Zinc chloride promoted efficient and facile BOC protection of amines

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Amines are efficiently protected as their BOC derivatives under mild reaction conditions when reacted with BOC anhydride in presence of ZnCl₂. The present method is applicable to a variety of amines including aliphatic, aromatic as well as heteroaromatic amines. This protocol appears to be competitive and in some cases superior to previously reported procedures that work under basic conditions.

Keywords: Amine protection, N-BOC protected amine, ZnCl₂, Lewis acid

The development of mild and selective methods for the protection / deprotection of functional groups continue to be an important tool in synthetic organic chemistry. The BOC group has been used extensively for the protection of amines due to its ease of formation, stability under basic conditions and ease of removal. BOC protected aryl amines are important intermediates in organic synthesis and have been used for the directed lithiation of aromatic rings and preparation of unsymmetrical ureas, etc.

Aryl amines are particularly difficult to protect with the BOC group because of the reduced nucleophilicity of the nitrogen atom when compared to primary or secondary aliphatic amines. Thus, their synthesis often requires the Curtius rearrangement of aryl azides followed by trapping with tert-butylalcohol. However, recent reports have demonstrated that the reaction of aryl amines with one equivalent of di-tertiary butytldicarbonate (BOC₂O) requires extended reaction times, elevated temperature, or the addition of a base, i.e., DMAP, aq. NaOH (Ref 9), pyridine and NaHMDSe. On the other hand, methods using a Lewis acid catalyst to perform BOC protection are rare. Till date, only few reports on such reactions are found. i.e., Yttrium-zirconium based strong Lewis acid is used for BOC protection. However, the preparation of this catalyst is quite elaborate. Recently, LiClO₄ (Ref 13), Zn(ClO₄)₂ (Ref 14) and ZrCl₄ (Ref 15) have also been reported for BOC protection of amines.

In the past few years zinc chloride has emerged as a mild Lewis acid for various organic transformations such as Beckmann rearrangement, thiophenols, cycloaddition reaction, substitution, addition reactions and selective reduction. Furthermore, ZnCl₂ is also used in the synthesis of 1,2-diarylacetlenes, fluoroalkylated quinolines, 4-aryl-1,2,3,4-tetrahydroisoquinolines, N-arylation of pyridine-3(2H)one, Ferrier reaction, alkylation of imines with terminal alkynes and nitration of aromatic compounds. Although ZnCl₂ has been extensively used as Lewis acid in various organic transformations, it has not been used for the protection of amines as their BOC derivatives. This prompted the use of ZnCl₂ for the BOC protection of amines. Herein is reported the ZnCl₂ promoted selective BOC protection of amines under mild condition with high yield. (Scheme I).

A variety of amines were treated with BOC₂O in the presence of ZnCl₂, the corresponding N-BOC-protected amines were obtained in excellent yields. The substrates examined in the present studies and the results obtained are summarized in Table I. Thus the present procedure for introducing the BOC protecting group is quite general as a wide range of amines underwent reaction smoothly with BOC₂O. In the case of 2-chloroaniline (entry 1i) and 3-nitro aniline (entry 1j) the yields are low (20%). It contributes to the low reactivity of these deactivated anilines. It is noteworthy that the reaction is chemoselective and the amine being more nucleophilic than alcohol underwent reaction faster giving corresponding N-BOC protected product in high yield (94%). Moreover, it is important to highlight that any side reaction, such as biscardonylation or the formation of isocyanate or

\[
\text{R–NH₂} \xrightarrow{(BOC)₂O, ZnCl₂} \text{CH₂Cl₂, RT} \xrightarrow{\text{aq. NaOH}} \text{R–NHBOC}
\]

(Scheme I)

Note

The preparation / deprotection of functional groups is an important tool in synthetic organic chemistry.
Table I — ZnCl₂ promoted BOC protection of the amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (Min)</th>
<th>Yield (%)</th>
<th>Reaction condition</th>
</tr>
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<tr>
<td>1</td>
<td>NH₂</td>
<td>NHBOC</td>
<td>15</td>
<td>94</td>
<td>CH₂Cl₂ RT</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>15</td>
<td>92</td>
<td>CH₂Cl₂ RT</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>15</td>
<td>92</td>
<td>CH₂Cl₂ RT</td>
</tr>
<tr>
<td>4</td>
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<td></td>
<td>20</td>
<td>94</td>
<td>CH₂Cl₂ RT</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
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<td>94</td>
<td>CH₂Cl₂ RT</td>
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<tr>
<td>6</td>
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<td>20</td>
<td>94</td>
<td>CH₂Cl₂ RT</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>20</td>
<td>90</td>
<td>CH₂Cl₂, RT</td>
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<tr>
<td>8</td>
<td></td>
<td></td>
<td>20</td>
<td>92</td>
<td>CH₃CN:H₂O(1:1)</td>
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<tr>
<td>9</td>
<td></td>
<td></td>
<td>1440</td>
<td>20</td>
<td>CH₂Cl₂, RT</td>
</tr>
</tbody>
</table>

