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A facile protocol for *N*-Cbz protection of amines in PEG-600

Chun Lin Zhang, Dong Feng Zhang, Hong Yi Zhao, Zi Yun Lin, Hai Hong Huang *

Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, China

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Abstract

An efficient and eco-friendly protocol for the chemoselective *N*-benzyloxycarbonylation of amines was described. The reaction of amines with benzyl chloroformate (Cbz-Cl) in the presence of PEG-600 at room temperature afforded the corresponding *N*-Cbz derivatives in excellent yields. The method is applicable to the *N*-Cbz protection of aliphatic (acyclic and cyclic) and aromatic amines.

Keywords: Benzyl chloroformate (Cbz-Cl); *N*-Cbz protection; Amines; PEG-600

The protection of amines with the benzyloxycarbonyl (Cbz) group is a common protocol in multistep organic syntheses since it is not only stable to basic and most aqueous acidic conditions, but also can be easily removed by catalytic hydrogenation without any side reactions [1]. Generally *N*-Cbz protection of aryl and/or alkyl amines is carried out by the treatment of amines with benzyl chloroformate (Cbz-Cl) in the presence of 4-(dimethylamino)-pyridine (DMAP) [1]. Considering the very attractive nature of the *N*-Cbz protection, recently various efficient methods for the *N*-benzyloxycarbonylation of amines have been developed, including β-cyclodextrin in aqueous medium [2], $La(NO_3)_3{\cdot}6H_2O$ [3], tetrabutylammonium bromide (TBAB) [4], or silica-sulfuric acid [5] as a catalyst under solvent-free conditions, using ionic liquid tetrapropylammonium L-prolinate ([TPA][L-Pro]) as a reaction medium [6], the use of molecular iodine [7], and in aqueous micellar media [8]. However, to the best of our knowledge, the utility of polyethylene glycol (PEG) as a reaction medium for the preparation of *N*-Cbz derivatives has not been thoroughly investigated.

In recent years, PEG and its solutions have been widely used as the beneficial reaction medium in many organic transformations due to their excellent profiles, such as inexpensive, nontoxic, biodegradable, recyclable and water soluble, which facilitate the easy removal from reaction product [9]. Very recently, a PEG-mediated facile method for the chemoselective *N*-Boc protection of amines was reported [10]. These attractive features of PEG prompted us to investigate the *N*-benzyloxycarbonylation of amines with Cbz-Cl using PEGs as the reaction medium at room temperature.

Our initial attempt was to examine the effect of PEG molecular weight on the effectiveness in the reaction of 4-bromoaniline (1.0 mmol) with Cbz-Cl (1.2 mmol) in PEGs (1 mL) to form the corresponding *N*-Cbz derivative at room temperature (Scheme 1). For PEGs with low molecular weight liquid (MW $<$ 600), we selected PEG-600, PEG-400 and PEG-200 as the solvent respectively. In general, all of them showed very good reactivity with excellent yields (88–96%), the higher the MW of PEGs, the better the yield of the reaction (Table 1).

* Corresponding author.
E-mail address: joyce@imm.ac.cn (H.H. Huang).

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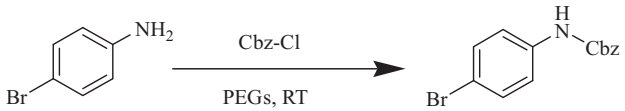


Scheme 1.

Table 1
Effect of PEG molecular weight on the yield of *N*-Cbz product at room temperature.

Entry	Solvent	Time (min)	Yield[a] (%)
1	PEG-200	10	88
2	PEG-400	10	91
3	PEG-600	10	96

[a] Yields of products isolated after column chromatography.

