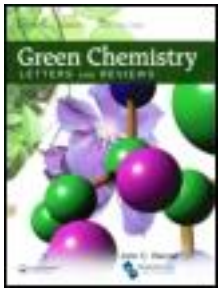

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A simple and eco-sustainable method for the O-Boc protection/deprotection of various phenolic structures under water-mediated/catalyst-free conditions

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A 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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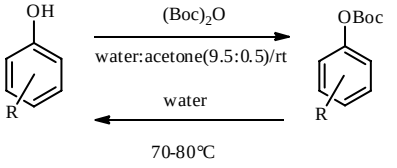
A greener, efficient, and chemoselective protocol for *O*-Boc protection/deprotection of a wide range of phenol derivatives is reported under catalyst-free conditions in water-related systems. Unlike previous reports, no additional reagents or catalysts were used, and workup fulfils green chemistry requirements, 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 $BiCl_3$ [9], $Zn(OAc)_2$ [10], 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydroisoquinoline (BBDI) [3,4] and $NaTiO_4$ [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 (CBr_4) as catalyst and their regeneration from the *O-tert*-Boc derivatives using the complex system CBr_4–PPh_3. 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_2O	0.75	95
MeOH	72	10
EtOH	72	4
MeCN	72	0
THF	72	0
CH_3Cl	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, CH_3Cl, and CCl_4) 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.

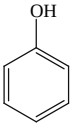
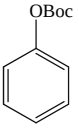
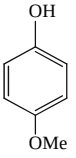
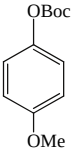
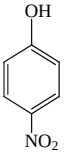
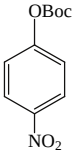
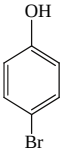
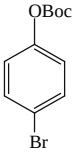
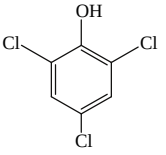
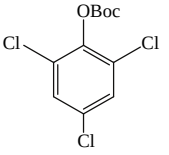
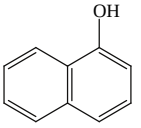
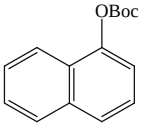
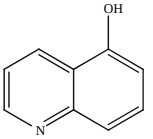
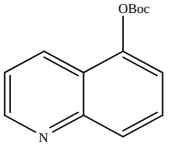
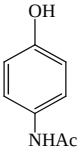
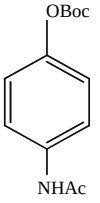
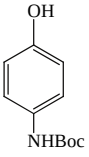
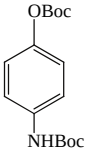
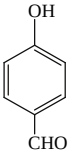
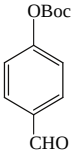
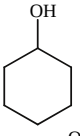
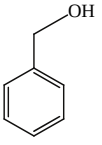
			O-Boc protection[a]	*O*-Boc deprotection[b]
Entry	Substrate	Product	*T* (min)/yield (%)	*T* (min)/yield (%)
1			45/95	8/98
2			30/87	3/95
3			70/96	5/100
4			55/90	8/90
5			90/93	10/89

Table 2 (*Continued*)

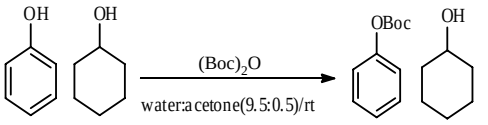
Entry	Substrate	Product	*O*-Boc protection[a] *T* (min)/yield (%)	*O*-Boc deprotection[b] *T* (min)/yield (%)
6			120/85	10/98
7			90/90	6/97
8			65/97	6/99
9			70/95	2/100
10			50/90	3/100
11		–	–/–	–/–
12		–	–/–	–/–

[a]1 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.
[b]All 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 *N*H-Boc, *N*H-Ac, CHO, NO_2, and OCH_3 can be observed in Table 2, showing the absence of undesired products such as *N*-Boc at *N*H-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.