— Contd
urea was not observed. Surprisingly, when these reaction conditions was applied to protect 6-aminoquinoline, 8-aminoquinoline, 2-ethyl aniline and 4-isopropyl aniline, the desired product does not form but only a white complex is obtained which may be due to complexation with ZnCl$_2$. Whereas, 3-aminoquinoline (entry 1p) gives only 10% of BOC protected product after 24 hr of the reaction. The BOC protection of tryptamine (entry 1k), 2-aminophenol (entry 1h) and β-alanine (entry 1o) is carried out in acetonitrile / water (1:1) as they are not soluble in CH$_2$Cl$_2$. The reaction with 0.25 equiv or 0.5 equiv of ZnCl$_2$ is very slow. Therefore, the reaction is carried out using 1:1:1 molar ratio of substrate, reactant and Lewis acid.

To check the effect of other Lewis acids under the present reaction conditions, the BOC protection of aniline, 4-aminopyridine and 3-nitroaniline was carried out using InCl$_3$ (20% mol) as Lewis acid. Although, the InCl$_3$ also promotes the BOC protection of amines, it took a relatively longer time to complete the reaction, i.e., aniline took 3 hr to afford the corresponding BOC protected aniline, 4-aminopyridine gives the required product in 5 hr whereas, 3-nitroaniline gave only traces of BOC protected compound even after 24 hr. The plausible mechanism can be visualized as the activation of carbonyl group of BOC anhydride by the attack of ZnCl$_2$ followed by nucleophilic attack of amine on the BOC anhydride. This facilitates the extrusion of tert-butanol and carbon dioxide as leaving entities eventually leading to the formation of N-BOC protected amines (Scheme II).

**Experimental Section**

Melting points were determined in open capillaries and are uncorrected. Reagents grade chemicals were purchased from commercial sources and used as

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**Table I — ZnCl$_2$ promoted BOC protection of the amines — Contd**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (Min)</th>
<th>Yield (%)</th>
<th>Reaction condition</th>
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<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
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<td>92</td>
<td>CH$_2$Cl$_2$, RT</td>
</tr>
<tr>
<td>14</td>
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<td><img src="image8" alt="Image" /></td>
<td>60</td>
<td>90</td>
<td>CH$_2$Cl$_2$, RT</td>
</tr>
<tr>
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<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
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<td>990</td>
<td>CH$_3$CN:HO(1:1)</td>
</tr>
<tr>
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<td><img src="image12" alt="Image" /></td>
<td>120</td>
<td>10</td>
<td>CH$_2$Cl$_2$, RT</td>
</tr>
</tbody>
</table>

(a) Products were characterized by comparison with spectroscopic data. (b) Isolated Yields.
General procedure for the BOC protection of amines

To a solution of amine (1 mmol) in dichloromethane (10 mL), BOC₂O (1 mmol) and ZnCl₂ (1 mmol) were added and the reaction mixture was stirred for the specified time given in Table I. After completion of the reaction as indicated by the TLC, the solvent was removed under reduced pressure and the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine. The organic layer separated and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue obtained was purified by column chromatography over silica gel by using 10% EtOAc:Hexane as eluent to give the pure product.

In conclusion, ZnCl₂ promotes the protection of amines as BOC derivatives. The present method works with various aromatic, aliphatic and hetero aromatic amines under mild conditions. Moreover, this protocol appears to be competitive and in some cases superior to previously reported procedures that require basic conditions. Although Zn(ClO₄)₂·6H₂O has been reported for the BOC protection of amines, the present procedure is superior as compared to the method reported with Zn(ClO₄)₂·6H₂O. In particular, with aniline (entry 1d) the present results are superior as the reaction is complete in 20 min whereas Zn(ClO₄)₂·6H₂O required 12 hr to complete the
reaction. In the case of heterocyclic amines, excellent yields were obtained in short reaction time as compared to literature methods.

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References