Encouraged by this promising result, we attempted to extend the generality of the reaction by using PEG-600 as the reaction medium. Various aliphatic (acyclic and cyclic) amines and different aromatic amines with electron-withdrawing and electron-donating substituent afforded the corresponding *N*-Cbz derivatives in excellent yields (80–96%) with a short reaction time (5–15 min) (Table 2) [11]. As it can be seen from Table 2, PEG-600 was compatible with various functional groups in aromatic amines such as –Cl, –F, –Br, –OH, $–NO_2$, $–OCH_3$, $–CH_3$ and –Ac. Actually, there is no obvious difference on the yields of aromatic amines with different substituents. But for cyclic aliphatic amines, the yields of entries 17 and 20 were relatively lower than those of other amines, perhaps caused by the steric hindrance effect. The perfect chemoselectivity was also observed as only the *N*-Cbz derivatives were obtained without competitive formation of *O*-Cbz compounds, for example, amino phenol (Table 2, entry 10) and amino alcohols (Table 2, entries 12, 15 and 19).

In order to prove the reusability of PEG, recovered PEG-600 was recycled for the reaction of 4-bromoaniline with Cbz-Cl successively for two times without obvious reduced yield (Table 2, entry 1).

To investigate the effect of PEG, we studied the model reaction between 4-bromoaniline (1 mmol) and Cbz-Cl (1.2 mmol) in different conventional solvents (1 mL), such as CH_2Cl_2, THF, Et_2O, CH_3CN and EtOH. However, in the

Table 2
N-Benzyloxycarbonylation of amines in PEG-600 at room temperature.

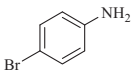
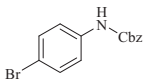
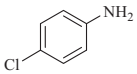
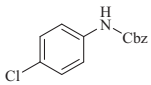
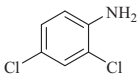
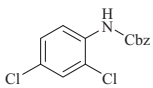
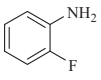
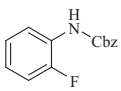
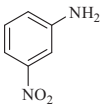
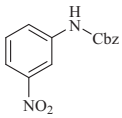
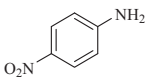
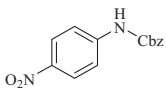
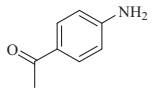
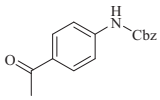
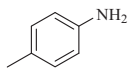
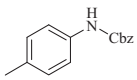
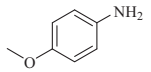
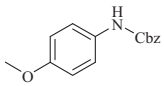
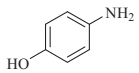
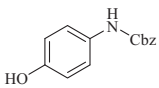
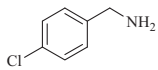
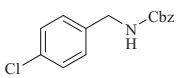
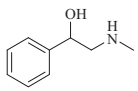
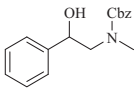
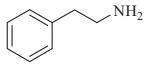
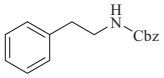
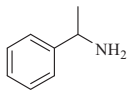
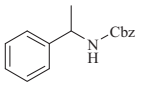
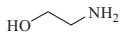
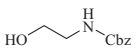
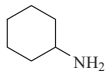
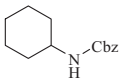
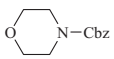
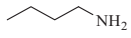
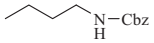
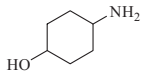
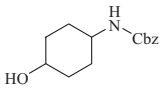
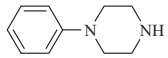
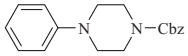
Entry	Amine	Product[a]	Time (min)	Yield[b] (%)
1			10	96, 94[d], 91[e]
2			10	96.7
3			15	93
4			8	96.2
5			10	92.8
6			10	91.8

Table 2 (*Continued*)

Entry	Amine	Product[a]	Time (min)	Yield[b] (%)
7			8	89
8			10	84.5
9			10	87.8
10			11	93[c]
11			10	85.4
12			10	85.5[c]
13			10	89.3
14			10	84.2
15			5	89[c]
16			7	87.9
17			10	81.8
18			5	90.7
19			6	84.6[c]
20	*trans* 	*trans* 	10	80.3

