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N-Benzyloxycarbonylation of amines in the ionic liquid [TPA][L-Pro] as an efficient reaction medium

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Abstract

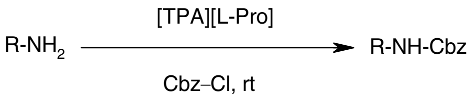
An efficient method for the N-benzyloxycarbonylation of amines is described. The reaction of amines with Cbz-Cl in the ionic liquid [TPA][L-Pro] afforded the corresponding *N*-Cbz derivatives in excellent yields. The method is versatile for the preparation of a wide variety of *N*-Cbz derivatives of aliphatic and aromatic amines.

Keywords: Amines; N-Benzyloxycarbonylation; Ionic liquid; [TPA][L-Pro]

The protection and deprotection of amines is very important in multi-step organic syntheses. Among the amine protecting groups, the benzyloxycarbonyl (Cbz) group is a very important and useful functionality.[1] The *N*-Cbz group is stable in the presence of a wide range of nucleophiles in alkaline as well as aqueous acidic conditions. It can be easily removed by catalytic hydrogenation without any side reactions to give the parent amine. In addition, Cbz also serves as a stable protecting group in peptide chemistry.[2] Limited methods are available for the conversion of amino groups to *N*-Cbz derivatives. Among them, reaction of an aryl/alkyl amine and benzyloxycarbonyl chloride (Cbz-Cl) in the presence of 4-(dimethylamino)pyridine (DMAP) is the most commonly employed method.[1] Recently, $La(NO_3)_3{\cdot}6H_2O$,[3] LiHMDS in THF–HMPA,[4] and β-cyclodextrin in aqueous medium[5] have been reported for this transformation. However, the utility of a catalyst-free ionic liquid for the preparation of *N*-Cbz derivatives has not been investigated at all.

In recent years, the use of ionic liquids (ILs) as green solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapour pressure, easy recyclability and reusability.[6–8] Maschmeyer and co-workers[9] reported the synthesis of ionic liquids using quaternary ammonium hydroxide and chiral carboxylic acids. These salts are promising additives as different alkyl residues in the $(R_4N)^+$ ammonium cation lead to different charge densities and hydrophobicity. Recently, we reported the facile synthesis of β-keto-sulfones using tetrapropylammonium L-prolinate [TPA][L-Pro] as an efficient reaction medium.[10,11] In continuation of our efforts to develop new organic transformations,[12–19] we observed that at room temperature, [TPA][L-Pro] is as an efficient reaction medium for the N-benzyloxycarbonylation of amines with Cbz-Cl.

Herein, we describe an efficient and high yielding protocol for the N-benzyloxycarbonylation of amines (Scheme 1). We prepared[11] the ionic liquid tetrapropylammonium L-prolinate [TPA][L-Pro] from readily available tetrapropylammonium hydroxide and L-proline in aqueous



Scheme 1.

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Table 1
N-Benzyloxycarbonylation of amines in the ionic liquid [TPA][L-Pro]

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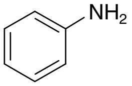
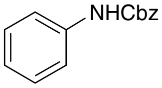
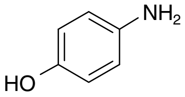
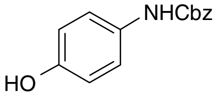
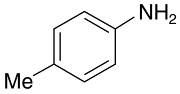
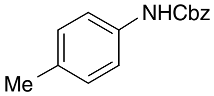
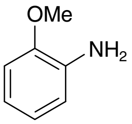
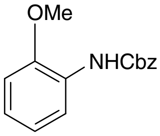
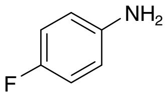
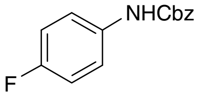
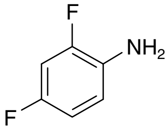
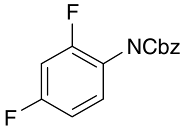
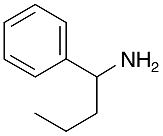
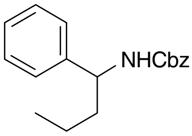
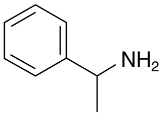
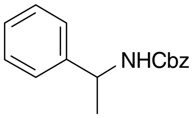
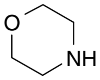
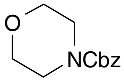
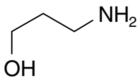
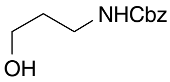
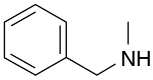
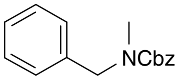
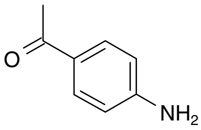
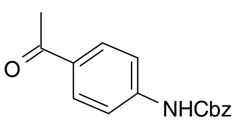
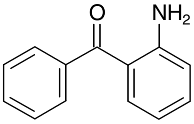
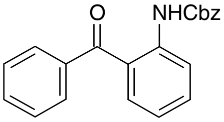
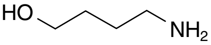
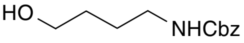
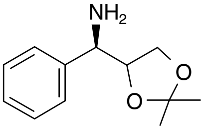
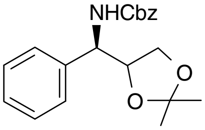
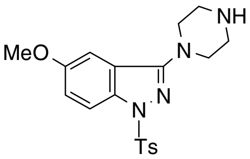
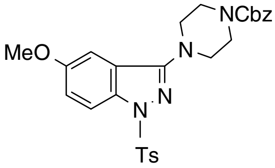
1			2	95
2			5	95
3			5	93
4			5	95
5			5	93
6			5	90
7			5	90
8			2	92
9			5	92
10			2	93
11			10	95
12			5	95

