

# Efficient and expeditious chemoselective BOC protection of amines in catalyst and solvent-free media

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**Abstract** A green and eco-friendly route for the almost quantitative BOC protection of a large variety of aliphatic and aromatic amines, amino acids, and amino alcohols is reported in catalyst and solvent-free media under mild reaction conditions. The products were confirmed by <sup>1</sup>H, <sup>13</sup>C NMR, IR spectroscopy, and in some cases, elemental analysis. This protocol does not require any water quenches, solvent separations, and purification steps, such as recrystallization and column chromatography.

Keywords Protection  $\cdot$  N-BOC  $\cdot$  Catalyst and solvent-free  $\cdot$  Reaction temperature  $\cdot$  Rotary evaporator

## Introduction

It is universally recognized that there is increasing interest in more eco-friendly practical approaches for pharmaceutical and fine chemical syntheses. This advanced growth area is recognized as green chemistry/sustainable technology [1–4]. This demands a paradigm shift from traditional concepts and focuses mainly on yield and commercial value, whilst eliminating the usage of solvents and catalysts to enhance green chemistry. In recent years, the amine functionality has been identified in a broad range of biologically active molecules, and the protection of the amine functionality is important in their synthetic applications. The nitrogen-containing carbamate or BOC amine compounds, shown in Fig. 1, are frequently found in

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Fig. 1 Some important biologically active N-BOC amines

pharmaceutical and biologically active molecules in organic synthesis [5]. One of the more significant routes to protection involves the use of BOC anhydride, which has been studied over various catalytic and solvent systems [6-21]. Some examples include DMAP, Lewis acid catalysts such as Zr(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O; Brønsted acid ionic liquids [(HMIm)BF<sub>4</sub>]; functionalized silica,  $H_3PW_{12}O_{40}$ , and montmorillonite K10. The above studies showed that some processes required long reaction times, some were carried out under harsh reaction conditions, and others required purification steps such as column chromatography. In addition, these processes involving catalysts and solvents sometimes required purification of the solvents, as well as catalyst washing, post reaction. Chankeshwara and Chakraborti [22] studied the N-BOC protection of amines in the absence of a catalyst, but used water as a solvent. Raju et al. [23] reported N-BOC amine and hydrazine synthesis at room temperature without a catalyst or solvent, and thereafter recrystallized the product using a suitable solvent. Mojtahedi et al. [24] reported on N-BOC protection of amines without a catalyst and under solvent-free conditions; however, the product was isolated after purification by column chromatography. Jia et al. [25] also reported, in a similar way, the synthesis of N-BOC amines without a catalyst and solvent, but purification with column chromatography was carried out after reaction, likely to remove the t-butanol from the reaction mixture considering that the reactions were carried out mostly at room temperature.

Various routes to N-BOC protection are reported and shown in Scheme 1. Route 1 shows the reaction proceeding in an aqueous medium or in an organic solvent to produce BOC amines after some purification technique [22, 26, 27]. Route 2 proceeds in the presence of a catalyst and solvent to obtain products after purification such as column chromatography [11, 14, 15, 17, 18, 29, 30, 34, 35]. This route may require a catalyst washing step after the reaction. Route 3 proceeds via the use of a catalyst to obtain a product but after some form of purification step [28, 31–33]. The most attractive pathway, from an environmental perspective, is route 4 where N-BOC protection takes place in the absence of a catalyst or solvent. In keeping with this philosophy, we report a very simple and highly efficient synthesis method for the protection of amines with BOC anhydride under catalyst and solvent-free conditions. This reaction proceeds via a simple mixing of stoichiometric amounts of the reactants to give products in quantitative yield, whilst simultaneously removing the formed by-products.



Scheme 1 Synthesis of N-BOC amines by various routes

### **Experimental**

The chemicals were procured in reagent grade and used without further purification. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded employing a Brüker Advance 400 MHz instrument with CDCl<sub>3</sub> as a solvent. The Fourier transformed infrared spectra were recorded using the attenuated total reflectance (ATR) technique on a Perkin Elmer Universal spectrometer at room temperature between 400 and 4000 cm<sup>-1</sup>. Elemental analyses were performed on a Thermal-Scientific Flash 2000 CHNS analyzer. The reactions were carried out in a 50 mL RB flask under reduced pressure for 10 min at 80 °C unless reported differently. In a typical experiment, 5 mmol of amine was added to 5 mmol of BOC anhydride, and the reaction was allowed to proceed for 10 min. The desired product was obtained in a rotary evaporator under vacuum conditions. In all cases, the products were found to be pure (NMR) and did not require any further purification. As confirmation, we carried out elemental analyses on some products, which are shown in Table 4. The BOC products were characterized by <sup>1</sup>H and <sup>13</sup>C NMR and IR spectroscopy. The results of these are presented in the supplementary information.

