

## Indion 190 수지에 의한 아민축매의 *N*-Boc protection의 실용적이며 친환경적 접근법

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(접수 2009. 3. 10; 수정 2009. 6. 30; 게재확정 2009. 7. 28)

### Practical and Green Approach for *N*-Boc Protection of Amines Catalyzed by Indion 190 Resin

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(Received March 10, 2009; Revised June 30, 2009; Accepted July 28, 2009)

**요 약.** Indion 190 수지의 존재하에서 di-*tert*-butoxypyrocarbonate (Boc)<sub>2</sub>O를 이용한 아민의 *N*-Boc protection의 효과적인, 화학적 선택성적인, 실용적인 실험안. 수지는 반응혼합물로부터 쉽게 분리되었고 활성의 감소 없이 재사용되었다. 간단한 workup, 온화한 조건, 짧은 반응시간, 높은 수율은 이 방법의 두드러진 특색들이다.

**주제어:** 아민, Indion 190 수지, Di-*tert*-butoxypyrocarbonate (Boc)<sub>2</sub>O, 화학적 선택성

**ABSTRACT.** An efficient, chemoselective and practical protocol for *N*-Boc protection of amines using di-*tert*-butoxypyrocarbonate (Boc)<sub>2</sub>O in presence of Indion 190 resin. Resin was easily separated from the reaction mixture by filtration and reused in subsequent reactions without any apparent loss of activity. Simple workup, mild condition, short reaction time and high yield are some of the striking features of the present process.

**Keywords:** Amines, Indion 190 resin, Di-*tert*-butoxypyrocarbonate (Boc)<sub>2</sub>O, Chemoselectivity

## INTRODUCTION

Protection and de-protection under mild reaction condition are crucial steps in organic synthesis. The protection of amines is an important step in synthetic organic chemistry. The *tert*-butoxycarbonyl (Boc) is widely used as a protecting group for amino functional group in organic synthesis.<sup>1-6</sup> Aryl amines protected in its Boc forms are important intermediates in organic synthesis. It has been used for the direct lithiation of aromatic rings and the preparation of

unsymmetrical urea's amongst others.<sup>7,8</sup> There are varieties of *N*-Boc protection strategies available in the literature.<sup>9,10</sup> *N*-Boc has gain importance, due to its resistance towards basic and nucleophilic stability as well as stability towards catalytic hydrogenation.<sup>11</sup> In recent years, various methods have been developed for the protection of amines in their *N*-Boc form, either in the presence of base (DMAP,<sup>12-14</sup> aq. NaOH,<sup>15,16</sup> NaHMDS<sup>17</sup>) or Lewis acid catalyst such as Zr(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O,<sup>18</sup> ZrCl<sub>4</sub>,<sup>19</sup> LiClO<sub>4</sub>,<sup>20</sup> Yttria, Zirconia,<sup>21</sup> Bronsted acid ionic liquid,<sup>22</sup> thiourea,<sup>23</sup> and

Iodine  $\text{CsF}^{24}$  are also employed for *N*-Boc protection. However, despite the potential utility of these catalysts, many of these methodologies are associated with several shortcomings such as extended reaction time,<sup>25</sup> elevated temperatures,<sup>26</sup> tedious work-up, anhydrous organic solvents and non-recyclability of the catalyst.

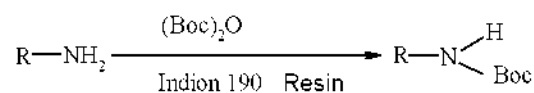
It is a need to develop an efficient and selective protecting reagent which can work under mild condition. By using solid catalyst Indion 190 resin, we have successfully carried out the *N*-Boc protection, which can be used for wide variety of substrates. We found that Indion 190 resin possesses unique properties such as physical and chemical stability, nontoxicity, noncorrosiveness, reusability, environmental compatibility and selectivity. Indion 190 resin can be handled easily and separated from the reaction mixture by simple filtration, washed with water, dried in oven and reused as per the experimental convenience. The recovered catalyst was consecutively reused several times without any variations in the yield of the product.