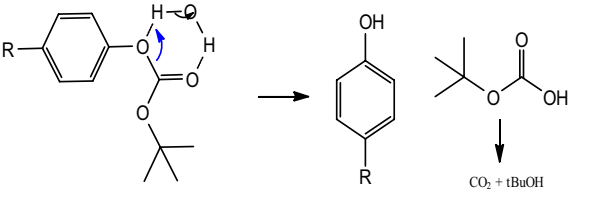
Encouraged by these experimental results, the protocol conditions were also applicable to the resorcinol and hydroquinone **13** and **14** containing two hydroxyl groups. The *O*-*tert*-butoxycarbonylation of **13** and **14** using 1 equiv. of $(Boc)_2O$ in the same conditions affords a mixture of 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 **14b** in 68%) (Scheme 2).

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, *N*H-Ac, *N*H-Boc, NO_2, 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 *N*H-Boc and *N*H-Ac can find interesting applications in protecting group chemistry.

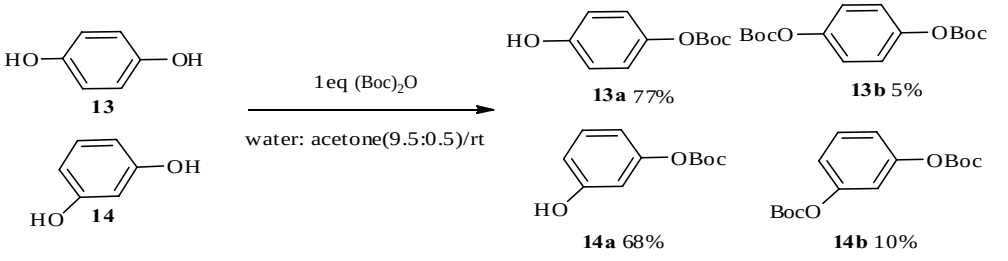
To demonstrate the general act of water as catalyst for the reaction, we used a depressurized system under argon atmosphere to avoid dissolving CO_2 in water, released during the removal of the Boc group. Therefore, we propose the following mechanism, where water can provide hydrogen bonding with the 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 CO_2 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



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

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. 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 $(Boc)_2O$ 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 (3×5mL), 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 ond solid form.

Tert-butyl 4-acetamidophenyl carbonate [11]
Yield 97%; R_f ($CHCl_3$–MeOH 95:5) 0.7; RMN^{1}H 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 ($2CH_{B,C}$), 121.47 ($2CH_{A,D}$), 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^{1}H δ (ppm) (250 MHz, $CDCl_3$): 1.51 (s, 9H, NHCOO*t*-Bu), 1.56 (s, 9H, OCOO*t*-But), 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, $J = 2.0$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 ($2CH_{B,C}$), 121.59 ($CH_{A,D}$), 136.00 (C_{CNHBoc}), 146.34 (C_{COBoc}), 152.03 ($C_{NCOOtBu}$), 152.76 ($C_{OCOOtBu}$).

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 (3×5mL) 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.

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Efficient deprotection of Boc group in amines and sulfamides using Dawson heteropolyacid catalyst

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ABSTRACT

A series of sulfamides containing two protecting groups have been synthesized starting from *N*-benzoylaminoacids derivatives of (glycine, alanine, valine, leucine, phenylalanine), chlorosulfonylisocyanate and primary amines. Selective deprotection of the cyclic or linear sulfamides and amines has been achieved by treatment with heteropolyacid, which is easily recoverable and reusable. This method represents a reasonable alternative to the previous reported deprotection procedures.

1. Introduction

The development of mild and chemoselective methods for the protection and deprotection of functional groups continues to be significant tool in organic synthesis. The *tert*-butyloxycarbonyl (Boc) group is extensively used in peptide and heterocyclic synthesis for amine protection. It is stable against hydrolysis under basic conditions and to many other nucleophic reagents. It is easily introduced using commercially available di-*tert*-butyldicarbonate (*Tert*-BuOCO)$_2$O under standard basic conditions. Deprotection is generally achieved under acid conditions, as extensively described in Greene's protective group in organic synthesis [1,2]. A variety of reagents have been employed to affect this transformation including strong acids (Trifluoacetic acid"TFA", HCl, HBr, H_2SO_4, $HNO_3$and Lewis acids (BF_3.Et_2O and ZnBr)). Cleavage of the Boc moiety can be obtained under basic conditions only in special cases, where the amine is highly activated, such as a pyrrole [3]. Thermal deprotection have also been reported [4,5]. The deprotection can also be effected with mildly acidic conditions such as Montmorillonite K10 clay catalyst [6] and silica gel (in low pressure) [7]. Many of these methods suffer from disadvantages such high acidity, expensive reagents and using more excessive amounts of catalysts, high temperature and slow rate reaction.