#### **Result and discussion**

The results of the N-BOC protection of various amines are shown in Table 1, and the proposed mechanism for BOC protection of amines in catalyst and solvent-free media is shown in Scheme 2 [24]. The reaction conditions enhance easy attack of

Entry	Reactant	Product	Con. (%)	Yield (mol %)
1	NH <sub>2</sub>	H.N.C.	100	99
2	NH <sub>2</sub>		100	99
3	NH <sub>2</sub> Br	H N C	100	99
4	NH <sub>2</sub>		100	98
5	NH <sub>2</sub>	H.N.L.	100	98
6	NH <sub>2</sub> Cl	H.N.CI	100	99
7	NH <sub>2</sub> CH <sub>3</sub> CH <sub>3</sub>	H <sub>N</sub> L <sub>O</sub> L CH <sub>3</sub>	100	98
8	H <sub>3</sub> C CH <sub>3</sub>		100	98
9	CH <sub>3</sub>		100	98
10	NH <sub>2</sub> NH <sub>2</sub>		100	99
11	NH <sub>2</sub>		100	99
12	NH2	H N N N N N N N N N N N N N N N N N N N	100	98
13		HO	100	98
14	HO-NH2		100	98

Table 1 Catalyst and solvent free BOC protection of various amines<sup>a</sup>

Table 1 c	ontinued
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Entry	Reactant	Product	Con. (%)	Yield (mol %)
15	NH <sub>2</sub>	HNLOK	100	99
16	NH <sub>2</sub>	~~~ <sup>H</sup> yo+	100	96
17	NH <sub>2</sub>	~~NyO+	100	96
18	₩H <sub>2</sub>		100	95
19	NH <sub>2</sub>	~~ <sup>N</sup> yo+	100	96
20	NH <sub>2</sub> OH		100	97
21	H <sub>2</sub> N NH <sub>2</sub>	Kon Horn Horn	100	97
22	H <sub>2</sub> N NH <sub>2</sub>	Kol how how	100	96
23	N N H	L'N X	100	98
24	⊂ N OH H OH	CN-CH	100	98
25	H <sub>2</sub> NOH	Ч° Ч № С ОН	100	97
26	H H		100	99
27	O H H	°, o' ∩, n, , , , , , , , , , , , , , , , , ,	100	97

Reaction conditions: Amine (5 mmol), BOC anhydride (5 mmol) carried out using a rotary evaporator at  $80^{\circ}$ C

 $^{\rm a}\,$  Reaction conditions: Amine (5 mmol), BOC anhydride (5 mmol) carried out using a rotary evaporator at 80  $^{\circ}{\rm C}$ 

the electron deficient carbonyl carbon in BOC anhydride by the nucleophilic lone pair on the nitrogen atom of the amine. The major advantage of our process involves the efficient removal of by-products such as t-butanol and  $CO_2$  during the course of the reaction without the need to purify the reaction products, thus giving analytically

Reaction temperature (°C)	Yield (mol%)					
	Aniline- BOC	4-Chloro aniline-BOC	4-Bromo aniline-BOC	4-Iodo aniline-BOC	3,4-Dimethyl aniline-BOC	
RT <sup>a</sup>	60	3	10	55	95	
50 <sup>a</sup>	78	10	40	72	99	
80 <sup>b</sup>	99	99	99	98	99	

Table 2 Protection of aniline derivatives with BOC<sub>2</sub>O at various reaction temperatures

<sup>a</sup> Yield based on <sup>1</sup>H NMR analysis

<sup>b</sup> Isolated yields

pure products in almost quantitative yield. We also studied selected indole compounds using the same reaction conditions and found them to produce a quantitative yield towards the desired product (Table 1). However, we found them less reactive, based on the longer reaction time (30 min) required to obtain quantitative yields.

In respect to the reaction mechanism, the rate of the reaction can be favoured by influencing the nucleophilicity of the lone pair on the nitrogen atom. Hence, electron donating groups enhance the rate, whereas, in the case of electron withdrawing groups, a decrease in rate would be favored. This effect would be pronounced for aryl amines as demonstrated by the results shown in Table 2. In order to compare the rate of the reaction as a function of the substituent, we studied the protection of several amines at various reaction temperatures including room temperature, 50, and 80 °C. When the reaction was carried out at room temperature, the electron withdrawing substituents clearly show a lower rate when compared to the electron donating groups. In comparison, the un-substituted aniline gave a rate that is in between activating and deactivating aniline derivatives (Table 2).

