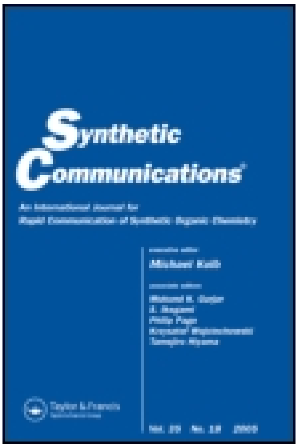

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: Tasneem & K. C. Rajanna (2011): Ferric Chloride-Promoted Efficient and Facile BOC Protection of Amines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:5, 715-719

To link to this article: http://dx.doi.org/10.1080/00397911003642641

Synthetic Communications®, 41: 715–719, 2011
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911003642641

FERRIC CHLORIDE–PROMOTED EFFICIENT AND FACILE BOC PROTECTION OF AMINES

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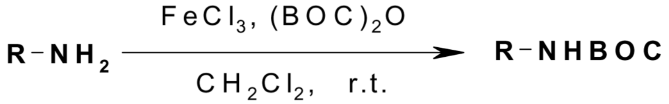
GRAPHICAL ABSTRACT



$$R{-}NH_2 \xrightarrow[CH_2Cl_2,\ r.t.]{FeCl_3,\ (BOC)_2O} R{-}NHBOC$$

Where R = aliphatic and aromatic compounds

Abstract *Amines are efficiently protected as their tertiary butyloxycarbonyl (BOC) derivatives under mild reaction condition when reacted with* $(BOC)_2O$ *in the presence of* $FeCl_3$*. The present method is applicable to a variety of amines including aliphatic, aromatic, and hetero aromatic amines.*

Keywords Amine protection; $FeCl_3$; Lewis acid; N-BOC

INTRODUCTION

The development of a mild and selective method for the protection and deprotection of functional groups continues to be important in synthetic organic chemistry.[1] The tertiary butyloxycarbonyl (BOC) group has been used extensively for the protection of amines because of its ease of formation, stability under basic conditions, and ease of removal.[2] BOC-protected aryl amines are important intermediates in organic synthesis and have been used for the direct lithiation of aromatic rings[3] and preparation of unsymmetrical urea.[4]

Aryl amines are particularly difficult to protect with the BOC group because of the reduced nucleophillicity 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 t-butyl alcohol.[5] However, recent reports have demonstrated that the reaction of aryl amines with 1 equivalent of di-tertiary butyldicarbonate $(BOC)_2O$ requires extended reaction times,[6] elevated

Received October 25, 2009.

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temperature,[7] or the addition of a base [i.e., dimethylaminopyridine (DMAP),[8] aqueous NaOH,[9] pyridine,[10] and NaHMDS.[11] On the other hand, methods using a Lewis acid catalyst to perform BOC protection are rare. Only a few studies on such reaction have been reported (i.e., yttrium-zirconium-based strong Lewis acid used for BOC protection). However, the preparation of this catalyst is quite elaborate.[12] Recently, $LiClO_4$,[13] $Zn(ClO_4)_2$,[14] $ZrCl_4$,[15] sulfamic acids,[16] and indium(III) halides[17] have been reported for BOC protection of amines.

In the past few years, ferric chloride has emerged as an oxidizing agent. It oxidizes a wide array of functionalities, such as certain phenols to quinines, dithiols to disulfides, and 2-hydroxycyclohexanone to 1,2-cyclohexanedione. Phenolic ethylamines and N-acetyloxyamides can be cyclized to indoles[18] and oxindoles respectively.[19] Dimerization of aryl lithium yields intermediates for cyclophane[20] and perylenequinone[21] synthesis. Inter- and intramolecular[22] ketone enolates can be converted to 1,4-diketones, and lithium salts of allylic sulfones afford 1,6-disulfones.

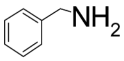
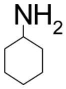
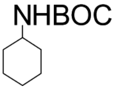
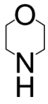
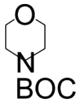
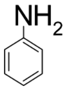
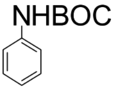
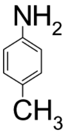
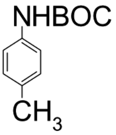
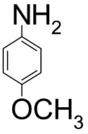
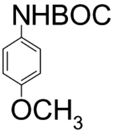
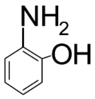
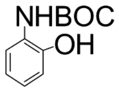
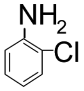
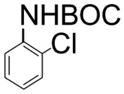
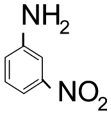
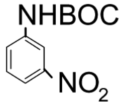
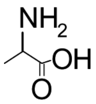
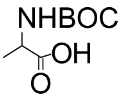
Although $FeCl_3$ has been extensively used as a Lewis acid in various organic transformations, it has not been used for the protection of amines as their BOC derivatives. This prompted us to use $FeCl_3$ for the BOC protection of amines. Herewith, we report that $FeCl_3$ promotes the selective BOC protection of amines under mild conditions with excellent yield.

