N-Boc Protection of Amines with Di-*tert*-butyldicarbonate in Water under Neutral Conditions in the Presence of β-Cyclodextrin[1]

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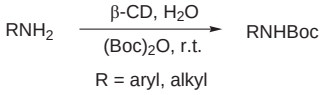
Abstract: A new protocol for protection of aryl and aliphatic amines was developed with $(Boc)_2O$ in the presence of β-cyclodextrin in water. A catalytic amount of β-cyclodextrin is specific for activation of amines. This procedure works well on a wide variety of both electron-rich and electron-deficient amines.

Key words: β-cyclodextrin, amines, Boc-anhydride, Boc-derivatives, water

Protection of amino groups is often required during the synthesis of peptides, amino acids and other natural products. Among the most widely used protecting groups,[2] the *tert*-butoxy carbonyl (Boc) has been recognized as the method of choice due to easy installation, removal, stability towards nucleophiles and strong basic conditions.[3] Di-*tert*-butyldicarbonate [Boc_2O] is widely applied to introduce the *tert*-butoxy carbonyl (Boc) protecting group.[4] Boc-protected aryl amines are important intermediates in organic synthesis and have been used for the directed lithiation of aromatic ring and preparation of unsymmetrical ureas amongst others.[5,6]

However, various reagents and methodologies developed over the years to introduce this group using Boc_2O have been carried out either in the presence of a base (DMAP,[7] aq NaOH,[8] NaHMDS[9]) or Lewis acid catalysts such as $Zr(ClO_4)_2 \cdot 6H_2O$,[10] $ZrCl_4$,[11] etc. These reports have demonstrated that the reaction of Boc_2O requires acidic or basic catalysts, extended reaction times,[12] elevated temperatures,[13] tedious work-up, and anhydrous organic solvents. Keeping in view of the various limitations in the introduction of Boc group, we felt the need to develop a cleaner synthetic methodology under neutral conditions.

Recently, organic reactions in aqueous media have acquired significance as they overcome the harmful effects of organic solvents and are environmentally benign. These reactions will be more sophisticated if they can be performed under supramolecular catalysis. In our efforts to develop chemical reactions under supramolecular catalysis involving cyclodextrins in water,[14] we report herein an efficient method for the preparation of *N*-Boc derivatives from amines using catalytic amount of β-cyclodextrin as a catalyst in water at room temperature under neutral conditions (Scheme 1).



Scheme 1

Cyclodextrins are cyclic oligosaccharides, which exert micro environmental effect. They catalyze reactions by supramolecular catalysis through non-covalent bonding as in enzymes. The attractive features of cyclodextrins in the modeling of chemical reactions prompted us to investigate the Boc protection of a variety of amines in the presence of β-cyclodextrin with Boc_2O in water. β-CD was used as a catalyst since it is inexpensive and could also be recovered and reused. In the absence of cyclodextrin under the same conditions, even under extended reaction times, the yields obtained were only to the extent of 20% (e.g., entry 3, Table 1: 9 h).

These reactions are efficiently carried with catalytic amount of β-cyclodextrin (0.1 mmol) in water followed by the addition of amines/amino acid esters and Boc_2O.[15] These reactions take place at room temperature without generation of any toxic waste products. All the products were characterized by ^1H NMR and IR spectroscopy, mass spectrometry, and by the comparison with the known compounds.[10,11]

Reaction rates and yields are governed by the nucleophilicity of the amines. In particular, anilines with fluoro and COMe groups give the protected derivative with lower yields considering their low reactivity (Table 1, entry 4 and 5), whereas the yields are comparatively better with the aliphatic amines (Table 1). In the case of amino acid esters the yields are in the range of 82–92% (Table 2).

In conclusion, we have developed a simple and efficient procedure for the direct protection of amines with Boc under mild conditions with an inexpensive and reusable catalyst (β-CD) at room temperature. This method works well with different substrates. The notable features of this methodology are cleaner reaction profiles, high yields, shorter reaction times and operational simplicity.

Acknowledgment

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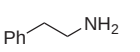
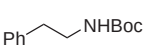
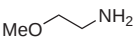
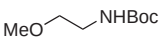
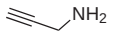
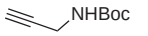
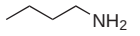
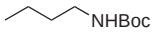
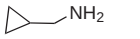
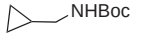
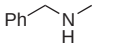
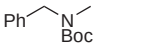
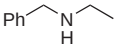
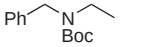
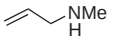
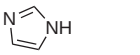
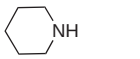
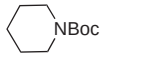
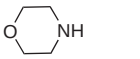
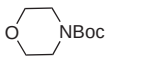
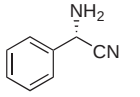
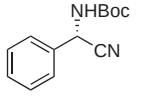
Table 1 Protection of Amines as Boc Derivatives

Entry	Starting material	Product[a]	Time		Yield (%)[b]
			min	h	
1	Ph-NH_2	Ph-NHBoc		2.5	75[c]
2	*o*-MeO-C_6H_4-NH_2	*o*-MeO-C_6H_4-NHBoc		3.0	76[c]
3	*p*-MeO-C_6H_4-NH_2	*p*-MeO-C_6H_4-NHBoc		1.5	78[c]
4	*p*-F-C_6H_4-NH_2	*p*-F-C_6H_4-NHBoc		4.0	60[c]
5	*p*-COMe-C_6H_4-NH_2	*p*-COMe-C_6H_4-NHBoc		4.0	50[c]
6	Bn-NH_2	Bn-NHBoc	7		96
7			8		94
8			5		96
9			10		91
10			4		90
11			5		94
12			12		90
13			10		91
14			5		93
15			4		89
16			8		92
17			7		90
18				2.5	73[c]

[a] All products were characterized by ^1H NMR and IR spectroscopy, and mass spectrometry.
[b] Isolated yields after purification.
[c] Remainder is starting material.

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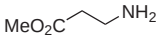
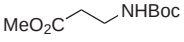
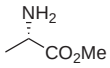
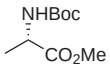
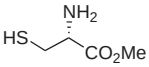
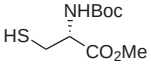
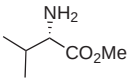
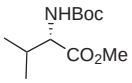
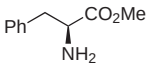
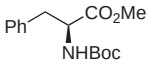
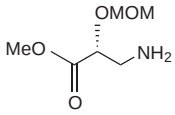
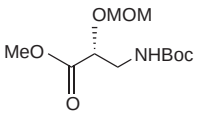
Table 2 β-CD-Catalyzed Protection of Amino Acid Esters

Entry	Substrate	Product[a]	Time (min)	Yield (%)[b]
1			20	92
2			15	90
3			20	88
4			10	87
5			25	82
6			20	90

[a] All products were characterized by ^{1}H NMR and IR spectroscopy, and mass spectrometry.
[b] Isolated yields after purification.

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(15) **General Procedure.**
β-Cyclodextrin (0.1 mmol of β-CD) was dissolved in H_2O (15 mL) at r.t. and the amine (1 mmol) dissolved in acetone–MeOH (1 mL) was added with stirring. Then $(Boc)_2O$ (1 mmol) was added and the reaction was stirred at r.t. for specific reaction times (Table 1). The reaction mixture was extracted with EtOAc and washed with brine. The organic phase was dried (Na_2SO_4), filtered and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography with EtOAc–hexane (1:9) as eluent. β-Cyclodextrin was recovered (95%) after lyophilization of the aqueous phase.