



# SILICA-BORIC ACID ( $\text{SiO}_2\text{-H}_3\text{BO}_3$ ): A MILD, EFFICIENT AND REUSABLE HETEROGENEOUS CATALYST FOR BOC PROTECTION OF AMINES

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## ABSTRACT

An efficient method for *N*-tert-butoxy carbonylation of amines using silica-boric acid ( $\text{SiO}_2\text{-H}_3\text{BO}_3$ ) as a new catalyst is described. The catalyst is air stable and can be readily separated from the reaction products and recovered for direct reuse.

**Keywords:** Silica-Boric Acid Catalyst, Protection of amines

## 1. Introduction

Protection and deprotection plays a pivotal role for the synthesis of complex organic molecules. Amine is one of the most important functional group present in plethora of biologically active compounds. So, its protection plays a crucial role while designing the syntheses of bioactive molecules. Till now, many protective groups have been developed for the amine functionality. Out of these, *N*-tert-butyloxycarbonyl (Boc) has emerged as the most commonly used strategies due to the ease of protection as well as deprotection. This group is stable for various base-catalyzed nucleophilic substitutions and catalytic hydrogenation reactions.<sup>1</sup> Various methods are available for the *N*-tert-butyloxycarbonylation (Boc) under basic as well as Lewis acidic conditions using di-*tert*-butyl-dicarbonate ( $\text{Boc}_2\text{O}$ ) that includes  $\text{I}_2$ ,<sup>2</sup>  $\text{ZrCl}_4$ ,<sup>3</sup>  $\text{HClO}_4\text{-SiO}_2$ ,<sup>4</sup>  $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ ,<sup>5</sup> ionic liquid,<sup>6</sup> Amberlyst-15,<sup>7</sup> sulfamic acid,<sup>8</sup> etc. However, most of the methods suffer from one or more drawbacks like highly basic conditions, elevated temperatures, long reaction times and high toxicity. To overcome these drawbacks still there is a need to develop a new catalyst system that can minimise these limitations. Recently, solid supported catalysts have attracted great deal of attention for

carrying out important organic transformations. Supported reagents have good thermal and mechanical stabilities. These are more advantageous over homogeneous catalysts as they can be easily recovered from reaction mixture by simple filtration and can be reused several times, making the process more economically and environmentally viable.<sup>9, 10</sup>

One of the few solid supported catalysts is silica supported boric acid ( $\text{SiO}_2\text{-H}_3\text{BO}_3$ ) as it is a simple, inexpensive reagent recently gaining momentum as a green catalyst in various organic transformations. It possesses environmentally benign properties such as non-toxicity, biocompatibility, recyclability, inexpensive and thermal stability. As an example, Parveen<sup>11</sup> *et al* utilized  $\text{SiO}_2\text{-H}_3\text{BO}_3$  as an efficient solid supported recyclable catalyst for the synthesis of tetrazoles in high yields. Next, this elegant catalyst have been successfully utilized for the synthesis of bis(indolyl)methane derivatives,<sup>12</sup>  $\beta$ -amino carbonyl compounds,<sup>13</sup> etc.

Encouraged by these advantages, we herein report for the first time use of silica-boric acid ( $\text{SiO}_2\text{-H}_3\text{BO}_3$ ) for *N*-Boc protection of amines.  $\text{SiO}_2\text{-H}_3\text{BO}_3$  catalyst was prepared using standard procedure<sup>14</sup> and the structure was confirmed using IR spectroscopy.

## 2. Experimental

**Preparation of silica supported boric acid:** Boric acid (3.0 g) was taken in a 250 ml round bottom flask with 60 mL water and heated to 60-80°C. Silica gel (60-120 mesh, 27.0 g) was added gradually with constant stirring and refluxed for 5 hrs. Water was evaporated under reduced pressure and the residue was stirred at 100°C for 6-7 hrs under vacuum to give free

flowing white powder of silica-boric acid. It was kept under vacuum for 48 h at room temperature (Scheme 15).

**General procedure for Boc protection of amines:** To a mixture of amine (1.0 mmol) and  $\text{Boc}_2\text{O}$  (1.0 mmol) was added  $\text{H}_3\text{BO}_3\text{-SiO}_2$  (10 mol%) and stirred at room temperature for appropriate time as given in Table 3. The progress of reaction was monitored by TLC. After completion, the reaction mixture was washed with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the pure products.

#### Spectral data of selected compounds

**(4-Methoxy-phenyl)-carbamic acid tert-butyl ester (entry 6, Table 3):** White solid, M.P. 93-95°C; IR (KBr)  $\nu$  3363, 3074, 1691, 1523, 825  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.48 (s, 9H), 3.74 (s, 3H), 6.20 (br s, 1H), 6.76 (d,  $J=8.76$  Hz, 2H), 7.24 (d,  $J=12.42$  Hz, 2H).

**Naphthalen-1-yl-carbamic acid tert-butyl ester (entry 8, Table 3):** Clear solid, M.P. 94-96°C; IR (neat):  $\nu$  3257, 3051, 1687, 1541, 765  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.52 (s, 9H), 6.83 (br s, 1H, NH), 7.38-7.88 (m, 7H).