## RESULTS AND DISCUSSION

Various catalysts such as  $\text{BiCl}_3$ ,  $\text{CdCl}_2$ , triethylamine, PTSA,  $\text{Bi}(\text{NO}_3)_3$ ,  $\text{CuCl}_2$  and Indion 190 resin were used for the reaction between aniline and  $(\text{Boc})_2\text{O}$ . The results obtained are summarized in Table 1.

A wide range of structurally diverse aromatic, aliphatic and heterocyclic amines have been used during the reaction and the corresponding results of the reaction yield and time are listed in Table 2.

It was observed that, when electron withdrawing group present along with amine group, reaction progresses slowly, but it is noteworthy that electron donating substituents on the aromatic ring enhance the rate of the reaction. This may be due to lone pair of electron of nitrogen of amine functional group



Scheme 1. *N*-Boc protection of amine

which involves in the conjugation with electron withdrawing group and hence, it is not easily available for the reaction with  $(\text{Boc})_2\text{O}$  to form *N*-Boc protected amines. Further, presence of electron withdrawing group leads effect on the yield of the product, which was found to less compare to those formed in absence of same. Chemo selectivity of Indion 190 resin facilitates the reaction selectively with amino group in presence of other functional groups like  $-\text{OH}$ ,  $-\text{SH}$ , etc. resulting in *N*-Boc product in high yield.

## EXPERIMENTAL

All commercial reagents were used as received without purification and all solvents were of reagent grade. The reaction mixture was stirred in a round bottom flask magnetically and was monitored by TLC using on 0.25 mm E-Merck silica gel 60 F<sub>254</sub> precoated plates, which were visualized with UV light. Melting points were taken in open capillaries. The IR spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr discs.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra in  $\text{DMSO}-d_6$  were recorded on VXR-300 MHz using TMS as internal standard.

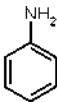
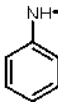
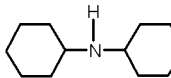
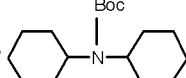
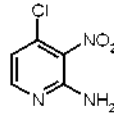
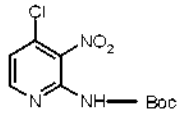
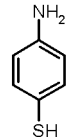
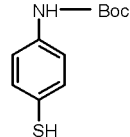
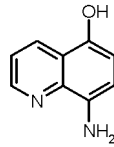
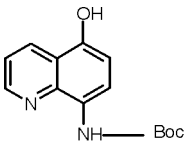
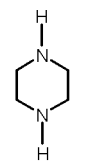
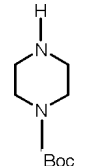
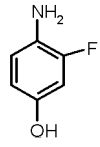
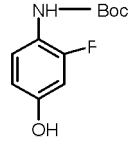
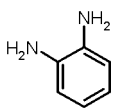
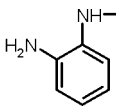
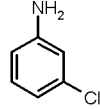
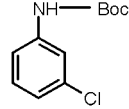


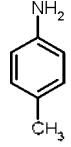
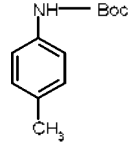
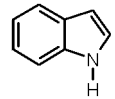
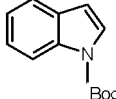
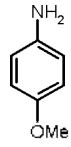
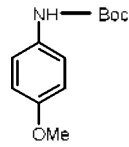
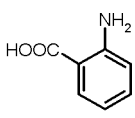
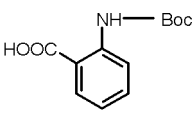
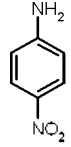
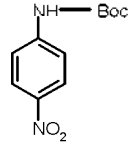
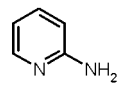
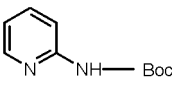
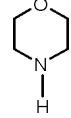
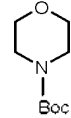
### General Experimental Procedure

Amine (0.01 mole) was added to the solution of  $(\text{Boc})_2\text{O}$  (0.01 mole). Indion 190 resin and *t*-butanol (15 mL) with constant stirring. After addition, the reaction mixture was heated at 50 °C till completion of the reaction. The reaction progress was monitored by TLC. After completion of the reaction, the catalyst was separated by filtration, washed with water, dried and reused. Evaporation of solvent

