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An efficient and facile synthesis of *N*-Cbz-β-aminoalkanesulfonamides

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An efficient method for the synthesis of *N*-Cbz-β-aminoalkanesulfonamides was described. *N*-Cbz-β-aminoalkanesulfonamides were readily prepared in good yields from a variety of amino alcohols, including optically active ones, via *N*-Cbz protection with benzyl chloroformate, Mitsunobu esterification reaction with thiolacetic acid, *N*-chlorosuccinimide oxidation, and ammonolysis process.

sulfonamides, amino alcohols, synthesis, Mitsunobu reaction, ammonolysis

1 Introduction

Aminoalkanesulfonamides have been recognized as important building blocks in combinatorial chemistry. Although α-aminoalkanesulfonamides are close mimetics of naturally occurring amino amides, few literature reported α-aminoalkanesulfonamides and their applications due to their readily labile properties [1]. Inversely, there is still growing interest in β-aminoalkanesulfonamides due to the fact that they can be considered as stable mimetics of tetrahedral transition states in hydrolysis and formation of esters and amides [2]. Therefore, they have been widely used as enzyme inhibitors [3, 4], antibacterial [5–7] and anticancer agents [8]. Additionally, *N*-protected β-aminoalkanesulfonamides as useful building blocks have been successfully employed in the synthesis of sulfonopeptides [1] and hybrid sulfonophosphinopeptides [9, 10]. Initially, β-aminoalkanesulfonamides were synthesized via the reaction of aminoalkanesulfinyl chlorides with ammonia or amines and subsequent oxidation with sodium periodate under the catalysis of $RuCl_3$ [4, 11–13]. Alternatively, they were prepared via the direct reaction of aminoalkanesulfonyl chlorides with ammonia or amines [14–16]. Aminoalkanesulfinyl chlorides were generally prepared from naturally occurring amino acids or amino alcohols via conversion of them into the corresponding thiolacetates and subsequent treatment with sulfuryl chloride in the presence of acetic anhydride [4, 11] or chlorine in an aqueous solution [12, 13], or prepared from cysteamine hydrochloride via the oxidation reaction with iodine to the corresponding disulfide, followed by treatment with chlorine in an aqueous solution [13–15]. Aminoalkanesulfonyl chlorides can be prepared via oxidation of thiols, thioacetates, or disulfides with phosgene [16, 17], triphosgene [18, 19], or chlorine in an aqueous solution [15, 20], or via reaction of β-aminoalkanesulfonic acids or β-aminoalkanesulfonates with phosgene [21, 22] or triphosgene [23], thionyl chloride [9, 24, 25], or oxalyl chloride [9, 26]. Although aminoalkanesulfinyl chlorides show higher reactivity than aminoalkanesulfonyl chlorides, the oxidation step did not always result in high yields and was difficult to optimize for use in solid phase synthesis. On the other hand, toxic transition metal $RuCl_3$ is necessary in the oxidation. For preparation of aminoalkanesulfonyl chlorides from thiols, thioacetates or disulfides, toxic gaseous rea-

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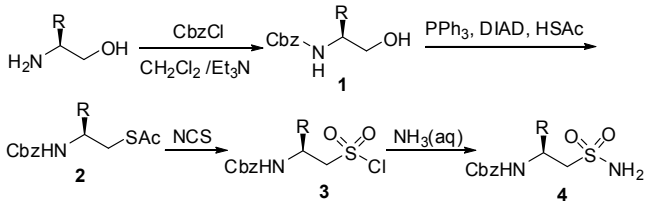


Scheme 1 Preparation of *N*-Cbz-β-aminoalkanesulfonamides.

gents, such as phosgene and chlorine, are generally used with difficulty to control the stoichometry and dangerous handle. In the methods with β-aminoalkanesulfonic acids or β-aminoalkanesulfonates as starting materials, it is generally difficult in the product isolation and purification in the preparation of β-aminoalkanesulfonic acids and β-aminoalkanesulfonates due to their strong polarity and solubility in water. They also showed poor solubility in the chloridation step and unsatisfactory reproducibility on a large scale, low yields sometimes. Therefore, it is worthy to develop a new efficient method for the preparation of this type of important sulfonamides. Herein, we present a convenient and facile synthetic method for the preparation of *N*-Cbz-β-aminoalkanesulfonamides in high yields by using mild reagents and reaction conditions (Scheme 1).

