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A Simple and Efficient Green Method for the Deprotection of *N*-Boc in Various Structurally Diverse Amines under Water-mediated Catalyst-free Conditions

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Abstract

A simple, efficient and eco-friendly protocol has been developed for the deprotection of *N*-Boc on structurally diverse amines. Selective removal of *N*-Boc groups was achieved with excellent yields using water around reflux temperatures. In the absence of any additional reagents, this method represents a reasonable alternative to previously reported deprotection procedures.

Keywords: boc, deprotection, water, green chemistry, amines, cyclosulfamides

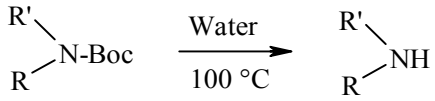
1. Introduction

The development of a simple and effective method, using an environmentally friendly approach as well as an economical process is in great demand in protective group chemistry. The introduction and removal of protecting groups has great significance in organic synthesis (Wuts & Greene, 2007). The development of protecting groups and the study of its consequent deprotection is a field of interest, often unavoidable need in the synthesis of complex molecular structures. The *tert*-butyloxycarbonyl (Boc) is still one of the most widely used in organic chemistry, used to protect primary or secondary amines as well as amino acids in peptides chemistry (Bodansky & Bodansky, 1994). The stability of *N*-Boc to catalytic hydrogenation and its resistance towards basic and nucleophilic attacks make Boc and other protecting groups (Bn, Fmoc and CBz) ideal orthogonal partners for the protection of amines during the synthesis of multifunctional targets (Agami et al., 2002; Lutz et al., 1998). Traditional methods for Boc-protection involve the reaction of amines with di-*tert*-butyl dicarbonate $(Boc)_2O$ in the presence of 4-(*N*,*N*-dimethylamino) pyridine (DMAP) (Basel et al., 2000) or inorganic bases (Handy et al., 2004). In the point of view, several strategies for the *N*-Boc deprotection have been developed these past years. A variety of reagents have been employed to effect this transformation, including strong acids, Lewis acids, and neutral conditions assisted by microware. *N*-Boc deprotection has been successful using mild acidic conditions (Wuts & Greene, 2007) such as trifluoacetic acid (TFA) in CH_2Cl_2, HCl in EtOAc, H_2SO_4 in t-BuOAc, TsOH and MsOH in *t*-BuOAc-CH_2Cl_2, aqueous phosphoric acid in THF (Li et al., 2003), or with Lewis acids such as $BF_3{\cdot}OEt_2$, TMSI, TMSOTf, $TiCl_4$, $SnCl_4$, $AlCl_3$, $Sn(OTf)_2$ and $ZnBr_2$ (Wuts & Greene, 2007; Bose et al., 2003). Montmorillonite K10 clay catalyst (Shaikh et al., 2000) and silica gel (under low pressure) (Applquist et al., 1996) or thermolytic conditions at high temperature (150 ^oC) (Rawal et al., 1987; Klai et al., 2004) have also shown to work. Cleavage of the Boc group can also be achieved in some cases under basic conditions, where the amine is highly activated, such as a pyrrole (Hasan et al., 1981; El Kazouli et al., 2006; Tom et al., 2004). Recently, microware-assisted *N*-Boc deprotection under mild basic conditions using $K_3PO_4{\cdot}H_2O$ in CH_3OH has been reported (Dandepally et al., 2009). However, many of these methods present disadvantages such as high acidity, the use of expensive reagents and more excessive amounts of catalysts and organic solvents, low

chemoselectivity as well as high temperatures. In addition, some of these catalysts cannot be recovered and used again. In recent years, organic reactions in water have received considerable attention. Compared to conventional solvents, water is preferred for organic reactions because of its unique properties. Moreover, it is cheap, non-toxic, non-explosive, and environmentally acceptable. Thus, the use of water over organic solvents in deprotection reactions has gained much importance in the area of sustainable development chemistry (Crieco, 1998; Li & Chang, 1997). However, reports for using of water as catalyst to promote organic reactions are very limited. Wang et al. (2009) reported special and efficient "green", catalyst- free, *N*-Boc deprotection in subcritical water, under pressure. Both aromatic and aliphatic *N*-Boc amines can be converted to the corresponding amines in high yields. The experiments were carried out with various time intervals (1-6 h), using distilled, deionized water (20 mL/mmol) at 150 ^{o}C. More recently, Thajudeen et al. (2010) described l-proline-based cyclic dipeptides from *N*-Boc-protected methyl esters under catalyst free conditions using water as a solvent. One-pot deprotection followed by cyclization has been used as the key steps. Based on these works, we've explored the deprotection of the Boc group using a catalyst-free water-mediator in the absence of any additional reagent under normal pressure, predicting chemoselectivity toward acid labile protecting group as methyl ester.

