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PEG-mediated Facile Protocol for *N*-Boc Protection of Amines

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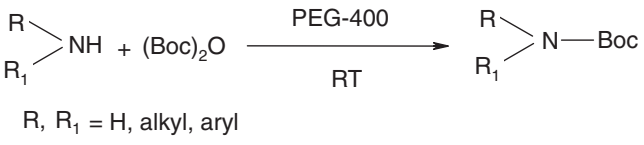
We have reported an efficient and eco-friendly protocol for the protection of various structurally and electronically divergent aryl and aliphatic amines using $(Boc)_2O$ in the presence of PEG-400 at room temperature. The reaction gave excellent yields with low as well as high molecular weight PEGs.

In recent years eco-friendly chemical processes have gained considerable interest in synthetic organic chemistry.[1] Hazardous, toxic, and volatile organic solvents are being continuously replaced either by the use of solvent-free techniques,[2] or by using water,[3] phase-transfer catalysts,[4] or ionic liquids.[5] The use of PEG as a reaction medium is highly beneficial as the system remains neutral, which helps insure a number of acid- and base-sensitive functional groups remain unchanged.[6]

Protection and deprotection of functional groups are important and frequently needed in modern organic chemistry. Particularly protection of amines is very important due to their high nucleophilicity and basicity. Among the widely used protecting groups for amines the *tert*-butoxycarbonyl (Boc)[7] group is extensively used since it can be easily removed by using an acid like TFA or HCl.[7a] Furthermore the Boc group is stable toward catalytic hydrogenation and extremely resistant to basic and nucleophilic reactions.[7c,8] Generally *N*-Boc protection of amines is carried out by the treatment of amines with di-*tert*-butoxypyrocarbonate ($(Boc)_2O$) in the presence of DMAP,[9] organic/inorganic bases,[10] or Lewis acids.[11] Other procedures have also been developed by the reaction of amines with *tert*-butyl-1-chloroalkyl carbonates in the presence of K_2CO_3 in H_2O–THF,[12] 4-dimethylamino-1-*tert*-butoxycarbonylpyridinium chloride/tetrafluoroborate in aqueous NaOH,[13] *tert*-butyl-2-pyridyl carbonate in the presence of Et_3N in H_2O–DMF,[14] or 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile in the presence of Et_3N in H_2O–dioxane.[15]

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

In continuation[16] of our efforts 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 $(Boc)_2O$ in the presence of PEG-400 at room temperature (Scheme 1).



Scheme 1.

Table 1. *N*-Boc protection of aniline with PEG-400 in various conditions at room temperature (Entry 3 gives the optimum conditions)

Entry	PEG-400 /mL	Solvent /mL	Time /min	Isolated yield/%
1	—	—	120	70
2	0.1	—	30	80
3	0.5	—	5	100
4	1.0	—	5	100
5	0.5	DCM (5)	10	75
7	0.5	EtOH (5)	10	95
8	0.5	THF (5)	10	88
9	0.5	CH_3CN (5)	10	90

Poly(ethylene glycol) (PEG) is commercially available, inexpensive, and nontoxic, possesses high thermal stability, and helps in maintaining a neutral reaction medium. Organic synthesis in PEG is an area of great significance in modern organic synthesis.[17]

In order to optimize the reaction conditions, we investigated the reaction with aniline (3 mmol), di-*tert*-butoxypyrocarbonate ($(Boc)_2O$) (3 mmol) and different quantities of PEG-400.[18] Further we also studied this reaction using various solvents. The optimized results are summarized in Table 1. We found that the best result was obtained with 0.5 mL of PEG-400 for 3 mmol of aniline in the absence of any solvent at room temperature within 5 min (Table 1, Entry 3). Using more than 0.5 mL of PEG-400 did not improve the yield of the product, and at the same time, 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 solvent and as a good promoter. We investigated our protocol with various PEGs with molecular weights 200, 400, 600, 4000, and 6000 (0.05 mol % each) for our model reaction with aniline (3 mmol) and di-*tert*-butoxypyrocarbonate ($(Boc)_2O$) (3 mmol). The reaction gave excellent yields with low as well as high molecular weight PEGs.

With the above result in hand, aliphatic, heterocyclic, and aromatic amines possessing both electron-donating and electron-withdrawing groups were employed for *N*-Boc protection and in all the cases, the yields were excellent (Table 2). This protocol is highly chemoselective as only the amine group is protected even in the presence of OH/SH groups and mono-*N*-Boc-protected products were obtained in excellent yields.