2 Experiments

2.1 Materials and measurements

Amino alcohols were purchased commercially. Dichloromethane was refluxed with calcium hydride and freshly distilled prior to use. Tetrahydrofuran was refluxed with sodium and diphenyl ketone until the color of system became blue and freshly distilled prior to use. TLC analysis was performed on glass pre-coated silica gel YT257-85 (10–40 μm) plate. Spots were visualized with UV light or iodine. Column chromatography was performed on silica gel zcx.II (200–300 mesh). Melting points were measured on a Yanaco MP-500 melting point apparatus. ^{1}H and ^{13}C NMR spectra of all compounds were recorded on a Brucker 400 NMR or Varian 300 plus spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal standard. HRMS data was carried out on an Agilent LC/MSD TOF mass spectrometer. IR spectra were determined on a Nicolet AVATAR 330 FT-IR spectrometer. Optical rotations were measured on a PerkinElmer Model 341 polarimeter with a thermally jacketed 10 cm cell (concentration *c* expressed as g/100 mL).

2.2 General procedure for synthesis of *N*-Cbz protected amino alcohols 1a–g

To a solution of an amino alcohol (50 mmol) in CH_2Cl_2 (165 mL) was added dropwise benzyl chloroformate (8.6 mL, 10.6 g, 60 mmol) at 0 °C, followed by Et_3N (35 mL, 25.3 g, 250 mmol). The resulting mixture was stirred at room temperature overnight. The resulting solution was washed with brine (100 mL × 3) and dried over anhydrous sodium sulfate. After concentration at reduced pressure, the residue was crystallized from the mixture of ethyl acetate and petroleum ether (60–90 °C) to give the corresponding *N*-Cbz amino alcohols. If the desired product was oil, it was purified by flash column chromatography on silica gel with petroleum ether (60–90 °C): ethyl acetate = 1:5 to 1:1 (*v*/*v*) as the eluent to afford the corresponding *N*-Cbz amino alcohol. Their analytic data are identical with those reported previously [27–33].

2.3 General procedure for synthesis of *N*-benzyloxycarbonylaminoalkyl thiolacetates 2a–g

To an efficiently stirred solution of triphenylphosphine (10.48 g, 40 mmol) in anhydrous THF (48 mL) was added dropwise a solution of diisopropyl azodicarboxylate (DIAD, 8.0 g, 40 mmol) in anhydrous THF (24 mL) at −10 °C over 30 min. The resulting mixture was stirred at −10 °C for another 0.5 h. A white precipitate appeared. A solution of Cbz-amino alcohol **1** (20 mmol) and thiolacetic acid (3.04 g, 40 mmol) in anhydrous THF (48 mL) was added dropwise over 45 min, and the reaction mixture was stirred overnight at −10 °C. After concentrated under reduced pressure, triphenylphosphine oxide was crystallized upon the addition of a mixture of ethyl acetate and petroleum ether (60–90 °C) in fridge. After filtration, the combined filtrate was concentrated in vacuo and subjected to silica gel column chromatography with petroleum ether (60–90 °C) (PE) : ethyl acetate (EA) = 20:1 to 5:1 (*v*/*v*) as the eluent to afford thiolacetate **2**.

*2-Benzyloxycarbonylaminoethyl thiolacetate (**2a**)*

Colorless needle crystals; yield: 82%; m.p. 36–37 °C; R_f = 0.29 (silica gel plate, PE: EA = 6:1, *v*/*v*). IR *v* (cm^{-1}): 3340 (NH), 1724 (C=O), 1692 (C=O), 1135 (S-CO). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 3.02 (t, *J* = 6.4 Hz, SCH_2), 3.36 (dt, *J* = 6.3, 6.4 Hz, 2H, NCH_2), 5.09 (s, 3H, OCH_2 & NH), 7.29–7.35 (m, 5H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 29.1, 30.5, 40.7, 66.7, 128.06, 128.1, 128.5, 136.4, 156.3, 195.7. HRMS (ESI) Calcd. for $C_{12}H_{16}NO_3S$ $[M+H]^+$ *m/z*: 254.0845; Found 254.0841.

