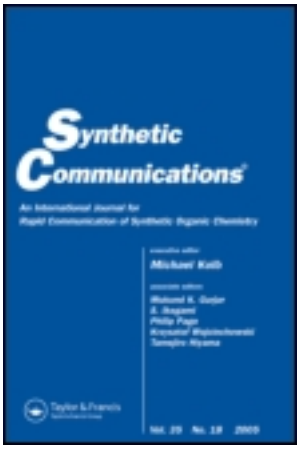

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Simple and Efficient Method for N-Boc Protection of Amines Using PEG-400 as a Reaction Medium Under Mild Conditions

Hongyao Zeng [a] , Yongjia Li [b] & Huawu Shao [a]

[a] Natural Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, ChinaGraduate School of Chinese Academy of Sciences, China

[b] College of Chemistry, Sichuan University, Chengdu, China

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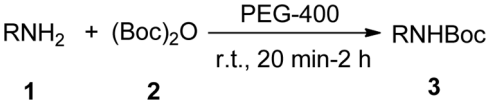
SIMPLE AND EFFICIENT METHOD FOR *N*-BOC PROTECTION OF AMINES USING PEG-400 AS A REACTION MEDIUM UNDER MILD CONDITIONS

Hongyao Zeng,[1] Yongjia Li,[2] and Huawu Shao[1]

[1]*Natural Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, China, and Graduate School of Chinese Academy of Sciences, China*
[2]*College of Chemistry, Sichuan University, Chengdu, China*

GRAPHICAL ABSTRACT



Abstract *Simple and efficient method for* N-*Boc protection of amines using PEG-400 as an ecofriendly reaction medium at room temperature is described. Various aromatic, heteroaromatic, and aliphatic amines were converted to the corresponding* N-tert-*butyl-carbamates in good to excellent yields in short times.*

Keywords Di-*tert*-butyl dicarbonate; *N-tert*-butoxycarbonylation; PEG-400; protection of amines

INTRODUCTION

The protection of amines plays an essential role in synthetic organic chemistry and medicinal chemistry, especially peptide synthesis.[1] Out of the vast array of available amine protecting groups, the *tert*-butoxycarbonyl (Boc) group has emerged as the most commonly and widely used strategy because of ease of protection and deprotection.[2] Various conventional base-mediated methods for the *N*-Boc protection of amines have been developed, for example, dimethylaminopyridine (DMAP),[3] NaHMDS,[4] K_2CO_3,[5] NaOH,[6] and Et_3N.[7] However, the base-catalyzed reactions often lead to the formation of side products such as isocyanate, urea, and *N,N*-di-Boc derivatives.[3b,8] Additionally, the unpleasant smell, high toxicity, requirement for large excess, and nonrecyclability of these catalysts makes the method objectionable, especially from the standpoint of green chemistry.

Lately several Lewis acids and heterogeneous catalysts such as $ZrCl_4$,[9] $LiClO_4$,[10] $Cu(BF_4)_2$,[11] $Zn(ClO_4)_2 \cdot 6H_2O$,[12] $La(NO_3)_3$,[13] $H_3PW_{12}O_{40}$,[14] I_2,[15]

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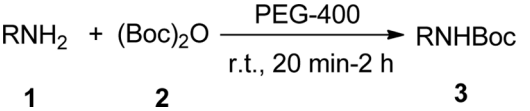
Address correspondence to Huawu Shao, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China. E-mail: shaohw@cib.ac.cn

and Montmorillonite K10[16] have been extensively investigated to achieve such transformations. Although these methods circumvented the problem associated with formation of the side products, many of Lewis acids are corrosive, moisture sensitive, and nonrecoverable reagents, and the synthesis of heterogeneous catalysts often involves long and tedious procedures. Moreover, most of these methodologies suffer from use of volatile organic solvents, long reaction time, elevated temperature, and/or substrate limitations. Therefore, new and mild methods for *N*-Boc protection are in demand. In recent years, polyethylene glycols (PEGs) have attracted great interest as powerful ecofriendly reaction media for various organic transformations[17] because they are relatively inexpensive, thermally stable, readily recyclable, and biodegradable.[18]

In continuation of our work on the utilization of PEG,[19] we report here a simple and efficient method for the *N*-Boc protection of amines using PEG-400 as an ecofriendly reaction medium at room temperature (Scheme 1).

