# A Library of Conformationally Restricted Saturated Heterocyclic Sulfonyl Chlorides

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**Abstract:** An approach to the synthesis of conformationally restricted saturated heterocyclic sulfonyl chlorides is described. Being guided by the principle of diversity-oriented conformational restriction, a mini-library of saturated heterocyclic sulfonyl chlorides was designed and synthesized. The library consists of nine members that are derivatives of azetidine, pyrrolidine, and piperidine. These compounds were prepared in 19–88% total yields on multigram scale starting from the corresponding Cbz-protected amino alcohols.

**Key words:** sulfonyl chlorides, nitrogen heterocycles, molecular rigidity, libraries, conformational restriction

Sulfonamides represent an important class of chemical compounds that have been used in modern drug discovery since its very beginning. In addition to the widely known antibacterials ('sulfa drugs'), sulfonamides, which are used as diuretics, ophthalmologicals, anticonvulsants, and COX-2 inhibitors, can be mentioned.[1] Most of the marketed sulfonamide drugs are benzene derivatives. In fact, only 5 out of 82 sulfamide drugs registered in MDDR[1] are derivatives of aliphatic sulfonic acids other than methanesulfonic acid. This is partially due to the limited availability of the corresponding starting materials, such as aliphatic sulfonyl chlorides, and is especially the case when cyclic functionalized saturated sulfonyl chlorides are considered. Meanwhile, compounds of this type possess an important feature referred to as '3D shape', which is related to the prevalence of saturated atoms, the limited number of rotatable bonds, and to the chirality of the molecules.[2] These properties were identified as being characteristic for both the drug molecules and natural products.

Another important feature that is peculiar for cyclic saturated molecules is their limited conformational flexibility, which is a property that is also believed to improve the biological effect of the compounds.[3] In the search for structures that provide optimal interaction with biological targets, libraries of conformationally restricted analogues (i.e., isomers and/or homologues) that allow the conformational space to be probed, are beneficial. This approach to the design of biologically relevant molecules is referred to as diversity-oriented conformational restriction.[3,4] The idea has been widely used in the design of conformationally restricted amino acids and diamines,[5] whereas conformationally constrained amino sulfonyl chlorides has received much less attention. The limited long-term stability of the latter compounds and some of their derivatives may be one of the reasons for this. Meanwhile, the used of acyclic amino sulfonyl chlorides has already been beneficial in the design of peptidomimetics and related compounds.[6,7]

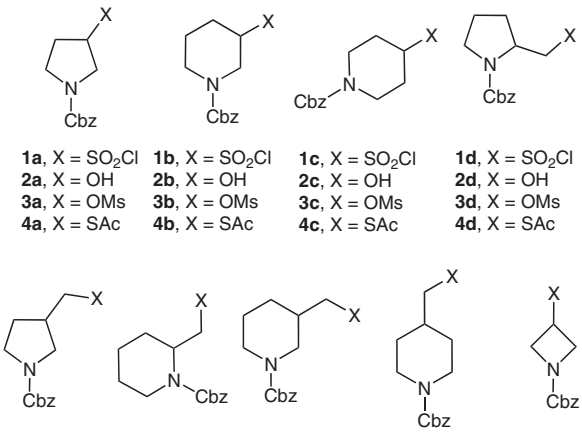


**Figure 1** Pyrrolidine- and piperidine-derived sulfonyl chlorides and their synthetic precursors

Being inspired by the ideas described above, herein we present a mini-library of saturated heterocyclic sulfonyl chlorides **1a–i** (Figure 1). Some of these compounds have been reported in the literature[7–10] (**1a** and **1d**) and their utility has even been proved. In particular, such compounds were used in the synthesis of peptidomimetics,[7] ligands for asymmetric catalysis,[11] and chiral auxiliaries.[12] The procedures reported for the synthesis of **1** commenced from the corresponding sulfonic acids and required the use of highly toxic phosgene. In this work, we wish to report a more practical, three-step approach to the multigram synthesis of sulfonyl chlorides **1a–i** starting from the corresponding Cbz-protected amino alcohols **2a–i**.[13]

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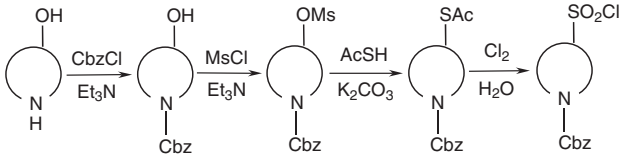
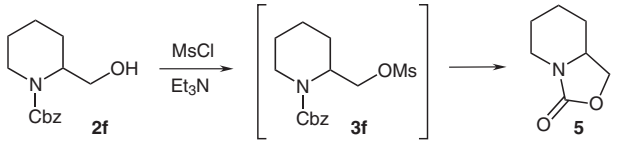
The reaction sequence involved rather robust transformations (Table 1). Mesylation of **2** yielded the corresponding products **3**; these were subjected to nucleophilic substitution with thioacetate in *N*,*N*-dimethylformamide at 55–80 °C to give **4**, which were oxidized to sulfonyl chlorides **1**.

