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## Solvent-free, instant, ambient, n-boc protection of amines -A green, recyclable heterogenous acid catalysis by Amberlite-IR 120

Vijay Kumar Pasala

Department of Chemistry, Osmania University, Hyderabad-500 007

### ABSTRACT

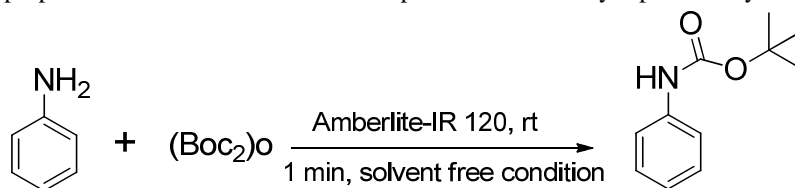
A facile and versatile method for the *N*-tert-butoxycarbonylation of amines with  $\text{Boc}_2\text{O}$  in the presence Amberlite-IR 120 under solvent-free conditions. This method is general for the preparation of *N*-Boc derivatives of both aliphatic (cyclic and acyclic) and aromatic amines.

**Keywords:** Amines,  $(\text{Boc})_2\text{O}$ , Amberlite-IR 120, solvent-free

### INTRODUCTION

Exploration of new reagents, new methodologies for the selective protection of functional groups and their deprotection has been on the radar for quite some time to make the reactions hassle-free, environment friendly and easy to handle. Among them heterogenous catalysis-with clays, solid supported catalysts-etc, is one area towards which a practicing chemist looks at. In a multistep organic synthesis involving amino group, the protection and deprotection is a major issue which is effectively solved by using Boc-protecting group<sup>1</sup>. The resulting carbamates are highly stable towards to alkaline conditions and very labile to even mildly acidic conditions rolling back to the starting amines<sup>2</sup>. Various reagents and methods are available for the *N*-tert-butoxycarbonylation of amines.<sup>3-11</sup> However, to avoid the problems coupled with a strong acid or a base initiating the side reactions, various Lewis acids have been introduced<sup>12-21</sup>. But most of them suffer with drawbacks such as long duration of reaction, high reaction temperature etc. In addition, many catalysts need special conditions for their preparation.

This demands for the development of ecofriendly and hassle-free method for the amino group protection. Heterogenous catalysis is one such area with the anticipated traits used in the recent times in both process and custom related synthesis of fine chemicals.<sup>22</sup> Amberlite-IR 120 resin has emerged as an efficient heterogeneous catalyst for chemical transformations<sup>23</sup> Amberlite IR-120 is one such heterogenous catalyst fitting into the above class with requisite properties for the execution of *N*-Boc protection with easy separation by simple filtration.



To begin with, aniline was reacted with di-*tert*-butyl dicarbonate in DCM in the presence of Amberlite-IR 120 at room temperature for 3 min to give the expected product in 95% yield. Further the reaction was verified in different solvents, but ended in no-improvement in the yields. In deed, highest yield was with DCM (95%) and the lowest was found with toluene and CH<sub>3</sub>CN (80%) (Table 1, entry 1&3). Actually all these attempts were inferior to solvent-free method where the yields were almost 100% (Table 1, entry 4).

**Table 1** *N-tert*-Butoxycarbonylation of amines in the presence of Amberlite-IR 120 under solvent-free conditions <sup>a</sup>

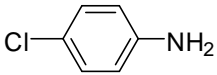
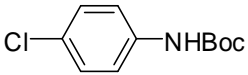
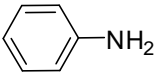
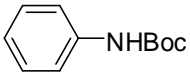
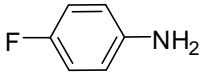
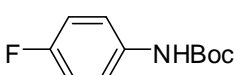
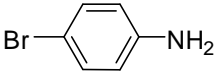
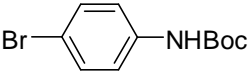
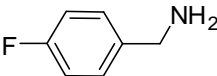
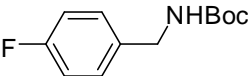
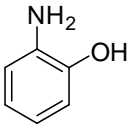
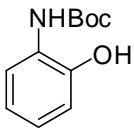
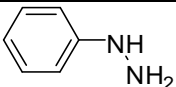
Entry	Solvent	Yield <sup>b</sup> (%)
1	DCM	95
2	CH <sub>3</sub> CN	92
3	Toluene	80
4	Dioxane	79
5	DMF	85
6	Solvent free	99, 98, 95, 94 <sup>b</sup>

<sup>a</sup> Reaction conditions: aniline (1mmol) and Boc<sub>2</sub>O (1 mmol); Amberlite-IR 120 (15%, w/w); r.t.; 1 min.