2. Results and Discussion

For the initial study of the deprotection, we chose aromatic and aliphatic *N*-Boc amine derivatives since many of these substrates are either commercially available or easily accessible. A series of *N*-Boc amines were subject to the deprotection conditions in water at 100 ^{o}C (Scheme 1). The results are established in Table 1. *N*-Boc deprotection was achieved in one single step by using deionized water under argon atmosphere.

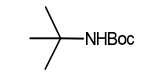
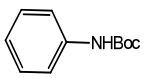
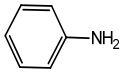
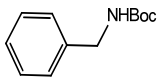
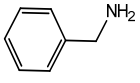
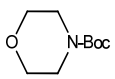
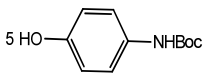
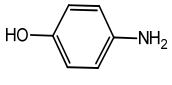
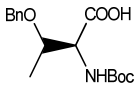
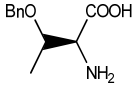


1-5 **1a-5a**

Scheme 1. Deprotection of the Boc group in diverse amines

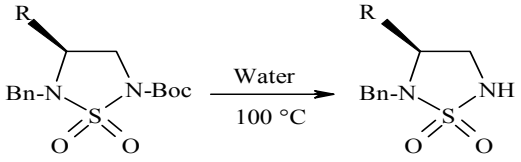
As seen by the results from Table 1, the isolated yields of 1a-6a are in between 90 and 97 % and the reactions completed after within 12 minutes. A comparative observation can be made with Wang et al. (2009) who heated to a temperature of 150 ^{o}C under pressure for the deprotection of *N*-Boc amines, whereas only 100 ^{o}C was needed for our approach and delivering excellent yields. We noticed that the Benzyl orthogonal group was conserved in the case of 6a.

Table 1. Deprotection of *N*-Boc amines[a]

Entry	Substrat	Product	Time (min)	Yield [b] (%)
1			5	93
2			7	94
3			10	90
4			8	95
5			8	97
6			12	90

[a] All reactions conducted with 1 mmol of substrate in 10 mL of water at 100°C
[b] isolated yield after purification.

Encouraged by these excellent preliminary results, we attempted the deprotection with a series of cyclosulfamides containing two orthogonal protecting groups a Benzyl and a Boc.

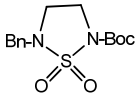
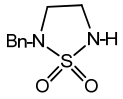
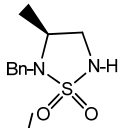
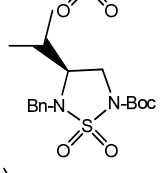
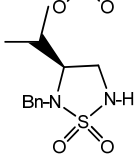
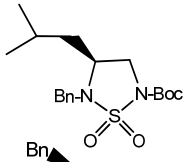
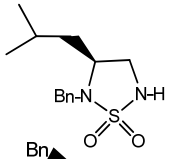
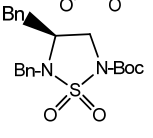


7-11 **7a-11a**

Scheme 2. Deprotection of the Boc group in *N*-Boc, *N*'-Bn- cyclosulfamides

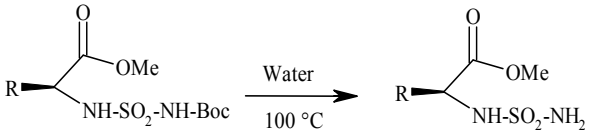
Using a typical procedure, *N*-Boc, *N*'-Bn cyclosulfamides (7-11) were dissolved in water and treated by increasing the temperature until reaching boiling point. Reaction progress was monitored by TLC, which showed complete transformations of 7-11 within 12 min at 100 ^{o}C, giving the corresponding deprotected *N*-H, *N*'-Bn cyclosulfamides 7a-11a in yields ranging from 90 % to 96 % (Scheme 2, Table 2). In every experiment, the benzyl group was preserved. The *N*-Boc, *N*'-Bn cyclosulfamides 7-11 syntheses were achieved starting from chlorosulfonyl isocyanate (CSI), *tert*-butanol and natural amino acids (Gly, Ala, Val, Leu, Phe), following the general procedure previously described (Régaïnia et al., 2000; Berredjem et al., 2003).

Table 2. Deprotection of *N*-Boc cyclosulfamides[a]

Entry	Substrat	Product	Time (min)	Yield [b] (%)
7			3	90
8			5	96
9			12	95
10			8	93
11			6	93

[a] All reactions conducted with 1 mmol of substrate in 10 mL of water at 100°C
[b] isolated yield after purification.

