

# Molecular Sieves as a New, Highly Efficient, Inexpensive and Reusable Catalyst for N-Ter-Butoxycarbonylation of Amines

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## Abstract

Molecular sieves was found to be a new catalyst for chemoselective N-tert-butoxycarbonylation of amines at room temperature and under solvent-free conditions for range of amines, which includes acyclic, aromatic and sterically hindered amines. Environmental benignity, cost effectiveness, and high yields are the important attributes of the present procedure.

**Keywords:** Amine protection; Molecular sieves; Lewis acid; N-BOC

## Introduction

Increasing importance of environmental concerns and promotion of green processes are forcing replacement of traditional acid/base catalysis. Protection and deprotection of functional groups is an important tool in synthetic organic chemistry [1,2]. BOC group has several advantages as protecting group for amines [3]. Though there are several methods available for BOC protection of amines, there is a need for green catalyst. Molecular sieves 4A<sup>o</sup> are advocated for this purpose. Aryl amines has reduced nucleophilicity compared to primary or secondary aliphatic amines, due to which BOC protection of aryl amines are not very easy. Existing methods for N-BOC protection has several disadvantages like extended reaction times, elevated temperatures [4], addition of bases like DMAP [5,6], NaOH [7], Pyridine [8], NaHMDS [9]. This is also same in the case of Lewis acid catalysis like LiClO<sub>4</sub> [10], Zn(ClO<sub>4</sub>)<sub>2</sub> [11], ZrCl<sub>4</sub> [12], sulfamic acids [13], and indium(III) halides [14] are reported for BOC protection of amines. Molecular sieves has wide spread applications in diverse areas. Thus they are not only used as adsorbents or desiccants, but also as catalyst in several organic reactions. It is used for trans-esterification, preparation of enamines, ketimines [15,16], synthesis of acetals [17], Oxidation of 2° alcohols [18]. The importance of molecular sieves in heterogeneous catalysis depends of its micro-porous structure. Modification of framework composition results in change of its acidic/ basic/ redox properties. Therefore, molecular sieves (MS), which have several catalytic sites inside their structures, have been successfully employed to promote N-BOC protection. In the present study we selected variety of amines and protected with Di-tert-butyl dicarbonate at 20-25°C in solvent free condition using molecular sieves 4A<sup>o</sup> as catalyst. Though reaction proceeds without catalyst in some reactions, Molecular sieves reduced reaction time significantly. In case of less nucleophilic substrates, reaction not proceeded without catalyst.

## Results and Discussion

When a variety of amines were treated with Di-tert-butyl dicarbonate in the presence of Molecular sieves 4A<sup>o</sup>, the corresponding N-BOC-protected amines were obtained in good yields (Table 1). 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 Di-tert-butyl dicarbonate. In the cases of L-tert-Leucine (Entry 1) and Diethanolamine (Entry 4), the yields are moderate (50-95%). It contributes to the low reactivity of these compounds. It is noteworthy that the reaction does not require any toxic reagents and Di-tert-butyl dicarbonate in equimolar ratio is

required. It is also important to note that aliphatic amines react much faster than aromatic or hindered amines. Moreover, it is important to highlight that no side reaction, such as bis-carbonylation or the formation of isocyanate or urea, was observed. When this reaction condition was applied to protect ammonia, S-phenyl ethyl amine, aniline, product formed with excellent yields. The BOC protection of diethanolamine (Entry 4) and L-tert-Leucine (Entry 1) was also carried out. The reaction with 2.5 mol% or 5 mol% of Molecular sieves 4A<sup>o</sup> was very slow and reactions not completed (Table 2). Therefore, the reaction was carried out using a 1:1:0.1 molar ratios of amine: Di-tert-butyl dicarbonate: Molecular sieves respectively. The reaction was carried out easily at room temperature (20-25°C) (Scheme 1). After reaction, filtered catalyst reused for 3 cycles. Catalyst activity not reduced till 3 cycles.

## Experimental

### Materials and methods

Commercially available reagents were used directly without any purification unless otherwise stated. Molecular sieves with porous size 4A<sup>o</sup> were used as catalyst. Reaction progress was monitored by silica gel aluminum sheets (60F-254) and RP-18 F254s using UV light as a visualizing agent. Silica gel 100-200 mesh size used to purify said compounds. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded on Bruker Avance 400 spectrometer with TMS as internal standard. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), or doublet of doublet (dd). The value of chemical shifts (δ) is given in ppm and coupling constants (J) in Hertz (Hz). Mass spectra were obtained using Agilent LC-MS instrument in electrospray positive and negative ionization modes.