### 3. Results and Discussion

Initially we studied the reaction of aniline with di-*tert*-butyl-dicarbonate ( $\text{Boc}_2\text{O}$ ) in the presence of  $\text{SiO}_2\text{-H}_3\text{BO}_3$  (10 mol%) under various solvent conditions at room temperature as depicted in Table 1. Firstly, we

carried out the reaction using acetone as a solvent and to our delight, the reaction was completed in 30 min with 80% yield. Next, we evaluated different solvents like methanol, chloroform, ethyl acetate and they also produced excellent results in short reaction time (Table 1). We also carried out the reaction in solvent free conditions (Table 1, entry 6), here the reaction time was shortened but, due to the formation of thick solid, the reaction was unable to complete. The best results were obtained when the reaction was carried out using ethanol as a solvent, here the desired product was obtained in 98% yield in 30 min (Table 1, entry 5).

**Table 1.** Effect of various solvents on the yield of the model reaction

Entry	Solvent	Time	Yield (%)
1.	Methanol	25 min	92
2.	Ethyl acetate	25 min	90
3.	Acetone	30 min	80
4.	Chloroform	25 min	92
5.	EtOH	30 min	98
6.	Neat	15 min	82

Comparison of our result with few of the reported procedures is presented in Table 2, which clearly indicates the efficiency of  $\text{SiO}_2\text{-H}_3\text{BO}_3$  in the synthesis of Boc protected amines. Here, in most of the cases, expensive catalyst system is required with long reaction time (entry 2-5) which limits the utility of the protocols.

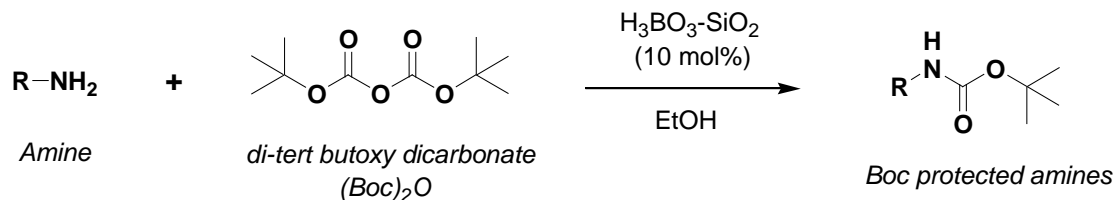
**Table 2.** Comparison of various catalysts employed for the N-Boc protection of aniline<sup>#</sup>

Entry	Catalyst (mol%)	Solvent	Time	Yield(%)	Ref.
1	Iodine	Neat	30 min	95%	2
2	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	$\text{CH}_2\text{Cl}_2$	12 h	92%	5
3	Sulfonic acid functionalized silica	$\text{CH}_2\text{Cl}_2$	45 min	83%	15
4	$\beta$ - cyclodextrin	$\text{H}_2\text{O}$	2.5 h	75%	16
5	Ytria-Zirconia	$\text{CH}_3\text{CN}$	14 h	90%	17
6	$\text{H}_3\text{BO}_3\text{-SiO}_2$	$\text{C}_2\text{H}_5\text{OH}$	20 min	98%	This work

<sup>#</sup>Reaction conditions: Aniline: (1:1),  $\text{Boc}_2\text{O}$ , room temperature.

Next, we evaluated the scope of the reaction with various aromatic amines. Several amines were treated with 1 eq. di-*tert*-butyl dicarbonate in presence of 10 mol% of  $\text{SiO}_2\text{-H}_3\text{BO}_3$

in ethanol as a solvent to obtain pure products without any column purification (Scheme 1). The results (reaction time and the product yields) are depicted in (Table 3).



Scheme 1.

Table 3. Synthesis of various Boc protected amines catalyzed by  $\text{SiO}_2\text{-H}_3\text{BO}_3$ 

Amine	Time	Product	Yield (%)
	20 min		98
	2.5 h		97
	45 min		95
	30 min		85
	40 min		90
	15 min		99
	45 min		86
	2 h		78
	50 min		65
	6 h		60
	45 min		86
	15 min		98

Anilines possessing electron withdrawing groups on the phenyl ring (such as chloro Table 3, entry 9, 10) shows decrease in product yields with longer reaction time. In contrast, aniline having electron donating groups on phenyl ring (methyl or methoxy, Table 3, entry 3-7) results in higher yields with rapid product formation. Position of substituents

on aniline does not affect much on the product yield but, the effect can be seen on the reaction time. For example, substituent on *ortho* position of aniline requires more time for the completion of reaction as compared to *para* positions due to the *ortho* effect (Table 3, entry 2).

#### 4. Conclusion

In conclusion, we described here a simple, convenient and environment-friendly protocol for the *tert*-butyloxycarbonylation of amines using catalytic amount of SiO<sub>2</sub>-H<sub>3</sub>BO<sub>3</sub>. The present protocol shows several advantages such as high yields, shorter reaction times, safe handling, clean reactions, excellent selectivity and low cost. We envisage that this new method would be used as an alternative to other existing methods for the Boc protection of amines.

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