*(S)-2-Benzyloxycarbonylaminopropyl thiolacetate (**2b**)*

Colorless needle crystals; yield: 68%; m.p. 66–67 °C; R_f = 0.31 (silica gel plate, PE:EA = 6:1, *v*/*v*); $[\alpha]^{20}_D$ = +30.8 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 3317 (NH), 1695 (C=O), 1135 & 1105 (S-CO); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.20 (d, *J* = 6.7 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.05 (d, *J* = 5.6 Hz, 2H, CH_2S), 3.84–4.00 (m, 1H, CHN), 4.81 (br s, 1H, NH), 5.09 (s, 2H, OCH_2), 7.26–7.35 (m, 5H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 20.0, 30.5, 34.9, 47.1, 66.5, 77.4, 128.0

(para and meta ArC), 128.5, 136.6, 155.7, 195.6. HRMS (ESI) Calcd. for $C_{13}H_{18}NO_3S$ $[M+H]^+$ *m/z*: 268.1002; Found 268.0996.

*(S)-2-Benzyloxycarbonylamino-3-methylbutyl thiolacetate (**2c**)*
Colorless crystals; yield: 57%; m.p. 89–90 °C; R_f = 0.3 (silica gel plate, PE:EA = 6:1, *v/v*); $[\alpha]^{20}_D$ = +94.9 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 3312 (NH), 1695 (C=O), 1130 & 1102 (S-CO). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, *J* = 6.9 Hz, 3H, CH_3), 0.96 (d, *J* = 6.9 Hz, 3H, CH_3), 1.75–1.86 (m, 1H, CH), 2.28 (s, 3H, CH_3), 2.94–3.09 (m, 2H, CH_2S), 3.60–3.70 (m, 1H, CHN), 4.80 (d, *J* = 9.4 Hz, 1H, NH), 5.05 (d, *J* = 12.3 Hz, 1H in OCH_2), 5.13 (d, *J* = 12.3 Hz, 1H in OCH_2), 7.25–7.41 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.9, 19.1, 30.4, 31.7, 32.0, 56.5, 66.5, 127.91, 127.96, 128.4, 136.6, 156.3, 196.0. HRMS (ESI) Calcd. for $C_{15}H_{22}NO_3S$ $[M+H]^+$ *m/z*: 296.1315; Found 296.1318.

*(S)-2-Benzyloxycarbonylamino-4-methylpentyl thiolacetate (**2d**)*
Colorless crystals; yield: 77%; m.p. 62–62.5 °C; R_f =0.4 (silica gel plate, PE:EA = 6:1, *v/v*); $[\alpha]^{20}_D$ = +29.4 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 3340 (NH), 1718 (C=O), 1696 (C=O), 1105 & 1027 (S-CO); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, *J* = 6.5 Hz, 6H, $2CH_3$), 1.24–1.43 (m, 2H, $CHCH_2$), 1.59–1.70 (m, 1H, $CH(CH_3)_2$), 2.29 (s, 3H, $COCH_3$), 2.96 (dd, *J* = 7.2, 13.8 Hz, 1H in CH_2S), 3.11 (dd, *J* = 4.7, 13.8 Hz, 1H in CH_2S), 3.90 (br s, 1H, CHN), 4.81 (d, *J* = 8.8 Hz, 1H, NH), 5.05 (d, *J* = 12.3 Hz, 1H in OCH_2), 5.11 (d, *J* = 12.3 Hz, 1H in OCH_2), 7.29–7.40 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.0, 22.9, 24.7, 30.4, 34.1, 43.4, 49.2, 66.5, 127.89, 127.9, 128.3, 136.5, 155.9, 195.5. HRMS (ESI) Calcd. for $C_{16}H_{24}NO_3S$ $[M+H]^+$ *m/z*: 310.1417; Found 310.1473.