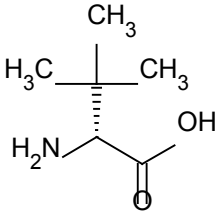
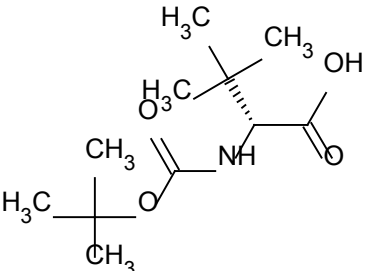
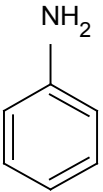
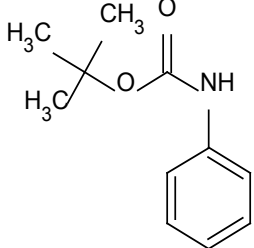
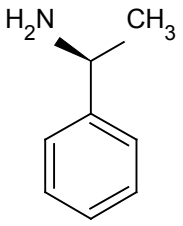
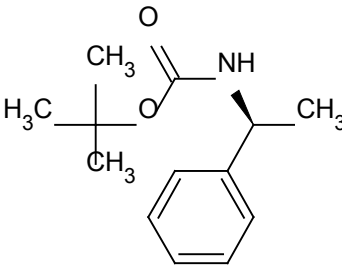
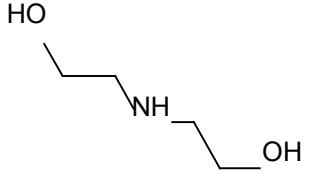
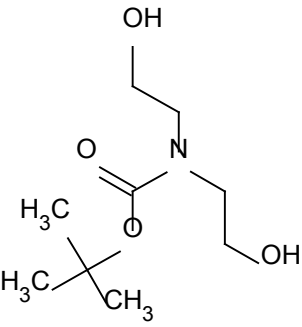
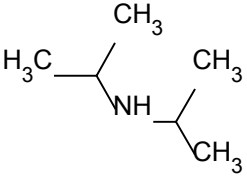
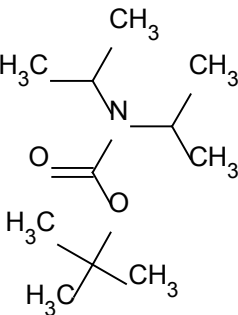
**General Procedure for BOC Protection of Amines:** Di-tert-butyl dicarbonate (1 mmol) and Molecular sieves 4A<sup>o</sup> (0.1 mmol) were added to a solution of amine (1 mmol), and the reaction mixture

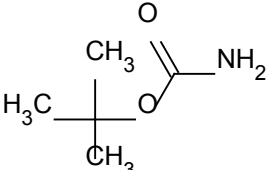
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| S No | Starting material   | Product  | Reaction time | Yield |
|------|---|--|---------------|-------|
| 1    |    |    | 12 h          | 28 %  |
| 2    |    |    | 30 min        | 75 %  |
| 3    |  |   | 15 min        | 95 %  |
| 4    |  |  | 5 h           | 51 %  |
| 5    |  |  | 3 h           | 80 %  |

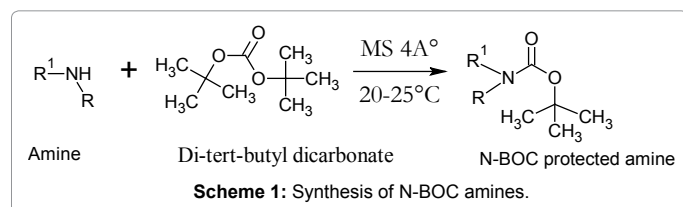
|   |                 |  |      |      |
|---|-----------------|--|------|------|
| 6 | NH <sub>3</sub> |  | 10 h | 98 % |
|---|-----------------|--|------|------|

Reaction condition: 1:1:0.1 Molar ratios of amine: Di-tert-butyl dicarbonate: Molecular sieves respectively at 20-25°C.

**Table 1:** Synthesized N-BOC protected amines.

| Catalyst loading |       |                        |
|------------------|-------|------------------------|
| S No             | Mol % | Remarks                |
| 1                | 0     | Reaction not started   |
| 2                | 2.5   | Reaction not completed |
| 3                | 5     | Reaction not completed |
| 4                | 10    | Reaction completed     |

**Table 2:** Study on catalyst loading.



was stirred for the time specified in Table 1. After completion of the reaction as indicated by thin-layer chromatography (TLC), and the reaction mixture was diluted with dichloromethane, and filter reaction mixture. Obtained filtrate 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. Details are summarized in Table 1.

## Conclusions

In conclusion, we have devised a method for *N*-tert-butoxycarbonylation of amines in the presence of Molecular sieves 4A° as a catalyst (10 mol%). This general method is a valuable addition to the existing *N*-tert-butoxycarbonylation protocols. More importantly, the present procedure offers a chemo selective with respect to amine and hydroxyl groups, and environmentally benign strategy by the use of Molecular sieves which could be easily handled, removed, and recycled.

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