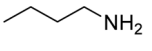
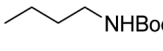
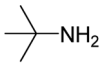
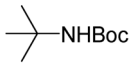
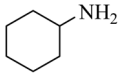
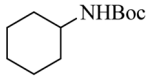
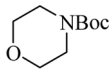
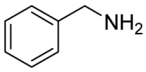
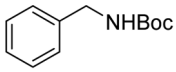
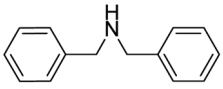
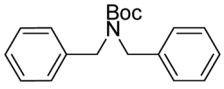
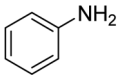
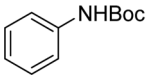
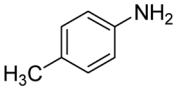
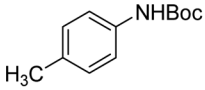
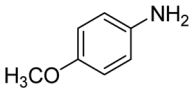
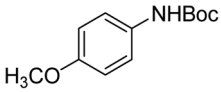
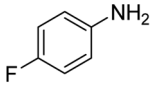
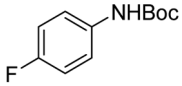
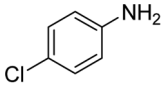
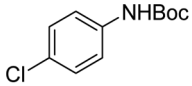
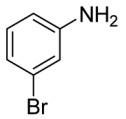
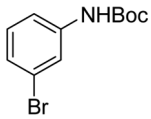
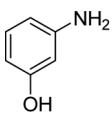
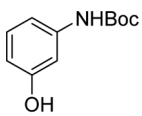
The reaction of aniline (2.0 mmol) with $(Boc)_2O$ (1.2 equiv) using PEG-400 (2.0 mL) as a reaction medium at room temperature gave the corresponding *N*-Boc aniline in 95% yield (Table 1, entry 7). This result encouraged us to extend the generality of the reaction. Various structurally diverse primary and secondary aliphatic, aromatic, alicyclic, heterocyclic, and glycosyl amines with di-*tert*-butyl dicarbonate gave the corresponding *N*-*tert*-butylcarbamates in good to excellent yields (Table 1). No competitive side reactions leading to formation of isocyanate, urea or *N,N*-di-Boc derivatives were detected by thin-layer chromatography (TLC), mass spectrometry (MS), and ^{1}H NMR analyses of the crude product. In general, alkylamines (Table 1, entries 1–5) reacted completely in very short times. In contrast, arylamines (Table 1, entries 7–14) proceeded in a sluggish manner. These results are not surprising because alkylamines are more nucleophilic than arylamines. Additionally, more sluggish reactions were also observed with arylamines containing electron-deficient or bulky groups (Table 1, entries 11–14). It is important to note that *N*-Boc protection in PEG-400 is highly chemoselective: the amino group is protected exclusively in presence of phenolic -OH (Table 1, entries 13 and 14), alcoholic -OH (Table 1, entries 23 and 24), or -Ac, -Ms, -Ts, and -Cbz groups (Table 1, entries 18–21, respectively).

However, in our study, it was observed that when the diamines were subjected to *N*-*tert*-butoxycarbonylation, *mono*-*N*-Boc-protected products were difficult to control even by using <1.0 equiv of $(Boc)_2O$ and short time, but di-*N*-Boc-protected products were easy to form with 2.2 equiv of $(Boc)_2O$ in a very short time (Table 1, entries 16 and 17), which is different from previous reports. Moreover, amino acid derivatives, such as α-amino alcohols and α-amino acid ester, were also converted into the corresponding *N*-Boc ester under similar reaction conditions (Table 1, entries 23–25). *N*-Boc-protected products were solely obtained and no *O*-Boc or oxazolidinone derivatives were observed.



