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Synthesis of spirocyclic β- and γ-sultams by one-pot reductive cyclization of cyanoalkylsulfonyl fluorides

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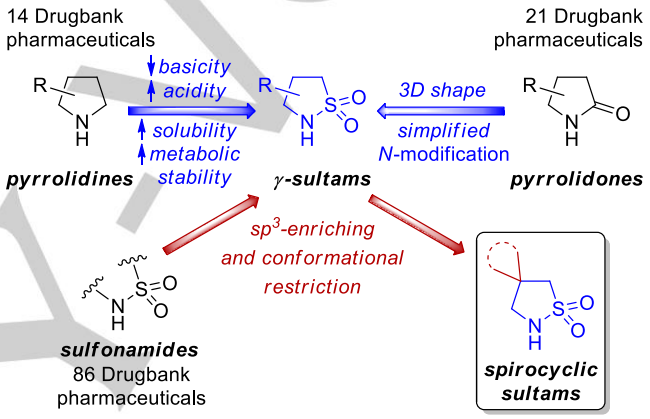
Dedicated to Prof. Andrey A. Tolmachev's 63th anniversary

Abstract: One-pot intramolecular cyclization of novel sp^3-enriched cyanoalkylsulfonyl fluorides into spirocyclic β- or γ-sultams is disclosed. The method relies on nitrile group reduction followed by sulfonylation of amino group thus formed upon mild conditions ($NaBH_4$, $NiCl_2 \cdot 6H_2O$ in MeOH). Cyclization proceeds smoothly with considerable efficiency (48–84%, 10 examples) on up to 30 g scale. The cyanoalkylsulfonyl fluoride intermediates can be obtained *via* S-nucleophilic substitution in β-functionalized alkanenitriles or double alkylation of α-alkylthioacetonitrile, followed by oxidative chlorination with Cl_2 and further reaction with KHF_2. The title mono- and bifunctional sultams are advanced sp^3-enriched building blocks for drug discovery and organic synthesis providing novel substitution patterns and frameworks mimicking saturated nitrogen heterocycles such as pyrrolidine/pyrrolidone.

Introduction

Since discovery of the first SO_2NH_2-containing antibacterial drug Prontosil in the 1932, sulfonamides have become indispensable in drug discovery with about a hundred of FDA-approved drugs present on the market to date.[1,2] Those include sulfanilamide antibiotics, also known as "*sulfa drugs*" (Sulfanilamide, Sulfamethoxazole), several important diuretics (*i.e.* Furosemide, Hydrochlorothiazide) etc.[3,4] In turn, cyclic sulfonamides (sultams) provide an example of promising scaffolds with manifold applications in modern drug discovery, *i.e.* anti-inflammatory drug piroxicam, its prodrug ampiroxicam,[5,6] or anticonvulsant sultiame.[7] γ-Sultam-based scaffolds provide important physico-chemical properties to as compared to other five-membered molecular frameworks (Scheme 1). In particular, unlike saturated nitrogen heterocycles (*i.e.* pyrrolidines), γ-sultams possess very low basicity, which is accompanied by increased acidity and enhanced aqueous solubility. On the other hand, γ-sultams are 3D-shaped, stable towards protease-catalyzed degradation[8] and can be easily modified by *N*-alkylation, which brings them closer to pyrrolidines as compared to isosteric γ-lactams (pyrrolidones) with planar amide moiety.



Scheme 1. Comparison of γ-sultams, pyrrolidines and pyrrolidones

Therefore γ-sultams can be considered as prominent building blocks for lead-oriented synthesis[9] – analogs of saturated nitrogen heterocycles[8] – which allow "escaping from flatland"[10,11] without considerable efforts.

A number of approaches to γ-sultams has been described in recent years (Scheme 2),[12–21] including intramolecular cyclization of 3-aminopropane-1-sulfonyl chlorides (**A**),[22–26] or aryl propane-1-sulfonates (**B**),[27,28] intramolecular *N*-alkylation of propane-1-sulfonamides (**C**),[29–37] double alkylation of alkanesulfonamides (**D**),[38,39] intramolecular *C*-alkylation of *N*-substituted methanesulfonamides (**E**),[40–43] cyclizations of *N*-allyl-1-halomethanesulfonamides (**F**),[44] and intramolecular aliphatic C–H sulfonamidations (**G**).[45]

Most of these methods have been used for the synthesis of monocyclic and fused bicyclic γ-sultams. While preparation of γ-sultams bearing a spirocyclic fragment at the C-5 position have been also presented in the literature,[46–50] their C-4-substituted counterparts are underrepresented to date, being limited by several 4,4′-spirobi(γ-sultam) derivatives.[51] Keeping in mind further possible applications in lead discovery projects, herein we have aimed at preparation of spirocyclic building blocks **1a**–**h** (Figure 1) with high sp^3-atom fraction bearing alicyclic or saturated heterocyclic moieties at the C-4 position of the sultam ring.

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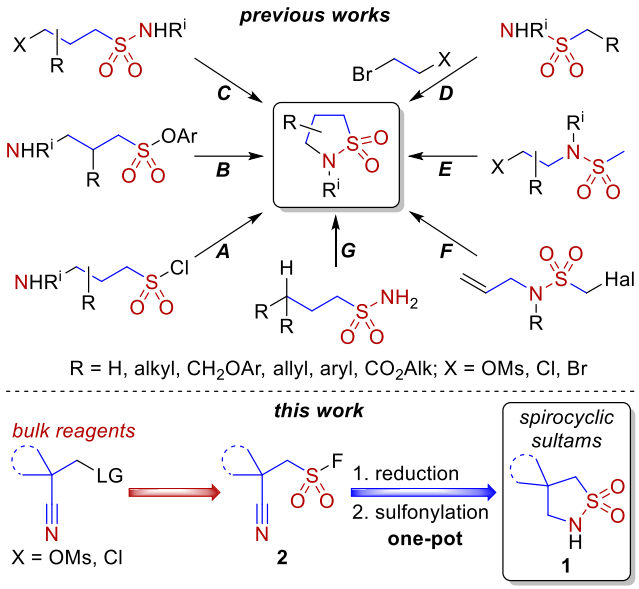


Scheme 2. Approaches to mono- and disubstituted γ-sultams

A proposed strategy to construct the spirocyclic scaffolds of **1** relied on reductive cyclization of previously unknown cyclic 2,2-disubstituted 2-cyanoethane-sulfonyl fluorides **2** derived from monocyclic ring systems (Scheme 2). Utility of the title methodology for the preparation of other spirocyclic derivatives (e.g. β-sultams) was also to be validated.

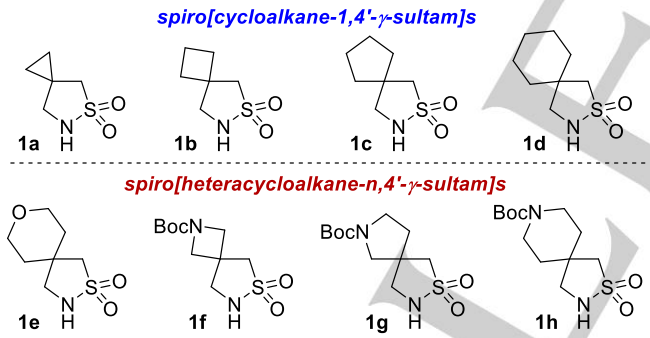
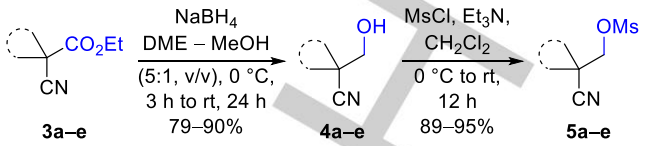


Figure 1. C-4-spirocyclic sultams **1a–h** – targets molecules of this study

Results and Discussion

The study commenced with preparation of 2,2-disubstituted 2-cyanoethanesulfonyl fluorides **2a–h**. The first step of the reaction sequence included reduction of homologous cyanoacetates **3a–d** and tetrahydropyran derivative **3e** with $NaBH_4$ in DME – MeOH, which resulted in the corresponding β-cyanoalcohols **4a–e** in 79–90% yield (Table 1). Mesylation of **4a–e** in the presence of Et_3N in CH_2Cl_2 led to corresponding mesylates **5a–e** (89–95% yield).

Table 1. Synthesis of intermediates **4** and **5**

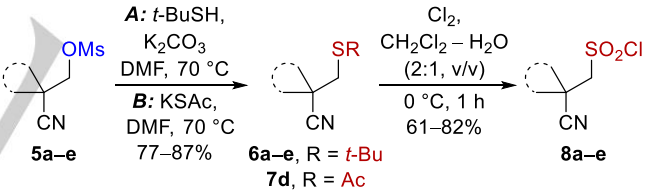


#		Starting material	Alcohol (yield, %)	Mesylate (yield, %)
1	$(CH_2)_2$	**3a**	**4a** (90)	**5a** (91)
2	$(CH_2)_3$	**3b**	**4b** (86)	**5b** (93)
3	$(CH_2)_4$	**3c**	**4c** (79)	**5c** (95)
4	$(CH_2)_5$	**3d**	**4d** (85)	**5d** (94)
5	$(CH_2)_2O(CH_2)_2$	**3e**	**4e** (81)	**5e** (89)

Subsequent incorporation of the sulfur atom was performed *via* nucleophilic substitution in mesylates **5a–e** with *t*-BuSH (Table 2). While most *tert*-butyl sulfides **6a–c** and **6e** were obtained in good yields (Table 2, Entries 1–3 and 5), cyclohexane derivative **6d** was formed in moderate yield (*ca.* 60%). Instead, when reaction was performed with KSAc, thioacetate **7d** was obtained in 87% yield (Entry 4).

tert-Butyl sulfides **6a–c** and **6e** and thioacetate **7d** smoothly underwent the oxidative chlorination with Cl_2 and the corresponding β-cyano sulfonyl chlorides **8a–e** were obtained in 61–82% yield.

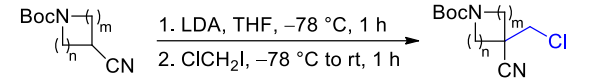
Table 2. Preparation of sulfonyl chlorides **8a–e**



#		Mesylate	Sulfide or thio-acetate (%)[a]	Sulfonyl chloride (%)[a]
1	$(CH_2)_2$	**5a**	**6a** (79)[b]	**8a** (61)
2	$(CH_2)_3$	**5b**	**6b** (83)[b]	**8b** (67)
3	$(CH_2)_4$	**5c**	**6c** (77)[b,c]	**8c** (71)
4	$(CH_2)_5$	**5d**	**7d** (87)[d]	**8d** (82)
5	$(CH_2)_2O(CH_2)_2$	**5e**	**6e** (85)[b]	**8e** (71)

[a] Isolated yields [b] Method **A**: *t*-BuSH, K_2CO_3, DMF, 70 °C (completion of the reaction was monitored by ^1H NMR) [c] Reaction was performed at 90 °C [d] Method **B**: KSAc, DMF, 70 °C, (completion of the reaction was monitored by ^1H NMR)

Synthesis of heterocyclic nitriles **5f–h** relied on chloromethylation of *N*-Boc protected 3-cyanoazetidine (**3f**), 3-cyanopyrrolidine (**3g**) and 4-cyanopiperidine (**3h**). The reaction was performed via metallation with LDA at –78 °C followed by reaction with $ClCH_2I$, which gave β-chloropropanenitriles **5f–h** in 90–95% yield (Scheme 3).