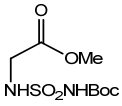
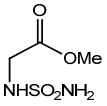
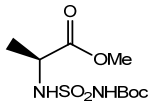
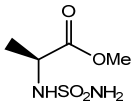
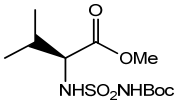
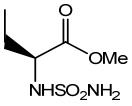
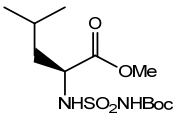
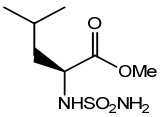
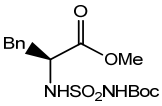
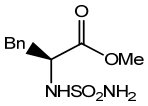
To scope the limitations of this reaction, we extended our study to the Boc-deprotection of various linear *N*-Boc carboxylsulfamides amino acid derivatives (Scheme 3). All *N*-protected compounds (12-16) were prepared by our team starting from amino acids and CSI as described previously (Aouf et al., 1991). The results of these experiments are summarized in Table 3, and show that the Boc cleavage was successful for all of the substrates giving the corresponding *N*-deprotected carboxylsulfamides in high yields ranging from 92 to 96 % within 10 minutes. Surprisingly, we did not observe the deprotection of the ester group, and the selectivity of the deprotection was confirmed by ^{1}H NMR, by the presence of a methyl ester group signal at 3.70 ppm. This could be considered advancement over the reported methods (Wang & Li., 2009; Wang et al., 2009) for *N*-Boc deprotection and can be avoid predicting that water molecule act as dual acid/base catalyst in height temperature.



12-16 **12a-16a**

Scheme 3. Deprotection of the Boc group in carboxysulfamides

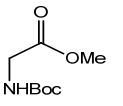
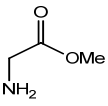
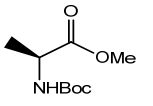
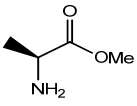
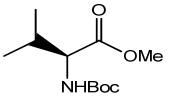
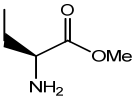
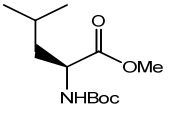
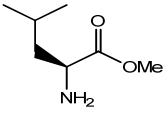
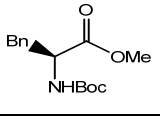
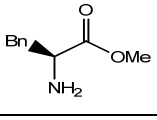
Table 3. Deprotection of *N*-Boc carboxysulfamides[a]

Entry	Substrat	Product	Time (min)	Yield [b] (%)
12			5	95
13			10	94
14			8	92
15			10	95
16			5	98

[a] All reactions conducted with 1 mmol of substrate in 10 mL of water at 100°C
[b] isolated yield after purification.

The reaction preserves stereochemical integrity of *N*-Boc amino ester derivatives (Table 4, entry 17-21), and the selectivity of this method can be valuable in organic chemistry applications, particularly in the synthesis of peptides.

Table 4. Deprotection of *N*-Boc aminoesters[a]

Entry	Substrat	Product	Time (min)	Yield [b] (%)
17			5	96
18			10	94
19			8	92
20			10	95
21			5	95

[a] All reactions conducted with 1 mmol of substrate in 10 mL of water at 100°C
[b] isolated yield after purification.

The generally accepted mechanism for the cleavage of the Boc group under acidic conditions involves the formation of carbone dioxide and a *tert*-butyl cation. We noticed a theory on water catalysis based on the study of molecular dynamics from Houk's et al. (2008) predicting that methyl ester hydrolyzed in water, which could act as a dual acid/base catalyst. When the temperature rises, the self-ionization of water is enhanced, where subcritical water can boast higher H^+ and OH^- concentration.

To demonstrate acting of water molecule on *N*-Boc deprotection, we have carrying out the reaction in deonized water under argon atmosphere with depressurized system, avoiding the dissolution of CO_2 released, which we think that decreasing of pH to 6.2 at 100 ^oC on bidistilled water effect the reaction. Furthermore, reaction was carried out on deionized water where pH decreases for 6.9 at rt to 6.6 at 100 ^oC. For these reasons, we found that water molecule could bear hydrogen-bonding with carbamate moiety than an acid (Wang & Li., 2009) or dual acid/base (Wang et al., 2009) catalyst advised.

Most of *N*-Boc amine derivatives are insoluble in water at room temperature, but become miscible when the temperature above 60 ^oC, which proves that substrate-water hydrogen-bonding occurs. Starting from 90 ^oC, the release of CO_2 is observed. The carbamate is firstly activated (electrophilic activation on carbonyl and nucleophilic activation on azotes atom), and then the hydroxide ion serves as a base which attacks the carboxyl, providing a tetrahedral intermediate. The geminal diol gives the deprotected amine, carbon dioxide and *t*-BuOH. The mechanism proposed by Qu et al. (2009) has been confirmed by our study.

