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RESEARCH LETTER

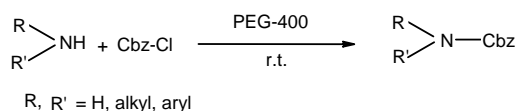
Polyethylene glycol mediated facile protocol for *N*-Cbz protection of amines

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We have reported an efficient and eco-friendly protocol for the protection of various structurally and electronically divergent aryl and aliphatic amines using Cbz-Cl in the presence of polyethylene glycol (PEG)-400 at room temperature. The reaction afforded excellent yields with low as well as high molecular weight PEGs.



Keywords: polyethylene glycol; amine protection; Cbz-Cl; eco-friendly

Introduction

In recent years, the development of eco-friendly organic syntheses is gaining considerable interest both in industrial and academic research (1). Hazardous, toxic, and volatile organic solvents are being continuously replaced by the use of solvent-free techniques (2), water (3), phase-transfer catalysts, or ionic liquids (4). The use of polyethylene glycol (PEG) as a reaction medium is highly beneficial as the system remains neutral, which helps in maintaining a number of acid- and base-sensitive functional groups remains unchanged (5).

Protection and deprotection of functional groups are important and frequently needed exercises in organic chemistry. Protection of amines is particularly very important due to their high nucleophilicity and basicity. Among the widely used protecting groups for amines, the benzyloxycarbonyl (Cbz) group is extensively used because it can be easily removed by catalytic hydrogenation (6–9). Furthermore, the Cbz group is stable toward basic and most aqueous acidic conditions (10). Generally *N*-Cbz protection of amines is carried out by the treatment of amines with benzyloxycarbonyl chloride (Cbz-Cl) in the presence of 4-(dimethylamino)pyridine or organic/inorganic bases (10). Recently, a few methods using β -cyclodextrin (11), molecular iodine (12), tetrabutylammonium bromide (13), and polymer-bound 1-hydroxybenzotriazole (14) has been re-

ported. However, these methods have various drawbacks such as requirement of anhydrous solvents and formation of side products. These drawbacks necessitate the development of efficient new synthetic methodologies.

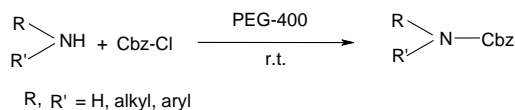
In general, PEG and their monomethyl ethers are inexpensive, thermally stable, non-toxic (15), and are widely used in food products (16) as well as in cosmetics (17). PEG is water miscible which facilitates its removal from reaction products. Recently, great attention has been focused on the use of PEG as a benign, alternative reaction medium in the synthesis of various organic compounds (5,18–28).

Results and discussion

In continuation of our investigations (29–32) in the development of new synthetic methodologies for carbon-heteroatom bond formation, herein we report an efficient and eco-friendly protocol for the protection of amines using Cbz-Cl in the presence of PEG-400 at room temperature (Scheme 1).

To optimize the reaction conditions, we investigated the reaction with aniline (1 mmol), benzyloxycarbonyl chloride (Cbz-Cl) (1 mmol), and different quantities of PEG-400. Furthermore, we studied this reaction using various solvents including tap water in the presence of PEG-400. The optimized results are summarized in Table 1. We found that the best result was obtained with 0.5 mL of PEG-400 for 1 mmol of

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Scheme 1.

aniline in the absence of any solvent at room temperature within 5 min (Table 1, entry 4). Using larger amounts of PEG-400 did not improve the yield of the product. In addition, low yield of the product was obtained in the absence of PEG-400 (Table 1, entry 1). Thus in this reaction 0.5 mL of PEG-400 acted as a good promoter. We investigated our protocol with PEGs of various molecular weights 200, 400, 600, 4000, and 6000 (0.05 mol% each) for our model reaction with aniline (1 mmol) and benzyloxycarbonyl chloride (Cbz-Cl) (1 mmol). The reaction afforded excellent yields with low as well as high molecular weight PEGs. With the above results in hand, a variety of amines such as aliphatic, aromatic, and heterocyclic were employed for *N*-Cbz protection. It was found that the yields were excellent in all the cases (Table 2). This protocol is highly chemoselective as the amine group is only protected even in the presence of OH/SH groups and mono *N*-Cbz protected products were obtained in excellent yields.

