View Article Online / Journal Homepage / Table of Contents for this issue

Boiling water-catalyzed neutral and selective *N*-Boc deprotection†

Jia Wang, Yan-Liang Liang and Jin Qu*

Received (in College Park, MD, USA) 26th May 2009, Accepted 8th July 2009
First published as an Advance Article on the web 31st July 2009
DOI: 10.1039/b910239f

A general protocol for removing Boc groups from various types of nitrogen is reported and a preliminary investigation of the reaction mechanism indicates that water acts as a dual acid/base catalyst at elevated temperature.

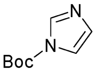
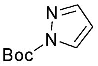
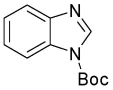
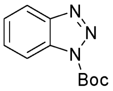
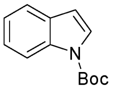
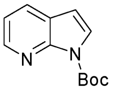
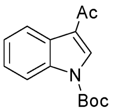
Water is the main solvent for life processes and there is growing interest in using it as a "green" solvent for organic transformations.[1] However, reports about using water as a catalyst to promote organic reactions are very limited. An early report from Breslow's research group pointed out that the Diels–Alder reaction can be remarkably accelerated in water owing to the hydrophobic interaction between water and nonpolar moieties.[2] As an emerging area, supercritical water (liquid water above 374 °C) and subcritical water (liquid water between 150 °C and 374 °C) under high pressure was applied to promote the traditionally acid-catalyzed reactions.[3] Recently, several reports showed that water could catalyze reactions by forming hydrogen bonds with substrates.[4] A most surprising result came from Prof. Jamison's research group, who discovered that the cascade epoxide-opening yielding ladder polyether could be efficiently promoted by water.[5] Our group reported that the generalized ring-opening reactions of epoxides and aziridines by nucleophiles may also be carried out in hot water (60–100 °C) without additional catalyst.[6]

The *tert*-butoxycarbonyl (Boc) group is one of the most widely used amino protecting groups. The most common method for its removal is treating the *N*-Boc substrates in TFA–CH_2Cl_2 (1 : 1),[7,8] but because of the toxicity and cost issues,[9] large scale *N*-Boc deprotections still use mineral acids such as sulfuric acid,[10] hydrochloric acid[11] and phosphoric acid.[12] Neutralization and the production of waste salt are inevitable; thus, a more environmentally benign method is still desired. We found that boiling water could efficiently catalyze the deprotection of *N*-Boc groups, which meet all requirements for a green chemical process. After our work was essentially completed, Prof. Jia's research group reported a catalyst-free *N*-Boc deprotection in subcritical water under pressure.[13] Several *N*-Boc aromatic amines and two *N*-Boc amino acids were deprotected in good to excellent yields. Our work included a much greater variation of substrates, and the utilization of manageable boiling water rather than subcritical water makes the present method safe and practical. The possibility of selective deprotection of *N*-Boc groups could be realized in molecules containing two kinds of *N*-Boc. Furthermore, research was carried out to understand the role water played in the reaction. We found that water acts as a dual acid/base catalyst rather than an acid catalyst, as suggested by Jia *et al.*[13] Thus we are responsible to present these findings.

The *N*-Boc group on aromatic heterocycles such as imidazole, pyrazole, benzimidazole and benzotriazole could be removed in quantitative yields within 10 min (entries 1–4, Table 1). *N*-Boc-indole gave free indole in quantitative yield under the same conditions, but complete reaction took 4 h (entry 5). For indole's electron-deficient analogs such as *N*-Boc-7-azaindole and *N*-Boc-3-acetylindole, the reaction could be completed in 1 h and 2 h, respectively (entries 6 and 7).

For the representative *N*-Boc aromatic amines examined, no obvious electronic substitution effect on the phenyl ring was observed. It appears that the substrates bearing hydrogen bond-forming functional groups (–OH, –OMe, –Ac, –NO_2, –NMe_2), which could enhance the solubility of the substrates in water, react faster (entries 5–12, Table 2) than those substrates without such functional groups (entries 1–4). As reported previously,[6] the reaction rate of epoxide hydrolysis was relevant to the amount of water that served as reaction medium. We tested this point again by measuring the reaction rates of two substrates with different solubilities in water

Table 1 Deprotection of *N*-Boc aromatic heterocycles[a]

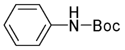
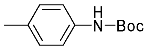
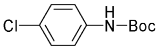
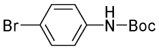
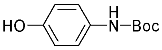
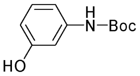
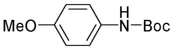
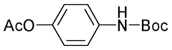
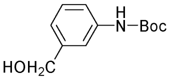
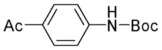
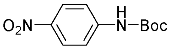
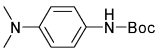
Entry	Substrate	Time	Yield (%)
1		10 min	99
2		10 min	99
3		10 min	99
4		5 min	99
5		4 h	99
6		1 h	99
7		2 h	99

[a] All reactions were conducted with 1 mmol of substrate in 10 mL of water at 100 °C.