3. Conclusions

In this work, we have developed a method for selective deprotection of the Boc group for various aliphatic, aromatic and heterocyclic amines, as well as cyclosulfamides and carboxylsulfamides. Based on our interesting results, we believe that the present study is a more eco-friendly approach compared to previous methods used. We are currently investigating the limitations of this technique and applying it to various structurally diverse *N*-Boc amines containing different orthogonal protecting groups. Relating results will be reported in our next communication.

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Appendix

General Procedure for the *N*-Boc Deprotection

(1 mmol) *N*-Boc amine, kept in a round-bottomed flask, is dissolved in (1 mL) water and stirred for the appropriate amount of time (Table). Progress of the different reactions is monitored by TLC and after periods no longer than 12 minutes at temperatures between 90-100 ^{o}C, the transformations are complete. Each reaction is then cooled to room temperature. Dichloromethane (5 mL) is added to the stirring mixture. The organic extract is dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give desired product after purification by silica gel column chromatography. ^{1}H and ^{13}C NMR were consistent with the predicted structures and were compared with those reported in literature. In all cases, products obtained after the usual work up gave satisfactory spectral data.

Experimental Section

All commercial chemicals and solvents were without further purification. All reactions were carried out under inert argon atmosphere. Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in a 250 MHz Brücker spectrometer. Microanalysis was performed in the microanalysis laboratory of ENSCM (Montpellier). Chemical shifts are reported in δ units (ppm) with 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 combination of these signals. Electron Ionisation mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ. High-resolution mass spectra were measured on a Jeol SX102 mass spectrometer and recorded in FAB positive mode. All reactions were monitored by TLC on silica Merck 60 F_{254} precoated aluminium plates and were developed by spraying with ninhydrin solution. Optical rotations were measured on a JUSCO DIP-370 digital polarimeter. Columns chromatographies were performed on Merck silica gel (230-400 mesh).

[(S) (+)] Methyl [N-sulfamoyl]-phenylalaninate 16a

(Yield 92%); R_f = 0.53 (CH_2Cl_2-MeOH, 9.1), (mp 64-65 ℃), $[\alpha]_D$ = + 45 (c = 1, MeOH), IR (KBr, ν cm^{-1}): 1745 (C=O), 1338 and 1152 (SO_2); 3312, 3245, 3482, (NH). ^{1}H NMR spectrum (250 MHz, $CDCl_3$): δ, ppm (*J*, Hz): 7.25 (m, 5H, Ar-H), 5.60 (d, 1H, *J* = 8.8 Hz, NH), 4.90 (s, 2H, NH_2), 4.40 (dt, *J* = 5.5 Hz and *J'* = 8.8 Hz, 1H, C*H); 3.65 (s, 3H, OCH_3); 3.00 and 3.20 (2dd, (ABX system) ^{1}J = 5.7, ^{2}J = 7.00 and *Jgem* = 13.8, 2H, CH_2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ, ppm (*J*, Hz): 39.50, 52.50, 58.60, 127.70, 129.80, 129.90, 137.30, 173.50.Mass Spectrum (ESI^+, 30 eV), m/z (I_{rel}, %): 259 $[M+H]^+$ (100). Anal. Calcd for $C_{10}H_{14}N_2O_2S$; C,46.51; H, 5.42; N, 10.85. Found; C, 46.49; H, 5.39; N, 10.80.

N^5–Benzyl-1, 2, 5-thiadiazolidine 1,1-dioxide 7a

(Yield 92 %); R_f = 0.64 (CH_2Cl_2-MeOH, 95-5); (mp 98-100 ℃). IR (KBr) v, cm^{-1}: 3267, 3335, 3298 (NH); 1325 and 1141 (SO_2). ^{1}H NMR spectrum, (250 MHz, $CDCl_3$): δ, ppm (*J*, Hz): 7.40 (m, 5H, ArH), 4.75 (t, *J* = 9.6, 1H, NH); 4.20 (s, 2H, $PhCH_2$), 3.84 (t, *J* = 6.4, 2H, CH_2); 3.62 (m, 2H, CH_2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ, ppm (*J*, Hz): 134, 129.5, 128.8, 127.3, 51.2, 43.3, 42.5. Mass spectrum (ESI+, 30 eV), m/z (I_{rel}, %): 213 $[M+H]^+$, (100), 91 $[Bn]^+$ (77). Anal. Calcd for $C_9H_{12}N_2O_2$; C, 50.94; H, 5.66; N, 13.20. Found; C, 50.90; H, 5.71; N, 13.28.