In our previous work, we reported the cleavage reaction of the Boc group in heterocyclic compounds by fusion method [8]. In thepursuit of our researchfocussedto the development of new reagents and methods for the *N*-Boc deprotection, we attempt to use the Dawson heteropolyacid (HPA) as catalyst. Heteropolyacids have been reported as versatilegreen catalysts for a variety of reactions [9]. The large field of research in heteropolyanion (HPAn) chemistry has been devoted to the preparation, structure characterization, and analytical applications of these compounds [10,11]. Surprisingly, in spite of their importance, Dawson HPA is not extensively used in organic synthesis, except in few examples described in literature [12-17]. Heydari et *al.* [18] reported the *N*-*tert*-butoxycarbonylation of amines using commercially available Kegg in heteropolyacids ($H_3PW_{12}O_{40}$). Except very few examples, no reference reported the use the HPA in protecting group chemistry.

In this paper, we report a deprotection study of the Boc group in cyclosulfamides, linear sulfamides and amines carried out using a heteropolyacid with Wells-Dawson structure in dichloromethane.

2. Experimental

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 Bruker spectrometer. Microanalyses were performed in the microanalysis laboratory of ENSCM (Montpellier). Spectral data are reported in δ unit (ppm) relative to tetramethyl silane (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 massspectra were measured on a Jeol SX102 mass spectrometer and recorded in FAB (Fast atom bombardement) positive mode.

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Scheme 1

All reactions were monitored by thin layer chromatography (TLC) on silica Merck 60 F_{254}precoated aluminium plates and were developed by spraying with ninhydrin solution. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Columns chromatographies were performed on Merck silica gel (230-400 mesh).

2.1. Synthesis

The heteropolyanions precursor's $K_6P_2W_{18}O_{62}.10H_2O$ and $K_6P_2W_{12}Mo_6O_{62}.14H_2O$ as well as their acids forms were synthesized according to published procedures [19-20] and purity was confirmed by infrared and ^{31}P NMR spectroscopy. Heteropolyacid (HPA) potassium salt (10 g) was dissolved in 50 mL of HCl 0.5 N. To the obtained solution, we added 30 mL of concentrated HCl (d = 1.184 g/cm^3) and 100 mL of ether. After stirring, the heavy phase was deposed in decanted bulb. The heteropolyacid was extracted. 5mL of water was added to the heteropolyacid and stirred. The heteropolyacid was obtained by vapour diffusion over a period of 3 days.

2.1.1. N^2-Boc-4-alkyle-N^5-benzyl-1,2,5-thiadiazolidine 1,1-dioxide (1-5)

The synthesis of the compounds, starting from chlorosulfonyl isocyanate (CSI), *tert*-butyl alcohol and methyl esters of amino acids (Gylcine, L-alanine, L-leucine and L-phenyalanine) has been previously reported [19].

2.1.2. Synthesis of compounds 1a-5a

N^2-Boc-4-alkyle-*N*^{5}-benzyl-1,2,5-thiadiazolidine 1,1-dioxide (1 mmol) was dissolved in CH_2Cl_2, 10% of heteropolyacid catalyst was added and the mixture was stirred at room temperature for a few minutes. The suspension was filtered, the solution was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum, and the crude product was subjected to column chromatography (DCM:MeOH, 9:1). Deprotected compounds (**1a**-**5a**) were obtained in 90-95% yield. The heteropolyacid was recuperated by filtration and used again (Scheme 1).