RESULTS AND DISCUSSION

When a variety of amines were treated with $(BOC)_2O$ in the presence of $FeCl_3$, the corresponding N-BOC-protected amines were obtained in excellent yields. The substrates were examined in our studies, and the results obtained are summarized in Table 1. Thus the present procedure to introduce the BOC protecting group is quite general as a wide range of amines underwent reaction smoothly with $(BOC)_2O$. In the cases of 2-chloroaniline (entry h) and 3-nitroaniline (entry i), the yields are poor (20%). It contributes to the low reactivity of these deactivated anilines. It is noteworthy that the reaction is chemoselective in the case of 2-amino phenol (entry g) as the amine; being more nucleophilic than alcohol, it underwent reaction faster, giving corresponding N-BOC-protected product in good yield. Moreover, it is important to highlight that no side reaction, such as biscarbonylation or the formation of isocyanate or urea, was observed. Surprisingly, when this reaction condition was applied to protect 6-aminoquinoline, 8-aminoquinoline, 2-ethyl aniline, and 4-isoproyl aniline, product formation did not occur; only a white complex was obtained, which may be due to complexation with $FeCl_3$. The BOC protection of 2-aminophenol (entry g) and β-alanine (entry j) was carried out in acetonitrile/water (1:1) as they are not soluble in dichloromethane. The reaction with 0.25 equivalent or 0.5 equivalent of $FeCl_3$ was very slow. Therefore, the reaction was carried out using a 1:1:1 molar ratio. The reaction was carried out easily at room temperature (rt) (Scheme 1).

To check the effect of other Lewis acids in the present reaction condition, the BOC protection of aniline, 4-aminopyridine, and 3-nitroaniline was carried out using $AlCl_3$ (20% mol) as Lewis acid. Although $AlCl_3$ promotes the BOC protection of amines, comparatively it takes a longer reaction time to complete the reaction (i.e., aniline takes 3 h to afford the corresponding BOC-protected aniline, 4-aminopyridine gave the required product in 5 h, and 3-nitroaniline gave only traces of BOC-protected

Table 1. $FeCl_3$ promoted BOC protection of amines

Entry	Substrate	Product[a]	Reaction condition/Time	Yield[b] (%)
a			CH_2Cl_2, 15 min, rt	94
b			CH_2Cl_2, 15 min, rt	92
c			CH_2Cl_2, 15 min, rt	92
d			CH_2Cl_2, 20 min, rt	94
e			CH_2Cl_2, 20 min, rt	94
f			CH_2Cl_2, 20 min, rt	94
g			ACN/H_2O (1:1), 20 min, rt	92
h			CH_2Cl_2, 24 h, rt	20
i			CH_2Cl_2, 5 h, rt	20
j			ACN/H_2O (1:1), 1 h, rt	90

[a] Products were characterized by comparison with spectroscopic data.

[b] Isolated yields.

$$R{-}NH_2 \xrightarrow[CH_2Cl_2,\quad r.t.]{FeCl_3,\ (BOC)_2O} R{-}NHBOC$$

Scheme 1. R = aliphatic and aromatic compounds.

compound after 24 h). The plausible mechanism can be visualized as the activation of carbonyl group of BOC anhydride by the attack of $FeCl_3$ followed by nucleophillic attack of amine to the BOC anhydride. This facilitates the extrusion of t-butanol and carbon dioxide as leaving entities, eventually leading to the formation of N-BOC-protected amines.

CONCLUSION

In summary, $FeCl_3$ promotes the protection of amines as BOC derivatives. The present method works with various aromatic and aliphatic amines under mild conditions. Moreover, this protocol appears to be competitive and in some cases superior to previously reported procedures that work under basic conditions. The results show the completion of the reaction in 20–30 min with good to excellent yield as compared to the various methods reported in literature. The present method also offers advantages such as environmental safety, readily available, inexpensive laboratory benchtop reagents, and mild reaction conditions with simple workup. Thus, it is believed that the present method is a major step forward in the protection of amines.

EXPERIMENTAL

General Procedure for BOC Protection of Amines

$(BOC)_2O$ (1 mmol) and $FeCl_3$ (1 mmol) were added to a solution of amine (1 mmol) in dichloromethane (10 ml), and the reaction mixture was stirred for the time specified in Table 1. After completion of the reaction as indicated by thin-layer chromatography (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. It was then separated, dried over Na_2SO_4, and evaporated under reduced pressure. The residue obtained was purified by column chromatography on silica gel by using 10% EtOAc–hexane as eluent to give the pure product.

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