[a] All products were identified by NMR, and mass spectroscopy.
[b] Yields of products isolated after column chromatography.
[c] These compounds were also confirmed by IR.
[d] The second run.
[e] The third run.

presence of above these solvents, a white gel was formed, unlike a homogeneous solution obtained using the PEG-600 as the reaction medium. Thin-layer chromatographic (TLC) analysis of the crude mixture showed a highly polar product at the baseline. Careful scrutiny of the polar product led us to conclude that it was the hydrochloride salt of 4-bromoaniline that gave the white precipitate. The yields were comparatively lower than that in PEG-600 (Table 3).

Table 3
Effect of solvent on the yield of *N*-Cbz product at room temperature.

Entry	Solvent	Time (min)	Yield[a] (%)
1	CH_2Cl_2	10	57
2	THF	10	59
3	EtOH	10	76
4	CH_3CN	10	57
5	Et_2O	10	60
6	PEG-600	10	96

[a] Yields of products isolated after column chromatography.

Therefore, we concluded that PEG-600, employed as a promoter and good eco-friendly solvent in our procedure, could shift the equilibrium toward the right.

In summary, we have achieved an efficient, high-yielding and excellent chemoselective method for protection of amines by Cbz group at room temperature in PEG-600, an easily recyclable and highly effective reaction medium. This approach is general and applicable to a wide range of alkyl and aryl amines.

Acknowledgment

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[11] Typical experimental procedure: a mixture of amine (1.0 mmol), benzyl chloroformate (Cbz-Cl) (1.2 mmol) and PEG-600 (1.0 mL) was stirred at room temperature for an appropriate time (see Table 2). After completion of the reaction as monitored by TLC, water was added to the reaction mixture. The above mixture was extracted with ethyl acetate, and concentrated under reduced pressure to give a crude product which was further purified by silica gel column chromatography to afford the corresponding *N-Cbz* derivatives. The PEG-600 was recovered from aqueous solution by direct distillation of water. Spectral data for selected compounds: entry 3: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 8.4 Hz), 7.41–7.35 (m, 6H), 7.23 (d, 1H, J = 8.4 Hz), 7.15 (brs, 1H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.85, 135.58, 133.48, 128.76, 128.71, 128.60, 128.49, 128.25, 127.93, 122.53, 120.63, 67.55; HRMS (ESI-TOF$^+$): m/z $[M+H]^+$ calcd. for $C_{14}H_{12}Cl_2NO_2$: 296.0240; found: 296.0250. Entry 10: ^{1}H NMR (300 MHz, CD_3OD): δ 7.35–7.24 (m, 5H), 7.15 (d, 2H, J = 8.4 Hz), 6.65 (d, 2H, J = 8.7 Hz), 5.09 (s, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 156.37, 154.66, 138.28, 131.95, 129.51, 129.05, 128.92, 122.18, 116.29, 67.42; HRMS (ESI-TOF$^+$): m/z $[M+H]^+$ calcd. for $C_{14}H_{14}NO_3$: 244.0968; found: 244.0974; IR (KBr) ν: 3304, 3060, 2945, 1701, 1538, 1239, 1066, 828 cm^{-1}. Entry 19: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H), 5.09 (s, 2H), 3.66–3.50 (m, 3H), 2.01 (m, 4H), 1.37 (m, 2H), 1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.62, 136.53, 128.53, 128.13, 69.72, 66.61, 49.31, 33.84, 31.03; HRMS (ESI-TOF$^+$): m/z $[M+H]^+$ calcd. for $C_{14}H_{20}NO_3$: 250.1438; found: 250.1438; IR (KBr) ν: 3389, 3341, 2948, 2862, 1687, 1533, 1265, 1229, 1064 cm^{-1}.