N^5*-Benzyl-1,2,5-thiadiazolidine 1,1-dioxide* (**1a**): Yield: 92%. R_f = 0.64 (CH_2Cl_2:MeOH, 95:5). M.p.: 98-100 °C. FT-IR (KBr, cm^{-1}): 3267, 3335, 3298 ν(NH), 1325, 1141 ν(SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 7.40 (m, 5H, ArH), 4.75 (t, *J* = 9.6 Hz, 1H, NH), 4.30 (s, 2H, $PhCH_2$), 3.84 (t, *J* = 6.4 Hz, 2H, CH_2), 3.62 (m, 2H, CH_2). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 134.0, 129.5, 128.8, 127.3, 51.2, 43.3, 42.5. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 213 $[M+H]^+$ (100), 91 $[Bn]^+$ (77). Anal. calcd. for $C_9H_{12}N_2O_2S$: C, 50.94; H, 5.66; N, 13.20. Found: C, 50.90; H, 6.71; N, 13.28%.

N^5*-Benzyl-4-methyl 1, 2, 5-thiadiazolidine-1,1-dioxide* (**2a**): Yield: 95%. R_f = 0.62 (CH_2Cl_2:MeOH, 95:5). M.p.: 100-102 °C. $[\alpha]_D$ = -18° (c = 1, $CHCl_3$). FT-IR (KBr, cm^{-1}): 3339, 3308, 3267 ν(NH), 1332, 1153 ν(SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 7.40 (m, 5H, ArH), 4.75 (d, *J* = 9.6 Hz, 1H, NH), 4.40 (d, 1H, *J* =15.2 Hz, $PhCH_2$), 4.10 (d, 1H, *J* = 15.2 Hz, $PhCH_2$), 3.90 (m, 2H, CH_2), 3.62 (m, 1H, CH_{asy}), 1.25 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 135.2, 128.5, 127.4, 124.1, 51.3, 47.2, 42.4, 21.7. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 227 $[M+H]^+$ (100). Anal. calcd. for $C_{10}H_{14}N_2O_2S$: C, 53.09; H, 6.19; N, 12.39. Found: C, 53.00; H, 6.23; N, 12.31%.

N^5*-Benzyl-4-isopropyl 1, 2, 5-thiadiazolidine 1,1-dioxide* (**3a**): Yield: 96%. R_f = 0.62 (CH_2Cl_2:MeOH, 95:5). M.p.: 104-106 °C. $[\alpha]_D$ = +23° (c = 1, EtOH). FT-IR (KBr, cm^{-1}): 3331, 3314, 3252 ν(NH), 1345 and 1165 ν(SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 7.40 (m, 5H, ArH), 4.88 (s, 1H, NH), 4.35 (d, *J* = 13.8 Hz, 1H, CH_2-Ph), 3.95 (d, *J* = 13.8 Hz, 1H, CH_2-Ph), 3.40 (m, 3H, *CH and CH_2), 2.8 (m, 1H, CH *i*Pr), 0.90 and 1.00 (2d, *J* = 6.7 Hz, 6H, $2CH_3$). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 139.2, 128.3, 129.4, 12.5, 51.2, 50.6, 32.3, 23.5, 19.4, 18.2. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 255 $[M+H]^+$ (72), 91 $[Bn]^+$ (80). Anal. calcd. for $C_{12}H_{18}N_2O_2S$: C, 56.69; H, 7.08; N, 11.02. Found: C, 56.67; H, 7.14; N, 10.95%.

N^5*-Benzyl-4-isobutyl 1, 2, 5-thiadiazolidine 1,1-dioxide* (**4a**): Yield: 92%. R_f = 0.60 (CH_2Cl_2:MeOH, 95:5). M.p.: 117-119 °C. $[\alpha]_D$ = +3° (c = 1, EtOH). FT-IR (KBr, cm^{-1}): 3327, 3242, 3273 ν(NH), 1332, 1161 ν(SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 7.35 (m, 5H, ArH), 4.45 (d, 1H, *J* = 7.4 Hz, NH), 4.35 (d, *J* = 13.8 Hz, 1H, CH_2-Ph), 4.10 (d, *J* = 13.8 Hz, 1H, CH_2-Ph), 3.80 (m, 1H, CH_{asy}), 2.90 (dd, *J* = *J'* = 6.9 Hz, 1H, CH_2), 2.35 (dd, *J* = *J'* = 6.9 Hz, 1H, CH_2), 1.60 (m, 1H, CH-*i*Bu), 1.45 (m, 2H, CH_2), 0.90 and 0.95 (2d, *J* = 6.2 Hz, 6H, $2CH_3$). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 138.7, 127.5, 127.4, 125.5, 54.3, 52.3, 42.2, 23.5, 19.2, 17.4. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 269 $[M+H]^+$ (76), 91$[Bn]^+$ (56). Anal. calcd. for $C_{13}H_{20}N_2O_2S$: C,58.21; H, 7.46; N, 10.45. Found: C, 58.31; H, 7.53; N, 10.41%.