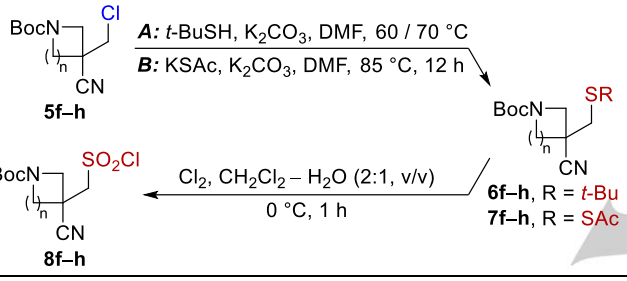
3f, n = m = 1
3g, n = 1, m = 2
3h, n = m = 2

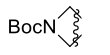
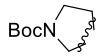
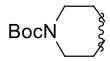
5f, n = m = 1, 90%
5g, n = 1, m = 2, 95%
5h, n = m = 2, 90%

Scheme 3. Synthesis of β-chloropropanenitriles **5f–h**

Reactions of heterocyclic derivatives **5f–h** with *S*-nucleophiles proceeded analogously to synthesis of **5a–e** (Table 3). As it was found, synthesis of thioacetates **7f** and **7h** was more efficient as compared to corresponding *tert*-butyl sulfides **6f** and **6h**. Moreover, the chlorination step proceeded with better outcome for thioacetates **7f** and **7h** than for sulfides **6f** and **6h**.

Table 3. Preparation of sulfonyl chlorides **8f–h**



#	Cyclic substituent	Chloride	Sulfide or thioacetate (%)[a]	Sulfonyl chloride (%)[a]
1		**5f**	**6f** (73)[b]	**8f** (60)
2			**7f** (80)[c]	**8f** (63)[c]
3		**5g**	**7g** (97)[c]	**8g** (71)[c]
4		**5h**	**6h** (71)[b]	**8h** (73)
5			**7h** (93)[c]	**8h** (84)[c]

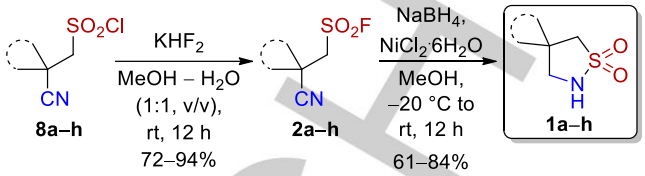
[a] Isolated yields [b] Method **A**: *t*-BuSH, K_2CO_3, DMF, 60 °C (for **6f**) or 70 °C (for **6h**), (completion of the reaction was monitored by ^{1}H NMR) [c] Method **B**: KSAc, DMF, 85 °C, 12 h

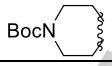
Due to limited stability of the SO_2Cl derivatives **8** under reductive conditions, they were transformed into the target sulfonyl fluorides **2** by reaction of **8a–h** with KHF_2 in MeOH – H_2O (1:1, v/v) (Table 4). The reaction proceeded smoothly at rt and gave exclusively **2a–h** in good to excellent yields (72–94%, 85% average yield).

The key intramolecular reductive cyclization of SO_2F-derivatives **2a–h** was performed with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$, and the spirocyclic sultams **1a–h** were obtained exclusively in the one-pot reaction in 61–84% yield (Table 4).

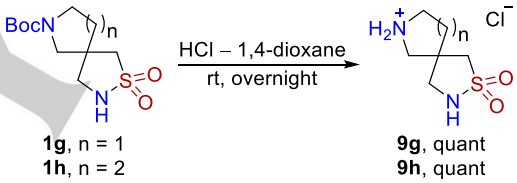
Moreover, *N*-Boc-protecting group cleavage was successfully performed for the case of monoprotected bifunctional sultams **1g** and **1h**. Deprotection proceeded smoothly with 4 M HCl – 1,4-dioxane at rt and gave corresponding hydrochlorides **9g** and **9h**, both in quantitative yield (Scheme 4).

Table 4. Intramolecular reductive cyclization of **2a–h**



#		Sulfonyl chloride	Sulfonyl fluoride (%)[a]	Sultam (%)[a]
1	$(CH_2)_2$	**8a**	**2a** (87)	**1a** (61)
2	$(CH_2)_3$	**8b**	**2b** (89)	**1b** (71)
3	$(CH_2)_4$	**8c**	**2c** (94)	**1c** (82)
4	$(CH_2)_5$	**8d**	**2d** (94)	**1d** (78)
5	$(CH_2)_2O(CH_2)_2$	**8e**	**2e** (90)	**1e** (84)
6		**8f**	**2f** (77)	**1f** (74)
7		**8g**	**2g** (72)	**1g** (75)
8		**8h**	**2h** (80)	**1h** (78)

[a] Isolated yields



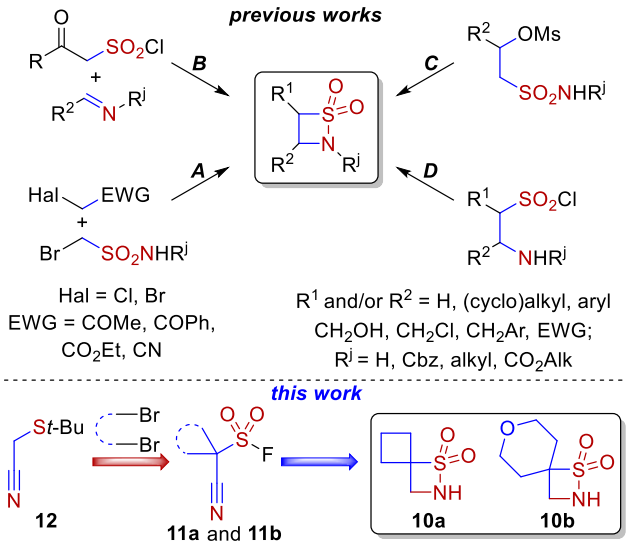
1g, n = 1
1h, n = 2

9g, quant
9h, quant

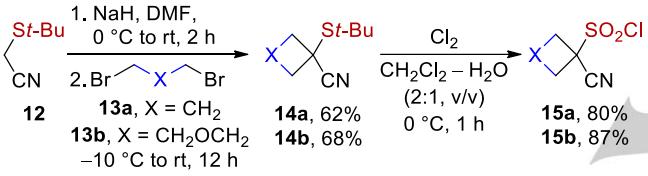
Scheme 4. *N*-Deprotection of sultams **1g** and **1h**

Being inspired by aforementioned results, we have evaluated the developed approach for synthesis of analogous spirocyclic β-sultams. It should be noted that known approaches to β-sultams (Scheme 5) relied on intermolecular reactions of α-bromomethyl sulfonamides with α-halocarbonyl compounds (**A**),[52] [2 + 2] cycloadditions of sulfonyl chlorides with imines (**B**),[53–55] intramolecular alkylation of sulfonamides bearing a leaving group at the β-position (**C**),[56,57] and intramolecular cyclization of β-amino sulfonyl chlorides (**D**).[44,58–66] As in the case of γ-sultams, the intramolecular reductive cyclization of substituted α-cyano sulfonyl fluorides has never been reported to date. To demonstrate possibility of such cyclyzations, spirocyclic β-sultams **10a** and **10b** were selected as the synthetic targets.

Synthesis of corresponding cyanomethanesulfonyl fluorides **11a** and **11b** relied on the double alkylation of easily accessible 2-(*tert*-butylthio)acetonitrile **12** (Scheme 6). The NaH-mediated reaction of **12** with 1,3-dibromopropane **13a** in DMF gave cyclobutane derivative **14a** in 62% yield, while 1-bromo-2-(2-bromoethoxy)ethane **13b** was used for preparation of tetrahydropyrane-derived sulfide **14b** (68% yield). The oxidative chlorination proceeded smoothly for sulfides **14a** and **14b**, and



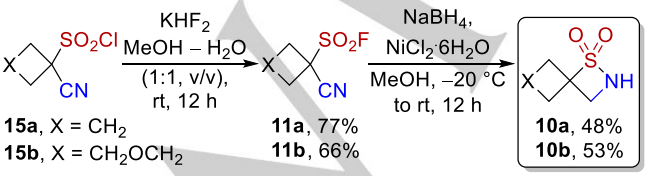
Scheme 5. Approaches to β-sultams



Scheme 6. Synthesis of cyanomethanesulfonyl chlorides **15a** and **15b**

correspondding sulfonyl chlorides **15a** and **15b** were isolated in 80% and 87% yield, respectively.

Finally, sulfonyl chlorides **15a** and **15b** were successfully transformed into corresponding fluorides **11a** and **11b** in 77% and 66% yield, respectively (Scheme 7). To our delight, intramolecular cyclizations of **11a** and **11b** into β-sultams proceeded smoothly upon the common conditions, despite the fact that **10a** and **10b** were obtained in slightly lower yields (58% and 63% yield, respectively) as compared to γ-counterparts **1a–h**, that were synthesized with 75% average yield. This might be contributed to the general fact that the four-membered rings are formed less efficiently than the five-membered ones.



Scheme 7. Synthesis of β-sultams **10a** and **10b**

Molecular structure of sultam **1h** was obtained by X-Ray diffraction studies of single crystals (Figure 2). It was shown that the γ-sultam ring in the molecule of **1h** adopts envelope conformation in the solid state, with the nitrogen atom outstanding of the mean plane formed by other ring atoms by 0.604 Å. This is somewhat different from the case of the corresponding spirocyclic derivative **16** (Figure 3): although the pyrrolidine ring also adopts the envelope conformation, it is the spirocyclic carbon atom which outstands from the mean plane formed by other five-membered ring atoms by 0.575 Å. Exit vector plot (EVP) analysis[67–70] of the corresponding bifunctional scaffolds shows that despite some differences, their overall geometry is similar and corresponds to truly three-dimensional relative disposition of the corresponding groups attached to the variation points (Table 5).

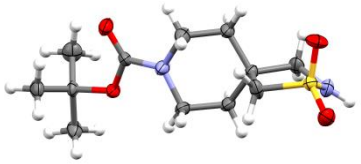


Figure 2. ORTEP diagram of sultam **1h** (thermal ellipsoids are shown at 50% probability level)

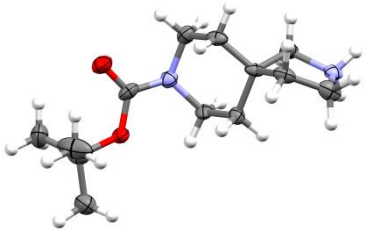
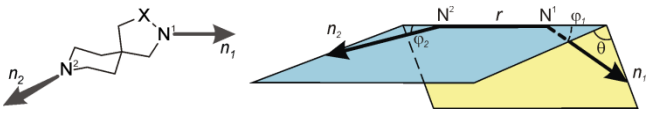


Figure 3. ORTEP diagram of spirocyclic pyrrolidine **16** (thermal ellipsoids are shown at 30% probability level)

Table 5. EVP analysis of the spirocyclic scaffods of **1h** and **16**



#	X	*r*, Å	φ_1, deg	φ_2, deg	$\lvert\theta\rvert$, deg
1	CH_2	4.96	43.8	11.4	71.0
2	SO_2	5.39	37.4	24.0	48.4

Conclusions

Intramolecular reductive cyclization of alicyclic and saturated heterocyclic cyanoalkylsulfonyl fluorides is an efficient approach for the preparation of spirocyclic β- and γ-sultams. The protocol includes using $NaBH_4$ in presence of $NiCl_2{\cdot}6H_2O$ in MeOH for nitrile group reduction, that is accompanied with intramolecular sulfonylation of amino group with the side chain SO_2F-functional

group. The method is scalable (up to 30 g), equally suitable for both α- and β-cyano-substituted sulfonyl fluorides, and leads exclusively to β-(48–53% yield, 2 examples) and γ-sultams (61–84% yield, 8 examples), respectively.

