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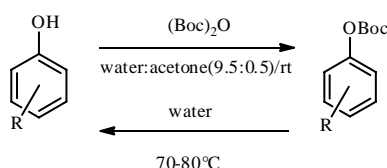
A simple and eco-sustainable method for the *O*-Boc protection/deprotection of various phenolic structures under water-mediated/catalyst-free conditions

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A greener, efficient, and chemoselective protocol for *O*-Boc protection/deprotection of a wide range of phenol derivatives is reported under catalyst-free conditions in water-related systems. Unlike previous reports, no additional reagents or catalysts were used, and workup fulfils green chemistry requirements, making the present method even more interesting.



Keywords: catalyst-free; *O*-Boc protection/deprotection; phenol; water-related system

Introduction

Efforts have been made to identify mild and efficient chemoselective methods for the protection/deprotection of functional groups, crucial interest to organic multi-step synthesis [1,2]. *Tert*-butyl carbamates are widely used as amine-protecting groups in various fields of organic synthesis due to its stability toward nucleophilic conditions and due to its easy removal in various environments. The insertion of Boc group is usually achieved using di-*tert*-butyl dicarbonate (Boc)₂O, being the best available reagent used for protecting substrates containing a labile-hydrogen moiety such as phenol-type [3,4].

Acylation is a common approach in protecting hydroxyl groups [5,6], but its regeneration requires harsh conditions incompatible with polyfunctional molecules. Furthermore, *O*-*tert*-butoxycarbonylation is a suitable and preferred alternative process to protect hydroxyl group [1,2] due to both sustainable compatibility toward reaction conditions applied in organic synthesis and regeneration practices conducted under soft conditions.

In the last decade, various methods and reagents have been developed to achieve the protection/deprotection of Boc group on phenol functionality. The introduction of Boc moiety into phenols is

generally achieved by the reaction of (Boc)₂O in the presence of a phase transfer catalyst [7], 4-dimethylaminopyridine (DMAP) as catalyst [8] and using Lewis acids such as BiCl₃ [9], Zn(OAc)₂ [10], 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) [3,4] and NaTiO₄ [11], or using 6,7-dimethoxyisoquinoline [12] as an organocatalyst.

On the other hand, the *O*-Boc deprotection is carried out under mild acidic conditions such as trifluoroacetic acid (TFA) [13] and the use of a large excess of base [14]. In spite of their importance, there are a few methods available for the protection/deprotection of *O*-Boc groups under eco-sustainable conditions. Recently, Chankeshwara et al. [15] reported the *O*-*tert*-butoxycarbonylation of functionalized phenols using carbon tetrabromide (CBr₄) as catalyst and their regeneration from the *O*-*tert*-Boc derivatives using the complex system CBr₄-PPh₃. More recently, Procopio et al. [16] described a new method for the protection/deprotection of the *O*-*tert*-butoxy carbonates of alcohols and phenols using mesoporous silica-supported (Er^{III}-MCM-41).

However, these conditions are not chemoselective, require harsh conditions, long reaction time, and nucleophilic organocatalysts used sometimes involve the generation of side products in significant

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Table 1. Evaluation of different solvents for *O*-Boc protection of phenol under catalyst-free conditions.

Solvents	Time (h)	Yield (%)
H ₂ O	0.75	95
MeOH	72	10
EtOH	72	4
MeCN	72	0
THF	72	0
CH ₃ Cl	72	0
CCl ₄	72	0

quantities such as symmetrical carbonates, cyclic carbonates, and carbonic-carbonic anhydrides [8].

In recent years, organic reactions in water have received considerable attention (17–20). The use of water as a solvent offers several advantages such as improving reactivity and selectivity, mild reaction conditions, and minimization of energy requirements [21].

Thus, in the continuation of our previous work on the use of catalyst-free water-related system for the *N*-Boc protection/deprotection (22–24), we herein report an efficient protocol for *O*-*tert*-butoxycarbonyl

protection/deprotection of phenol derivatives under catalyst-free conditions and in aqueous media, meeting all requirements for a green chemical process.