N^5*-3-Dibenzyl-1,2,5-thiadiazolidine 1,1-dioxide* (**5a**): Yield: 93.2%. R_f = 0.52 (CH_2Cl_2). M.p.: 97-98 °C. $[\alpha]_D$ = -23° (c = 1, EtOH). FT-IR (KBr, cm^{-1}): 3269 ν(NH), 1338, 1172 ν(SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 7.52 (m, 10H, ArH), 4.90 (t, *J* = 9.6 Hz, 1H, NH), 4.40 (m, 1H, CH_{asy}), 4.10 (d, *J* = 13.6 Hz, 1H, CH_2-Ph), 4.35 (d, *J* =13.6 Hz, 1H, CH_2-Ph), 2.90 (m, 2H, CH_2), 3.50 and 3.20 (2dd, , *J* = 18.3, *J'* = 4.7 and *J''*= 7.3 Hz, 2H, CH_2-Ph). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 138.7, 137.3, 129.2, 128.3, 127.5, 127.1, 125.5, 124.5, 57.3, 54.2, 52.1, 42.7. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 303 $[M+H]^+$ (100), 91 $[Bn]^+$ (67). Anal. calcd. for $C_{16}H_{18}N_2O_2S$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.51; H, 5.92; N, 9.29%.

2.1.3. N-tert **-butyloxycarbonyl,** *N'***-benzylsulfamide** *(6)*

The synthesis of the compound **6**, starting from CSI, *tert*-butyl alcohol and benzylamine with a reaction of carbamoylation-sulfamoylation affording *N*-Boc-benzyl sulfamide, that has been previously reported [19].

2.1.4. Synthesis of N'-Benzylsulfamide (6a)

N-Boc, *N'*-benzylsulfamide (1 mmol) was dissolved in was CH_2Cl_2, 10% of heteropolyacid catalyst was added and the mixture was stirred at room temperature for a few minutes. The suspension was filtered, the solution was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum, and the crude product was subjected to column

Scheme 2

chromatography (DCM:MeOH, 9:1). *N'-Benzylsulfamide* **6a** was obtained in 92% yield. The heteropolyacid was recuperated by filtration and used again (Scheme 2).

N'-Benzylsulfamide (**6a**): Yield: 92%. R_f = 0.43 ($CHCl_2$:MeOH, 9:1). M.p.: 86-88 °C. FT-IR (KBr, cm^{-1}): 3335, 3298, 3265 ν(NH), 1354, 1142 ν(SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 7.32 (m, 5H, Ar-H), 6.05 (t, *J* = 6.7 Hz, 1H, NH), 5.80 (s, 2H, NH_2), 4.28 (d, *J* = 6.7 Hz, 2H, CH_2-Ph). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 52.5, 127.7, 129.8, 129.9, 138.2. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 187 $[M+H]^+$ (100). Anal. calcd. for $C_7H_{10}N_2O_2S$: C, 45.16; H, 5.37; N, 15.05. Found: C, 45.12; H, 5.40; N, 15.12%.

2.1.5. Methyl esters of [(N-(N-Boc)-sulfamoyl] amino acids (7-11)

The synthesis of the compounds, starting from CSI *tert*-butyl alcohol and methyl esters of amino acids (Gylcine, L-alanine, L-leucine, and L-phenyalanine) has been previously reported [20,21].

2.1.6. Synthesis of compounds (7a-11a)

N-Boc linear sulfamides (**7**-**11**) (1 mmol) was dissolved in CH_2Cl_2, 10% of heteropolyacid catalyst was added and the mixture was stirred at room temperature for a few minutes. The suspension was filtered, the solution was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum, and the crude product was subjected to column chromatography (DCM:MeOH, 9:1). Deprotected compounds (**7a**-**11a**) were obtained in 92-95% yield. The heteropolyacid was recuperated by filtration and used again (Scheme 3).