**Table 1** Synthesis of Sulfonyl Chlorides **1a–i**

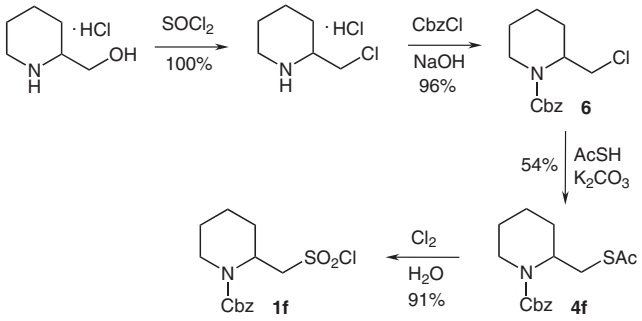



| Sulfonyl chloride | Yield (%) of the step 2 → 3 | 3 → 4 | 4 → 1 | Total yield from 2 (%) |
|---|---|---|---|---|
| **1a** | 96 | 60 | 75 | 43 |
| **1b** | 86 | 28 | 80 | 19 |
| **1c** | 90 | 56 | 81 | 41 |
| **1d** | 100 | 90 | 57 | 51 |
| **1e** | 100 | 95 | 93 | 88 |
| **1g** | 90 | 97 | 88 | 77 |
| **1h** | 73 | 91 | 62 | 41 |
| **1i** | 90 | 64 | 62 | 36 |

The method gave excellent results in the case of primary alcohols **2d**, **2e**, **2g**, and **2h**, with the corresponding sulfonyl chlorides **1d**, **1e**, **1g** and **1h** being obtained in 51, 88, 77, and 41% overall yields, respectively. Even the synthesis of rather strained azetidine-containing sulfonyl chloride **1i** was successful (36% yield starting from **2i**). Surprisingly, the procedure did not work in the case of **1f**. In our hands, mesylate **3f**, formed initially from the alcohol **2f**, underwent intramolecular cyclization to give oxazolidinone **5**[14] (Scheme 1). It is worth noting that the corresponding pyrrolidine derivative **3d** did not show any tendency to undergo analogous transformations. Hence, stereoelectronic factors seem to be crucial for the reaction outcome. We attempted to use a freshly prepared solution of **3f** in the next step. Again, compound **5** was formed as the major product, and no trace of **4f** was detected. We succeeded in the preparation of compound **4f** only via the Cbz-protected chloride **6** (Scheme 2). Chlorination of **4f** proceeded smoothly to give the target sulfonyl chloride **1f** in 91% yield.

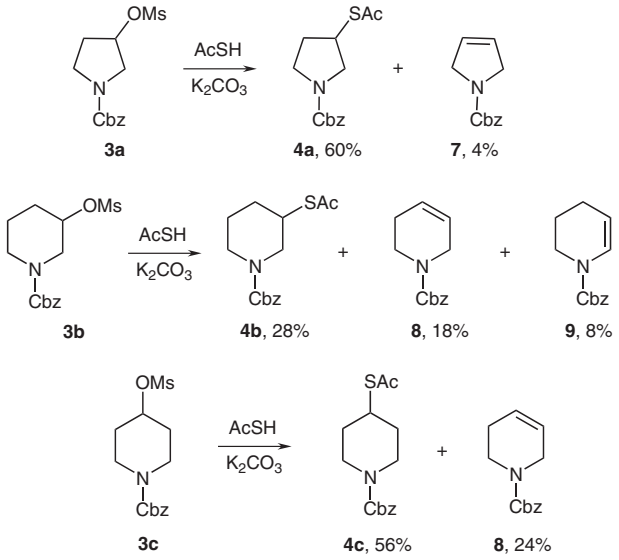



**Scheme 1**




**Scheme 2**

In the case of secondary alcohols **2a–c**, the corresponding mesylates **3a–c** were obtained in good yields. However, reaction of **3a–c** with thioacetate under the conditions described above was accompanied by elimination, giving the corresponding alkenes **7–9**[15] as byproducts (Scheme 3). Although these byproducts were easily separated by column chromatography, their formation diminished the yields of **4a–c**, especially in the case of 3-substituted piperidine derivative **4b** (28%). Chlorination of **4a–c** gave the corresponding sulfonyl chlorides **1a–c** (43, 19, and 41%, respectively, starting from **2**).