Preparation of the previously unknown β-cyano sulfonyl fluorides was performed *via* mesylation of β-hydroxy nitriles or chloromethylation of heterocyclic nitriles, followed by incorporation of the sulfur atom *via* nucleophilic substitutions with *t*-BuSH or KSAc. Subsequent oxidative chlorination with Cl_2 and reaction with KHF_2 gave SO_2F-derivatives. To obtain α-cyano sulfonyl fluorides, double alkylation of 2-(*tert*-butylthio)acetonitrile was used, which was followed by the transformations mentioned above for the homologous counterparts.

The title mono- and bifunctional sultams can be considered as analogs of common saturated nitrogen heterocycles – advanced building blocks for modern organic chemistry and lead-oriented synthesis. In particular, replacement of spirocyclic pyrrolidine derivatives with the corresponding three-dimensional sulfonamide analogues can be envisaged, which is confirmed by crystallographic studies and exit vector plot (EVP) analysis of the corresponding bifunctional scaffods.

Experimental Section

The solvents were purified according to the standard procedures.[71] Compounds **3a–h**, **12**, **13a**, **13b** and **16** were available from Enamine Ltd. All other starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are shown in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Single crystals of **1h** and **16**·(**16**·CO_2)·H_2O were obtained by slow evaporation of their solutions in hexanes – THF (1:1, v/v) and MeCN, respectively. CCDC 1990716 (**1h**) and CCDC 1990717 (**16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the preparation of 4a–e. To a solution of ester **3a–e** (0.360 mol) in dimethoxyethane - MeOH (600 mL, 5:1, v/v), $NaBH_4$ (27.2 g, 0.720 mol) was added in portions at 0 °C over 3 h. The reaction mixture was warmed up to rt and stirred for 24 h. The resulting solution was diluted with H_2O (700 mL), and extracted with CH_2Cl_2 (3×400 mL). Combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*.

1-(Hydroxymethyl)cyclopropanecarbonitrile (4a).[72,73] The crude compound was purified by distillation in *vacuo*. Yield 31.5 g (90%); colorless liquid; bp 60–63 °C / 0.2 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 2H), 2.99 (s, 1H), 1.28 – 1.17 (m, 2H), 1.01 – 0.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 122.5, 65.5, 12.7, 12.0. GC/MS (EI): *m/z* = 66 [M-CH_2OH]$^+$, 97 [M]$^+$. Anal. Cald. for C_5H_7NO: C 61.84; H 7.27; N 14.42. Found: C 62.19; H 7.62; N 14.36.

1-(Hydroxymethyl)cyclobutanecarbonitrile (4b). The crude compound was purified by distillation in *vacuo*. Yield 34.4 g (86%); colorless liquid; bp 67–70 °C / 0.2 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 2H), 2.79 (s, 1H), 2.49 – 2.41 (m, 2H), 2.19 – 2.09 (m, 3H), 2.04 – 1.97 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.6, 65.8, 37.3, 28.4, 16.7. GC/MS (EI): *m/z* = 111 [M]$^+$. Anal. Cald. for C_6H_9NO: C 64.84; H 8.16; N 12.60. Found: C 65.11; H 8.55; N 12.44.

1-(Hydroxymethyl)cyclopentanecarbonitrile (4c). The crude compound was purified by distillation in *vacuo*. Yield 35.6 g (79%); colorless liquid; bp 82–84 °C / 0.2 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (s, 2H), 2.75 (s, 1H), 2.12 – 1.97 (m, 2H), 1.89 – 1.62 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.8, 66.7, 45.2, 34.7, 24.8. GC/MS (EI): *m/z* = 125 [M]$^+$. Anal. Cald. for $C_7H_{11}NO$: C 67.17; H 8.86; N 11.19. Found: C 67.26; H 8.88; N 11.41.

1-(Hydroxymethyl)cyclohexanecarbonitrile (4d).[74,75] Yield 42.6 g (85%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 2H), 2.57 (s, 1H), 2.01 (d, *J* = 13.3 Hz, 2H), 1.82 – 1.71 (m, 3H), 1.61 (td, *J* = 13.3, 3.4 Hz, 2H), 1.27 (td, *J* = 13.3, 3.4 Hz, 2H), 1.23 – 1.07 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 122.9, 68.8, 42.2, 31.9, 25.4, 22.6. GC/MS (EI): *m/z* = 122 [M–CN]$^+$, 139 [M]$^+$. Anal. Cald. for $C_8H_{13}NO$: C 69.03; H 9.41; N 10.06. Found: C 68.73; H 9.32; N 9.98.

4-(Hydroxymethyl)tetrahydro-2*H*-pyran-4-carbonitrile (4e). The crude compound was purified by distillation in *vacuo*. Yield 41.2 g (81%); colorless oil; bp 108–111 °C (0.2 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (dq, *J* = 12.2, 1.9 Hz, 2H), 3.67 (td, *J* = 12.2, 1.9 Hz, 2H), 3.61 (s, 2H), 2.79 (s, 1H), 1.87 (dd, *J* = 13.7, 1.9 Hz, 2H), 1.60 (ddd, *J* = 13.7, 12.2, 4.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.9, 68.4, 64.5, 40.0, 31.7. GC/MS (EI): *m/z* = 141 [M]$^+$. Anal. Cald. for $C_7H_{11}NO_2$: C 59.56; H 7.85; N 9.92. Found: C 59.19; H 8.1; N 10.29.

General procedure for the preparation of 5a–e. Et_3N (34.1 mL, 24.8 g, 0.245 mol) was added to the corresponding alcohol **4a–e** (0.204 mol) in CH_2Cl_2 (200 mL), and the resulting solution was cooled to 0 °C. Then, MsCl (17.4 mL, 25.7 g, 0.224 mol) was added dropwise at 0 °C, the reaction mixture was stirred at rt for 12 h, and washed with H_2O (200 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated in *vacuo*. Unless other is specified, the crude compound was purified by column chromatography on silica gel using 40 g RediSep column (flow rate: 40 mL / min, rack: 16 mm × 150 mm tubes) and gradient hexanes – *t*-BuOMe as eluent.

(1-Cyanocyclopropyl)methyl methanesulfonate (5a). Yield 32.5 g (91%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 2H), 3.05 (s, 3H), 1.42 – 1.33 (m, 2H), 1.17 – 1.08 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.8, 71.7, 38.1, 13.5, 10.2. LC/MS (CI): *m/z* = 176 [M+H]$^+$. Anal. Cald. for $C_6H_9NO_3S$: C 41.13; H 5.18; N 7.99; S 18.3. Found: C 41.08; H 4.83; N 7.84; S 18.40.

(1-Cyanocyclobutyl)methyl methanesulfonate (5b). Yield 35.9 g (93%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (s, 2H), 3.09 (s, 3H), 2.60 – 2.52 (m, 2H), 2.28 – 2.17 (m, 3H), 2.13 – 2.05 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.6, 70.1, 37.9, 34.9, 28.8, 16.6. GC/MS (EI): *m/z* = 95 [M-OSO_2CH_3]$^+$, 189 [M]$^+$. Anal. Cald. for $C_7H_{11}NO_3S$: C 44.43; H 5.86; N 7.40; S 16.94. Found: C 44.14; H 5.88; N 7.35; S 16.55.

(1-Cyanocyclopentyl)methyl methanesulfonate (5c). Yield 39.4 g (95%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (s, 2H), 3.09 (s, 3H), 2.22 – 2.08 (m, 2H), 1.96 – 1.82 (m, 2H), 1.82 – 1.69 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 122.6, 70.9, 42.7, 37.9, 35.2, 24.5. GC/MS (EI): *m/z* = 108 [M-OMs]$^+$, 203 [M]$^+$. Anal. Cald. for $C_8H_{13}NO_3S$: C 47.27; H 6.45; N 6.89; S 15.77. Found: C 47.66; H 6.53; N 6.94; S 16.09.

(1-Cyanocyclohexyl)methyl methanesulfonate (5d). Yield 41.7 g (94%); colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (s, 2H), 3.07 (s, 3H), 2.00 (d, *J* = 12.9 Hz, 2H), 1.81 – 1.74 (m, 3H), 1.60 (qt, *J* = 12.9, 3.4 Hz, 2H), 1.32 (td, *J* = 12.9, 3.4 Hz, 2H), 1.19 (qt, *J* = 12.2, 4.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.8, 72.8, 39.7, 37.7, 31.9, 25.0, 22.2. GC/MS (EI): *m/z* = 122 [M-OMs]$^+$, 217 [M]$^+$. Anal. Cald. for $C_9H_{15}NO_3S$: C 49.75; H 6.96; N 6.45; S 14.76. Found: C 49.86; H 7.17; N 6.28; S 15.09.

(4-Cyanotetrahydro-2*H*-pyran-4-yl)methyl methanesulfonate (5e). The crude compound was purified by flash chromatography (5 bar) on silica gel using 40 g column gradient hexanes – *t*-BuOMe as eluent. Yield 39.8 g (89%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (s, 2H), 3.99 (dd, *J* = 12.3, 4.5 Hz, 2H), 3.69 (t, *J* = 12.3 Hz, 2H), 3.11 (s, 3H), 1.91 (d, *J* = 13.2 Hz, 2H), 1.69 (td, *J* = 13.2, 4.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.9, 72.0, 63.9, 37.8, 37.7, 31.6. GC/MS (EI): *m/z* = 124 [M-OMs]$^+$, 141 [M–H_2C=SO_2]$^+$, 219 [M]$^+$. Anal. Cald. for $C_8H_{13}NO_4S$: C 43.82; H 5.98; N 6.39; S 14.62. Found: C 44.00; H 6.35; N 6.43; S 14.68.

General procedure for the preparation of chloromethyl derivatives 5f–h. 2.1 M LDA (31.4 mL, 65.9 mmol) in THF was added dropwise to a solution of corresponding nitrile **3f–h** (54.9 mmol) in THF (100 mL) at –78 °C under argon atmosphere. The reaction mixture was stirred at –78 °C for 1 h, and a solution of $ClCH_2I$ (14.9 g, 82.3 mmol) in THF (30 мл) was added dropwise at –78 °C. The resulting mixture was warmed up to rt, stirred for 1 h, and H_2O (100 mL) was added. The misture was extracted with EtOAc (2×100 mL), combined organic layers were dried over Na_2SO_4, and evaporated in *vacuo*.

***tert*-Butyl 3-(chloromethyl)-3-cyanoazetidine-1-carboxylate (5f).** The crude compound was purified by column chromatography on silica gel using 80 g RediSep column (flow rate: 60 mL / min, rack: 16 mm × 150 mm tubes) and gradient hexanes – *t*-BuOMe as eluent. Yield 11.4 g (90%); yellowish solid; mp 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (d, *J* = 9.1 Hz, 2H), 3.96 (d, *J* = 9.1 Hz, 2H), 3.84 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 119.1, 81.3, 56.3, 46.2, 33.0, 28.4. LC/MS (CI): *m/z* = 131 [M–CO_2–(H_3C)$_2$C=CH_2+H]$^+$. Anal. Calcd. for $C_{10}H_{15}ClN_2O_2$: C 52.07; H 6.55; N 12.14; Cl 15.37. Found: C 52.17; H 6.19; N 12.39; Cl 15.17.