Results and discussion

In order to determine the best reaction system model, we chose phenol (Table 2, Entry 1) as model substrate and treated it with (Boc)₂O (1 mmol) under catalyst-free conditions in aqueous media at room temperature, and the expected product was obtained in excellent yield. To find the role of water in *O*-Boc protection, the reaction was performed in several polar solvents at room temperature (Table 1). The best result was obtained with water, affording *tert*-butyl phenyl carbonate in 95% yield after 45 min. The reaction was carried out under catalyst-free conditions in polar protic solvents (MeOH and EtOH), affording, respectively, expected products in 10% and 4% yields after 72 h. The *O*-*tert*-butoxycarbonylation in polar aprotic solvents (THF, MeCN, CH₃Cl, and CCl₄) did not give any significant results. The readings of these results show well the efficacy of water in the *O*-Boc protection of phenol. Whereas, when the reaction carried using

Table 2. *O*-Boc protection/deprotection of hydroxy compounds.

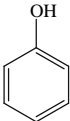
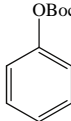
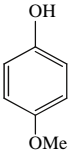
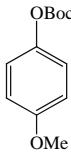
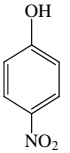
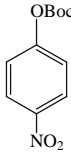
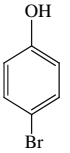
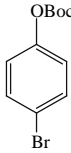
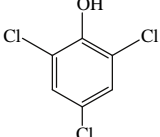
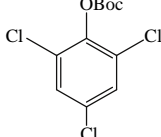
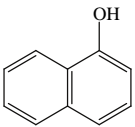
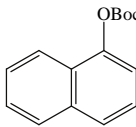
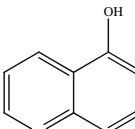
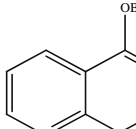
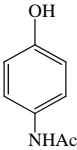
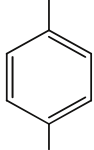
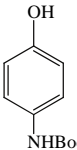
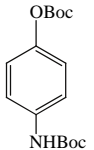
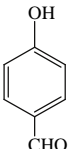
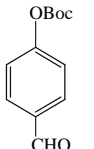
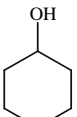
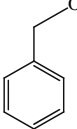
Entry	Substrate	Product	<i>O</i> -Boc protection ^a	<i>O</i> -Boc deprotection ^b
			<i>T</i> (min)/yield (%)	<i>T</i> (min)/yield (%)
1			45/95	8/98
2			30/87	3/95
3			70/96	5/100
4			55/90	8/90
5			90/93	10/89

Table 2 (Continued)

Entry	Substrate	Product	<i>O</i> -Boc protection ^a	<i>O</i> -Boc deprotection ^b
			<i>T</i> (min)/yield (%)	<i>T</i> (min)/yield (%)
6			120/85	10/98
7			90/90	6/97
8			65/97	6/99
9			70/95	2/100
10			50/90	3/100
11		–	–/–	–/–
12		–	–/–	–/–

^a1 mmol of substrate was treated with 1 mmol of (Boc)₂O in 5 mL (9.5/0.5) of (water:acetone) under neat at room temperature.

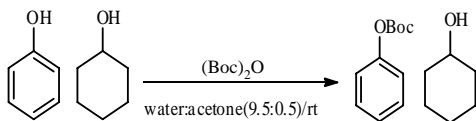
^bAll reactions were carried out in depressurized systems under argon atmosphere; 1 mmol of substrate was dissolved in 10 mL of freshly bidistilled water.

polar and protic solvents under catalyst-free conditions, the corresponding carbonate is in failure. Only the properties of water molecule cause “electrophilic activation” making the carbonyl group more susceptible to the nucleophilic attack of phenol. What may be explained the role of water compared to other solvents.

The amount of aqueous media has a significant effect on the reaction rate and product yield. The minimal required amount for *O*-Boc protection is 5 mL/mmol (water:acetone 9.5:0.5). Increasing the amount of water to 7–10 mL/mmol affects the

reaction rate by prolonging reaction time by 1.5–4 h in *tert*-butyl phenyl carbonate conversion, which could be explained by the outsized dispersion of reagents in the solution.