Experimental

To a magnetically stirred mixture of Cbz-Cl (1 mmol) and PEG-400 (0.5 mL), amine (1 mmol) was added at room temperature. After stirring the reaction mixture for a specified time (Table 2), diethyl ether (20 ml) was added to the reaction mixture. The organic phase

was separated and washed aqueous saturated NaHCO₃ (5 ml), dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography on silica gel using hexane-ethyl acetate (7:3) as eluent. All the known compounds were characterized by comparing their physical and spectral data with those reported (10–13).

The data for the selected *N*-Cbz products (Table 2, entries 10, 13, and 18) are given below.

(4-Hydroxy-phenyl)-carbamic acid benzylester (Entry 10, Table 2)

Mp: 138–140°C; FT-IR (KBr): 3332, 3082, 2952, 2870, 1732, 1605, 1583, 1510, 1380, 1326, 1237, 1027, 635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃ + DMSO-*d*₆): 8.56 (brs, 1H), 7.22–7.35 (m, 5H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 8.1 Hz, 2H), 5.14 (s, 2H), 3.62 (s, 1H); ¹³C NMR (100 MHz, CDCl₃ + DMSO-*d*₆): 65.2, 114.6, 119.9, 127.2, 127.5, 129.7, 135.8, 152.3, 153.2; ESI-MS = 242 (M-H)⁺; Anal. Calcd for C₁₄H₁₃NO₃: C, 69.12; H, 5.39; N, 5.76; Found: C, 69.07; H, 5.42; N, 5.70.

(4-Acetyl-phenyl)-carbamic acid benzy ester (Entry 13, Table 2)

Mp: 125–127°C; FT-IR (KBr): 3323, 3200, 2930, 2870, 1721, 1662, 1601, 1585, 1521, 1290, 1045, 745 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 7.91 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.33–7.40 (m, 5H), 7.06 (s, 1H), 5.20 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): 26.3, 67.1, 117.7, 128.8, 129.7, 132.0, 135.6, 142.4, 152.9, 196.9; ESI-MS: *m/z* = 268 (M-H)⁺;

Table 1. *N*-Cbz protection of aniline with variety of polyethylene glycols (PEGs) in various conditions at room temperature (entry 3 gives the optimum conditions).

Entry	PEGs	Quantity of PEG (mL)	Solvent (mL)	Time (min)	Yield (%) Isolated
1	–	–	–	120	40
2	–	–	Tap water	100	45
3	PEG-400	0.1	–	30	80
4	PEG-400	0.5	–	5	93
5	PEG-400	1.0	–	5	93
6	PEG-400	0.5	DCM (5)	10	92
7	PEG-400	0.5	EtOH (5)	10	70
8	PEG-400	0.5	THF (5)	10	85
9	PEG-400	0.5	CH ₃ CN (5)	10	75
10	PEG-400	0.5	Tap water	10	92
11	PEG-200	0.5	–	5	92
12	PEG-600	0.5	–	5	92
13	PEG-4000	0.5	–	5	93
14	PEG-4000	0.1	–	5	93
15	PEG-6000	0.5	–	5	93
16	PEG-6000	0.1	–	5	93

Table 2. PEG-400 mediated *N*-Cbz protection of amines at room temperature.