**Scheme 3**

With a single exception, sulfonyl chlorides **1** showed remarkable long-term stability. In particular, solid compounds (**1c** and **1g–i**) remained unchanged after the storage at ambient temperature for up to six months. Compounds **1a**, **1b**, **1d**, and **1e**, which were obtained as oils, showed some degradation under these conditions, but their NMR data were still satisfactory. Sulfonyl chloride **1f** was less stable and contained less than 50% of undegraded compound after storage at ambient temperature for a week. We recommend that this compound be stored at –20 °C and for it to be used within a few days of preparation. It should be noted that traces of HCl significantly reduced the long-term stability of the samples. Therefore,

HCl should be carefully removed upon the purification of **1**.

In conclusion, a mini-library of conformationally restricted saturated heterocyclic sulfonyl chlorides was designed and synthesized from the readily available Cbz-protected amino alcohols in 19–88% total yields.

Solvents were purified according to standard procedures. Compounds **2a–i**[16] and 2-(chloromethyl)piperidine hydrochloride[17] were prepared according to methods reported in the literature. All other starting materials were purchased from Acros, Merck, or Fluka. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. $^1$H and $^{13}$C NMR spectra were recorded with a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for $^1$H and 124.9 MHz for $^{13}$C). Chemical shifts (δ) are reported in ppm downfield from TMS ($^1$H, $^{13}$C) as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Kyiv National Taras Shevchenko University. Mass spectra were recorded with an Agilent 1100 LCMSD SL instrument [chemical ionization (APCI)].

**Benzyl 2-(Chloromethyl)piperidine-1-carboxylate (6)**
2-(Chloromethyl)piperidine hydrochloride[17] (0.1 mol) was suspended in a mixture of 1 M aq NaOH (300 mL) and $Et_2O$ (200 mL). Benzyl chloroformate (0.1 mol) was added dropwise with stirring, and the resulting mixture was stirred overnight. The organic phase was separated, washed with brine (50 mL), dried over $Na_2SO_4$, and evaporated to dryness.

Yield: 96%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.35–7.37 (m, 4 H), 7.29–7.34 (m, 1 H), 5.15 (s, 2 H), 4.50 (br s, 1 H), 4.11 (br s, 1 H), 3.57–3.67 (m, 2 H), 2.79–2.86 (m, 1 H), 1.93 (br s, 0.5 H), 1.90 (br s, 0.5 H), 1.61–1.68 (m, 3 H), 1.41–1.53 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.6, 136.7, 128.5, 128.0, 127.9, 67.3, 51.8, 42.3, 39.7, 25.4, 25.0, 18.7.

Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; Cl, 13.24; N, 5.23. Found: C, 63.04; H, 6.51; Cl, 13.08; N, 4.96.

MS (APCI): $m/z$ = 268 $[M + H]^+$, 226, 142.

**Synthesis of 3a–i; General Procedure**
Compound **2** (1 mol) was dissolved in $CH_2Cl_2$ (1 L). Methanesulfonyl chloride (1.05 mol) was added dropwise at 0 °C and the resulting mixture was stirred for 0.5 h, then washed with sat. aq $NaHCO_3$ (2 × 300 mL), brine (300 mL), dried over $Na_2SO_4$, and evaporated. The crude product was purified by column chromatography (hexanes–EtOAc, 3:2).

**Benzyl 3-[(Methylsulfonyl)oxy]pyrrolidine-1-carboxylate (3a)[18]**
Yield: 100 g (96%); yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.34 (m, 5 H), 5.25 (m, 1 H), 5.12 (s, 2 H), 3.76 (d, $J$ = 13.0 Hz, 0.5 H), 3.72 (d, $J$ = 13.0 Hz, 0.5 H), 3.63 (dd, $J$ = 13.0, 4.2 Hz, 1 H), 3.47–3.62 (m, 2 H), 3.00 (s, 3 H), 2.23–2.32 (m, 1 H), 2.06–2.18 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 154.6 and 154.5, 136.6 and 136.5, 128.5, 128.0, 127.93 and 127.89, 79.7 and 79.2, 67.0, 52.3 and 52.0, 43.8 and 43.5, 38.6, 32.5 and 31.6.

Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71. Found: C, 52.53; H, 5.48; N, 4.91; S, 11.05.

MS (APCI): $m/z$ = 300 $[M + H]^+$, 256, 158, 91 $[C_7H_7^+]$.