After successful completion of *N*-Boc protection of various amines in excellent yields under the above optimized conditions, we planned to evaluate the effectiveness of this protocol for *N*-Boc protection of chiral amines, α-amino acid esters, and β-amino alcohols (Table 3). In all cases, the corresponding optically pure[19] (as determined by the optical rotation and comparison with literature values) *N*-Boc products were ob-

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

Entry	Amine	Time/min	Yield/%
1	Aniline	5	100
2	4-Methylaniline	5	100
3	2,4-Dimethylaniline	40	100
4	2,4,6-Trimethylaniline	40	95
5	4-Methoxyaniline	15	100
6	4-Benzyloxyaniline	10	100
7	3-Chloroaniline	10	95
8	4-Bromoaniline	10	95
9	4-Bromo-2-methylaniline	30	95
10	4-Fluoroaniline	30	90
11	4-Aminophenol	90	95
12	4-Aminobenzenethiol	90	90
13	4-Aminoacetophenone	360	90
14	2-Aminobenzoic acid	360	95
15	Indole	30	100
16	Indole-3-carbaldehyde	120	98
17	4-Aminopyridine	15	100
18	2-Aminopyridine	15	100
19	*n*-Butylamine	5	100
20	Isopropylamine	10	100
21	Benzylamine	5	100
22	Morpholine	5	100
23	Piperidine	5	100
24	Cyclohexylamine	5	100
25	Phenylhydrazine	5	100

Table 3. PEG-400-mediated *N*-Boc protection of chiral amines, esters of α-amino acids and β-amino alcohols at room temperature

Entry	Amine	Time/min	Yield/%
1	(*S*)-α-Methylbenzylamine	5	100
2	(*R*)-α-Methylbenzylamine	5	100
3	L-NH–Pro–OMe	5	100
4	L-NH_2–Phe–OMe	15	95
5	L-NH_2–Tyr–OMe	30	95
6	L-His–OMe	15	95
7	L-Phenylalaninol	15	95

tained in excellent yields. It is noteworthy that the reaction with phenylalaninol resulted in chemoselective formation of the *N*-Boc-protected products without formation of *O*-Boc-protected products.[20]

In conclusion, we have developed a simple and efficient protocol for *N*-Boc protection of amines in high yields in the presence of PEG-400 at room temperature. In this reaction PEG-400 acted as a very efficient "green" promoter and this methodology works equally well with both low and high molecular weight PEGs. Therefore this is a very general and environmentally benign eco-friendly procedure, which would prove beneficial to both academic and industrial fields.

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18 **General experimental procedure for *N*-Boc protection of amines**: To a magnetically stirred mixture of $(Boc)_2O$ (3 mmol) and PEG-400 (0.5 mL), amine (3 mmol) was added at room temperature. After stirring the reaction mixture for the specified time (Tables 2 and 3), water (20 mL) was added to the reaction mixture. In many cases, the products were solidified. The products, thus obtained, were filtered and dried to get pure compounds. In a few cases the products were not solidified, in such occasions the reaction mixture was extracted with diethyl ether and the organic layer was dried over anhydrous sodium sulfate. Then the combined ethereal solution was concentrated under vacuum to afford the corresponding *N*-Boc products. In all the cases, the products were found to be sufficiently pure (HPLC) and did not require any further efforts for purification. All the known compounds were characterized by comparing their physical and spectral data with those of reported compounds. The data of the unknown *N*-Boc products (Table 2, Entries 13 and 16) is given below.
(4-Acetylphenyl)carbamic acid *tert*-butyl ester (Table 2, Entry 13): Mp: 141–143 °C. FT-IR (KBr): 3101, 2998, 2974, 1719, 1663, 1587, 1320, 1240, 1153, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.52 (s, 9H), 2.55 (s, 3H), 6.76 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.92 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 28.9, 80.7, 118.6, 127.3, 131.1, 148.9, 156.2, 196.6. LCMS: m/z 236 $[M + 1]^+$. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%. Found: C, 66.32; H, 7.29; N, 5.91%.
3-Formylindole-1-carboxylic acid *tert*-butyl ester (Table 2, Entry 16): Mp: 123–125 °C. FT-IR (KBr): 3019, 2979, 2814, 1720, 1680, 1590, 1399, 1243, 1101, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (9H, s), 7.34–7.43 (m, 2H), 8.15 (d, $J = 8$ Hz, 1H), 8.22 (s, 1H), 8.28 (dd, $J = 1.2$, 7.2 Hz, 1H), 10.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 80.4, 115.0, 119.2, 120.8, 121.8, 123.2, 123.9, 137.4, 137.8, 155.2, 184.4. LCMS: m/z 246 $[M + 1]^+$. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.16; N, 5.71%. Found: C, 68.51; H, 6.17; N, 5.69%.

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