***tert*-Butyl 3-(chloromethyl)-3-cyanopyrrolidine-1-carboxylate (5g).** The crude compound was purified by column chromatography on silica gel using 80 g RediSep column (flow rate: 60 mL / min, rack: 16 mm × 150 mm tubes) and gradient hexanes – *t*-BuOMe as eluent. The compound was obtained as *ca*. 1:1 mixture of rotamers. Yield 12.8 g (95%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 – 3.76 (m, 1H), 3.71 – 3.62 (m, 2H), 3.58 (s, 2H), 3.49 (d, *J* = 11.6 Hz, 1H), 2.47 – 2.33 (m, 1H), 2.23 – 2.08 (m, 1H), 1.46 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 120.2, 80.7, 53.5 and 53.4, 46.0, 45.0, 44.3 and 44.1, 34.7 and 33.9, 28.5 ppm. GC/MS (EI): *m/z* = 144/146 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 171/173 [M–O*t*-Bu]$^+$, 188/190 [M–H_2C=$C(CH_3)_2$]$^+$, 209 [M–Cl]$^+$, 244/246 [M]$^+$. Anal. Calcd. for $C_{11}H_{17}ClN_2O_2$: C 53.99; H 7.00; N 11.45; Cl 14.49. Found: C 54.07; H 7.33; N 11.50; Cl 14.79.

***tert*-Butyl 4-(chloromethyl)-4-cyanopiperidine-1-carboxylate (5h).** The crude compound was purified by column chromatography on silica gel using 80 g RediSep column (flow rate: 60 mL / min, rack: 16 mm × 150 mm tubes) and gradient $CHCl_3$ – MeCN as eluent. Yield 12.8 g (90%); colorless solid; mp 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 – 4.07 (m, 2H), 3.56 (s, 2H), 3.13 – 2.93 (m, 2H), 2.04 (d, *J* = 12.9 Hz, 2H), 1.49 (td, *J* = 12.9, 4.4 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 119.9, 80.4, 49.6, 41.0, 40.7, 32.9, 28.5. GC/MS (EI): *m/z* = 185/187 [M–O*t*-Bu]$^+$, 258/260 [M]$^+$. Anal. Calcd. for $C_{12}H_{19}ClN_2O_2$: C 55.70; H 7.40; N 10.83; Cl 13.70. Found: C 55.67; H 7.36; N 11.07; Cl 13.85.

General procedure for the preparation of *tert*-butyl sulfides 6a–h. A mixture of the corresponding mesylate or chloride (0.124 mol), *t*-BuSH (16.8 mL, 13.4 g, 0.149 mol) and K_2CO_3 (20.6 g, 0.149 mol) in DMF (200 mL) was heated at 70 °C. Completion of the reaction was monitored by ^{1}H NMR. Then, the reaction mixture was diluted with H_2O (400 mL) and extracted with EtOAc (3×200 mL). Combined organic layers were washed with H_2O (2×200 mL), dried over Na_2SO_4 and evaporated in *vacuo*. Unless other is specified, the crude compound was purified by column chromatography on silica gel using 40 g RediSep column (flow rate: 40 mL / min, rack: 16 mm × 150 mm tubes) and gradient hexanes – *t*-BuOMe as eluent.

1-((*tert*-Butylthio)methyl)cyclopropanecarbonitrile (6a). Yield 16.6 g (79%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 2H), 1.30 (s, 9H), 1.29 – 1.25 (m, 2H), 0.96 – 0.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 122.7, 42.6, 33.5, 30.9, 14.5, 10.2. GC/MS (EI): *m/z* = 169 [M]$^+$. Anal. Cald. for $C_9H_{15}NS$: C 63.85; H 8.93; N 8.27; S 18.94. Found: C 63.79; H 8.9; N 8.41; S 18.97.

1-((*tert*-Butylthio)methyl)cyclobutanecarbonitrile (6b). The crude compound was purified by flash chromatography (5 bar) on silica gel using 80 g column gradient hexanes – *t*-BuOMe as eluent. Yield 18.9 g (83%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (s, 2H), 2.54 – 2.48 (m, 2H), 2.21 – 2.13 (m, 3H), 2.06 – 1.98 (m, 1H), 1.33 (d, *J* = 1.1 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.8, 42.5, 36.0, 35.5, 31.9, 30.9, 16.5. GC/MS (EI): *m/z* = 183 [M]$^+$. Anal. Cald. for $C_{10}H_{17}NS$: C 65.52; H 9.35; N 7.64; S 17.49. Found: C 65.53; H 9.24; N 7.49; S 17.47.

1-((*tert*-Butylthio)methyl)cyclopentanecarbonitrile (6c). The reaction was performed at 90 °C. The crude compound was purified by flash chromatography (5 bar) on silica gel using 40 g column gradient hexanes – *t*-BuOMe as eluent. Yield 18.8 g (77%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 2H), 2.17 – 2.06 (m, 2H), 1.87 – 1.76 (m, 2H), 1.75 – 1.65 (m, 4H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 124.5, 43.5, 42.6, 37.9, 35.9, 30.8, 24.4. GC/MS (EI): *m/z* = 197 [M]$^+$. Anal. Cald. for $C_{11}H_{19}NS$: C 66.95; H 9.71; N 7.1; S 16.25. Found: C 67.18; H 9.35; N 7.05; S 16.49.

4-((*tert*-Butylthio)methyl)tetrahydro-2*H*-pyran-4-carbonitrile (6e). Yield 22.5 g (85%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (ddd, *J* = 12.2, 4.6, 1.9 Hz, 2H), 3.62 (td, *J* = 12.2, 1.9 Hz, 2H), 2.66 (s, 2H), 1.87 (dd, *J* = 13.4, 1.9 Hz, 2H), 1.62 (ddd, *J* = 13.4, 12.2, 4.6 Hz, 2H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.6, 64.6, 42.8, 37.9, 37.6, 35.0, 30.8. GC/MS (EI): *m/z* = 157 [M–H_2C=$C(CH_3)_3$]$^+$, 198 [M–Me]$^+$, 213 [M]$^+$. Anal. Cald. for $C_{11}H_{19}NOS$: C 61.93; H 8.98; N 6.57; S 15.03. Found: C 61.84; H 9.13; N 6.89; S 15.02.

***tert*-Butyl 3-((*tert*-butylthio)methyl)-3-cyanoazetidine-1-carboxylate (6f).** The reaction was performed at 60 °C. The crude compound was purified by flash chromatography (5 bar) on silica gel using 40 g column gradient hexanes – *t*-BuOMe as eluent. Yield 25.7 g (73%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (d, *J* = 8.8 Hz, 2H), 3.87 (d, *J* = 8.8 Hz, 2H), 2.94 (s, 2H), 1.39 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 120.6, 80.7, 57.6, 43.2, 34.2, 31.0, 30.8, 28.3. GC/MS (EI): *m/z* = 229 [M–H_2C=$C(CH_3)_3$]$^+$, 284 [M]$^+$. Anal. Cald. for $C_{14}H_{24}N_2O_2S$: C 59.12; H 8.51; N 9.85; S 11.27. Found: C 58.73; H 8.18; N 9.48; S 11.35.

***tert*-Butyl 4-((*tert*-Butylthio)methyl)-4-cyanopiperidine-1-carboxylate (6h).** The compound existed as a mixture of *ca*. 1:1 rotamers. Yield 27.5 g (71%); colorless crystals; mp 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 – 4.02 (m, 2H), 3.01 (t, *J* = 10.9 Hz, 2H), 2.70 (s, 1H) and 2.69 (s, 1H), 1.96 (d, *J* = 13.4 Hz, 2H), 1.60 – 1.49 (m, 2H), 1.44 (s, 4.5H) and 1.43 (s, 4.5H), 1.32 (s, 4.5H) and 1.32 (s, 4.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 121.4, 80.1, 42.9, 40.7, 39.0, 37.3, 34.4, 30.8, 28.4. GC/MS (EI): *m/z* = 212 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 239 [M–O*t*-Bu]$^+$, 256 [M–H_2C=$C(CH_3)_2$]$^+$. Anal. Cald. for $C_{16}H_{28}N_2O_2S$: C 61.5; H 9.03; N 8.97; S 10.26. Found: C 61.23; H 8.63; N 9.20; S 10.56.

General procedure for the preparation of thioacetates 7d and 7f–h. KSAc (19.8 g, 0.174 mol) was added to a solution of the corresponding mesylate or chloride (0.124 mol) in DMF (625 mL). The reaction mixture was stirred at 85 °C for 12 h, then cooled to rt and evaporated in vacuo at

85 °C to *ca.* 150 mL volume. The residue was diluted with H_2O (1000 mL) and extracted with EtOAc (4×125 mL). Combined organic layers was washed with brine (4×125 mL), dried over Na_2SO_4 and evaporated in *vacuo*.

***S*-((1-Cyanocyclohexyl)methyl) ethanethioate (7d).** The crude compound was purified by column chromatography on silica gel using 40 g RediSep column (flow rate: 40 mL / min, rack: 16 mm × 150 mm tubes) and gradient hexanes – *t*-BuOMe as eluent. Yield 21.3 g (87%); yellowish liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.12 (s, 2H), 2.39 (s, 3H), 1.98 (d, *J* = 13.2 Hz, 2H), 1.80 – 1.69 (m, 3H), 1.59 (q, *J* = 13.2 Hz, 2H), 1.36 – 1.26 (m, 2H), 1.21 – 1.12 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9, 122.0, 40.3, 37.6, 34.8, 30.5, 25.0, 22.9. GC/MS (EI): *m/z* = 122 [M–SAc]$^+$, 155 [M–$H_2CCC(O)$]$^+$, 182 [M–Me]$^+$, 197 [M]$^+$. Anal. Cald. for $C_{10}H_{15}NOS$: C 60.88; H 7.66; N 7.10; S 16.25. Found: C 61.08; H 8.01; N 7.23; S 16.35.

***tert*-Butyl 3-((acetylthio)methyl)-3-cyanoazetidine-1-carboxylate (7f).** The crude compound was purified by column chromatography on silica gel using 80 g RediSep column (flow rate: 60 mL / min, rack: 16 mm × 150 mm tubes) and gradient $CHCl_3$ – MeCN as eluent. Yield 26.8 g (80 %); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (d, *J* = 8.9 Hz, 2H), 3.85 (d, *J* = 8.9 Hz, 2H), 3.43 (s, 2H), 2.42 (s, 3H), 1.43 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 155.5, 120.2, 81.0, 57.5, 34.0, 31.6, 30.7, 28.4. GC/MS (EI): *m/z* = 228 [M–$CH_2CC(O)$]$^+$, 197 [M–O*t*-Bu]$^+$. Anal. Calcd. for $C_{12}H_{18}N_2O_3S$: C 53.31; H 6.71; N 10.36; S 11.86. Found: C 53.29; H 6.92; N 10.18; S 11.75.

***tert*-Butyl 3-((acetylthio)methyl)-3-cyanopyrrolidine-1-carboxylate (7g).** The crude compound was purified by flash chromatography (5 bar) on silica gel using 80 g column gradient hexanes – *t*-BuOMe as eluent. Yield 34.2 g (97%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (d, *J* = 8.7 Hz, 2H), 3.92 (d, *J* = 8.7 Hz, 2H), 2.95 (t, *J* = 9.3, 6.5 Hz, 2H), 2.35 (s, 3H), 2.15 (dd, *J* = 9.3, 6.5 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.1, 155.5, 120.7, 80.9, 57.9 (2C), 36.4, 30.7, 30.5, 28.4, 24.7. LC/MS (CI): *m/z* = 185 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 229 [M–H_2C=$C(CH_3)_2$+H]$^+$, 307 [M+Na]$^+$. Anal. Calcd. for $C_{13}H_{20}N_2O_3S$: C 54.91; H 7.09; N 9.85; S 11.27. Found: C 54.88; H 7.44; N 9.97; S 11.52.