*(S)-2-Benzyloxycarbonylamino-3-phenylpropyl thiolacetate (**2e**)*
Colorless solids; yield: 42%; m.p. 92–93 °C; R_f =0.4 (silica gel plate, PE:EA = 6:1, *v/v*); $[\alpha]^{20}_D$ = +20.6 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 3327 (NH), 1689 (C=O), 1134 & 1082 (S-CO).^1H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H, CH_3), 2.80 (dd, *J* = 7.1, 13.6 Hz, 1H in CH_2Ph), 2.92 (dd, *J* = 6.3, 13.6 Hz, 1H in CH_2Ph), 2.97 (dd, *J* = 7.8, 14.1 Hz, 1H in CH_2S), 3.08 (dd, *J* = 4.7, 14.1 Hz, 1H in CH_2S), 4.05 (m, 1H, CHN), 4.90 (d, *J* = 7.2 Hz, 1H, NH), 5.06 (s, 2H, OCH_2), 7.16–7.36 (m, 10H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 30.5, 32.6, 40.3, 52.5, 66.6, 126.7, 127.9, 128.0, 128.4, 128.6, 129.3, 136.5, 137.0, 155.7, 195.8. HRMS (ESI) Calcd. for $C_{19}H_{22}NO_3S$ $[M+H]^+$ *m/z*: 344.1315; Found 344.1320.

*(S)-2-Benzyloxycarbonylaminophenylethyl thiolacetate (**2f**)*
Colorless needle crystals; yield: 72%; m.p. 112–113 °C; R_f = 0.49 (silica gel plate, PE:EA = 6:1, *v/v*); $[\alpha]^{20}_D$ = +38.1 (*c*, 1.0, $CHCl_3$). IR *v* (cm^{-1}): 3331 (NH), 1686 (C=O), 1180 & 1141 (SCO). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H, CH_3), 3.21 (dd, *J* = 4.5, 13.8 Hz, 1H in CH_2S), 3.31 (dd, *J* = 9.0, 13.8 Hz, 1H in CH_2S), 4.88 (br s, 1H, NH), 5.04 (d, *J* = 12.3 Hz, 1H in OCH_2), 5.10 (d, *J* = 12.3 Hz, 1H in OCH_2), 5.35-5.51 (m, 1H, PhCH), 7.23–7.36 (m, 10H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 30.5, 34.9, 55.5, 66.8, 126.2, 127.9, 128.1, 128.4, 128.7 (2 carbons overlap), 136.4, 140.8, 155.7, 196.1. HRMS (ESI) Calcd. for $C_{18}H_{20}NO_3S$ $[M+H]^+$ *m/z*: 330.1158; Found 330.1148.

*(S)-1-Benzyloxycarbonylpyrrolidine-2-methyl thiolacetate (**2g**)*
Viscous oil; yield: 80%; R_f =0.44 (silica gel plate, PE:EA = 6:1, *v/v*); $[\alpha]^{20}_D$ = −52.5 (*c*, 1.0, $CHCl_3$). IR *v* (cm^{-1}): 1698 (C=O), 1133 & 1108 (S-CO). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.66–1.76 (m, 1H in CH_2), 1.77–1.85 (m, 1H in CH_2), 1.88–2.04 (m, 2H, CH_2), 2.30 (Rotamer), 2.34 (Rotamer) (s, 3H, CH_3), 3.01–3.29 (m, 2H, CH_2S), 3.44 (t, *J* = 6.4 Hz, 2H, NCH_2), 3.96–4.08 (m, 1H, NCH), 5.10-5.20 (m, 2H, OCH_2), 7.30–7.40 (m, 5H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 22.6, 23.4 (Rotamer), 28.8, 29.9 (Rotamer), 30.2, 31.0, 32.0 (Rotamer), 46.5, 46.9 (Rotamer), 56.2, 57.0 (Rotamer), 66.3, 66.6 (Rotamer), 127.5, 127.6, 127.7, 128.1, 136.5, 136.6, 154.5, 194.4, 194.8. HRMS (ESI) Calcd. for $C_{15}H_{20}NO_3S$ $[M+H]^+$ *m/z*: 294.1158; Found 294.1156.