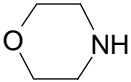
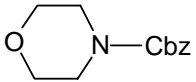
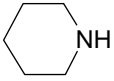
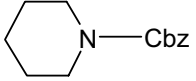
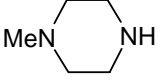
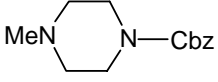
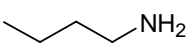
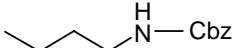
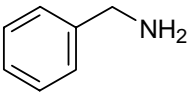
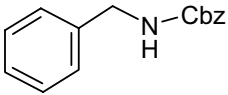
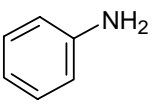
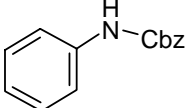
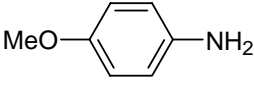
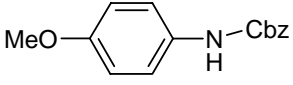
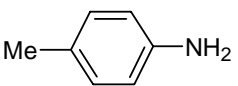
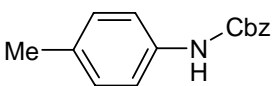
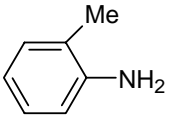
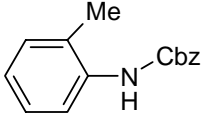
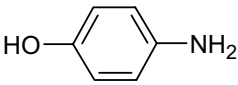
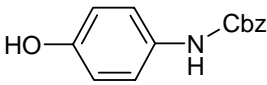
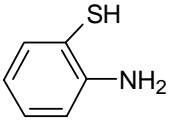
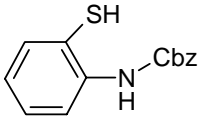
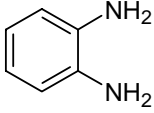
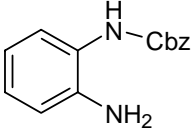
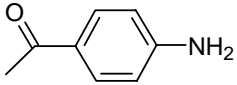
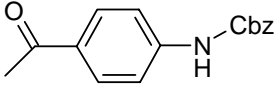
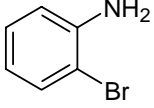
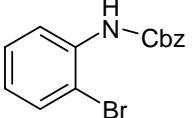
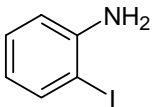
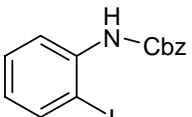
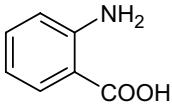
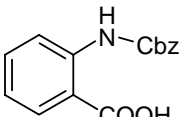
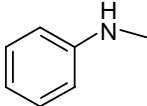
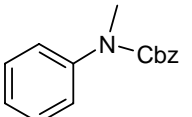
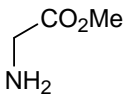
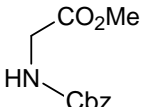
Entry	Amine	Product	Time (min)	Yield (%)
1			2	91
2			2	95
3			5	89
4			10	95
5			15	92
6			5	95
7			10	87
8			10	89
9			10	85
10			7	82
11			20	76

Table 2 (Continued)

Entry	Amine	Product	Time (min)	Yield (%)
12			15	89
13			7	89
14			20	80
15			20	80
16			30	72
17			7	90
18			6	90

PEG, polyethylene glycol.

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20; Found: C, 71.31; H, 5.66; N, 5.15.

Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90; Found: C, 60.69; H, 6.42; N, 5.87.

Benzyloxycarbonylamino-acetic acid methylester
(Entry 18, Table 2)

FT-IR (KBr): 3092, 2930, 2893, 1746, 1711, 1605, 1585, 1472, 1290, 1045, 625 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): 7.29–7.21 (m, 5H), 5.83 (brs, 1H), 5.03 (s, 2H), 4.08 (q, $J=7.2$ Hz, 2H), 3.82 (d, $J=5.6$ Hz), 1.15 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.6, 42.3, 60.8, 66.4, 127.5, 128.0, 136.0, 156.1, 169.7; ESI-MS: $m/z=236$ (M-H) $^+$; Anal.

Conclusion

In conclusion, we have developed a simple and efficient protocol for *N*-Cbz protection of amines in high yields in the presence of PEG-400 at room temperature. In this reaction, PEG-400 acted as an efficient “green” promoter. Therefore, this is a versatile and environmentally benign eco-friendly procedure that proves beneficial to both academic and industrial fields.

Acknowledgements

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