***tert*-Butyl 4-((acetylthio)methyl)-4-cyanopiperidine-1-carboxylate (7h).** The crude compound was purified by flash chromatography (5 bar) on silica gel using 80 g column gradient hexanes – *t*-BuOMe as eluent. Yield 34.4 g (93%); beige powder; mp 94–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 – 4.10 (m, 2H), 3.20 (s, 2H), 3.07 – 2.98 (m, 2H), 2.44 (s, 3H), 1.95 (d, *J* = 12.8 Hz, 2H), 1.56 – 1.51 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.5, 154.2, 120.7, 80.2, 40.7, 39.3, 36.9, 33.8, 30.5, 28.4. GC/MS (EI): *m/z* = 198 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 225 [M–O*t*-Bu]$^+$, 242 [M–H_2C=$C(CH_3)_2$]$^+$, 298 [M]$^+$. Anal. Cald. for $C_{14}H_{22}N_2O_3S$: C 56.35; H 7.43; N 9.39; S 10.74. Found: C 56.32; H 7.43; N 9.27; S 11.13.

Preparation of *tert*-butyl sulfides 14a and 14b. 2-(*tert*-Butylthio)acetonitrile (**12**, 20.0 g, 0.155 mol) was added dropwise to a suspension of NaH (60%, 13.0 g, 0.325 mol) in DMF (100 mL) at 0 °C under argon atmosphere. The resulting mixture was stirred at rt for 2 h, then cooled to –10 °C, and 1,3-dibromopropane (**13a**, 31.3 g, 0.155 mol) or 1-bromo-2-(2-bromoethoxy)ethane (**13b**, 35.9 g, 0.155 mol) was added dropwise at –10 °C. The reaction mixture was stirred at rt for 12 h, then diluted with H_2O (200 mL) and extracted with EtOAc (3×100 mL). Combined organic layers were washed with H_2O (2×70 mL), dried over Na_2SO_4, and evaporated in *vacuo*.

1-(*tert*-Butylthio)cyclobutanecarbonitrile (14a). The crude compound was purified by flash chromatography (5 bar) on silica gel using 80 g column gradient hexanes – $CHCl_3$ as eluent. Yield 16.3 g (62%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (ddt, *J* = 15.0, 8.7, 3.5 Hz, 2H), 2.47 – 2.40 (m, 2H), 2.35 – 2.25 (m, 1H), 2.21 – 2.11 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 123.4, 47.0, 37.4, 36.4, 31.5, 18.1. GC/MS (EI): *m/z* = 169 [M]$^+$. Anal. Calcd. for $C_9H_{15}NS$: C 63.85; H 8.93; N 8.27; S 18.94. Found: C 64.14; H 9.26; N 7.91; S 19.14.

4-(*tert*-Butylthio)tetrahydro-2*H*-pyran-4-carbonitrile (14b). The crude compound was purified by column chromatography on silica gel using 40g RediSep column (flow rate: 40 mL / min, rack: 16 mm × 150 mm tubes) and gradient *t*-BuOMe – MeOH as eluent. Yield 21.0 g (68%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (dt, *J* = 11.7, 3.8 Hz, 2H), 3.71 (dd, *J* = 11.7, 2.3 Hz, 2H), 2.15 (dq, *J* = 13.6, 2.3 Hz, 2H), 1.95 (ddd, *J* = 13.6, 11.7, 3.8 Hz, 2H), 1.51 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.3, 64.2, 48.1, 39.2, 38.0, 32.3. GC/MS (EI): *m/z* = 199 [M]$^+$. Anal. Calcd. for $C_{10}H_{17}NOS$: C 60.26; H 8.60; N 7.03; S 16.09. Found: C 60.01; H 8.88; N 7.03; S 16.19.

General procedure for the preparation of sulfonyl chlorides 8a–h, 15a and 15b. A solution of the corresponding *tert*-butyl sulfide **6** or thioacetate **7** (0.180 mmol) in CH_2Cl_2 – H_2O (450 mL, 2:1, v/v) was cooled to 0 °C, and Cl_2 was bubbled through the reaction mixture at 0 °C for 1 h (CAUTION! Gaseous Cl_2 is toxic, has irritating odor, strong oxidizing agent. The experiments with gaseous Cl_2 must be performed carefully and accurately, while the temperature of the reaction mixture should not exceed 5 °C). The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (300 mL). Combined organic phases were washed with H_2O (300 mL), dried over Na_2SO_4 and evaporated in *vacuo*. Unless other is specified, the crude compound was purified by column chromatography on silica gel using 80 g or 330 g RediSep column (flow rate: 60 mL / min or 100 mL / min, respectively, rack: 16 mm × 150 mm tubes) and hexanes – *t*-BuOMe followed by gradient hexanes – EtOAc as eluents.

(1-Cyanocyclopropyl)methanesulfonyl chloride (8a). Yield 19.7 g (61% from **6a**); colorless crystals; mp 71–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 2H), 1.69 – 1.61 (m, 2H), 1.44 – 1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.9, 69.1, 15.8, 5.9. GC/MS (EI): *m/z* = 80 [M–SO_2Cl]$^+$. Anal. Cald. for $C_5H_6ClNO_2S$: C 33.43; H 3.37; N 7.8; S 17.85; Cl 19.74. Found: C 33.15; H 3.52; N 7.65; S 18.17; Cl 19.70.

(1-Cyanocyclobutyl)methanesulfonyl chloride (8b). Yield 23.3 g (67% from **6b**); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 2H), 2.76 – 2.66 (m, 2H), 2.53 – 2.45 (m, 2H), 2.44 – 2.33 (m, 1H), 2.17 – 2.08 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.8, 70.1, 32.9, 32.8, 17.4. LC/MS (CI): *m/z* = 194/196 [M+H]$^+$. Anal. Cald. for $C_6H_8ClNO_2S$: C 37.21; H 4.16; N 7.23; S 16.56; Cl 18.31. Found: C 37.11; H 4.11; N 7.12; S 16.32; Cl 18.12.

(1-Cyanocyclopentyl)methanesulfonyl chloride (8c). The crude compound was purified by flash chromatography (5 bar) on silica gel using 80 g column gradient hexanes – *t*-BuOMe as eluent. Yield 26.5 g (71% from **6c**); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (s, 2H), 2.47 – 2.37 (m, 2H), 2.07 – 1.96 (m, 2H), 1.95 – 1.86 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 120.8, 71.0, 40.6, 38.5, 23.5. GC/MS (EI): *m/z* = 108 [M–SO_2Cl]$^+$, 207/209 [M]$^+$. Anal. Cald. for $C_7H_{10}ClNO_2S$: C 40.49; H 4.85; N 6.74; S 15.44; Cl 17.07. Found: C 40.45; H 4.6; N 6.48; S 15.36; Cl 16.97.

(1-Cyanocyclohexyl)methanesulfonyl chloride (8d). Yield 32.7 g (82% from **7d**); colorless solid; mp 55–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 2H), 2.25 (d, *J* = 13.0 Hz, 2H), 1.87 – 1.67 (m, 5H), 1.57 (td, *J* = 13.0, 3.7 Hz, 2H), 1.29 – 1.18 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.4, 72.7, 37.9, 35.1, 24.4, 22.4. GC/MS (EI): *m/z* = 122 [M–SO_2Cl]$^+$, 221/223 [M]$^+$. Anal. Cald. for $C_8H_{12}ClNO_2S$: C 43.34; H 5.46; N 6.32; S 14.46; Cl 15.99. Found: C 43.59; H 5.18; N 5.98; S 14.07; Cl 15.70.

(4-Cyanotetrahydro-2*H*-pyran-4-yl)methanesulfonyl chloride (8e). Yield 28.6 g (71% from **6e**); colorless powder; mp 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 – 4.00 (m, 1H), 4.00 – 3.96 (m, 3H), 3.76 (td, *J* = 12.1, 1.8 Hz, 2H), 2.13 (dd, *J* = 13.2, 1.9 Hz, 2H), 1.87 (ddd, *J* = 13.2, 12.1, 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 118.4, 72.0, 63.8, 35.6, 34.6. GC/MS (EI): *m/z* = 124 [M-SO_2Cl]$^+$, 223/225 [M]$^+$. Anal. Cald. for

$C_7H_{10}ClNO_3S$: C 37.59; H 4.51; N 6.26; S 14.33; Cl 15.85. Found: C 37.94; H 4.48; N 6.64; S 14.39; Cl 15.63.

***tert*-Butyl 3-((chlorosulfonyl)methyl)-3-cyanoazetidine-1-carboxylate (8f).** Yield 31.8 g (60% from **6f**) and 33.4 g (63% from **7f**); beige powder; mp 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (d, *J* = 9.3 Hz, 2H), 4.28 (s, 2H), 4.17 (d, *J* = 9.3 Hz, 2H), 1.45 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 117.8, 81.8, 68.1, 57.8, 28.3, 27.7 ppm. LC/MS (CI): *m/z* = 195/197 $[M–CO_2–(H_3C)_2C=CH_2+H]^+$. Anal. Calcd. for C10H15ClN2O4S: C 40.75; H 5.13; N 9.50; S 10.88; Cl 12.03. Found: C 40.44; H 5.25; N 9.21; S 10.93; Cl 12.15.

***tert*-Butyl 3-((chlorosulfonyl)methyl)-3-cyanopyrrolidine-1-carboxylate (8g).** Yield 39.5 g (71% from **7g**); yellow solid, mp 102–105 °C. The compound existed as *ca*. 1:1 mixture of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 – 3.97 (m, 3H), 3.71 – 3.48 (m, 3H), 2.67 – 2.52 (m, 1H), 2.36 – 2.18 (m, 1H), 1.47 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 118.4, 81.2, 68.2, 54.8, 43.9 and 43.5, 39.6 and 38.9, 36.3 and 35.8, 28.5. LC/MS (CI): *m/z* = 209/211 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$, 253/255 $[M–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{11}H_{17}ClN_2O_4S$: C 42.79; H 5.55; N 9.07; S 10.38; Cl 11.48. Found: C 42.75; H 5.73; N 9.28; S 10.23; Cl 11.21.

***tert*-Butyl 4-((chlorosulfonyl)methyl)-4-cyanopiperidine-1-carboxylate (8h).** The crude compound was purified by column chromatography on silica gel using 80 g RediSep column (flow rate: 60 mL / min, rack: 16 mm × 150 mm tubes) and gradient $CHCl_3$ – MeCN as eluent. Yield 42.4 g (73% from **6h**) and 48.8 g (84% from **7h**); yellow solid, mp 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 – 4.00 (m, 2H), 3.97 (s, 2H), 3.17 – 3.01 (m, 2H), 2.17 (dd, *J* = 12.9, 2.2 Hz, 2H), 1.69 (td, *J* = 12.9, 4.4 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 118.2, 80.8, 71.9, 40.2, 36.8, 34.2, 28.5. Anal. Calcd. for $C_{12}H_{19}ClN_2O_4S$: C 44.65; H 5.93; N 8.68; S 9.93; Cl 10.98. Found: C 44.52; H 5.55; N 8.54; S 10.10; Cl 10.72.

1-Cyanocyclobutane-1-sulfonyl chloride (15a). Yield 25.9 g (80%); yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 – 3.00 (m, 2H), 2.93 – 2.81 (m, 2H), 2.42 – 2.25 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 115.1, 66.9, 30.9, 15.6. GC/MS (EI): *m/z* = 179/181 $[M]^+$. Anal. Cald. for $C_5H_6ClNO_2S$: C 33.43; H 3.37; N 7.80; S 17.85; Cl 19.74. Found: C 33.48; H 3.33; N 7.74; S 17.59; Cl 19.38.

4-Cyanotetrahydro-2*H*-pyran-4-sulfonyl chloride (15b). Yield 32.8 g (87%); yellowish crystals; mp 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 – 4.17 (m, 2H), 3.75 – 3.66 (m, 2H), 2.45 – 2.33 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.4, 71.5, 63.5, 30.2. LC/MS (CI): *m/z* = 111 $[M–SO_2Cl]^+$, 210/212 $[M+H]^+$. Anal. Cald. for $C_6H_8ClNO_3S$: C 34.38; H 3.85; N 6.68; S 15.29; Cl 16.91. Found: C 34.39; H 4.11; N 6.80; S 15.00; Cl 16.92.