2.4 General procedure for synthesis of 2-benzyloxycarbonylaminoalkanesulfonamides 4a–g

NCS (16 g, 120 mmol) was dissolved to a mixture of 2 M HCl (8 mL) and MeCN (40 mL). The resulting solution was cooled to 10 °C. A solution of thiolacetate **2** (30 mmol) in MeCN (8 mL) was added dropwise to the cooled solution at below 20 °C. The resulting solution was stirred at the same temperature for 30 min, and then diluted with isopropyl ether (156 mL). The organic layer was washed with aq. NaCl (12%, 3 × 78 mL) and then dried over anhydrous Na_2SO_4. After concentration in vacuo, the crude sulfonyl chloride **3** was obtained as colorless solids or pale yellow oil, and used directly without further purification. The sulfonyl chloride **3** was dissolved in dry dichloromethane (20 mL) and the resulting solution was added dropwise into ammonia (100 mL) under stirring at −10 °C. After addition, the resulting mixture was stirred for another 1 h at −10 °C. The solution was concentrated in vacuo to afford the crude product **4**. Further recrystallization from ethanol gave rise to *N*-Cbz-β-aminoalkanesulfonamide as colorless crystals.

*(S)-2-Benzyloxycarbonylaminopropanesulfonamide (**4a**)*
Colorless needle crystals; yield: 81%; m.p. 142–143 °C; Lit. [9] m.p. 138.5–140 °C; R_f = 0.26 (silica gel plate, PE:EA = 1:1, *v/v*). ^1H NMR (400 MHz, DMSO-d_6) δ: 3.12 (t, *J* = 7.0 Hz, 2H, CH_2), 3.40 (dt, *J* = 6.8, 7.0 Hz, 2H, CH_2), 5.02 (s, 2H, CH_2), 6.90 (s, 2H, NH_2), 7.30–7.39 (m, 6H, ArH, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 36.2, 54.4, 66.0, 128.2,

128.3, 128.8, 137.4, 156.5.

*(S)-2-Benzyloxycarbonylaminopropanesulfonamide (**4b**)*

Colorless needle crystals; yield: 63%; m.p. 150–151 °C; R_f = 0.57 (silica gel plate, PE:EA = 1:1, *v*/*v*); $[\alpha]^{20}_D$ = +10.8 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 1668 (C=O), 1342 & 1142 (SO_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.24 (d, *J* = 6.6 Hz, 3H, CH_3), 3.04 (dd, *J* = 7.5, 13.9 Hz, 1H in CH_2S), 3.25 (dd, *J* = 5.3, 13.9 Hz, 1H in CH_2S), 4.01(ddq, *J* = 5.3, 6.6, 7.5 Hz, 1H, CHN), 5.03 (s, 2H, OCH_2), 6.90 (s, 2H, NH_2), 7.28–7.42 (m, 6H, ArH & NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 20.4, 43.2, 59.8, 65.3, 127.7, 127.8, 128.3, 137.0, 155.2. HRMS (ESI) Calcd. for $C_{11}H_{17}N_2O_4S$ $[M+H]^+$ *m/z*: 273.0904; Found 273.0902.