Methyl [N-sulfamoyl]-glycinate (**7a**): Yield: 95%. R_f = 0.56 (CH_2Cl_2:MeOH, 9:1). M.p.: 61-62 °C. FT-IR (KBr, cm^{-1}): 1738 ν(C=O), 1351, 1139 ν(SO_2), 3320, 3265 ν(NH). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 6.62 (s, 2H, NH_2), 6.05 (t, *J* = 6.8 Hz, 1H, NH), 4.35 (d, *J* = 6.8 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 52.8, 58.0, 160.2. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 191 $[M+Na]^+$ (100%). Anal. calcd. for $C_3H_8N_2O_4S$: C, 21.43; H, 4.76; N, 16.66. Found: C, 21.38; H, 4.79; N, 16.64%.

[(S)(-) Methyl [N-sulfamoyl]-alaninate (**8a**): Yield: 92%. R_f = 0.46 (CH_2Cl_2:MeOH, 9:1). M.p.: 67-68 °C. $[\alpha]_D$= -18° (c = 1, EtOH). FT-IR (KBr, cm^{-1}): 3290, 3372 ν(NH), 1746 ν(C=O), 1341, 1149 ν(SO_2), 3330, 3270, 3250 ν(NH). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 6.95 (d, *J* = 8.6 Hz, 1H, NH), 5.40 (s, 2H, NH_2), 4.20 (m, 1H, C*H), 3.65 (s, 3H, OCH_3), 1.45 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 19.3, 51.3, 53.2, 171.2. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 183 $[M+H]^+$ (80), 365 $[2M+H]^+$(20). Anal. calcd. for $C_4H_{10}N_2O_4S$: C, 26.37; H, 5.49; N, 15.38. Found: C, 26.42; H, 5.44; N, 15.43%.

[(S)(+) Methyl [N-sulfamoyl]-valinate (**9a**): Yield: 92%. R_f = 0.49 (CH_2Cl_2:MeOH, 9:1). M.p.: 52-54 °C. $[\alpha]_D$ = +9.5° (c = 1, EtOH). FT-IR (KBr, cm^{-1}): 1748 ν(C=O), 1352, 1158 ν(SO_2), 3332, 3258, 3274 ν(NH). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 5.73 (d, *J* = 8.3 Hz, 1H, NH), 5.04 (s, 2H, NH_2), 3.90 and 3.95 (dd, *J*= 4.8 and *J'*= 4.8 Hz, 1H, C*H), 3.80 (s, 3H, OCH_3), 2.20 (m, 1H, CH_β), 0.9 and 1.1 (2d, *J* = 6.8 Hz, 6H, $2CH_3$). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 19.7, 20.0, 30.3, 56.7, 62.2, 175.6. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 211 $[M+H]^+$ (100). Anal. calcd. for $C_6H_{14}N_2O_2S$: C, 34.28; H, 6.66; N, 13.33. Found: C, 34.42; H, 6.71; N, 13.12%.

[(S)(-)] Methyl [N-sulfamoyl]-leucinate (**10a**): Yield: 95%. R_f = 0.47 (CH_2Cl_2:MeOH, 9:1). M.p.: 58-60 °C. $[\alpha]_D$ = -21.5° (c = 1, MeOH). FT-IR (KBr, cm^{-1}): 1751 ν(C=O), 1348, 1154 ν(SO_2), 3310, 3251, 3282 ν(NH). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 5.20 (s, 1H, NH exch), 5.20 (s, 2H, NH_2), 4.25 (t, *J* = 7.4 Hz, 1H, C*H), 3.66 (s, 3H, OCH_3), 1.85 (m, 1H, iPr), 1.55 (m, 2H, $CH_{2\beta}$), 0.93 and 0.75 (2d, *J* = 2.9 Hz, 6H, $2CH_3$). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 21.05, 22.50, 23.50, 41.90, 52.20, 57.4, 172.28. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 225 $[M+H]^+$ (100). Anal. calcd. for $C_7H_{16}N_2O_2S$: C, 37.50; H, 7.14; N, 12.50. Found: C, 37.46; H, 7.13; N, 12.54%.