General procedure for the preparation of sulfonyl fluorides 2a–h, 11a and 11b. KHF_2 (0.900 mol) was added at rt to the corresponding sulfonyl chloride **8** or **15** (90.0 mmol) in MeOH–H_2O (240 mL, 1:1, v/v). The resulting mixture was stirred at rt for 12 h, then diluted with H_2O (240 mL) and extracted with CH_2Cl_2 (3×200 mL). Combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*. Unless other is specified, the crude compound was purified by column chromatography on silica gel using 40 g, 80 g or 330 g RediSep column (flow rate: 40 mL / min, 60 mL / min, or 100 mL / min, respectively, rack: 16 mm × 150 mm tubes) and gradient hexanes – *t*-BuOMe as eluent.

(1-Cyanocyclopropyl)methanesulfonyl fluoride (2a). The crude compound was purified by flash chromatography (5 bar) on silica gel using 40 g column gradient hexanes – *t*-BuOMe as eluent. Yield 12.8 g (87%); colorless crystals; mp 56–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (d, *J* = 4.1 Hz, 1H), 1.64 – 1.58 (m, 1H), 1.34 – 1.29 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.9, 55.5 (d, *J* = 17.9 Hz), 15.4, 5.1. ^{19}F{H} NMR (376 MHz, $CDCl_3$) δ 57.0. GC/MS (EI): *m/z* = 163 $[M]^+$. Anal. Cald. for $C_5H_6FNO_2S$: C 36.81; H 3.71; N 8.58; S 19.65. Found: C 36.61; H 4.08; N 8.23; S 19.54.

(1-Cyanocyclobutyl)methanesulfonyl fluoride (2b). Yield 14.2 g (89%); colorless crystals; mp 43–44 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (d, *J* = 4.2 Hz, 2H), 2.73 – 2.59 (m, 2H), 2.50 – 2.37 (m, 2H), 2.37 – 2.26 (m, 1H), 2.17 – 2.02 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.1, 56.37 (d, *J* = 16.1 Hz), 32.4, 32.1, 17.1. ^{19}F{H} NMR (376 MHz, $CDCl_3$) δ 61.3. GC/MS (EI): *m/z* = 177 $[M]^+$. Anal. Cald. for $C_6H_8FNO_2S$: C 40.67; H 4.55; N 7.91; S 18.09. Found: C 40.37; H 4.79; N 7.63; S 17.89.

(1-Cyanocyclopentyl)methanesulfonyl fluoride (2c). The crude compound was purified by flash chromatography (5 bar) on silica gel using 40 g column gradient hexanes – *t*-BuOMe as eluent. Yield 16.2 g (94%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 2H), 2.47 – 2.32 (m, 2H), 2.03 – 1.91 (m, 2H), 1.92 – 1.81 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.1, 56.9 (d, *J* = 16.5 Hz), 39.7, 38.3, 23.5. ^{19}F{H} NMR (470 MHz, $CDCl_3$) δ 62.1. GC/MS (EI): *m/z* = 108 $[M–SO_2F]^+$, 191 $[M]^+$. Anal. Cald. for $C_7H_{10}FNO_2S$: C 43.97; H 5.27; N 7.33; S 16.77. Found: C 43.8; H 5.39; N 7.36; S 16.75.

(1-Cyanocyclohexyl)methanesulfonyl fluoride (2d). Yield 17.4 g (94%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (d, *J* = 3.2 Hz, 2H), 2.25 (d, *J* = 12.9 Hz, 2H), 1.86 – 1.68 (m, 5H), 1.54 (td, *J* = 12.9, 3.6 Hz, 2H), 1.32 – 1.18 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 119.4, 58.7 (d, *J* = 16.3 Hz), 36.7, 35.0, 24.4, 22.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ 65.4. GC/MS (EI): *m/z* = 122 $[M–SO_2Cl]^+$, 205 $[M]^+$. Anal. Cald. for $C_8H_{12}FNO_2S$: C 46.82; H 5.89; N 6.82; S 15.62. Found: C 46.67; H 6.22; N 6.98; S 15.56.

(4-Cyanotetrahydro-2*H*-pyran-4-yl)methanesulfonyl fluoride (2e).. Yield 16.8 g (90%); colorless crystals; mp 143–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (dd, *J* = 12.2, 4.3 Hz, 2H), 3.78 (t, *J* = 12.2 Hz, 2H), 3.67 (s, 2H), 2.14 (d, *J* = 13.2 Hz, 2H), 1.86 (td, *J* = 13.2, 4.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 118.5, 63.8, 58.4, 58.2, 34.6, 34.5. ^{19}F{H} NMR (470 MHz, $CDCl_3$) δ 65.5. GC/MS (EI): *m/z* = 124 $[M-SO_2F]^+$, 207 $[M]^+$. Anal. Cald. for $C_7H_{10}FNO_3S$: C 40.57; H 4.86; N 6.76; S 15.47. Found: C 40.44; H 4.94; N 6.58; S 15.37.

***tert*-Butyl 3-cyano-3-((fluorosulfonyl)methyl)azetidine-1-carboxylate (2f).** The crude compound was purified by flash chromatography (5 bar) on silica gel using 80 g column gradient hexanes – *t*-BuOMe – MeCN as eluent. Yield 19.3 g (77%); yellowish powder; mp 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (d, *J* = 9.3 Hz, 2H), 4.12 (d, *J* = 9.3 Hz, 2H), 3.99 (d, *J* = 4.1 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 117.8, 81.8, 57.6, 55.0 (d, *J* = 18.3 Hz), 28.3, 27.1. ^{19}F{H} NMR (376 MHz, $CDCl_3$) δ 62.3. LC/MS (CI): *m/z* = 277 $[M-H]^-$. Anal. Calcd. for $C_{10}H_{15}FN_2O_4S$: C 43.16; H 5.43; N 10.07; S 11.52. Found: C 42.99; H 5.75; N 10.24; S 11.82.

***tert*-Butyl 3-cyano-3-((fluorosulfonyl)methyl)pyrrolidine-1-carboxylate (2g).** Yield 18.9 g (72%); yellow solid, mp 134–136 °C. The compound existed as *ca*. 1:1 mixture of rotamers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.85 – 4.68 (m, 2H), 3.86 (dd, *J* = 11.9, 4.8 Hz, 1H), 3.53 (t, *J* = 9.8 Hz, 1H), 3.47 – 3.37 (m, 2H), 2.49 – 2.41 (m, 1H), 2.28 – 2.13 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.2 and 152.9, 119.6, 79.5, 54.1, 52.8 (d, *J* = 15.0 Hz), 43.7 and 43.5, 38.6 and 37.8, 35.2 and 34.4, 28.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ 60.9 and 60.8. LC/MS (CI): *m/z* = 193 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$, 237 $[M–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{11}H_{17}FN_2O_4S$: C 45.20; H 5.86; N 9.58; S 10.97. Found: C 45.23; H 5.85; N 9.83; S 10.82.

***tert*-Butyl 4-cyano-4-((fluorosulfonyl)methyl)piperidine-1-carboxylate (2h).** The crude compound was purified by column chromatography on silica gel using 330 g RediSep column (flow rate: 100 mL / min, rack: 16 mm × 150 mm tubes) and gradient $CHCl_3$ – MeCN as eluent. Yield 22.1 g (80%); yellow solid, mp 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 2H), 3.65 (d, *J* = 3.5 Hz, 2H), 3.18 – 3.01 (m, 2H), 2.17 (dd, *J* = 13.1, 2.7 Hz, 2H), 1.67 (td, *J* = 13.1, 4.3 Hz, 2H), 1.45 (s, 9H) ppm. ^{13}C

NMR (126 MHz, $CDCl_3$) δ 154.2, 118.3, 80.8, 58.2 (d, *J* = 17.0 Hz), 40.1, 35.7, 34.2, 28.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ 65.0 ppm. GC/MS (EI): *m/z* = 206 [M-CO_2-$(H_3C)_2C=CH_2$]$^+$, 233 [M –O*t*-Bu]$^+$. Anal. Calcd. for $C_{12}H_{19}FN_2O_4S$: C 47.05; H 6.25; N 9.14; S 10.47. Found: C 47.16; H 6.35; N 8.95; S 10.56.

1-Cyanocyclobutane-1-sulfonyl fluoride (11a). The crude compound was purified by flash chromatography (5 bar) on silica gel using 120 g column gradient hexanes – $CHCl_3$ as eluent. Yield 11.3 g (77%); colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.12 – 3.01 (m, 2H), 2.99 – 2.88 (m, 2H), 2.50 – 2.33 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 114.4 (d, *J* = 1.8 Hz), 54.9 (d, *J* = 19.2 Hz), 30.5, 16.5. $^{19}F\{H\}$ NMR (470 MHz, $CDCl_3$) δ 41.8. GC/MS (EI): *m/z* = 163 [M]$^+$. Anal. Calcd. for $C_5H_6FNO_2S$: C 36.81; H 3.71; N 8.58; S 19.65. Found: C 36.98; H 3.56; N 8.46; S 19.43.

4-Cyanotetrahydro-2*H*-pyran-4-sulfonyl fluoride (11b). The crude compound was purified by HPLC using gradient H_2O – MeCN as eluent. Yield 11.5 g (66%); yellowish crystals; mp 57–59 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (ddd, *J* = 12.4, 4.2, 1.9 Hz, 2H), 3.71 (td, *J* = 12.4, 2.4 Hz, 2H), 2.40 – 2.26 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.0, 63.4, 60.6 (d, *J* = 18.2 Hz), 30.4. $^{19}F\{H\}$ NMR (376 MHz, $CDCl_3$) δ 39.4. GC/MS (EI): *m/z* = 193 [M]$^+$. Anal. Cald. for $C_6H_8FNO_3S$: C 37.3; H 4.17; N 7.25; S 16.6. Found: C 37.41; H 4.31; N 7.56; S 16.97

General procedure for the preparation of sultams 1a–h, 10a and 10b. A mixture of the corresponding sulfonyl fluoride **2** or **11** (0.140 mol) and $NiCl_2$*$6H_2O$ (36.6 g, 0.154 mol) in MeOH (300 mL) was cooled to –20 °C. Then, $NaBH_4$ (18.5 g, 0.490 mol) was added in portions at –20 °C (NOTE: the temperature should not exceed –10 °C). The resulting mixture was warmed up to rt and stirred for 12 h. The precipitate was filtered off and washed with MeOH (3×500 mL), and the filtrate was evaporated in *vacuo*. The residue was dissolved in EtOAc - H_2O (1000 mL, 1:1, v/v), the organic phase was separated, and the aqueous phase was extracted with EtOAc (500 mL). Combined organic phases were dried over Na_2SO_4 and evaporated in *vacuo*. Unless other is specified, the crude compound was purified by column chromatography on silica gel using 40 g, 80 g or 330 g RediSep column (flow rate: 40 mL / min, 60 mL / min or 100 mL / min, respectively, rack: 16 mm × 150 mm tubes) and gradient *t*-BuOMe – MeOH as eluent.

5-Thia-6-azaspiro[2.4]heptane 5,5-dioxide (1a). The crude compound was purified by flash chromatography (5 bar) on silica gel using 330 g column gradient *t*-BuOMe – MeOH as eluent. Yield 12.6 g (61%); colorless crystals; mp 72–74 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 1H), 3.21 (s, 2H), 3.07 (s, 2H), 0.97 – 0.81 (m, 2H), 0.81 – 0.63 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.4, 51.4, 20.3, 11.8. LC/MS (CI): *m/z* = 148 [M+H]$^+$. Anal. Cald. for $C_5H_9NO_2S$: C 40.80; H 6.16; N 9.52; S 21.78. Found: C 40.52; H 5.84; N 9.89; S 21.58.