State key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China. E-mail: qujin@nankai.edu.cn; Fax: +86-22-23499254; Tel: +86-22-23499247

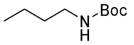
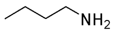
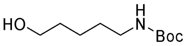
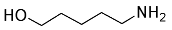
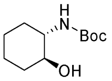
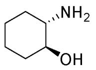
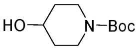
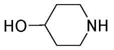
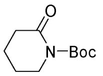
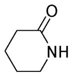
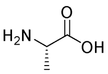
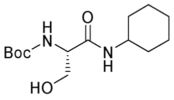
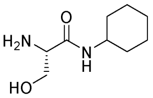
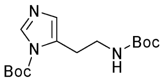
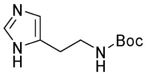
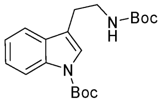
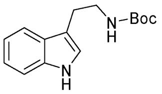
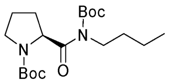
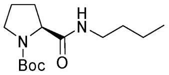
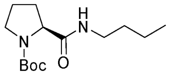
† Electronic supplementary information (ESI) available: Experimental details and analytical data. See DOI: 10.1039/b910239f

Table 2 Deprotection of *N*-Boc aromatic amines[a]

Entry	Substrate	Time/h	Yield (%)
1[b]		10	99
2[b]		10	99
3		10	99
4		14	97
5[b]		2	97
6		1	95
7[b]		6	99
8		3	91
9		1.5	98
10		2.5	97
11		3.5	94
12[b]		8	99

[a] All reactions were conducted with 1 mmol of substrate in 20 mL of water at 100 °C. [b] The reaction was conducted under nitrogen atmosphere.

Table 3 Deprotection of *N*-Boc aliphatic amines and amides[a]

Entry	Substrate	Product	Time	Yield (%)
1			13 h	87
2			4.5 h	99
3			6.5 h	93
4			10 h	97
5			0.5 h	97
6			4 h	99
7			4 h	99
8			10 min	94
9[b]			4 h	77
10			9 h	76

[a] All reactions were conducted with 1 mmol of substrate in 20 mL of water at 100 °C. [b] The sticky substrate (1 mmol) was firstly dissolved in 1 mL of 1,4-dioxane and then 19 mL of water was added.

(Fig. 1). The reaction rate of the less soluble *N*-Boc-4-chloroaniline strongly depended on the amount of water. For the more soluble *N*-Boc-3-hydroxymethylaniline, the amount of water was not important once the minimum volume of water needed for efficient conversion was reached. We suppose that the electronic substitution effect was masked by the solubility effect of the substrate, the effect which we think to be predominantly determining the rate of the deprotection.

N-Boc protected aliphatic amines with some solubility in water reacted smoothly (the deprotection of hydrophobic substrates is sluggish). The deprotection of relatively insoluble *N*-Boc-*n*-butylamine needed 13 h (entry 1, Table 3), but when a hydroxyl group is present in the substrate, such as in *N*-Boc-5-amino-1-pentanol, *N*-Boc-*trans*-2-hydroxyl cyclohexylamine and *N*-Boc-4-hydroxypiperidine (entries 2–4), the reaction proceeded faster and high yields were obtained. Deprotection of the *N*-Boc lactam is a desired method in organic synthesis.[14] For a *N*-Boc lactam, removal of Boc group was effected without hydrolysis of the lactam ring (entry 5). However, several acid-liable protecting groups such as THP, TMS and acetal cannot survive under the present conditions.

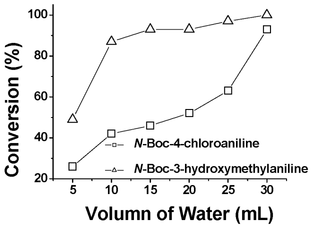


Fig. 1 Deprotection of 1 mmol of *N*-Boc-4-chloroaniline (□) and *N*-Boc-3-hydroxymethylaniline (△) in different volumes of water at 100 °C (the conversion was measured separately at 6 h and 1 h).