*(S)-2-Benzyloxycarbonylamino-3-methylbutanesulfonamide (**4c**)*

Colorless solids; yield: 80%; m.p. 113–114 °C; R_f = 0.66 (silica gel plate, PE:EA = 1:1, *v*/*v*); $[\alpha]^{20}_D$ = +17.2 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 1696 (C=O), 1327 & 1143 (SO_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.81 (d, *J* = 6.6 Hz, 6H, $2CH_3$), 0.82 (d, *J* = 6.6 Hz, 6H, $2CH_3$), 1.85 (dhept, *J* = 5.3, 6.6 Hz, 1H, CH), 3.10 (d, *J* = 6.0 Hz, 2H, CH_2S), 3.85–3.94 (m, 1H, CHN), 5.03 (s, 2H, OCH_2), 6.81 (s, 2H, NH_2), 7.30–7.36 (m, 6H, ArH & NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 17.3, 18.6, 31.6, 51.9, 56.0, 65.1, 127.5, 127.6, 128.3, 137.2, 155.8. HRMS (ESI, *m/z*) Calcd. for $C_{13}H_{21}N_2O_4S$ $[M+H]^+$ *m/z*: 301.1217; Found 301.1214.

*(S)-2-Benzyloxycarbonylamino-4-methylpentanesulfonamide (**4d**)*

Colorless solids; yield: 70%; m.p. 128–129 °C; R_f = 0.77 (silica gel plate, PE:EA = 1:1, *v*/*v*); $[\alpha]^{20}_D$ = −7.5 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 1683 (C=O), 1326 & 1152 (SO_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.86 (d, *J* = 6.3 Hz, 6H, $2CH_3$), 1.42–1.48 (m, 2H, CH_2), 1.56–1.65 (m, 1H, CH), 3.04 (dd, *J* = 6.0, 13.8 Hz, 1H in CH_2S), 3.22 (dd, *J* = 6.3, 13.8 Hz, 1H in CH_2S), 3.94-4.05 (m, 1H, CHN), 5.02 (s, 2H, CH_2), 6.81 (s, 2H, NH_2), 7.29-7.36 (m, 6H, ArH & NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.4, 23.1, 24.1, 42.7, 45.4, 59.2, 65.1, 127.5, 127.7, 128.2, 137.1, 155.5. HRMS (ESI) Calcd. for $C_{14}H_{22}N_2O_4S$ $[M+H]^+$ *m/z*: 315.1373; Found 315.1370.

*(S)-2-Benzyloxycarbonylamino-3-phenylpropanesulfonamide (**4e**)*

Colorless solids; yield: 74%; m.p. 168–169 °C; R_f = 0.57 (silica gel plate, PE:EA = 1:1, *v*/*v*); $[\alpha]^{20}_D$ = −14.4 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 1683 (C=O), 1326 & 1152 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.81 (dd, *J* = 9.0, 13.5 Hz, 1H in CH_2), 3.02 (dd, *J* = 5.1, 13.5 Hz, 1H in CH_2), 3.14 (dd, *J* = 6.0, 14.0 Hz, 1H in CH_2S), 3.25 (dd, *J* = 6.4, 14.0 Hz, 1H in CH_2S), 4.15 (dddd, *J* = 5.1, 6.0, 6.4, 9.0 Hz, 1H, NCH), 5.0 (s, 2H, OCH_2), 6.90 (s, 2H, NH_2), 7.20–7.40 (m, 11H, ArH & NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 39.2, 48.7, 58.1, 65.0, 126.2, 127.3, 127.6, 128.1, 128.2, 129.2, 137.1, 138.0, 155.3. HRMS (ESI) Calcd. for $C_{17}H_{21}N_2O_4S$ $[M+H]^+$ *m/z*: 349.1217; Found 349.1213.

*(S)-2-Benzyloxycarbonylamino-2-phenylethanesulfonamide (**4f**)*

Colorless flaky crystals; yield: 69%; m.p. 150–150.5 °C; R_f = 0.54 (silica gel plate, PE:EA = 1:1, *v*/*v*); $[\alpha]^{20}_D$ = +41.4 (*c*, 1.0, MeOH). IR *v* (cm^{-1}): 1701 (C=O), 1340 & 1142 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.26 (dd, *J* = 3.3, 14.2 Hz, 1H in SCH_2), 3.55 (dd, *J* = 9.0, 14.2 Hz, 1H in SCH_2), 4.98 (d, *J* = 12.7 Hz, 1H in OCH_2), 5.03 (d, *J* = 12.7 Hz, 1H in OCH_2), 5.11 (ddd, *J* = 3.3, 8.2, 9.0 Hz, 1H, CHN), 6.92 (s, 2H, NH_2), 7.20–7.40 (m, 10H, ArH), 8.02 (d, *J* = 8.2 Hz, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 50.9, 59.8, 65.3, 126.2, 127.2, 127.6, 127.7, 128.2, 128.4, 136.9, 142.1, 155.1. HRMS (ESI) Calcd. for $C_{16}H_{18}N_2NaO_4S$ $[M+Na]^+$ *m/z*: 357.0879; Found 357.0873.