6-Thia-7-azaspiro[3.4]octane 6,6-dioxide (1b). Yield 16.0 g (71%); colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.53 (s, 1H), 3.36 (d, *J* = 5.7 Hz, 2H), 3.17 (s, 2H), 2.25 – 2.18 (m, 2H), 2.13 – 2.06 (m, 2H), 1.99 – 1.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 58.7, 54.6, 44.6, 32.3, 16.0. GC/MS (EI): *m/z* = 161 [M]$^+$. Anal. Cald. for $C_6H_{11}NO_2S$: C 44.7; H 6.88; N 8.69; S 19.89. Found: C 45.02; H 6.89; N 8.51; S 19.72.

2-Thia-3-azaspiro[4.4]nonane 2,2-dioxide (1c). Yield 20.1 g (82%); colorless powder; mp 61–64 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (s, 1H), 3.20 (d, *J* = 6.3 Hz, 2H), 3.06 (s, 2H), 1.83 – 1.76 (m, 2H), 1.75 – 1.70 (m, 2H), 1.69 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 59.0, 54.1, 50.8, 37.8, 23.9. LC/MS (CI): *m/z* = 176 [M+H]$^+$. Anal. Cald. for $C_7H_{13}NO_2S$: C 47.98; H 7.48; N 7.99; S 18.29. Found: C 47.92; H 7.81; N 7.95; S 18.67.

2-Thia-3-azaspiro[4.5]decane 2,2-dioxide (1d). Yield 20.7 g (78%); Colorless liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 4.94 (t, *J* = 6.8 Hz, 1H), 3.11 (dd, *J* = 6.5, 1.7 Hz, 2H), 2.97 (d, *J* = 1.7 Hz, 2H), 1.69 (dd, *J* = 14.0, 6.5 Hz, 2H), 1.60 – 1.53 (m, 2H), 1.52 – 1.44 (m, 3H), 1.39 – 1.31 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.9, 53.7, 44.3, 36.3, 25.3, 22.7. GC/MS (EI): *m/z* = 189 [M]$^+$. Anal. Cald. for $C_8H_{15}NO_2S$: C 50.77; H 7.99; N 7.4; S 16.94. Found: C 50.99; H 8.34; N 7.41; S 17.07.

8-Oxa-2-thia-3-azaspiro[4.5]decane 2,2-dioxide (1e). Yield 22.5 g (84%); colorless powder; mp 85–86 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 4.85 (s, 1H), 3.88 – 3.74 (m, 2H), 3.61 – 3.48 (m, 2H), 3.22 (d, *J* = 6.1 Hz, 2H), 3.10 (s, 2H), 1.87 – 1.71 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 64.4, 57.2, 53.5, 41.7, 36.2. GC/MS (EI): *m/z* = 191 [M]$^+$. Anal. Cald. for $C_7H_{13}NO_3S$: C 43.96; H 6.85; N 7.32; S 16.76. Found: C 43.61; H 6.91; N 7.71; S 16.70.

***tert*-Butyl 6-thia-2,7-diazaspiro[3.4]octane-2-carboxylate 6,6-dioxide (1f).** Yield 27.2 g (74%); colorless powder; mp 146–147 °C.^1H NMR (500 MHz, $CDCl_3$) δ 5.10 (s, 1H), 4.04 (d, *J* = 9.1 Hz, 2H), 3.92 (d, *J* = 9.2 Hz, 2H), 3.54 (s, 2H), 3.32 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 80.4, 59.2, 56.2, 52.8, 38.5, 28.3. LC/MS (CI): *m/z* = 163 [M–CO_2–$(H_3C)_2C=CH_2$+H]$^+$. Anal. Cald. for $C_{10}H_{18}N_2O_4S$: C 45.79; H 6.92; N 10.68; S 12.22. Found: C 46.19; H 6.55; N 10.92; S 12.22.

***tert*-Butyl 2-thia-3,7-diazaspiro[4.4]nonane-7-carboxylate 2,2-dioxide (1g).** The compound existed as *ca*. 1:1 mixture of rotamers. Yield 29.0 g (75%); colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (s, 0.5H) and 4.96 (s, 0.5H), 3.61 – 3.38 (m, 4H), 3.37 – 3.23 (m, 2H), 3.15 (q, *J* = 13.3 Hz, 2H), 2.11 (s, 1H) and 2.04 (s, 1H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 154.4 and 154.3, 80.1, 56.3 and 56.2, 55.9 and 55.4, 51.4, 48.8 and 48.6, 44.6 and 44.2, 36.1 and 35.6, 28.4. LC/MS (CI): *m/z* = 177 [M–CO_2–$(H_3C)_2C=CH_2$+H]$^+$. Anal. Cald. for $C_{11}H_{20}N_2O_4S$: C 47.81; H 7.30; N 10.14; S 11.60. Found: C 48.04; H 7.67; N 10.35; S 11.74.

***tert*-Butyl 2-thia-3,8-diazaspiro[4.5]decane-8-carboxylate 2,2-dioxide (1h).** Yield 31.7 g (78%); colorless powder; mp 173–174. ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (s, 1H), 3.69 (d, *J* = 13.7 Hz, 2H), 3.21 (s, 2H), 3.18 – 3.10 (m, 2H), 3.06 (s, 2H), 1.79 (dt, *J* = 8.7, 4.2 Hz, 2H), 1.66 (ddd, *J* = 13.7, 9.4, 4.2 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 80.1, 56.7, 53.0, 42.5, 40.5, 35.5, 28.4. LC/MS (CI): *m/z* = 235 [M–$H_2C=C(CH_3)_3$+H]$^+$, 291 [M+H]$^+$. Anal. Cald. for $C_{12}H_{22}N_2O_4S$: C 49.64; H 7.64; N 9.65; S 11.04. Found: C 49.49; H 7.67; N 9.65; S 11.21.

1-Thia-2-azaspiro[3.3]heptane 1,1-dioxide (10a). Yield 9.89 g (48%); colorless crystals; mp 167–169 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 1H), 3.24 (s, 2H), 2.78 (ddt, *J* = 14.3, 8.9, 5.4 Hz, 2H), 2.42 – 2.32 (m, 2H), 2.00 – 1.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 80.0, 43.1, 28.5, 15.6. GC/MS (EI): *m/z* = 147 [M]$^+$. Anal. Cald. for $C_5H_9NO_2S$: C 40.8; H 6.16; N 9.52; S 21.78. Found: C 40.88; H 6.52; N 9.81; S 21.98.

7-Oxa-1-thia-2-azaspiro[3.5]nonane 1,1-dioxide (10b). The crude compound was purified by flash chromatography (5 bar) on silica gel using 220 g column gradient *t*-BuOMe – MeOH as eluent. Yield 13.1 g (53%); colorless crystals; mp 129–131 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 3.67 (ddd, *J* = 11.8, 6.1, 4.0 Hz, 2H), 3.57 (ddd, *J* = 11.8, 8.0, 3.4 Hz, 2H), 3.04 (d, *J* = 3.4 Hz, 2H), 2.13 (ddd, *J* = 13.9, 6.1, 3.4 Hz, 2H), 1.98 (ddd, *J* = 13.9, 8.0, 4.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 78.0, 64.9, 42.1, 31.7. GC/MS (EI): *m/z* = 177 [M]$^+$. LC/MS (CI): *m/z* = 178 [M+H]$^+$. Anal. Cald. for $C_6H_{11}NO_3S$: C 40.66; H 6.26; N 7.9; S 18.09. Found: C 40.65; H 6.19; N 8.03; S 17.79.

Genreal procedure for preparation of hydrochlorides 9g and 9h. The corresponding *N*-Boc amine **1g** (950 mg, 3.44 mmol) or **1h** (1.00 g, 3.44 mmol) was added to 4 M HCl – 1,4-dioxane (10 mL) at rt. The reaction mixture was stirred at rt for 12 h, then evaporated in *vacuo* to dryness. The precipitate thus obtained was dried in *vacuo*.

2-Thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide hydrochloride (9g). Yield 732 mg (100%); yellowish solid; mp 187–189 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 2H), 7.27 (t, *J* = 6.5 Hz, 1H), 3.29 – 3.15 (m, 8H), 2.05 (qt, *J* = 13.7, 7.1 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.9, 53.1, 51.0, 49.7, 43.9, 35.3. LC/MS (CI): *m/z* = 177 [M–HCl+H]$^+$. Anal. Cald. for $C_6H_{13}ClN_2O_2S$: C 33.88; H 6.16; N 13.17; S 15.07; Cl 16.67. Found: C 33.53; H 6.52; N 13.46; S 15.45; Cl 16.39.

2-Thia-3,8-diazaspiro[4.5]decane 2,2-dioxide hydrochloride (9h). Yield 780 mg (100%); colorless crystals; mp 241–244 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 2H), 7.27 (t, J = 6.9 Hz, 1H), 3.16 – 3.10 (m, 4H), 3.02 (d, J = 6.9 Hz, 2H), 2.96 (t, J = 11.0 Hz, 2H), 1.90 – 1.85 (m, 2H), 1.80 (dt, J = 11.9, 5.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.5, 52.5, 41.9, 40.6, 32.0. LC/MS (CI): m/z = 191 [M–HCl+H]$^+$. Anal. Calcd. for $C_7H_{15}ClN_2O_2S$: C 37.08; H 6.67; N 12.36; S 14.14; Cl 15.64. Found: C 37.10; H 6.96; N 12.66; S 14.26; Cl 15.83.