The use of water eliminates the drawbacks found in reported protocols as well as replaces the use of toxic solvents undesired by most pharmaceutical companies [25]. Various phenols were converted to the *O*-*tert*-Boc derivatives in excellent yield after 30–120 min, proving the advantage of this procedure. No side product was formed as previously cited [8]. The

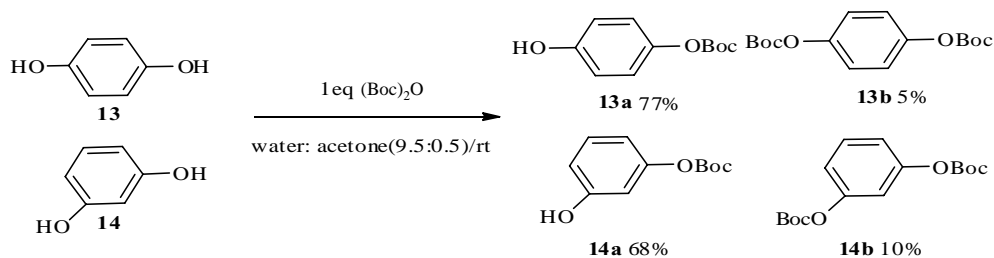


Scheme 1. Water-mediated chemoselective *O*-*tert*-butoxycarbonylation of phenol.

compatibility of the reaction conditions in the presence of other functional groups such as *NH*-Boc, *NH*-Ac, CHO, NO₂, and OCH₃ can be observed in Table 2, showing the absence of undesired products such as *N*-Boc at *NH*-Ac or *N*-di-Boc and without damaging substituted functional groups. This study encourages the development of the general strategy used in this method. We tried to test the reaction conditions on aliphatic hydroxyls, but no *O*-Boc formation was observed at room temperature over time. This may confirm the advantage of this method over reported procedures. The chemoselectivity of *O*-Boc formation on phenol derivatives rather than on aliphatic hydroxyl groups was also verified by studying the reactivity when applying our protocol conditions on mixtures containing both compounds. This showed that only phenol substrates were affected and that aliphatic hydroxyl groups were left intact. When phenol and cyclohexanol were tested using previous conditions, no *tert*-butyl cyclohexyl carbonate was formed (Scheme 1).

The reaction was affected by the nature of the substituent in the aromatic ring; the electron-donating effect of the methoxy (Table 2, entry **2**) increased the rate of the reaction compared to entry **1**. On the contrary, electron-withdrawing substituents impede the process.

Encouraged by these experimental results, the protocol conditions were also applicable to the resorcinol and hydroquinone **13** and **14** containing two hydroxyl groups. The *O*-*tert*-butoxycarbonylation of **13** and **14** using 1 equiv. of (Boc)₂O in the same conditions affords a mixture of mono-*O*-*t*-Boc and di-*O*-*t*-Boc within 30 min. A significant amount of the mono-*O*-*t*-Boc was formed (**13a** in 77% and **14a** in 68%) (Scheme 2).



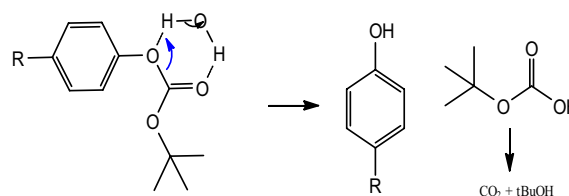
Scheme 2. *O*-*tert*-butoxycarbonylation of bisubstituted phenol.

We further investigated the *O*-Boc deprotection, finding that heating water (80°C) could efficiently catalyze the deprotection of the *O*-Boc group on phenol derivatives in good to excellent yields within 10 min (Table 2). Moreover, it seems obvious that the electronic effect of substituents does not have any significant influence on the deprotection reaction's speed in comparison to the *O*-Boc protection.

By enhancing the solubility of substrates in water with hydrogen bond-forming groups such as OMe, *NH*-Ac, *NH*-Boc, NO₂, reaction yields are increased which is in perfect accord with Prof. Qu's research group concerning the *N*-Boc deprotection in boiling water [26]. The chemoselective *O*-Boc deprotection in the presence of other moieties such as *NH*-Boc and *NH*-Ac can find interesting applications in protecting group chemistry.

To demonstrate the general act of water as catalyst for the reaction, we used a depressurized system under argon atmosphere to avoid dissolving CO₂ in water, released during the removal of the Boc group. Therefore, we propose the following mechanism, where water can provide hydrogen bonding with the carbonyl and *tert*-butyl oxygen atoms, leading to an electrophilic activation, intermolecular rearrangement, and regeneration of the parent phenol and *tert*-butyl hydrogen carbonate, followed by the elimination of CO₂ and *t*-BuOH.