*(S)-1-Benzyloxycarbonylpyrrolidine-2-methanesulfonamide (**4g**)*

Viscous oil; yield: 60%; R_f = 0.49 (silica gel plate, PE:EA = 1:1, *v*/*v*); $[\alpha]^{20}_D$ = −21.6 (*c*, 1.0, $CHCl_3$). IR *v* (cm^{-1}): 1686 (C=O), 1358 & 1158 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.87–1.97 (m, 2H, CH_2), 2.02–2.14 (m, 2H, CH_2), 3.08 (dd, *J* = 8.1, 14.0 Hz, 1H in SCH_2), 3.40–3.48 (m, 2H, NCH_2), 3.57 (dd, *J* = 4.6, 14.0 Hz, 1H in SCH_2), 4.38–4.46 (m, 1H, CH), 5.12 (s, 2H, OCH_2), 5.45 (s, 2H, NH_2), 7.29–7.40 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.5, 30.7, 46.1, 54.0, 57.7, 67.2, 127.7, 128.1, 128.5, 136.4, 155.4. HRMS (ESI) Calcd. for $C_{13}H_{19}N_2O_4S$ $[M+H]^+$ *m/z*: 299.1060; Found 299.1054.

3 Results and discussion

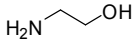
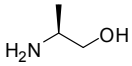
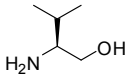
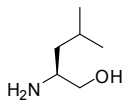
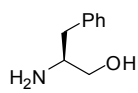
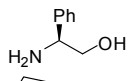
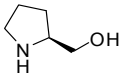
Commercially available β-amino alcohols first were protected their amino group with benzyl chloroformate (CbzCl) to give the corresponding *N*-Cbz-β-amino alcohols **1a**–**g** in satisfactory to perfect yields from 48% to 98% by referring the method described by Veitia *et al*. (Table 1, column 3) [34]. The workup procedure was modified. The reaction solution was first washed with brine to remove water soluble byproducts. After being dried over sodium sulfate and concentrated under reduced pressure, the crude residue was crystallized conveniently from the mixture of ethyl acetate and hexanes instead of the reported column chromatographic purification to afford the corresponding *N*-Cbz amino alcohols **1a**–**f** except for **1g** due to its oily property.

After synthesizing the *N*-Cbz-amino alcohols **1**, we next focused on the conversion of the *N*-Cbz-amino alcohols **1** to their thiolacetates **2.** To the best of our knowledge, there are two main approaches for the conversion**.** The first one is an

indirect method. The *N*-Cbz-amino alcohols **1** were first converted to their mesylates via reaction with methanesulfonyl chloride, and then the mesylates were further displaced with sodium or potassium thiolacetate. In the second approach, the thiolacetates were synthesized directly from *N*-Cbz-amino alcohols **1** and thiolacetic acid via the Mitsunobu reaction. Liskamp's group had attempted the two approaches previously [17] and found that the Mitsunobu reaction is more efficient than the indirect one. However, the purification process in the Mitsunobu reaction was usually very tedious and not reproducible on a larger scale (> 10 mmol). Additionally, the yields were unsatisfactory due to the formation of the Michael adduct of thiolacetic acid to DEAD (diethyl azodicarboxylate). Our group modified the method to avoid the formation of the Michael adduct. In our procedure, DEAD and triphenylphosphine were mixed first to form a white precipitate of the active intermediate, the adduct of DEAD and triphenylphosphine, and subsequently a solution of an *N*-Cbz-amino alcohol and thiolacetic acid was added slowly into the reaction mixture [35, 36]. Following our modified procedure, a series of thiolacetates **2a**–**g** were prepared in satisfactory to good yields from 42% to 82% (Table 1).