**Benzyl 3-[(Methylsulfonyl)oxy]piperidine-1-carboxylate (3b)**
Yield: 86%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.34–7.39 (m, 4 H), 7.29–7.33 (m, 1 H), 5.13 (br s, 2 H), 4.74 (br s, 1 H), 3.77 (dd, $J$ = 13.6, 5.2 Hz, 1 H), 3.57–3.63 (m, 2 H), 3.31–3.36 (m, 1 H), 2.98 (br s, 1.5 H), 2.90 (br s, 1.5 H), 1.91–1.96 (m, 2 H), 1.79–1.87 (m, 1 H), 1.50–1.59 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.2, 136.6, 128.5, 128.1, 127.9, 75.1 and 74.8, 67.3, 60.3, 41.2 and 47.8, 43.8, 38.6, 30.2, 21.4.

Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.91; H, 5.84; N, 4.51; S, 10.09.

MS (APCI): $m/z$ = 314 $[M + H]^+$, 270.

**Benzyl 4-[(Methylsulfonyl)oxy]piperidine-1-carboxylate (3c)**
Yield: 90%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.31–7.41 (m, 5 H), 5.13 (s, 2 H), 4.90 (sept, $J$ = 3.7 Hz, 1 H), 3.72–3.77 (m, 2 H), 3.34–3.44 (m, 2 H), 3.01 (s, 3 H), 1.96 (br s, 2 H), 1.83 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.1, 136.6, 128.5, 128.1, 127.9, 77.2, 67.3, 40.6, 38.8, 31.6.

Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.28; H, 5.90; N, 4.25; S, 9.97.

MS (APCI): $m/z$ = 314 $[M + H]^+$, 270, 91 $[C_7H_7^+]$.

**Benzyl 2-{[(Methylsulfonyl)oxy]methyl}pyrrolidine-1-carboxylate (3d)**
Yield: 100%; yellowish oil.

For spectral and physical data, see Jones et al.[19]

**Benzyl 3-{[(Methylsulfonyl)oxy]methyl}pyrrolidine-1-carboxylate (3e)**
Yield: 100%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.27–7.39 (m, 5 H), 5.12 (s, 2 H), 4.18 (dd, $J$ = 9.3, 6.6 Hz, 1 H), 4.08–4.16 (m, 1 H), 3.58–3.64 (m, 1 H), 3.49–3.57 (m, 1 H), 3.38–3.46 (m, 1 H), 3.18–3.24 (m, 1 H), 2.98 (s, 3 H), 2.58–2.67 (m, 1 H), 2.00–2.09 (m, 1 H), 1.66–1.80 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 154.6, 136.7, 128.4, 127.9, 127.8, 127.8, 70.0, 66.7, 48.3, 48.0, 45.3, 44.8, 38.3, 37.3, 37.2, 27.9, 27.0.

Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.37; H, 6.33; N, 4.60; S, 9.92.

MS (APCI): $m/z$ = 314 $[M + H]^+$, 270, 91 $[C_7H_7^+]$.

**Benzyl 3-{[(Methylsulfonyl)oxy]methyl}piperidine-1-carboxylate (3g)**
Yield: 90%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.34–7.36 (m, 4 H), 7.27–7.32 (m, 1 H), 5.12 (s, 2 H), 4.09–4.12 (m, 1 H), 3.97–4.06 (m, 2 H), 3.89 (br d, $J$ = 11.2 Hz, 1 H), 2.96 (br s, 3 H), 2.89–3.00 (m, 1 H), 2.78–2.89 (m, 1 H), 1.95 (br s, 1 H), 1.80–1.83 (m, 1 H), 1.66 (br s, 1 H), 1.49 (br s, 1 H), 1.29–1.36 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.2, 136.7, 128.4, 127.9, 127.8, 70.9, 67.0, 46.2, 44.4, 37.2, 35.4, 26.5, 23.8.

Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28; S, 9.79. Found: C, 54.71; H, 6.42; N, 4.45; S, 9.93.

MS (APCI): $m/z$ = 328 $[M + H]^+$, 284, 188, 91 $[C_7H_7^+]$.

**Benzyl 4-{[(Methylsulfonyl)oxy]methyl}piperidine-1-carboxylate (3h)**
Yield: 73%; white solid; mp 73–74 °C ($CCl_4$).

$^1$H NMR ($CDCl_3$): δ = 7.35–7.38 (m, 4 H), 7.30–7.33 (m, 1 H), 5.13 (s, 2 H), 4.25 (br s, 2 H), 4.07 (d, $J$ = 6.4 Hz, 2 H), 3.01 (s, 3 H),

2.80 (br s, 2 H), 1.90–1.99 (m, 1 H), 1.77 (d, $J$ = 12.5 Hz, 2 H), 1.22–1.28 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.2, 136.8, 128.6, 128.1, 128.0, 73.3, 67.2, 43.6, 37.4, 36.0, 28.3.

Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28; S, 9.79. Found: C, 55.16; H, 6.63; N, 4.08; S, 10.04.

MS (EI): $m/z$ = 327 $[M]^+$, 282, 220, 192, 91 $[C_7H_7^+]$.

**Benzyl 3-[(Methylsulfonyl)oxy]azetidine-1-carboxylate (3i)**
Yield: 90%; white solid; mp 51–52 °C.

$^1$H NMR ($CDCl_3$): δ = 7.32–7.39 (m, 5 H), 5.21–5.26 (m, 1 H), 5.11 (s, 2 H), 4.35–4.38 (m, 2 H), 4.19 (dd, $J$ = 10.2, 3.8 Hz, 2 H), 3.06 (s, 3 H).

$^{13}$C NMR ($CDCl_3$): δ = 156.1, 136.3, 128.6, 128.3, 128.1, 67.4, 67.1, 56.8, 38.4.

Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91; S, 11.24. Found: C, 50.35; H, 5.02; N, 5.16; S, 11.07.

MS (APCI): $m/z$ = 286 $[M + H]^+$, 242, 91 $[C_7H_7^+]$.

**Synthesis of 4a–i; General Procedure**
Ethanethioic acid (1.5 mol) was added dropwise to a suspension of $K_2CO_3$ (1.5 mol) in DMF (1 L) at 10–20 °C, followed by **3** (for **4a–e** and **4g–i**) or **6** (for **4f**) (1 mol). The resulting mixture was heated at 55–80 °C for 5–10 h (reaction monitored by TLC), then cooled, diluted with $H_2O$ (3 L), and extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with brine (3 × 300 mL), dried over $Na_2SO_4$, and evaporated. The crude product was purified by column chromatography (hexanes–EtOAc, 4:1).

**Benzyl 3-(Acetylthio)pyrrolidine-1-carboxylate (4a)**
Yield: 25 g (60%); yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.33–7.38 (m, 4 H), 7.30–7.33 (m, 1 H), 5.13 (s, 2 H), 3.98 (quint, $J$ = 6.1 Hz, 1 H), 3.84 (dd, $J$ = 11.4, 6.8 Hz, 1 H), 3.46–3.58 (m, 2 H), 3.38 (dd, $J$ = 11.8, 5.2 Hz, 0.5 H), 3.31 (dd, $J$ = 11.2, 5.7 Hz, 0.5 H), 2.32 (s, 3 H), 2.25–2.37 (m, 1 H), 1.85–1.94 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 195.2 and 195.0, 154.6, 136.84 and 136.78, 128.5, 128.03, 127.95, 66.9, 51.8 and 51.6, 45.2 and 44.8, 41.2 and 40.6, 32.1 and 31.0, 30.7.

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 59.87; H, 6.41; N, 5.03; S, 11.36.

MS (APCI): $m/z$ = 280 $[M + H]^+$, 236, 91 $[C_7H_7^+]$.

**Benzyl 3-(Acetylthio)piperidine-1-carboxylate (4b)**
Yield: 28%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.32–7.37 (m, 4 H), 7.30–7.32 (m, 1 H), 5.06–5.20 (m, 2 H), 3.86 (br d, $J$ = 12.8 Hz, 1 H), 3.55–3.65 (m, 2 H), 3.30 (br s, 2 H), 2.27 (br s, 3 H), 1.95–2.03 (m, 1 H), 1.54–1.73 (m, 3 H).

$^{13}$C NMR ($CDCl_3$): δ = 194.6, 155.2, 136.9, 128.5, 128.0, 127.9, 67.2, 49.0, 44.2, 40.2, 30.8, 30.3, 24.4.

Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77; S, 10.93. Found: C, 61.27; H, 6.64; N, 4.83; S, 11.14.

MS (APCI): $m/z$ = 294 $[M + H]^+$, 250, 235, 208, 160, 91 $[C_7H_7^+]$.

**Benzyl 4-(Acetylthio)piperidine-1-carboxylate (4c)**
Yield: 56%; yellowish oil.

For spectral and physical data, see Rosenberg et al.[20]

**Benzyl 2-[(Acetylthio)methyl]pyrrolidine-1-carboxylate (4d)[21]**
Yield: 264 g (90%); yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.34–7.41 (m, 4 H), 7.28–7.32 (m, 1 H), 5.10–5.20 (m, 2 H), 4.02 (br s, 1 H), 3.42–3.52 (m, 2 H), 3.27 (d, $J$ = 12.0 Hz, 0.5 H), 3.15–3.20 (m, 1 H), 3.01–3.05 (m, 0.5 H), 2.32–2.34 (2 × s, 3 H), 1.88–2.00 (m, 2 H), 1.78–1.84 (m, 1 H), 1.67–1.75 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 195.2 and 194.8, 154.8, 136.8 and 136.9, 128.5, 128.0, 127.9 and 127.8, 67.0 and 66.7, 56.6 and 57.4, 47.2 and 46.9, 32.3 and 31.4, 30.5, 30.2 and 29.2, 23.7 and 22.9.

Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77; S, 10.93. Found: C, 61.48; H, 6.40; N, 4.59; S, 10.93.

MS (APCI): $m/z$ = 294 $[M + H]^+$, 235, 208, 160, 91 $[C_7H_7^+]$.

**Benzyl 3-[(Acetylthio)methyl]pyrrolidine-1-carboxylate (4e)**
Yield: 95%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.31–7.36 (m, 4 H), 7.26–7.30 (m, 1 H), 5.07–5.13 (AB system, 2 H), 3.47–3.62 (m, 2 H), 3.31–3.38 (m, 1 H), 3.01–3.09 (m, 1 H), 2.85–2.98 (m, 2 H), 2.28–2.41 (m, 1 H), 2.31 (s, 3 H), 1.98–2.04 (m, 1 H), 1.55–1.66 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 195.2, 154.7, 137.0, 128.4, 127.9, 127.8, 66.7, 50.9 and 50.5, 45.7 and 45.2, 39.0 and 38.2, 31.5, 31.0 and 30.3, 30.6.

Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77; S, 10.93. Found: C, 61.07; H, 6.81; N, 4.93; S, 10.62.

MS (APCI): $m/z$ = 294 $[M + H]^+$, 250 $[M^+ – CH_3CO]$, 91 $[C_7H_7^+]$.

**Benzyl 2-[(Acetylthio)methyl]piperidine-1-carboxylate (4f)**
Yield: 54%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.34–7.37 (m, 4 H), 7.29–7.32 (m, 1 H), 5.10–5.16 (m, 2 H), 4.43 (br s, 1 H), 4.05–4.10 (m, 1 H), 3.18–3.22 (m, 1 H), 3.08–3.12 (m, 1 H), 2.86 (m, 1 H), 2.25 (s, 3 H), 1.61–1.69 (m, 5 H), 1.41 (br s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 195.3, 155.5, 136.9, 128.4, 127.9, 127.8, 67.1, 50.0, 39.4, 30.5, 29.1, 27.6, 25.3, 18.8.

Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56; S, 10.43. Found: C, 62.74; H, 7.16; N, 4.39; S, 10.60.

MS (APCI): $m/z$ = 308 $[M + H]^+$, 264, 222, 91 $[C_7H_7^+]$.

**Benzyl 3-[(Acetylthio)methyl]piperidine-1-carboxylate (4g)**
Yield: 61 g (97%); yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.30–7.35 (m, 4 H), 7.23–7.28 (m, 1 H), 5.09 (s, 2 H), 3.90–4.13 (m, 2 H), 2.76–2.87 (m, 2 H), 2.73 (dd, $J$ = 13.6, 7.4 Hz, 1 H), 2.55 (br s, 0.5 H), 2.66 (br s, 0.5 H), 2.27 (s, 3 H), 1.80–1.85 (m, 1 H), 1.63 (br s, 2 H), 1.41 (br s, 1 H), 1.14–1.24 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 194.9, 154.9, 136.7, 128.2, 127.7, 127.5, 66.8, 48.5, 44.2, 36.0, 31.9, 30.4, 29.9, 24.1 and 24.6.

Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56; S, 10.43. Found: C, 62.36; H, 7.02; N, 4.74; S, 10.09.

MS (APCI): $m/z$ = 308 $[M + H]^+$, 264, 222.

**Benzyl 4-[(Acetylthio)methyl]piperidine-1-carboxylate (4h)**
Yield: 170 g (91%); yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.31–7.34 (m, 4 H), 7.26–7.30 (m, 1 H), 5.10 (s, 2 H), 4.16 (br s, 2 H), 2.80 (d, $J$ = 6.6 Hz, 2 H), 2.72 (br s, 2 H), 2.30 (s, 3 H), 1.67–1.76 (m, 2 H), 1.56–1.65 (m, 1 H), 1.09–1.20 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 195.4, 155.1, 136.9, 128.5, 127.9, 127.8, 67.0, 43.9, 36.4, 34.9, 31.2, 30.6.

Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56; S, 10.43. Found: C, 62.69; H, 7.11; N, 4.46; S, 10.47.