Mechanistic proposal: *O*-Boc deprotection



Experimental

All commercial chemicals and solvents were used without further purification. All reactions were carried out under an inert argon atmosphere. Melting points

were determined in open capillary tubes on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in a 250 MHz Brücker spectrometer. Chemical shifts are reported in δ units (ppm) with Trimethylsilane (TMS) as reference. All coupling constants (J) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and combinations of these signals. All reactions were monitored by Thin layer chromatography (TLC) on silica Merck 60 F254 percolated aluminum plates. Column chromatography was performed on Merck silica gel (230–400 mesh).

General procedure of O-Boc protection on phenols derivatives

To 1 mmol of substrate dissolved in 3.5 mL of water:acetone (9.5:0.5) was added dropwise 1 mmol of $(\text{Boc})_2\text{O}$ in 1.5 mL of the same solvent. The mixture was stirred at room temperature. The reaction was monitored by TLC. After the appropriate time, the reaction mixture was extracted with ethyl acetate ($3 \times 5\text{mL}$), the organic layer was separated and dried with anhydrous Na_2SO_4 , and the solvent was eliminated in vacuo. The products was purified in a silica gel column (hexane:diethylether 3:1) to give O-Boc phenols in oil and solid form.

Tert-butyl 4-acetamidophenyl carbonate [11]

Yield 97%; R_f (CHCl_3 – MeOH 95:5) 0.7; RMN^1H δ (ppm) (250 MHz, CDCl_3): 1.55 (s, 9H, O-*t*-Bu), 2.07 (s, 3H, CH_3CONH), 7.04 (d, 2H, H_A , H_D , $J = 2.1$ Hz), 7.43 (d, 2H, H_B , H_C , $J = 2.1$ Hz), 8.43 (s, 1H, NH). RMN^{13}C δ (ppm) (62.89 MHz, CDCl_3): 24.12 (CH_3), 27.65 (3CH_3), 83.67 (C), 121.03 ($2\text{CH}_{B,C}$), 121.47 ($2\text{CH}_{A,D}$), 135.85 (C_{CNHAc}), 147.00 (C_{COBoc}), 169.04 (C_{COMe}).

Tert-butyl (4-((tert-butoxycarbonyl)oxy)phenyl) carbamate [12]

Yield 95%; R_f (CHCl_3 – MeOH 95:5) 0.63; RMN^1H δ (ppm) (250 MHz, CDCl_3): 1.51 (s, 9H, $\text{NHCOO}t\text{-Bu}$), 1.56 (s, 9H, $\text{OCOO}t\text{-Bu}$), 6.68 (s, 1H, NH), 7.08 (d, 2H, H_A , H_D , $J = 2.2$ Hz), 7.43 (d, 2H, H_B , H_C , $J = 2.0\text{Hz}$). RMN^{13}C δ (ppm) (62.89 MHz, CDCl_3): 27.67 (3CH_3), 28.30 (3CH_3), 80.53 (C), 83.40 (C), 119.35 ($2\text{CH}_{B,C}$), 121.59 ($\text{CH}_{A,D}$), 136.00 (C_{CNHboc}), 146.34 (C_{COBoc}), 152.03 ($\text{C}_{\text{NCOO}t\text{Bu}}$), 152.76 ($\text{C}_{\text{OCOO}t\text{Bu}}$).

General procedure of O-Boc deprotection on phenols derivatives

One millimoles of O-Boc-phenol and 10 mL of freshly double distilled water were loaded into 50 mL round-

bottomed flask related with depressurized system. The reaction mixture was heated at 80°C for particular time and conducted under argon atmosphere. After completion, the mixture was extracted with ethyl acetate ($3 \times 5\text{mL}$) and concentrated in vacuum, all products were obtained pure.

Conclusions

In summary, we report an efficient method for chemoselective O-Boc protection/deprotection of various phenolic structures under catalyst-free conditions, in aqueous media, and in high yields. The present protocol avoids the use of organocatalysts and prevents the generation of side products, has a discrete advantage by having a short reaction time, is easy of manipulation, is chemoselective to phenol hydroxyls rather than aliphatic alcohols, enabling greener reactions in multi-step synthesis.

Acknowledgements

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