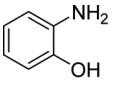
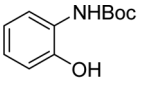
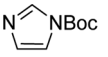
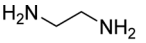
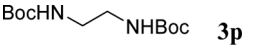
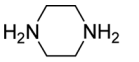
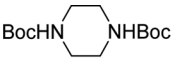
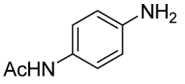
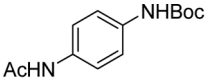
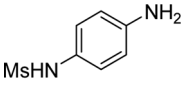
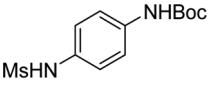
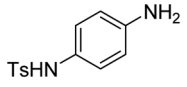
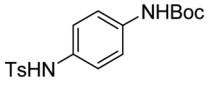
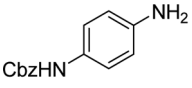
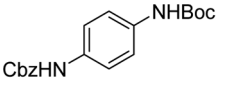
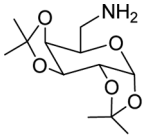
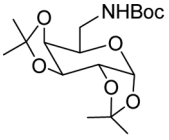
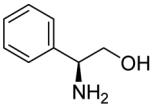
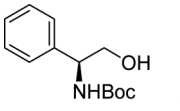
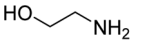
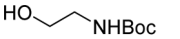
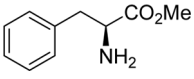
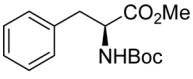
Scheme 1. *N*-Boc protection form amines in PEG-400.

Table 1. *N*-Boc protection of amines in PEG-400[a]

Entry	Amine	Product	Time	Yield[b,c] (%)
1	 **1a**	 **3a**	20 min	86
2	 **1b**	 **3b**	15 min	90
3	 **1c**	 **3c**	20 min	95
4	 **1d**	 **3d**	20 min	98
5	 **1e**	 **3e**	30 min	97
6	 **1f**	 **3f**	1.5 h	90
7	 **1g**	 **3g**	2 h	95, 92,[d] 88[e]
8	 **1h**	 **3h**	1.5 h	96
9	 **1i**	 **3i**	2 h	88
10	 **1j**	 **3j**	2 h	93
11	 **1k**	 **3k**	2.5 h	92
12	 **1l**	 **3l**	2.5 h	87
13	 **1m**	 **3m**	2.5 h	85

(*Continued*)

Table 1. Continued

Entry	Amine	Product	Time	Yield[b,c] (%)
14	 **1n**	 **3n**	3 h	81
15	 **1o**	 **3o**	2.5 h	87
16	 **1p**	 **3p**	<5 min	98[f]
17	 **1q**	 **3q**	<5 min	98[f]
18	 **1r**	 **3r**	2 h	86
19	 **1s**	 **3s**	2 h	87
20	 **1t**	 **3t**	2 h	87
21	 **1u**	 **3u**	2.5 h	85
22	 **1v**	 **3v**	10 min	96
23	 **1w**	 **3w**	30 min	95
24	 **1x**	 **3x**	15 min	98
25	 **1y**	 **3y**	40 min	91

[a]The amines (2.0 mmol) were treated with $(Boc)_2O$ (1.2 equiv) in PEG-400 (2.0 mL) at room temperature under neat conditions.

[b]Isolated yield of the corresponding *N*-Boc derivative.

[c]The products were characterized by IR, ^1H NMR, and MS analyses.

[d]The second run.

[e]The third run.

[f]The reaction was carried out with 2.4 equiv of $(Boc)_2O$.

In summary, we have developed an environmentally friendly method for *N*-Boc protection of variously amines. PEG-400 has been found to be an efficient and recyclable reaction medium for the chemoselective transformation of amines to *N*-(*tert*-butoxycarbonyl) amines. Compared to the previously reported methods, this protocol offers several advantages including exceedingly mild conditions, operational simplicity, short reaction time, and good yield.

EXPERIMENTAL

Reactions were monitored by TLC using silica-gel HSGF254 plates. Flash chromatography was performed using silica gel HG/T2354-92. ^{1}H NMR and ^{13}C NMR (600 and 150 MHz, respectively) spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). Melting points were determined with an X-6 (Beijing Fukai Co., Ltd.) melting-point apparatus and are uncorrected. Electrospray ioinization–high-resolution mass spectrographic (ESI-HRMS) spectra were recorded on a BioTOF Q.

