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

Roubila Belghiche, Zinelaabidine Cheraiet, Malika Berredjem, Mostefa Abbessi and Nour-Eddine Aouf *

Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Sciences Faculty, Chemistry Department, Badji Mokhtar Annaba University, 23000, Algeria

**Corresponding author at: Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Sciences Faculty, Chemistry Department, Badji Mokhtar Annaba University, 23000, Algeria. Tel.: +213.38872789; fax: +213.38872789. E-mail address: noureddineaouf@yahoo.fr (N-E. Aouf).*

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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 have reported the fusion method for the *N*-Boc deprotection [8]. More recently, we have developed the catalyst-free water-related system for the *N*-Boc protection/deprotection [9,10]. In the continuity of our research, we have focussed to 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 versatile green catalysts for a variety of reactions [11]. The large field of research in heteropolyanion (HPAn) chemistry has been devoted to the preparation, structure characterization, and analytical applications of these compounds [12,13]. Surprisingly, in spite of their importance, Dawson HPA is not extensively used in organic synthesis, except in few examples described in literature [14-19]. Heydari et *al.* [20] reported the *N*-*tert*-butoxycarbonylation of amines using commercially available Keggin 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.

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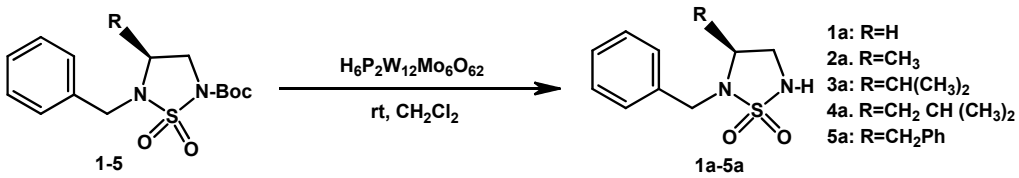


Scheme 1

High-resolution massspectra were measured on a Jeol SX102 mass spectrometer and recorded in FAB (Fast atom bombardement) positive mode. 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 chroma-tographies were performed on Merck silica gel (230-400 mesh).

2.1. Synthesis

The heteropolyanions precursor's $K_6P_2W_{18}O_{62}.14H_2O$ and $K_6P_2W_{12}Mo_6O_{62}.14H_2O$ as well as their acids forms were synthesized according to published procedures [21,22] and purity was confirmed by infrared and ^{31}P NMR spectroscopy. Heteropolyanion 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 [21].

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%.

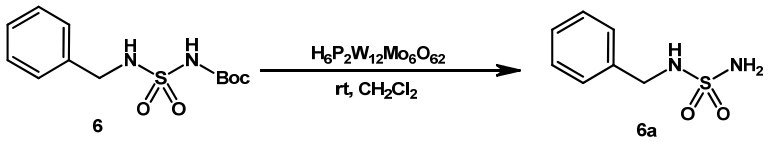
N^5*-3-Dibenzyl-1,2,5-thiadiazolidine 1,1-dioxide* (**5a**): Yield: 93.2%. R_f = 0.52 (CH_2Cl_2). M.p.: 97-98 °C. $[\alpha]_D$ = -23° (c = 1, EtOH). FT-IR (KBr, cm^{-1}): 3269 ν(NH), 1338, 1172 ν(SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 7.52 (m, 10H, ArH), 4.90 (t, *J* = 9.6 Hz, 1H, NH), 4.40 (m, 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 [21].

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,



Scheme 2

and the crude product was subjected to column 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 [22,23].

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%.

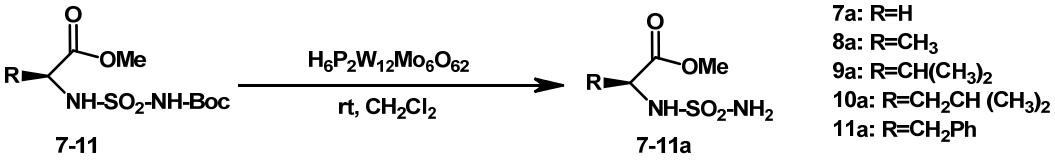
2.1.7. General procedure of the deprotection of N-Boc amines (12-16)

To a mixture of *N*-Boc amine (**12-16**) (1 mmol) and $H_6P_2W_{18}O_{62}.14H_2O$ (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).

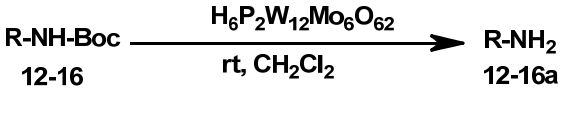
[(2S)(3S)(+)]2-amino-3-(benzyloxy)butanoic acid (**16a**): Yield: 90%. R_f = 0.58 (CH_2Cl_2:MeOH, 9:1). M.p.: 94-95 °C. $[\alpha]_D$ = +32° (c = 1, MeOH). FT-IR (KBr, cm^{-1}): 1708 ν(C=O), 3308, 3241, 3479 ν(NH). ^1H NMR (250 MHz, $CDCl_3$, δ, ppm): 11.10 (s, 1H, OH), 7.25-7.40 (m, 5H, Ar-H), 5.10 (s, 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.

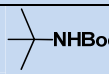
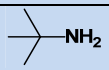
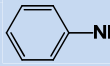
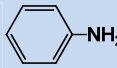
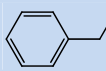
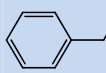
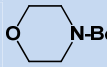
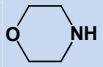
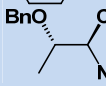
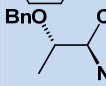


Scheme 3



Scheme 4

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

Entry	Substrat	Product	This study		Literature [27]	
			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 $H_6P_2W_{18}O_{62}.14H_2O$ 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 heteropolyanion ($H_6P_2W_{12}Mo_6O_{62}$) (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%) [24].

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 [25,26]. 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 [21].

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 [20], 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.* [27] 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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