Catalyst-free water-mediated *N*-Boc deprotection

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ABSTRACT

A catalyst-free water-mediated *N*-Boc deprotection of *N*-Boc-amines is reported. In the absence of any additional reagents, the free amines were formed from a variety of aromatic and aliphatic *N*-Boc-amines as well as from some *N*-Boc-amino acid derivatives.

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The choice of the protection and deprotection strategy is of high importance in synthetic chemistry of multifunctional molecules including the total synthesis of natural products. A large variety of protective groups have been developed along with numerous methods for their removal. Among them, the *tert*-butoxycarbonyl (*t*-Boc) group is frequently used as a protecting group for amine in synthetic organic/peptide chemistry due to its stability towards catalytic hydrogenolysis and extreme resistance to basic and nucleophilic conditions. For these reasons, many methods for *N*-Boc deprotection have been reported, in particular, under strong acidic conditions (e.g., CF_3COOH,[1] HCl,[2] HNO_3,[3] and H_2SO_4,[4] etc.[5]) and Lewis acid (e.g., $ZnBr_2$,[6] $BiCl_3$,[7] $Ce(NH_4)_2(NO_3)_6$,[8] montmorillonite K-10,[9] etc.[10]). In some cases, basic conditions have also been described.[11] However, these methodologies have various drawbacks such as the need for costly and cumbersome neutralization, using more excessive amounts of catalysts, and auxiliary substances (e.g., solvents, acids, and Lewis acids). In addition, some of these catalysts are more expensive and cannot be recovered and used again. As a result, attempts to find alternative methodologies for this transformation which do not suffer from the severe drawbacks of the conventional procedures are still very desirable.

In recent years, much attention has been focused on searching more 'green' or environmentally friendly chemical processes. Water is cheap, non-toxic, non-combustible, non-explosive, and environmentally acceptable.[12] Therefore, chemists have been interested in investigating the possibility of using water as solvent for organic reactions, sometimes with surprising and unforeseen results.[13]

In the present work, we wish to report a catalyst-free water-mediated *N*-Boc deprotection. In the absence of any additional reagents, the scope of this procedure is explored for the deprotection of a series of *N*-Boc derivatives of aromatic and aliphatic amines.

Our initial experiments were carried out by using *N*-Boc-aniline[14] as model substrate. As can be seen from Scheme 1 and Table 1, the *N*-Boc deprotection performed on this model substrate at 30 °C and 80 °C was not observed (Table 1, entries 1 and 2). However, at 130 °C and 150 °C, the free aniline was afforded in the yields of 39% and 86% after 4 h (Table 1, entries 4 and 6). We also discovered that the shortening of reaction time resulted in incomplete *N*-Boc deprotection (Table 1, entry 5). The critical amount of water required was found to be 1 mL/mmol of the *N*-Boc-amine. The use of a lesser amount of water led to incomplete conversion, but the use of >1 mL/mmol did not have a significant influence on the reaction rate and product yield. These results indicated that the removal of *N*-Boc group from *N*-Boc-aniline could be achieved in high performance in water without any additional reagents.

It is well known that subcritical water ($150 < T < 370$ °C, $0.4 < p < 22$ MPa) can boast of a higher H^+ and OH^- ion concentration than ambient water since the ion product in subcritical water is much higher than in ambient water.[15] Accordingly, subcritical water can replace the catalysts in some acid- and base-catalyzed reactions.[13b,16] The present hydrothermal reaction at 150 °C is close to the subcritical water condition. So we deduce that hydro-
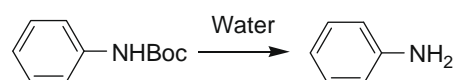
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E-mail address: xsjia@mail.shu.edu.cn (X. Jia).

Scheme 1.

Table 1
Effect of temperature on the water-mediated deprotection of N-Boc-aniline[a]

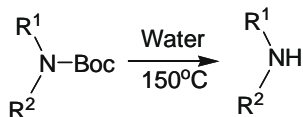| Entry	Temp (°C)	Time (h)	Isolated yield (%)
1	30	4	0
2	80	4	0
3	130	2	12
4	130	4	39
5	150	2	38
6	150	4	86

[a] Unless otherwise noted, all reactions proceeded with 1 mmol N-Boc-aniline and 1 mL distilled, deionized water. No additional reagents were added.

nium ions formed by the dissociation of water may be a catalyst in the present system. In the reference experiment, when the deprotection of N-Boc-aniline was performed under water-free condition (also heated for 4 h at 150 °C), no deprotection product was observed and 90% unreacted N-Boc-aniline was recovered. Furthermore, we also isolated a byproduct (oxanilide, 8%), which was not found under hydrothermal condition. These observations indicate that water acts as the catalyst and plays crucial role in this transformation.