Table 1. Effect of different catalyst on the yield and reaction time for *N*-Boc protection of aniline

Entry	Catalyst	Time (hr.)	Yield (%)
1	$\text{BiCl}_3$	2	87
2	$\text{CdCl}_2$	2	74
3	PTSA	2	63
4	$\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$	2.5	75
5	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	2.5	72
6	Triethylamine	2.5	80
7	Indion 190 resin	1.5	95

Table 2. Effect of nature of amines as well as presence of different functional group along with amine, on the Indion 190 catalyzed *N*-Boc protection of various amines

Entry	Substrate	Product	Time (h)	Yield (%)	Entry	Substrate	Product	Time (h)	Yield (%)
1			1.5	95	10			2	93
2			2.5	93	11			2	90
3			1.5	93	12			2	96
4			2	95	13			2	90
5			2	92	14			1.5	92
6			2	93	15			2.5	75
7			1.5	95	16			3.5	67
8			3	79	17			2	75
9			2	92					

imparts solid crude product. The product was purified by column chromatography, using ethyl acetate-petroleum ether (2:8) eluent. The physical and spectral data of known compounds are in agreement with those reported in the literature.<sup>9,10,25</sup>

### Spectral data of *N*-Boc amines

Entry 1: IR (KBr) 3310, 3230, 1690, 1530, 1480, 1470, 1250  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (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 (DMSO- $d_6$ )  $\delta$  (ppm) 28.25, 79.96, 118.74, 122.34, 129.60, 136.64, 156.10; M.P. 134-136

Entry 2: IR (KBr): 3315, 3200, 1580, 1540, 1520, 1490, 1410, 1260, 782, 650, 590  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\text{CDCl}_3$  ( $\delta$ -ppm) 1.53 (s, 9 H), 7.25 (d, 1 H,  $J = 7.5$  Hz), 8.56 (d, 1 H,  $J = 7.5$  Hz), 8.11 (s, 1 H, NH);  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  ( $\delta$ -ppm) 28.73, 82.10, 118.20, 129.22, 142.10, 151.90, 152.10, 157.89; M.P. 159-161

Entry 3: IR (KBr): 3610, 3325, 3250, 1590, 1570, 1520, 1490, 1470, 1255  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR DMSO- $d_6$  ( $\delta$ -ppm) 1.49 (s, 9 H), 6.90 (d, 1 H,  $J = 7.0$  Hz), 8.03 (d, 1 H,  $J = 7.0$  Hz), 7.55 (m, 1 H), 8.52 (d, 1 H), 8.84 (d, 1 H), 8.64 (s, 1 H, OH), 10.17 (s, 1 H, NH);  $^{13}\text{C}$  NMR DMSO- $d_6$  ( $\delta$ -ppm) 28.25, 111.60, 113.10, 114.80, 120.86, 130.50, 134.27, 139.55, 149.23, 152.13, 158.19; M.P. 215-217

Entry 4: IR (KBr): 3640, 3340, 3210, 1580, 1570, 1510, 1390, 1200  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\text{CDCl}_3$  ( $\delta$ -ppm) 1.51 (s, 9 H), 6.39 (s, 1 H), 6.47 (d, 1 H,  $J = 7.5$  Hz), 6.56 (d, 1 H,  $J = 7.5$  Hz), 7.26 (s, 1 H, OH), 7.57 (s, 1 H, NH);  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  ( $\delta$ -ppm): 28.32, 84.12, 104.63, 112.80, 122, 124.10, 151.85, 157.60, 166.15; M.P. 147-149

## CONCLUSION

In conclusion, Indion 190 resin was found to be an efficient catalyst for *N*-Boc protection of amines. The main advantages of the present synthetic protocols are mild reaction conditions, high chemo selectivity, ecofriendly recyclable catalyst and easy reaction work-up procedure. These advantages make the present method useful for large-scale operations.

**Acknowledgments.** The authors are grateful to Ion Exchange (India) Ltd, Mumbai for providing gift samples of Indion 190 resin and University Grant Commission, New Delhi for financial support. The authors are thankful to Dr. S. T. Gadade, Principal, C. K. Thakur College, for providing laboratory and other facilities.

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