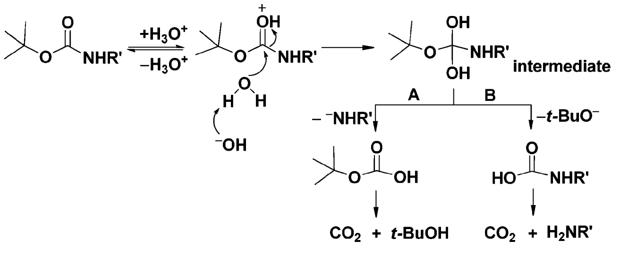
Cleavage of *N*-Boc groups on amino acid and peptidic substrates was also tested. For *N*-Boc alanine methyl ester (entry 6, Table 3), both the Boc group and methyl ester were unmasked within 4 h; this phenomenon was also observed in the deprotection of *N*-Boc phenylalanine methyl ester in subcritical water.[13] For *N*-Boc serine cyclohexylamide (entry 7), only the Boc group was removed after 4 h. No racemization of the α-carbon on the amino acid was found in the above two cases.

The reactivities of different types of *N*-Boc are not the same in boiling water. Strong acidic reagents cannot differentiate this and remove all Boc groups at the same time. The current condition is neutral and if the reaction is stopped at certain point, the more liable Boc group can be removed (Boc group on aromatic heterocycle or lactam) prior to the less reactive Boc group (Boc group on aliphatic amine). For N^{α},N^{im}-diBoc-histamine and N^{α},N^{ind}-diBoc-tryptamine (entries 8 and 9, Table 3), the heteroaromatic Boc group was selectively removed, while the *N*-Boc on the aliphatic amine remained intact.[15] Also, the Boc moiety on the amide nitrogen can be selectively removed from *N*,*N*′-bis-Boc-proline-*n*-butylamide (entry 10).

The *N*-Boc group could be removed under thermal conditions (180 °C).[16] We found the deprotection of *N*-Boc-3-hydroxymethylaniline did not occur in refluxing 1-propanol (b.p. = 97 °C), which indicates the deprotection does not automatically initiate at 100 °C. Neither did the deprotection occur in refluxing methanol, suggesting that the polar solvent effect does not account for the reactivity observed in water. To obtain further insight into the reaction mechanism, the *N*-Boc deprotection was performed in D_2O and monitored by ^1H NMR spectroscopy.† We found that with the decrease of the Boc group signal, the *t*-butanol signal increased, suggesting that the *N*-Boc group decomposed into *tert*-butanol rather than *iso*-butene, the product of *N*-Boc deprotection in strong acidic conditions. It is possible that the *t*-BuOH was from the water-trapped *tert*-butyl cation, but considering the reaction conditions are neutral, it is quite unlikely that refluxing water plays the role of a strong acid (such as TFA).

We noticed a recent theory on water catalysis based on molecular dynamics studies from Prof. Houk's research group. They predicted that ester hydrolysis in water is catalyzed by a water molecule acting as a dual acid/base catalyst.[17] Judging by the facts that methyl ester (entry 6, Table 3) is also hydrolyzed in boiling water, it is likely that the *N*-Boc cleavage in water may also undergo a similar pathway (Scheme 1).[18] When the water temperature rises, the self-ionization of water is enhanced (the $-\log K_w$ value of water at 100 °C is 12, while that of ambient water is 14), and both H^+ and OH^- are more abundant. The carbamate is firstly activated by protonation of the carbonyl oxygen by a hydronium ion, and water (hydroxide ion serving as a base) attacks the carboxyl, providing a tetrahedral intermediate, the geminal diol (attempts of monitoring the formation of this intermediate by ^1H NMR and MS did not succeed),† which then expels an amide ion (pathway **A**) or *tert*-butyloxide (pathway **B**) depending on which one is the better leaving group. The *N*-Boc on aromatic heterocycles should be deprotected through pathway **A** because aromatic heterocycle anions are better leaving groups. This pathway can easily explain the finding that boiling water may also remove methoxycarbonyl on imidazole, while aniline methyl carbamate cannot be deprotected in boiling water because neither the methoxide nor aniline anion is good leaving group. So, the deprotection of *tert*-butoxycarbonyl on aromatic and aliphatic amines should go through pathway **B**, which was also proposed by Coudert's group when using Bu_4NF as an *N*-Boc deprotection reagent.[8c]

Carrying out the organic reaction in water alone is the highest level of green chemical process. Our *N*-Boc deprotection also avoids the use of mineral acid and prevents the production of unwanted waste salt resulting from the subsequent neutralization. Moreover, the neutral reaction conditions enable the selective deprotection of one *N*-Boc group in molecules with two *N*-Boc protected sites. The investigation of the role of water suggested that it should act as a dual acid/base catalyst. Accordingly, this report demonstrates the potential of this most ancient dual acid/base catalyst in catalyzing organic transformations, which has not been essentially explored.



Scheme 1 Proposed mechanism of *N*-Boc deprotection.

