12] The *tert*-butoxycarbonylation of aniline with **1** was examined first. However, no reaction occurred and **1** was recovered. As described above, it was found that the *tert*-butoxycarbonylation at **4c** (pK_a=10.8)[13] proceeds under more mild conditions compared with those of **4a** (pK_a=18.0).[13] With these results in hand, we concluded that reactivity is proportional to the acidity of the substrates. Because the conjugate acid **6a** (pK_a=3.6)[13] of aniline (pK_a=30.6)[13] is stronger acid than **4a**, we tried the *tert*-butoxycarbonylation of aniline hydrochloride (**6a**). Treatment of **6a** with **1** in benzene at room temperature afforded *N*-Boc aniline **7a**, as expected, in 81% yield (Table 2, entry 1). The use of dimethoxyethane (DME) instead of benzene as solvent dramatically increased the yield of **7a** (entry 2). A similar treatment of *p*-methoxyaniline hydrochloride (**6b**) with **1** afforded *N*-Boc aniline **7b** in high yield (entry 3). On the other hand, the reaction of *p*-nitroaniline hydrochloride (**6c**) with **1** resulted in low yields. Although this reason remains unclear, a decomposition of **1** may occur due to a stronger acidity of **6c** compared with that (pK_a=3.6)[13] of **6a**. Actually, an evolution of gas presumed to be isobutylene was observed in a reaction flask. A high degree of chemoselectivity was also demonstrated by using **6d** of the coexistence of an aliphatic hydroxyl group, as shown in entry 4.

Table 1. *tert*-Butoxycarbonylation of **4a–d** with **1–3**



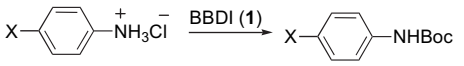
4a-d
a, X = H
b, X = OMe
c, X = NO_2
d, X = CH_2OH

5a-d
a, X = H
b, X = OMe
c, X = NO_2
d, X = CH_2OH

Entry	Reagent	Substrate (X)	Temp	Time (h)	Prod.	Yield (%)[a]
1	**1**	**4a** (H)	Reflux	1	**5a**	99
2	**2**	**4a** (H)	Reflux	2	**5a**	21
3	**3**	**4a** (H)	Reflux	5	**5a**	2
4	**1**	**4b** (OMe)	Reflux	1	**5b**	92
5	**1**	**4c** (NO_2)	rt	3	**5c**	96
6	**2**	**4c** (NO_2)	rt	3	**5c**	21
7	**3**	**4c** (NO_2)	rt	3	**5c**	17
8	**1**	**4d** (CH_2OH)	Reflux	3	**5d**	91

[a] Isolated yields.

Table 2. *tert*-Butoxycarbonylation of **6** with **1**



6a-e
a, X = H
b, X = OMe
c, X = NO_2
d, X = CN
e, X = CH_2CH_2OH

7a-e
a, X = H
b, X = OMe
c, X = NO_2
d, X = CN
e, X = CH_2CH_2OH

Entry	Substrate (X)	Temp	Solvent	Prod.	Yield (%)[a]
1	**6a** (H)	rt	Benzene	**7a**	81
2	**6a** (H)	rt	DME	**7a**	97
3	**6b** (OMe)	rt	DME	**7b**	98
4	**6c** (NO_2)	rt	DME	**7c**	19
5	**6c** (NO_2)	−10 °C	DME	**7c**	38
6	**6d** (CN)	rt	DME	**7d**	75
7	**6e** (CH_2CH_2OH)	rt	DME	**7e**	97

[a] Isolated yields.

The *tert*-butoxycarbonylation of α-amino acids ester hydrochlorides (pK_a=7.6–8.7)[14] as the weaker conjugate acid was next examined. Screening experiments were conducted with L-Met–OMe·HCl **8a** as a model compound using **1** in DME. The use of 3 equiv of **1** gave the best yield (93%, Table 3, entry 1), whereas the use of 2 and 1.2 equiv of **1** resulted in 82% and 33% yields, respectively. The use of diethyl ether (reflux) and chloroform as solvents provided similar results (95% and 92%), respectively, whereas dioxane resulted in a low yield (53%). Moreover, the decrease of the amounts of **1** was examined. Consequently, the treatment of **8a** with **1** (2 equiv) in acetonitrile at 0 °C provided **9a** in 97% yield (entry 3). On the basis of these results, the standard condition for the *tert*-butoxycarbonylation of several α-amino acid ester hydrochlorides **8** with **1** (3 equiv) was in DME at room temperature (A) or in diethyl ether under reflux (B). Thirdly, the use of 2 equiv of **1** in acetonitrile at 0 °C was carried out (C). Thus the *tert*-butoxycarbonylation of various α-amino acids occurs, and the corresponding *N*-Boc L-amino acid esters were obtained in high yields as shown in Table 3. The identification of *N*-Boc L-amino acid esters was confirmed by comparison of ^{1}H NMR and IR data and $[\alpha]_D$