[(S)(+)] Methyl [N-sulfamoyl]-phenylalaninate (**11a**): Yield: 92%. R_f = 0.53 (CH_2Cl_2:MeOH, 9:1). M.p.: 64-65 °C. $[\alpha]_D$ = +45° (c = 1, MeOH). FT-IR (KBr, cm^{-1}): 1745 ν(C=O), 1338 and 1152 ν(SO_2), 3312, 3245, 3482 ν(NH). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 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), 3.00-3.20 (2dd, (ABX system), J_1 = 5.7, J_2 = 7.00 and J_{gem} =13.8 Hz, 2H, CH_2). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 39.5, 52.5, 58.6, 127.7, 129.8, 129.9, 137.3, 173.5. MS (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%.

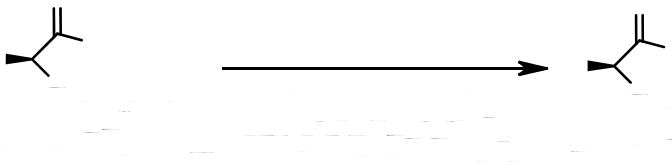
2.1.7. General procedure of the deprotection of N-Boc amines (12-16)

To a mixture of *N*-Boc amine (**12**-**16**) (1 mmol) and $H_6P_2W_{18}O_{62}.H_2O$ (10 % mmol) in 5 mL of CH_2Cl_2 was stirred at room temperature for 20 min. The catalyst was removed by filtration and was washed with toluene (1 mL). The solution was concentrated and the residue was generally subjected to column chromatography on silica to give the corresponding amine. The products **12a** triethylamine, **13a** aniline, **14a** benylamine, **15a** morpholine are commercially available and were identified by comparison of analytical data (TLC and IR) with those reported or with authentic samples prepared by the conventional method (Scheme 4).

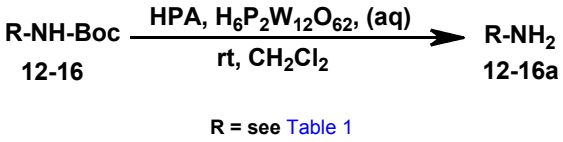
[(2S)(3S)(+)]2-amino-3-(benzyloxy)butanoic acid (**16a**): Yield: 90%. R_f = 0.58 (CH_2Cl_2:MeOH, 9:1). M.p.: 94-95 °C. $[\alpha]_D$ = +32° (c = 1, MeOH). FT-IR (KBr, cm^{-1}): 1708 ν(C=O), 3308, 3241, 3479 ν(NH). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 11.10 (s, 1H, OH), 7.25-7.40 (m, 5H, Ar-H), 5.10 (s, 2H, NH_2), 4.60 (s, 2H, OCH_2), 3.85 (d, *J* = 6.2 Hz, 1H, CH), 3.57 (m, 1H, CH), 1.20 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (62.89 MHz, $CDCl_3$, δ, ppm): 17.8, 60.9, 72.6, 85.3, 127.7, 128.2, 128.9, 137.3, 174.5. MS (ESI+, 30 eV, *m/z*, (I rel, %)): 210 $[M+H]^+$ (100). Anal. calcd. for $C_{11}H_{15}NO_3$: C,63.15; H, 7.18; N, 6.70. Found: C, 63.09; H, 7.18; N, 6.80%.

3. Results and discussion

In recent years, there has been great interest in the reactions performed under heterogeneous catalysis, because of the possibility of recovering and recycling the acid catalyst, largely reducing the environmental impact.

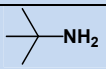
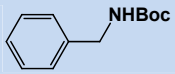
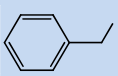


Scheme 3



Scheme 4

Table 1. Dawsonheteropolyacid catalysed cleavage of *N*-Boc amines.

Entry	Substrat	Product	This study		Literature [25]	
			Time (min)	Yield (%)	Time (h)	Yield (%)
12			8	88	-	-
13			10	92	4	86
14			12	92	4	86
15			4	85	-	-
16			10	94	-	-

The structure of Wells-Dawson (W.D.) heteropolyacid $H_6P_2W_{18}O_{62}{\cdot}24H_2O$ consists of a close-packed framework of octahedral WO_6 surrounding a central P atom, two identical 'half unit' PW_9 are linked through the oxygen atom. These proprieties make them suitable catalytic materials in homogeneous and heterogeneous liquid-phase reaction replacing the conventional liquid-acid. For reasons of the relative solubility in organic solvents, we are especially interested to the acid form of heteropolyacid ($H_6P_2W_{12}Mo_6O_{62}$) (HPA)was prepared starting from an aqueous solution of α-$K_6P_2W_{12}Mo_6O_{62}$ salt, which was treated with diethyl ether and a concentrated HCl solution (37%) [22].