This work was financially supported by The National Natural Science Foundation of China (20402007, 20772065), the 111 Project (B06005) and the 863 Project of the Ministry of Science and Technology of China (2006AA020502). We thank Prof. Chi Zhang for helpful discussions.

Notes and references

1 For recent reviews on organic reactions in water, see: (*a*) *Organic Reactions in Water*, ed. U. M. Lindström, Blackwell, Oxford, UK, 2007; (*b*) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*c*) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68; (*d*) U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751.

2 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816.

3 N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725.

4 (*a*) N. Shapiro and A. Vigalok, *Angew. Chem., Int. Ed.*, 2008, **47**, 2849; (*b*) N. Azizi and M. R. Saidi, *Org. Lett.*, 2005, **7**, 3649; (*c*) S. V. Chankeshwara and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 3259; (*d*) G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 2433.

5 (*a*) I. Vilotijevic and T. F. Jamison, *Science*, 2007, **317**, 1189; (*b*) C. J. Morten and T. F. Jamison, *J. Am. Chem. Soc.*, 2009, **131**, 6678.

6 Z. Wang, Y.-T. Cui, Z.-B. Xu and J. Qu, *J. Org. Chem.*, 2008, **73**, 2270.

7 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, 3rd edn, 1999 and references cited therein.

8 For other recently reported *N*-Boc deprotection methods, see: (*a*) A. Kuttan, S. Nowshudin and M. N. A. Rao, *Tetrahedron Lett.*, 2004, **45**, 2663; (*b*) A. Thaqi, A. McCluskey and J. L. Scott, *Tetrahedron Lett.*, 2008, **49**, 6962; (*c*) U. Jacquemard, V. Bénéteau, M. Lefoix, S. Routier, J.-Y. Mérour and G. Coudert, *Tetrahedron*, 2004, **60**, 10039; (*d*) J. Choy, S. Jaime-Figueroa, L. Jiang and P. Wagner, *Synth. Commun.*, 2008, **38**, 3840.

9 (*a*) R. A. Houghten, A. Beckman and J. M. Ostresh, *Int. J. Peptide Protein Res.*, 1986, **27**, 653; (*b*) H. R. Brinkman, Jr., J. J. Landi, Jr., J. B. Paterson, Jr. and P. J. Stone, *Synth. Commun.*, 1991, **21**, 459; (*c*) H. Miel and S. Rault, *Tetrahedron Lett.*, 1997, **38**, 7865.

10 P. Strazzolini, N. Misuri and P. Polese, *Tetrahedron Lett.*, 2005, **46**, 2075.

11 (*a*) G. Han, M. Tamaki and V. J. Hruby, *J. Peptide Res.*, 2001, **58**, 338; (*b*) D. S. Coffey, M. K. N. Hawk, S. W. Pedersen, S. J. Ghera, P. G. Marler, P. N. Dodson and M. L. Lytle, *Org. Process Res. Dev.*, 2004, **8**, 945.

12 (*a*) B. Li, R. Bemish, R. A. Buzon, C. K.-F. Chiu, S. T. Colgan, W. Kissel, T. Le, K. R. Leeman, L. Newell and J. Roth, *Tetrahedron Lett.*, 2003, **44**, 8113; (*b*) B. Li, M. Berliner, R. Buzon, C. K.-F. Chiu, S. T. Colgan, T. Kaneko, N. Keene, W. Kissel, T. Le, K. R. Leeman, B. Marquez, R. Morris, L. Newell, S. Wunderwald, M. Witt, J. Weaver, Z.-J. Zhang and Z.-L. Zhang, *J. Org. Chem.*, 2006, **71**, 9045.

13 G. Wang, C.-J. Li, J. Li and X.-S. Jia, *Tetrahedron Lett.*, 2009, **50**, 1438.

14 S. Calimsiz and M. A. Lipton, *J. Org. Chem.*, 2005, **70**, 6218.

15 (*a*) K. Ravinder, A. V. Reddy, K. C. Mahesh, M. Narasimhulu and Y. Venkateswarlu, *Synth. Commun.*, 2007, **37**, 281; (*b*) T. Apelqvist and D. Wensbo, *Tetrahedron Lett.*, 1996, **37**, 1471.

16 V. H. Rawal and M. P. Cava, *Tetrahedron Lett.*, 1985, **26**, 6141.

17 (*a*) H. Gunaydin and K. N. Houk, *J. Am. Chem. Soc.*, 2008, **130**, 15232; (*b*) X.-Y. Zhang and K. N. Houk, *J. Org. Chem.*, 2005, **70**, 9712.

18 The possible effect of CO_2 dissolved in water was evaluated by conducting the reactions in double distilled water, Milli-Q® Water and degassed water under a nitrogen atmosphere, but no difference in reactivity was found.