The structures of all thiolacetates **2** were characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectrometries. As observed generally, duplicated peaks appeared in the NMR spectra of product **2g**, indicating that it exists in two rotamers in its solution because the steric hindrance between Cbz and acetylthiomethyl groups inhibits its single bond to rotate freely. This is confirmed in the further reactions. After further oxidation and aminolysis, the duplicated peaks disappeared (vide post product **4g**), revealing that the steric hindrance between Cbz and methanesulfonamide groups is less than that between Cbz and acetylthiomethyl groups.

Table 1 Synthesis of compounds **1**, **2** and **4**

Entry	Amino alcohol	Yield (%)		
		1	**2**	**4**
1	 **a**	63	82	81
2	 **b**	48	68	63
3	 **c**	72	57	80
4	 **d**	92	77	70
5	 **e**	98	42	74
6	 **f**	86	72	69
7	 **g**	85	80	60

The crucial step is the preparation of *N*-Cbz-β-aminoalkanesulfonyl chlorides, which were mainly prepared previously via chlorination of the corresponding sulfonic acid with thionyl chloride [9, 24, 25], or oxalyl chloride [9, 26], or oxidation of thioacetates or disulfides via phosgene [16, 17], triphosgene [18, 19], or chlorine in an aqueous solution [15, 20]. Recently, Nishiguchi and his coworkers described a new and very useful reaction for the conversion of thiols, disulfides, thioacetates, and thiocarbamates to the corresponding sulfonyl chlorides in good yields via *N*-chlorosuccinimide (NCS) oxidation in dilute hydrochloric acid [37, 38]. However, aliphatic thiols and disulfides, electron-rich 4-methoxybenzyl and allyl thioacetates gave rise to the corresponding sulfonyl chlorides in relatively low yields, even without the desired products in the method. We envisioned that the above method could be applied in the preparation of functionalized *N*-Cbz-β-aminoalkanesulfonyl chlorides. As an attempt, the thioacetate **2a** was converted to *N*-Cbz-β-aminoethanesulfonyl chloride (**3a**) completely on TLC monitoring. The sulfonyl chloride **3a** was then subject to ammonolysis without further purification to afford the desired product *N*-Cbz-β-aminoethanesulfonamide (**4a**) in 81% overall yield of two steps. We also attempted to use NBS (*N*-bromosuccinimide) instead of NCS in the oxidation. However, no desired reaction occurred. With the successful method in hand, a series of *N*-Cbz-β-aminoalkanesulfonamides **4** were synthesized in satisfactory to good overall yields (Table 1). The approach for the preparation of *N*-Cbz-β-aminoalkanesulfonyl chlorides via the oxidation of the *N*-Cbz-aminoalkyl thiolacetates with NCS not only improves the reaction rate and product yields, but also uses a nontoxic and solid reagent NCS, convenient to control stoichiometry of the oxidizing agent. Compared with the chlorine oxidation method, the current method is more convenient, practical, and simple in controlling stoichiometry of the chlorinating reagents in the laboratory preparation. Additionally, except for 2-aminoethanol (**1a**), all of the other amino alcohols are optically active and their configuration is retained during the Mitsunobu substitution, NCS oxidation, and ammonolysis process without racemization because all reactions do not affect the chiral carbon atom. To the best of our knowledge, the current method is the best to synthesize *N*-Cbz-β-aminoalkanesulfonamides.

4 Conclusions

We developed a highly efficient and convenient method for the synthesis of useful *N*-Cbz-β-aminoalkanesulfon- amides from commercially available vicinal amino alcohols via the *N*-Cbz protection, the Mitsunobu esterification, *N*-chlorosuccinimide oxidation, and ammonolysis process. The cur-

rent method is an efficient, nontoxic, simple, and reproducible route to synthesize *N*-Cbz-β-aminoalkanesulfonamides.

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