Table 1 (*continued*)

Entry	Substrate	Product[a]	Time (min)	Yield[b] (%)
13			5	94
14			2	96
15			5	90
16			10	95

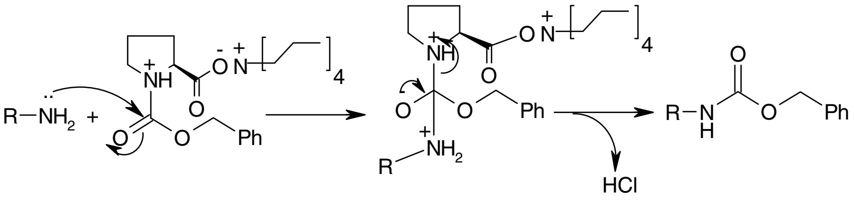
[a] Products were characterized by ^{1}H NMR and EIMS spectral data.

[b] Isolated yields after column chromatography.

medium at 60 °C. In general, all the reactions were carried out by the addition of the amines (1 mmol) to Cbz-Cl (1.2 mmol) in [TPA][L-Pro] at room temperature to give the corresponding *N*-benzyloxycarbamates in excellent yields (90–96%, Table 1). The time required for the reaction was comparatively short (2–10 min). Only the amino groups were protected while OH groups remained intact, for example, 4-aminophenol (entry 2), 3-amino propanol (entry 10) and 4-amino butanol (entry 14). In a chemoselective experiment, a 1:1 mixture of an aliphatic amine (benzyl amine) and an aromatic amine (aniline) (1 mmol each) was reacted with Cbz-Cl (1 mmol) in the presence of [TPA][L-Pro]. Only the aliphatic amine was derivatized and the aromatic amine was left intact. Further, aromatic amines containing electron-withdrawing groups also gave the desired derivatives in good yields. Labile functionalities such as acetonide protected 1,2-diols were compatible in this conversion. The protocol is highly chemoselective, involves simple experimental procedures, mild reaction conditions and gives excellent yields of Cbz-protected amines. We believe that the IL polarizes the carbonyl group of Cbz-Cl and facilitates the reaction (Scheme 2).

In conclusion, we have described an efficient method for the protection of amines as their *N*-benzyloxycarbonyl derivatives in the ionic liquid [TPA][L-Pro] at room temperature in excellent yields. The method has advantages of reduced reaction time and simple experimental work-up making it a useful addition to existing methodologies.

Typical experimental procedure: A mixture of amine (1 mmol) and benzyloxycarbonyl chloride (Cbz-Cl) (1.2 mmol) was taken in the ionic liquid [TPA][L-Pro] (1 mL) and the reaction was stirred at room temperature for the appropriate amount of time (Table 1). After completion of the reaction as monitored by TLC, water (5 mL) was added. The product was extracted into ethyl acetate (3 × 20 mL) and the combined organic layer was washed with saturated sodium bicarbonate followed by brine, and then dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was further purified by silica gel column chromatography. The ionic liquid was recovered from the aqueous layer by removing the water under reduced pressure or freeze dried and reused without loss of its activity for the next run.



Scheme 2. A Plausible mechanism.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.108.

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