MS (APCI): $m/z$ = 308 $[M + H]^+$, 264, 222.

**Benzyl 3-(Acetylthio)azetidine-1-carboxylate (4i)**
Yield: 64%; beige solid; mp 86–87 °C.

For spectral and physical data, see Rosenberg et al.[20]

**Synthesis of 1a–i; General Procedure**
Compound **1** (1 mol) was dissolved in $CH_2Cl_2$ (2000 mL). $H_2O$ (500 mL) was added, the resulting mixture was cooled (ice bath), and chlorine was bubbled through at 0–10 °C with stirring for 4–6 h (reaction monitored by TLC). The organic phase was separated, washed with $H_2O$ (2 × 500 mL), sat. aq $NaHCO_3$ (2 × 500 mL), and brine (300 mL), dried over $Na_2SO_4$, and evaporated. The crude product was purified by column chromatography (hexanes–EtOAc, 1:1).

**Benzyl 3-(Chlorosulfonyl)pyrrolidine-1-carboxylate (1a)**
Yield: 16 g (75%); yellowish oil.

For spectral and physical data, see Giordano et al.[7a]

**Benzyl 3-(Chlorosulfonyl)piperidine-1-carboxylate (1b)**
Yield: 12.6 g (80%); yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.32–7.39 (m, 5 H), 5.16 (s, 2 H), 4.75 (br s, 0.5 H), 4.64 (br s, 0.5 H), 4.08 (d, $J$ = 13.4 Hz, 1 H), 3.64 (br s, 1 H), 3.37 (br s, 0.5 H), 3.24 (br s, 0.5 H), 2.91 (ddd, $J$ = 14.0, 11.3, 2.7 Hz, 1 H), 2.47 (d, $J$ = 10.8 Hz, 1 H), 2.00 (d, $J$ = 9.6 Hz, 1 H), 1.93 (d, $J$ = 11.7 Hz, 1 H), 1.60 (br s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 154.8, 136.2, 128.6, 128.3, 128.0, 70.5, 67.8, 44.3, 43.8, 25.6, 24.0.

Anal. Calcd for $C_{13}H_{16}ClNO_4S$: C, 49.13; H, 5.07; Cl, 11.16; N, 4.41; S, 10.09. Found: C, 48.93; H, 4.87; Cl, 11.04; N, 4.60; S, 9.75.

MS (APCI, the sulfonic acid is registered): $m/z$ = 300 $[M + H]^+$.

**Benzyl 4-(Chlorosulfonyl)piperidine-1-carboxylate (1c)**
Yield: 16.9 g (81%); white solid; mp 73–74 °C.

$^1$H NMR ($CDCl_3$): δ = 7.32–7.39 (m, 5 H), 5.15 (s, 2 H), 4.41 (br s, 2 H), 3.66 (tt, $J$ = 11.7, 3.8 Hz, 1 H), 2.90 (br s, 2 H), 2.35 (br d, $J$ = 9.7 Hz, 2 H), 1.95 (br d, $J$ = 9.7 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.0, 136.4, 128.7, 128.4, 128.2, 72.3, 67.8, 42.7, 26.7.

Anal. Calcd for $C_{13}H_{16}ClNO_4S$: C, 49.13; H, 5.07; Cl, 11.16; N, 4.41; S, 10.09. Found: C, 49.17; H, 5.36; Cl, 11.38; N, 4.29; S, 10.18.

MS (APCI, the sulfonic acid is registered): $m/z$ = 300 $[M + H]^+$.

**Benzyl 2-[(Chlorosulfonyl)methyl]pyrrolidine-1-carboxylate (1d)**
Yield: 86 g (57%); yellowish oil.

For spectral and physical data, see previous reports.[7]

**Benzyl 3-[(Chlorosulfonyl)methyl]pyrrolidine-1-carboxylate (1e)**
Yield: 93%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.29–7.37 (m, 5 H), 5.13 (s, 2 H), 3.84 (dd, $J$ = 10.9, 7.2 Hz, 1 H), 3.71–3.80 (m, 2 H), 3.56–3.62 (m, 1 H), 3.38–3.44 (m, 1 H), 3.22 (dd, $J$ = 10.9, 8.5 Hz, 1 H), 2.86–2.95 (m, 1 H), 2.24–2.30 (m, 1 H), 1.75–1.83 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 154.6, 136.6, 128.6, 128.1, 128.0, 67.9, 67.1, 50.3, 45.1, 34.5, 30.7.

Anal. Calcd for $C_{13}H_{16}ClNO_4S$: C, 49.13; H, 5.07; Cl, 11.16; N, 4.41; S, 10.09. Found: C, 48.99; H, 5.31; Cl, 11.47; N, 4.27; S, 10.36.