Encouraged by these experimental results, a series of structurally diverse aromatic and aliphatic N-Boc-amines were treated in water at 150 °C (Scheme 2, Table 2). In most cases, the substrate N-Boc-amines underwent smooth conversion to corresponding free amino products in good to excellent yields. Moreover, behavior of the present strategy is also quite dependent on the type of substrate N-Boc-amines adopted. For the aromatic N-Boc-amines, the deprotection processes were affected dramatically by the substituents on the aromatic ring. Electron-donating substituents such as methyl, methoxy, and hydroxyl groups facilitate the reaction, allowing shorter reaction times (Table 2, entries 2–4). While electron-withdrawing substitutents such as chloro and nitro groups decrease the rate of the reaction (Table 2, entries 5 and 6). In particular, when nitro group was present in the aromatic ring, the reaction time must be prolonged to 10 h. The method is also applicable to the aliphatic N-Boc-amine, which could be converted to deprotection compound within 4 h (Table 2, entry 8).

In view of the importance of peptide synthesis, N-Boc-L-Ala and N-Boc-L-Phe-OMe were tested in this transformation (Table 2, entries 10 and 11). As can be seen from Table 2, the deprotection process for N-Boc-L-Ala was quite satisfactory because it could be quantitatively converted to its deprotection compound L-alanine within 2 h (entry 10). It is reasonable because the carboxyl group in N-Boc-L-Ala can dissociate H⁺ in water and the resulting higher H⁺ concentration facilitates this transformation. In contrast, when N-Boc-L-Phe-OMe was used as substrate, it is very interesting that both N-Boc and methyl ester groups were deprotected, that is, L-phenylalanine was achieved. The abilities of simultaneous cleavage of N-Boc and ester groups could be used to decrease the reaction steps in some instances and find applications in peptide synthesis. The prolonged reaction time (16 h) indicated that the cleavage of ester group was more difficult than that of N-Boc groups under present conditions.

In conclusion, we have described a catalyst-free water-mediated deprotection of N-Boc-amines.[17] Both aromatic and aliphatic N-Boc-amines can be converted to the corresponding free amines in high yield. The absence of acid/base and the use of water make present procedure environmentally friendly. We believe that our

Table 2
Water-mediated deprotection of N-Boc-amines[a]

Entry	N-Boc-amine	Time (h)	Isolated yield (%)
1	⬡—NHBoc	4	86
2	Me—⬡—NHBoc	4	88
3	MeO—⬡—NHBoc	4	96
4	HO—⬡—NHBoc	2	95
5	Cl—⬡—NHBoc	6	87
6	O₂N—⬡—NHBoc	10	97
7	naphthalene–NHBoc	8	88
8	⬡—CH₂—NHBoc	4	86
9	imidazole–NBoc	2	95
10	Me, NHBoc, HO₂C, H	2	100
11	Ph, NHBoc, MeO₂C, H	16	81[b]

[a] Unless otherwise noted, all reactions proceeded with 1 mmol N-Boc-amine and 1 mL distilled, deionized water at 150 °C. No additional reagents were added.
[b] Both N-Boc and methyl ester groups were deprotected.

method will find its use in organic chemistry, especially in large-scale industrial preparation.

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$$R^1 R^2 N\text{–}Boc \xrightarrow[150\,°C]{Water} R^1 R^2 NH$$

Scheme 2.

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17. *N*-Boc-amine(1 mmol) and distilled, deionized water (1 mL) were loaded into a 15 mL Teflon-lined stainless bomb, which was sealed and heated at 150 °C under hydrothermal condition for 2–16 h. Then the reaction mixture was cooled to room temperature. EtOAc (3 mL) was added and the mixture was stirred. The organic layer was separated, washed with water, and dried over anhydrous Na₂SO₄. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give corresponding amine. Because amino acids were water-soluble and did not dissolve in common organic solvents, the above purification strategy did not work when *N*-Boc amino acid derivatives were the substrates. For ʟ-alanine, after the reaction mixture was evaporated, the product was of sufficient purity (spectral data) and did not require further efforts of purification. For ʟ-phenylalanine, the product was purified by recrystallization in EtOH/H₂O. In addition, 4-aminophenol was purified directly by drying in vacuo to afford pure product. All the products are known and were characterized by comparison of their spectral data with those of authentic samples.
Selected data of ʟ-phenylalanine: IR (KBr): 3446, 3066, 3032, 2967, 1621, 1585, 1501 cm⁻¹. ¹H NMR (500 MHz, D₂O): δ = 7.40–7.28 (m, 5H), 3.96–3.94 (m, 1H), 3.27–3.06 (m, 2H). ¹³C NMR (125 MHz, D₂O): δ = 173.89, 135.02, 129.30, 129.06, 127.64, 55.98, 36.29.