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References

[1] J. Drews, *Science* **2000**, *287*, 1960–1964.
[2] A. Scozzafava, T. Owa, A. Mastrolorenzo, C. Supuran, *Curr. Med. Chem.* **2005**, *10*, 925–953.
[3] J. E. Lesch, *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine*, Oxford University Press, **2019**.
[4] E. J. Corey, B. Czakó, L. Kürti, *Molecules and Medicine*, John Wiley & Sons, **2007**.
[5] A. S. De Miranda, W. Bispo, Y. K. C. Da Silva, Magna Suzana Alexandre-Moreira, R. De Paula Castro, J. R. Sabino, L. M. Lião, L. M. Lima, E. J. Barreiro, *Molecules* **2012**, *17*, 14126–14145.
[6] T. J. Carty, A. Marfat, P. F. Moore, F. C. Falkner, T. M. Twomey, A. Weissman, *Agents Actions* **1993**, *39*, 157–165.
[7] N. Swiderska, D. Hawcutt, V. Eaton, F. Stockton, R. Kumar, R. Kneen, R. Appleton, *Seizure* **2011**, *20*, 805–808.
[8] S. Hanessian, H. Sailes, E. Therrien, *Tetrahedron* **2003**, *59*, 7047–7056.
[9] O. O. Grygorenko, D. M. Volochnyuk, S. V. Ryabukhin, D. B. Judd, *Chem. – A Eur. J.* **2020**, *26*, 1196–1237.
[10] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
[11] M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan, *Chem. Biol. Drug Des.* **2014**, *83*, 450–461.
[12] S. Mondal, S. Debnath, *Synthesis* **2014**, *46*, 368–374.
[13] O. O. Grygorenko, A. V. Biitseva, S. Zhersh, *Tetrahedron* **2018**, *74*, 1355–1421.
[14] M. V. Popova, A. V. Dobrydnev, *Chem. Heterocycl. Compd.* **2017**, *53*, 492–494.
[15] S. Debnath, S. Mondal, *Eur. J. Org. Chem.* **2018**, *2018*, 933–956.
[16] V. A. Rassadin, D. S. Grosheva, A. A. Tomashevskii, V. V. Sokolov, *Chem. Heterocycl. Compd.* **2013**, *49*, 39–65.
[17] K. C. Majumdar, S. Mondal, *Chem. Rev.* **2011**, *111*, 7749–7773.
[18] T. B. Samarakoon, J. K. Loh, A. Rolfe, L. S. Le, S. Y. Yoon, G. H. Lushington, P. R. Hanson, *Org. Lett.* **2011**, *13*, 5148–5151.
[19] A. Zhou, P. R. Hanson, *Org. Lett.* **2008**, *10*, 2951–2954.
[20] M. Jiménez-Hopkins, P. R. Hanson, *Org. Lett.* **2008**, *10*, 2223–2226.
[21] S. A. Zhersh, O. P. Blahun, I. V. Sadkova, A. A. Tolmachev, Y. S. Moroz, P. K. Mykhailiuk, *Chem. Eur. J.* **2018**, *24*, 8343–8349.
[22] R. J. Cherney, R. Mo, D. T. Meyer, K. D. Hardman, R.-Q. Liu, M. B. Covington, M. Qian, Z. R. Wasserman, D. D. Christ, J. M. Trzaskos, R. C. Newton, C. P. Decicco, *J. Med. Chem.* **2004**, *47*, 2981–2983.
[23] D. Enders, A. Moll, J. W. Bats, *Eur. J. Org. Chem.* **2006**, 1271–1284.
[24] R. Di Fabio, Y. St-Denis, F. M. Sabbatini, D. Andreotti, R. Arban, G. Bernasconi, S. Braggio, F. E. Blaney, A. M. Capelli, E. Castiglioni, E. Di Modugno, D. Donati, E. Fazzolari, E. Ratti, A. Feriani, S. Contini, G. Gentile, D. Ghirlanda, S. Provera, C. Marchioro, K. L. Roberts, A. Mingardi, M. Mattioli, A. Nalin, F. Pavone, S. Spada, D. G. Trist, A. Worby, *J. Med. Chem.* **2008**, *51*, 7370–7379.
[25] J. X. Qiao, C. H. Chang, D. L. Cheney, P. E. Morin, G. Z. Wang, S. R. King, T. C. Wang, A. R. Rendina, J. M. Luettgen, R. M. Knabb, R. R. Wexler, P. Y. S. Lam, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4419–4427.
[26] A. W. M. Lee, W. H. Chan, L. S. Jiang, K. W. Poon, *Chem. Commun.* **1997**, 611–612.
[27] É. S. Lipina, R. I. Bodina, T. P. Efimova, T. A. Novikova, V. V. Perekalin, *Pharm. Chem. J.* **1999**, *33*, 598–600.
[28] K. Hanaya, S. Yoshioka, S. Ariyasu, S. Aoki, M. Shoji, T. Sugai, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 545–550.
[29] W. F. Erman, H. C. Kretschmar, *J. Org. Chem.* **1961**, *26*, 4841–4850.
[30] A. J. Preston, J. C. Gallucci, L. A. Paquette, *J. Org. Chem.* **2006**, *71*, 6573–6578.
[31] C. Valente, R. C. Guedes, R. Moreira, J. Iley, J. Gut, P. J. Rosenthal, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4115–4119.
[32] E. H. White, H. M. Lim, *J. Org. Chem.* **1987**, *52*, 2162–2166.
[33] S. Hirashima, T. Oka, K. Ikegashira, S. Noji, H. Yamanaka, Y. Hara, H. Goto, R. Mizojiri, Y. Niwa, T. Noguchi, I. Ando, S. Ikeda, H. Hashimoto, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3181–3186.
[34] H. Jin, M. Wright, R. Pastor, M. Mish, S. Metobo, S. Jabri, R. Lansdown, R. Cai, P. Pyun, M. Tsiang, X. Chen, C. U. Kim, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1388–1391.
[35] K. X. Chen, B. Vibulbhan, W. Yang, L. G. Nair, X. Tong, K. C. Cheng, F. G. Njoroge, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1105–1109.
[36] M. Inagaki, T. Tsuri, H. Jyoyama, T. Ono, K. Yamada, M. Kobayashi, Y. Hori, A. Arimura, K. Yasui, K. Ohno, S. Kakudo, K. Koizumi, R. Suzuki, M. Kato, S. Kawai, S. Matsumoto, *J. Med. Chem.* **2000**, *43*, 2040–2048.
[37] D. Freitag, P. Metz, *Tetrahedron* **2006**, *62*, 1799–1805.
[38] V. A. Rassadin, D. S. Grosheva, I. A. Arefeva, A. A. Tomashevskiy, V. V. Sokolov, A. De Meijere, *Eur. J. Org. Chem.* **2012**, 5028–5037.
[39] V. A. Rassadin, A. A. Tomashevskii, V. V. Sokolov, A. A. Potekhin, *Chem. Heterocycl. Compd.* **2008**, *44*, 474–485.
[40] N. Lad, R. Sharma, V. E. Marquez, M. Mascarenhas, *Tetrahedron Lett.* **2013**, *54*, 6307–6309.
[41] E. Cleator, F. J. Sheen, M. M. Bio, K. M. Jos Brands, A. J. Davies, U. H. Dolling, *Tetrahedron Lett.* **2006**, *47*, 4245–4248.
[42] G. F. Cooper, *Synthesis* **1991**, *1991*, 859–860.
[43] N. Lad, R. Sharma, V. E. Marquez, M. Mascarenhas, *ChemInform* **2014**, *45*, no-no.
[44] S. M. Leit, L. A. Paquette, *J. Org. Chem.* **1999**, *64*, 9225–9229.
[45] D. Zhong, D. Wu, Y. Zhang, Z. Lu, M. Usman, W. Liu, X. Lu, W. B. Liu, *Org. Lett.* **2019**, *21*, 5808–5812.
[46] M. V. Popova, A. V. Dobrydnev, V. V. Dyakonenko, I. S. Konovalova, S. V. Shishkina, Y. M. Volovenko, *Tetrahedron* **2019**, *75*, 1231–1245.
[47] A. V. Dobrydnev, B. V. Vashchenko, I. S. Konovalova, K. O. Bisikalo, Y. M. Volovenko, *Monatsh. Chem.* **2018**, *149*, 1827–1833.
[48] M. S. Dyachenko, A. V. Dobrydnev, Y. M. Volovenko, *Mol. Divers.* **2018**, *22*, 919–927.
[49] A. V. Dobrydnev, B. V. Vashchenko, Y. M. Volovenko, *Tetrahedron Lett.* **2018**, *59*, 1581–1582.
[50] M. V. Popova, A. V. Dobrydnev, M. S. Dyachenko, C. Duhayon, D. Listunov, Y. M. Volovenko, *Monatsh. Chem.* **2017**, *148*, 939–946.
[51] E. Goethals, *Bull. des Sociétés Chim. Belges* **1963**, *72*, 750–760.
[52] W. R. S. Barton, L. A. Paquette, *Can. J. Chem.* **2004**, *82*, 113–119.
[53] M. Zajac, R. Peters, *Chem. Eur. J.* **2009**, *15*, 8204–8222.
[54] M. Zajac, R. Peters, *Org. Lett.* **2007**, *9*, 2007–2010.
[55] T. Iwama, A. Takagi, T. Kataoka, *Chem. Pharm. Bull.* **1998**, *46*, 757–766.
[56] C. Baldoli, P. Del Buttero, D. Perdicchia, T. Pilati, *Tetrahedron* **1999**, *55*, 14089–14096.
[57] M. E. Thompson, *J. Org. Chem.* **1984**, *49*, 1700–1703.
[58] H.-H. Otto, P. Schwenkkraus, *Tetrahedron Lett.* **1982**, *23*, 5389–5390.
[59] A. Meinzer, A. Breckel, B. A. Thaher, N. Manicone, H. H. Otto, *Helv. Chim. Acta* **2004**, *87*, 90–105.
[60] P. Schwenkkraus, S. Merkle, H. H. Otto, *Liebigs Ann.* **1997**, 1261–1266.
[61] P. Schwenkkraus, H. -H Otto, *Liebigs Ann. der Chemie* **1994**, *1994*, 251–257.
[62] P. Schwenkkraus, H. -H Otto, *Arch. Pharm.* **1993**, *326*, 519–523.
[63] D. Enders, S. Wallert, *Tetrahedron Lett.* **2002**, *43*, 5109–5111.
[64] D. Enders, S. Wallert, J. Runsink, *Synthesis* **2003**, 1856–1868.
[65] D. Enders, A. Moll, A. Schaadt, G. Raabe, J. Runsink, *Eur. J. Org. Chem.* **2003**, 3923–3938.
[66] D. Enders, A. Moll, *Synthesis* **2005**, 1807–1816.
[67] O. O. Grygorenko, P. Babenko, D. M. Volochnyuk, O. Raievskyi, I. V. Komarov, *RSC Adv.* **2016**, *6*, 17595–17605.

[68] O. O. O. Grygorenko, D. Demenko, D. M. Volochnyuk, I. V. Komarov, *New J. Chem.* **2018**, *42*, 8355–8365.
[69] V. V. Semeno, V. O. Vasylchenko, B. V. Vashchenko, D. O. Lutsenko, R. T. Iminov, O. B. Volovenko, O. O. Grygorenko, *J. Org. Chem.* **2020**, *85*, 2321–2337.
[70] Y. M. Sokolenko, Y. Y. Yurov, B. V. Vashchenko, O. V. Hryshchuk, Y. Filimonova, E. N. Ostapchuk, A. Artemenko, O. V. Zaremba, O. O. Grygorenko, *J. Org. Chem.* **2019**, *84*, 13908–13921.
[71] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.
[72] H. Tu, J. P. Powers, J. Liu, S. Ursu, A. Sudom, X. Yan, H. Xu, D. Meininger, M. DeGraffenreid, X. He, J. C. Jaen, D. Sun, M. Labelle, H. Yamamoto, B. Shan, N. P. C. Walker, Z. Wang, *Bioorg. Med. Chem.* **2008**, *16*, 8922–8931.
[73] Y. Rew, D. L. McMinn, Z. Wang, X. He, R. W. Hungate, J. C. Jaen, A. Sudom, D. Sun, H. Tu, S. Ursu, E. Villemure, N. P. C. Walker, X. Yan, Q. Ye, J. P. Powers, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1797–1801.
[74] Y. Kuroda, S. Harada, A. Oonishi, H. Kiyama, Y. Yamaoka, K. I. Yamada, K. Takasu, *Angew. Chem. Int. Ed.* **2016**, *55*, 13137–13141.
[75] H.-J. Liu, H. Wynn, *Tetrahedron Lett.* **1982**, *23*, 3151–3154.

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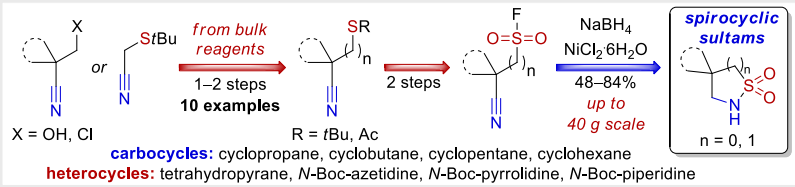

Multigram synthesis of spirocyclic γ- and β-sultams – advanced building blocks for organic synthesis and drug discovery – *via* one-pot reductive cyclization of cyclic cyano sulfonyl fluorides is developed.

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Spirocyclic sultams

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Synthesis of spirocyclic β- and γ-sultams by one-pot reductive cyclization of cyanoalkylsulfonyl fluorides