The preparation of cyclosulfamides (**1**-**5**) with orthogonal protecting group was performed in four steps starting from amino acids (Glycine, alanine, valine, leucine and phenyl alanine) and chlorosulfonylisocyanate as previously described [23,24]. The deprotection reaction was studied using compounds **1**-**5** as substrates. When *N*-Boc-cyclo-sulfamides (**1**-**5**) were treated with heteropolyacid (10%, w:w) in DCM at room temperature for 15-30 minutes, the deprotected cyclosulfamides were obtained in quantitative yield. The reaction was monitored by LC-MS.

As outlined in Scheme 2, the deprotection was envisioned in first reaction sequence starting from *N*-benzyl-*tert*-butyloxycarbonylsulfamide **6**. In a typical experimental procedure, heteropolyacid was added to a solution of reaction substrate in an organic solvent. The mixture was stirred at room temperature until reaction was complete (monitored by HPLC, typically 15 min). This requisite substrate was prepared by sulfamoylation of benzyl amine as previously described [19].

Chemoselective deprotection of compound **6** was carried out in heterogeneous system using heteropolyacid in dichloromethane to afford deprotected compound **6a** in good yield. In our previous studies [18], we described a convenient access to a series of sulfamides *N*,*N*'-disubstituted, (**7**-**11**) starting from amino acids and chlorosulfonylisocyanate in two steps (carbamoyaltion-sulfamoylation). The deprotection protocol giving linear sulfamides (**7a**-**11a**) is outlined in Scheme 3. Deprotection of compounds **7**-**11** was performed using the standardized reaction conditions, giving yields better than 92 %.

The reaction carried out with *N*-Boc amines **12**-**16** shown in Table 1 affordsthe corresponding commercially available amines using standard conditions. Carbamates **12**-**16** were deprotected cleanly to provide the corresponding amines with quantitative yields, all results summarized in Table 1.

Wang *et al.* [25] report the *N*-Boc deprotection of a variety of aromatic amines and amino ester under catalyst-free conditions in subcritical water with height pressure. The both removed of acid-sensitive groups (methyl ester and Boc), the prolonged reaction time, that the disadvantage of chemoselectivity.

The corresponding amines were obtained in excellent yields. The substrate examined in these studies and the results obtained are summarized in Table 1. The reaction preserves stereochemical integrity of *N*-Boc amino acids (**16**) and regioselectivity of compounds (**15**-**16**) containing two orthogonal protecting groups (Bn and Boc) (Bn =benzyl). The generally accepted mechanism for the Boc removal group

under acid conditions involves the formation of carbon dioxide and *tert*-butyl cation, which after losing a proton gives isobutene.

Concerning a possible reaction mechanism, we assume that the heteropolyacid-catalyzed proceed with exchange of protons with the product. However the relative insolubility of the heteropolyacid catalyst in dichloromethane allows for easy separation of the product by simple filtration, heteropolyacid was reused with only a gradual decrease in its activity observed.

The structures of all the compounds were unambiguously confirmed by usual spectroscopic methods. For the final derivatives, the different NMR spectra showed a signal of NH proton and disappearance of signal corresponding to the *tert*-butyl protons. These compounds exhibited characteristic absorption in the IR spectrum and disappearance of the absorption at 1702-1712 cm^{-1} (C=O).

3. Conclusion

In conclusion, the Wells-Dawson heteropolyacid can be used as an alternative reagent for the deprotection of *N*-Boc group under heterogeneous catalysis conditions. The reaction conditions are mild, and offer good selectivity among other acid/base sensitive groups including Benzyl and methyester. Advantages of this methodology are operational simplicity, no corrosive and reusable. We are exploring other organic synthesis applications for heteropolyacid catalyst, and will report the finding in due course.

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Graphical Abstract

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