#### **Reaction mechanism**

The same trend was observed when the temperature was increased to 50 °C. However, increasing the temperature further to 80 °C showed no influence of the substituents, with the rates being almost the same. These results show that the rate of reaction can be tuned by controlling the reaction temperature. The order of the rate is as follows,  $CH_3 > H > I > Br > Cl$  (Table 2), and these results correlate well with the inductive effect of these substituents,  $Cl > Br > I > H > CH_3$ .

The purity of compounds was confirmed by NMR analyses, and this was sufficient for the work presented; however, as an extra measure, we also carried out CHN analyses for some products obtained at 80 °C, as shown in Table 3. These results confirm the analytical purity of the products.

In order to compare the results obtained with those reported, we present several studies in Table 4 where aniline was N-BOC protected [11, 14, 15, 17, 18, 21, 28–35]. It can be seen from the data in the Table that the present protocol is highly efficient, albeit at 80 °C, and very expeditious when



Scheme 2 Reaction pathway for BOC amine formation under mild reaction conditions

Compound	Theoretical (%)			Found <sup>a</sup> (%)		
	С	Н	Ν	С	Η	Ν
H.N.C.K	68.37	7.82	7.25	67.37	7.46	7.16
H.N V	58.03	6.2	6.15	57.03	5.85	5.91
	41.4	4.42	4.39	41.24	4.16	4.15
H <sub>N</sub>	48.55	5.19	5.15	48.20	4.80	4.79
	70.56	8.65	6.33	69.57	7.91	6.26
CH <sub>3</sub>						

Table 3 Elemental analysis of selected BOC amines

 $^{\rm a}$  Deviation for some compounds due to adsorbed water (0.1–0.15 wt%)

compared to most. It must also be highlighted that all, but one, of the reported methods required purification to obtain the final product. As a result, the methodology reported here makes the process cost effective, efficient, and environmentally friendly, whilst giving excellent yields toward the product.

S. no.	Catalyst	Solvent	Reaction time (min)/room temperature	Yield (%)/purification cc (column chromatography)	References
1	Yttria-zirconia	CH <sub>3</sub> CN	840/RT	90/cc	[11]
2	Sulfonic acid- functionalized silica	CH <sub>2</sub> Cl <sub>2</sub>	45/RT	83/cc	[14]
3	β-cyclodextrin	H <sub>2</sub> O	150/RT	75/cc	[15]
4	Thiourea	Toluene	40/70 °C	95/cc	[17]
5	$H_{3}PW_{12}O_{40}$	$CH_2Cl_2$	8/RT	85/cc	[18]
6	Water	Water	30/35 °C	95	[21]
7	No catalyst	Neat	30/RT	95/cc	[25]
8	FeCl <sub>3</sub>	Neat	60/RT	89/cc	[28]
9	Zn(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	$CH_2Cl_2$	720/RT	92/cc	[29]
10	Saccharin sulfonic acid	Hexane	60/RT	97/cc	[30]
11	<i>N</i> -Sulfonic acid poly(4- vinylpyridinium) chloride	Neat	5/RT	93/cc	[31]
12	Pyridinium 2,2,2- trifluoroacetate ionic liquid	Neat	25/RT	95/cc	[32]
13	$I_2$	Neat	30/RT	98/cc	[33]
14	1,3-Disulfonic acid imidazolium hydrogen sulfate	Ethyl acetate	2/RT	98/cc	[34]
15	[H-Suc]HSO <sub>4</sub>	Ethyl acetate	6/RT	93/cc	[35]
16	No catalyst	Neat	10/RT	60 <sup>a</sup>	Present work
17	No catalyst	Neat	10/80 °C	99 <sup>b</sup>	Present work

Table 4 Comparison of N-BOC protection of aniline with  $(BOC)_2O$ —literature results with the present study

<sup>a</sup> Yield based on <sup>1</sup>H NMR analysis

<sup>b</sup> Isolated yield

# Conclusions

In the present investigation, a very simple method and green protocol is reported for a catalyst and solvent-free BOC protection of amines. This methodology is highly efficient and eco-friendly, chemoselective, with excellent yields and easy product isolation. We also show that at 80 °C the inductive effects of substituents have no effect on the rate of the BOC protection whilst at the lower temperatures, a higher rate was observed for the electron donating groups.

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