<sup>b</sup> Catalyst was used over four runs.

This success has encouraged exploring the universal application of this method on various primary, secondary aliphatic and aryl amines with di-*tert*-butyl dicarbonate in presence of Amberlite-IR 120 to give the corresponding *N-tert* butylcarbamates in good to excellent yields in 1-3 min (Table 2). Indeed, the rate of boc protection for aniline was highest with 99% yield in less than 1min (Table 2, entry 2) and it was reduced with the presence of either electron donating or withdrawing groups on aromatic ring (Table 2, entry 1,3-5). Aralkyl amines (Table 2,entry 8,9) exhibited similar rate as those of aromatic amines.

**Table 2** *N-tert*-Butoxycarbonylation of amines in the presence of Amberlyst-15 under solvent-free conditions<sup>a</sup>

Entry	Amine	Product	Time (min)	Yield <sup>b</sup> (%)
1			1	95
2			2	99
3			3	96
4			1	95
5			1	96
6			4	92
7			2	95

8			2	99
9			2	98
10			1	95
11			2	98
12			1	98
13			2	99
14			2	99
15			2	98
16			3	95

*a All the products were characterized by IR, NMR and mass spectroscopy and compared with those reported in the literature.*

*b Isolated yields after column chromatography.*

Further aliphatic (acyclic and cyclic) primary and secondary amines (Table 2; entries 11–16) gave the corresponding *N*-Boc products in 95–99% yields in 1–3 min. This method is selective and successfully applied for the selective protection of amine in the presence of hydroxyl group (Table 2; entries 6).

In conclusion, this paper describes the efficient general methodology for the protection of amines bestowed with characteristic features like selectivity, simple experimental procedure, inexpensive heterogeneous recyclable catalyst, solvent-free reaction conditions, short reaction times and high yields.

**General methods:** Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray.  $^1\text{H}$  NMR spectra was determined in  $\text{CDCl}_3$  or  $\text{DMSO-}d_6$  solution by using 400 MHz spectrometer. Proton chemical shifts ( $\delta$ ) are relative to tetramethylsilane (TMS,  $\delta = 0.00$ ) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants ( $J$ ) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer

### Experimental procedure

To a mixture of  $\text{Boc}_2\text{O}$  (1 mmol), Amberlyst-15 (15%, w/w) was added amine (1mmol) and stirred at room temperature for the described time (Table-1). The completion of the reaction was monitored by TLC and mixture was extracted into  $\text{CH}_2\text{Cl}_2$  (10 mL), facilitating the separation of catalyst by filtration. The filtrate was dried with anhydrous sodium sulphate and concentrated under vacuum. The residue was subjected to column chromatography to obtain pure product. The recovered catalyst was recycled for three times to furnish the product with a little variation in the yield (Table 1).

Entry 2: IR (KBr) 3310, 3230, 1690, 1530, 1480, 1470, 1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  (ppm) 1.51 (s, 9 H), 6.98 (m, 1 H), 7.21 (m, 2 H), 7.35 (m, 2 H), 9.1 (s, 1 H, NH);  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  (ppm) 28.25, 79.96, 118.74, 122.34, 129.60, 136.64, 156.10; M.P. 134-136.

Entry 11 Mp 91  $^\circ\text{C}$  (lit. 91-92  $^\circ\text{C}$ ). FTIR (KBr): 3354 NH, 3282 NH, 1726 C=O, 1698 C=O.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.43 (s, 9H, Boc), 5.92 (br s, 1H, PhNH), 6.71- 6.87 (m, 4H, Ph, BocNH), 7.13-7.21 (m, 2H, Ph).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  28.4 ( $\text{CH}_3$ , Boc), 81.1 (Cq, Boc), 113.3, 120.7, 129.1, 148.8 (Ph), 156.5 (C=O)

Entry 16 Colorless oil. FTIR (liq. film): 3351 NH, 1693 C=O.  $^1\text{H}$  NMR 200 MHz ( $\text{CDCl}_3$ )  $\delta$  0.93 (t,  $J = 7.2$  Hz, 3H,  $\text{CH}_3$ ), 1.34 (m, 2H,  $\text{CH}_2$ ), 1.45 (s, 11H, Boc +  $\text{CH}_2$ ), 3.12 (m, 2H,  $\text{CH}_2$ ), 4.83 (br, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  13.4, 19.6, 31.7, 39.7 (Bu), 27.7 (Boc), 77.8 (C, Boc), 155.6 (C=O, Boc).

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