MS (APCI, the sulfonic acid is registered): $m/z$ = 300 $[M + H]^+$.

**Benzyl 2-[(Chlorosulfonyl)methyl]piperidine-1-carboxylate (1f)**
Slowly decomposes upon storage at r.t.

Yield: 91%; yellowish oil.

$^1$H NMR ($CDCl_3$): δ = 7.36–7.39 (m, 4 H), 7.30–7.35 (m, 1 H), 5.13–5.18 (m, 3 H), 4.17 (br s, 1 H), 3.99 (m, 1 H), 3.87 (m, 1 H), 2.82 (br s, 1 H), 1.90 (br s, 1 H), 1.76–1.83 (m, 2 H), 1.70 (br s, 1 H), 1.46–1.52 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 154.9, 136.2, 128.6, 128.2, 128.2, 67.8, 65.0, 47.4, 40.0, 28.1, 24.8, 18.9.

Anal. Calcd for $C_{14}H_{18}ClNO_4S$: C, 50.68; H, 5.47; Cl, 10.68; N, 4.22; S, 9.66. Found: C, 50.78; H, 5.71; Cl, 10.75; N, 4.38; S, 9.37.

MS (APCI, the sulfonic acid is registered): $m/z$ = 314 $[M + H]^+$.

**Benzyl 3-[(Chlorosulfonyl)methyl]piperidine-1-carboxylate (1g)**
Yield: 106 g (88%); white solid; mp 81–82 °C.

$^1$H NMR ($CDCl_3$): δ = 7.39–7.41 (m, 4 H), 7.32–7.37 (m, 1 H), 5.28 (s, 2 H), 4.10 (dd, $J$ = 13.1, 2.3 Hz, 1 H), 3.84 (dt, $J$ = 13.1, 4.4 Hz, 1 H), 3.71 (br s, 1 H), 3.65 (dd, $J$ = 14.2, 6.1 Hz, 1 H), 3.15 (ddd, $J$ = 12.8, 9.7, 3.2 Hz, 1 H), 3.07 (br s, 1 H), 2.44 (br s, 1 H), 2.07 (m, 1 H), 1.70 (m, 1 H), 1.48–1.62 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.0, 136.5, 128.4, 127.9, 127.7, 68.1, 67.1, 48.0, 44.0, 32.4, 29.5, 23.5.

Anal. Calcd for $C_{14}H_{18}ClNO_4S$: C, 50.68; H, 5.47; Cl, 10.68; N, 4.22; S, 9.66. Found: C, 50.36; H, 5.42; Cl, 10.53; N, 4.08; S, 9.87.

MS (APCI, the sulfonic acid is registered): $m/z$ = 314 $[M + H]^+$.

**Benzyl 4-[(Chlorosulfonyl)methyl]piperidine-1-carboxylate (1h)**
Yield: 32 g (62%); white solid; mp 86–87 °C.

$^1$H NMR ($CDCl_3$): δ = 7.30–7.38 (m, 5 H), 5.12 (s, 2 H), 4.23 (br s, 2 H), 3.65 (d, $J$ = 6.4 Hz, 2 H), 2.86 (m, 2 H), 2.32–2.41 (m, 1 H), 1.97 (d, $J$ = 12.5 Hz, 2 H), 1.31–1.41 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.1, 136.6, 128.6, 128.1, 128.0, 71.2, 67.3, 43.5, 33.0, 31.2.

Anal. Calcd for $C_{14}H_{18}ClNO_4S$: C, 50.68; H, 5.47; Cl, 10.68; N, 4.22; S, 9.66. Found: C, 50.74; H, 5.60; Cl, 10.77; N, 4.35; S, 9.30.

MS (APCI, the sulfonic acid is registered): $m/z$ = 314 $[M + H]^+$.

**Benzyl 3-(Chlorosulfonyl)azetidine-1-carboxylate (1i)**
Yield: 62%; white solid; mp 53–54 °C.

$^1$H NMR ($CDCl_3$): δ = 7.35 (br s, 5 H), 5.13 (s, 2 H), 4.53 (br s, 1 H), 4.39–4.50 (m, 4 H).

$^{13}$C NMR ($CDCl_3$): δ = 155.8, 135.8, 128.6, 128.5, 128.2, 67.6, 60.8, 51.4.

Anal. Calcd for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.17; Cl, 12.24; N, 4.83; S, 11.07. Found: C, 45.79; H, 3.95; Cl, 12.56; N, 5.01; S, 11.08.

MS (APCI, the sulfonic acid is registered): $m/z$ = 286 $[M + H]^+$.

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