N-tert-Butoxycarbonylation of Amines

A mixture of amine (2.0 mmol) and $(BOC)_2O$ (2.4 mmol) in PEG-400 (2.0 mL) was vigorously stirred at room temperature for the appropriate time (Table 1) until TLC indicated total disappearance of the amine. After completion, the reaction mixture was poured into water and extracted into dry ether. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was purified by silica-gel column chromatography to afford the corresponding *N*-*tert*-butyl-carbamate. The PEG-400 was recovered from the aqueous layer and reused without loss of activity. The physical data (mp, IR, NMR) of the known compounds were found to be identical with those reported in the literature. Products **3r, 3 s, 3 t**, and **3 u** are new compounds. Spectral data for selected new compounds are as follows:

6-Deoxy-6-[(*tert*-butoxycarbonyl)amino]-1,2:3,4-bis-*O*-(1-methylethylidene)-α-D-galactopyranose (3v)

White solid, mp 116–117 °C (lit.[20] 122–123 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.32 (s, 3H), 1.33 (s, 3H), 1.43 (s, 9H), 1.44 (s, 3H), 1.50 (s, 3H), 3.16 (distorted br s, 1H), 3.44 (distorted br s, 1H), 3.91 (distorted br s, 1H), 4.19 (dd, $J = 1.4$ Hz, $J = 7.9$ Hz, 1H), 4.30 (dd, $J = 2.2$ Hz, $J = 4.8$ Hz, 1H), 4.59 (dd, $J = 2.1$ Hz, $J = 7.9$ Hz, Hz, 1H), 4.89 (br s, 1H), 5.51 (d, $J = 4.9$ Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 24.4, 25.0, 25.9, 26.0, 28.3, 41.2, 66.7, 70.6, 70.8, 71.7, 79.2, 96.3, 108.7, 109.4, 156.1; IR (KBr, cm^{-1}): *v* 3396, 2979, 2932, 1708, 1520, 1382, 1366, 1249, 1209, 1174, 1111, 1065, 1010.

tert-Butyl-4-acetamidophenylcarbamate (3r)

White solid, mp 182–183 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.51 (s, 9H), 2.15 (s, 3H), 6.43 (s, 1H), 7.10 (s, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 24.5, 28.3, 80.5, 119.2, 120.7, 133.2, 134.8, 152.8, 168.1; IR (KBr, cm^{-1}): v 3331, 2971, 2928, 1696, 1679, 1662, 1560, 1518, 1451, 1402, 1370, 1310, 1245, 1154, 1048, 1017, 901, 839, 774; ESI-HRMS Anal. calcd. for $C_{13}H_{18}N_2O_3Na$ $[M + Na]^+$ 273.1210; found: 273.1213.

tert-Butyl-4-(methylsulfonamido)phenylcarbamate (3s)

Light gray solid, mp 194–195 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.52 (s, 9H), 2.96 (s, 3H), 6.21 (s, 1H), 6.47 (s, 1H), 7.17 (d, $J = 8.8$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 28.6, 79.4, 119.5, 122.3, 132.8, 136.8, 153.3; IR (KBr, cm^{-1}): v 3333, 3193, 2970, 2927, 1702, 1602, 1532, 1400, 1368, 1326, 1311, 1249, 1219, 1150, 1059, 980, 910, 814, 777. ESI-HRMS anal. calcd. for $C_{12}H_{18}N_2O_4SNa$ $[M + Na]^+$ 309.0879; found: 309.0865.

tert-Butyl-4-(4-methylphenylsulfonamido)phenylcarbamate (3t)

White solid, mp 170–171 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H1.49 (s, 9H), 2.38 (s, 3H), 6.44 (s, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 8.2$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 2H), 7.59 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 21.5, 28.3, 80.8, 119.2, 123.9, 127.3, 129.6, 131.1, 136.0, 136.4, 143.8, 152.6; IR (KBr, cm^{-1}): v 3346, 3256, 2925, 1702, 1601, 1520, 1445, 1392, 1367, 1338, 1309, 1241, 1218, 1090, 1057, 912, 815, 714. ESI-HRMS anal. calcd. for $C_{18}H_{22}N_2O_4SNa$ $[M + Na]^+$ 385.1192; found: 385.1200.

tert-Butyl-4-(benzoyloxycarbonylamido)phenylcarbamate (3u)

White solid, mp 182–184 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.51 (s, 9H), 5.19 (s, 2H), 6.39 (s, 1H), 6.57 (s, 1H), 7.30 (s, 4H), 7.34 (t, 1H), 7.36–7.40 (overlap, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 28.3, 67.0, 119.4, 128.2, 128.3, 128.6, 136.1; IR (KBr, cm^{-1}): v 3359, 2983, 2927, 1702, 1606, 1544, 1527, 1499, 1311, 1242, 1219, 1167, 1065, 829, 744. ESI-HRMS anal. calcd. for $C_{19}H_{22}N_2O_4Na$ $[M + Na]^+$ 365.1472; found: 365.1462.

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