Synthesis of ω-Aminodithioesters

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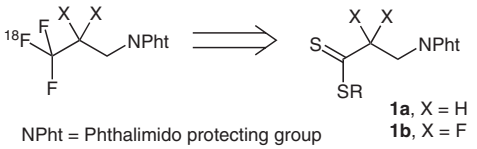
Abstract: ω-Aminodithioester derivatives were obtained from thionolactams by reaction with an alkyl triflate followed by thiolysis with hydrogen sulfide. The presence of an electron-withdrawing group was required on the N1 position (*p*-nitrophenyl or benzoyl) to favor the ring opening of γ-, δ- and ε-thionolactams. In the case of β-thionolactam, activation was provided by a CF_2 motif in C3 position

Key words: dithioesters, thionolactams, thioamidinium salts, thio-Pinner reaction



Scheme 1

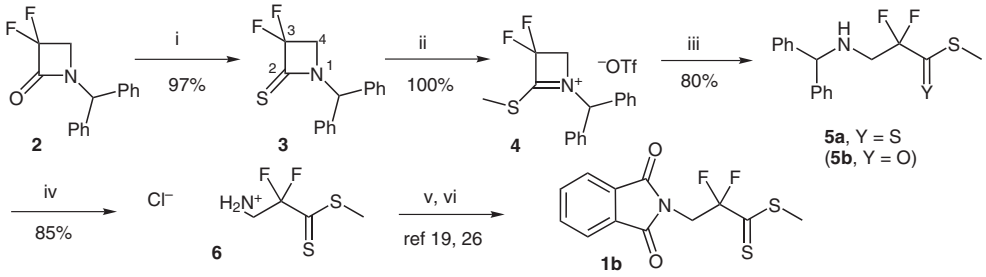
Dithioesters have attracted considerable attention in recent years as versatile tools for organic synthesis.[1–5] Methods of dithioester preparation have been known for a long time.[6] Generally, organometallic compounds or carbanions are treated with carbon disulfide followed by addition of an alkyl halide,[7–9] or reacted with aryl trithiocarbonates,[10] or alkyl dithiocarbonyl chlorides.[11] Another general approach was based on a Pinner-like reaction:[8] thiolysis with hydrogen sulfide of in situ-generated thiolimidoesters produced dithioesters.[12–17]

In the course of a program dedicated to the ^{18}F-radiolabeling of perfluorinated amine derivatives (to be incorporated in nitroimidazolic markers of hypoxia), we became interested in dithioester compounds **1a**,**b** (Scheme 1) as precursors of $[^{18}F]CF_3$ and $[^{18}F]C_2F_5$ motifs by an oxidative fluorodesulfurization reaction using 1,3-dibromo-5,5-dimethylhydantoin (DBH) and $[^{18}F]HF$·pyridine.[18,19]

We had already prepared **1a** (X = H; R = Et);[20] the key step for the dithioester formation was the nucleophilic substitution of a thioacyl-*N*-phthalimide intermediate[21] with ethanethiol. The same strategy could be applied for the synthesis of **1b**, but with lower yields.[19] In fact, the preparation of α-perfluorinated dithioesters was scarcely described in the previous literature and required particular methods.[22–25]

Just having in hand a practical synthesis of 3,3-difluoro-1-benzhydrylazetidin-2-one (**2**),[26,27] we decided to examine the possibility of using the corresponding azetidin-2-thione **3** as precursor of **1b**. Our plan was to transform the β-thionolactam into 2-thioalkyl-azetidinium salt **4** by selective S-alkylation; the subsequent thiolysis with hydrogen sulfide should create the dithioester function by nucleophilic addition on the C2 position followed by C2–N1 ring opening.

The precursor **3** was readily obtained by treatment of azetidinone **2** with Lawesson's reagent (Scheme 2). Reaction of **3** with methyl triflate quantitatively furnished the salt **4**, within 30 minutes at room temperature, in dichloromethane solution (control by ^1H NMR). Then a stream of hydrogen sulfide was bubbled into the solution of **4**; the dithioester **5a** was formed in about 80% yield, the side-product being the thiolester **5b** due to some competitive hydrolysis. After chromatographic purification, com-



Scheme 2 *Reagents and conditions*: (i) Lawesson's reagent, THF, reflux, 3 h; (ii) MeOTf, CH_2Cl_2, 20 °C, 30 min.; (iii) H_2S/DMF, 15 min; (iv) a) DDQ, toluene, 1 h; b) 0.1 N HCl, 15 min; (v) PYBOP, 2-carboxymethyl benzoic acid; (vi) cat. *p*-TsOH.

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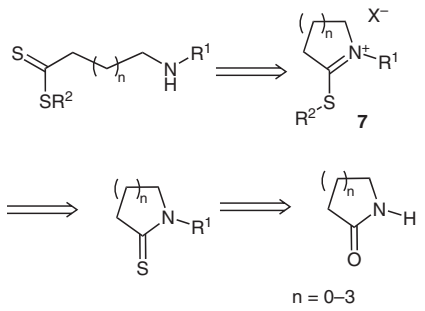
pound **5a** was N-deprotected by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by acidic hydrolysis of the resulting benzophenoneimine.[28] Methyl 3-amino-2,2-difluoropropanedithioate (**6**) was isolated in 85% yield as the hydrochloride salt and fully characterized (see experimental). The phthalimido derivative **1b** was prepared in two steps as usual.[19,26]

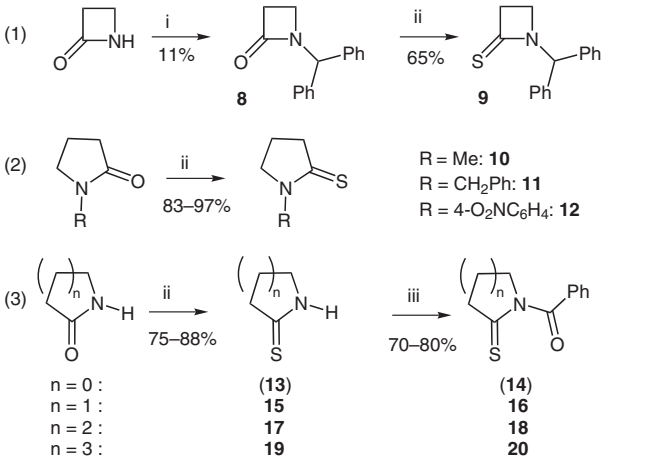
Our synthesis of β-aminodithioester **6** represents the first application of the Pinner reaction with hydrogen sulfide to a β-thionolactam precursor. The recent interest of polymer chemists in functional dithioesters[29,30] for their ability to control RAFT[31,32] (Reversible Addition–Fragmentation chain Transfer) radical polymerization, prompted us to explore further the scope of thionolactams as precursors of ω-aminodithioesters via the intermediate salts **7** (Scheme 3).



Scheme 3

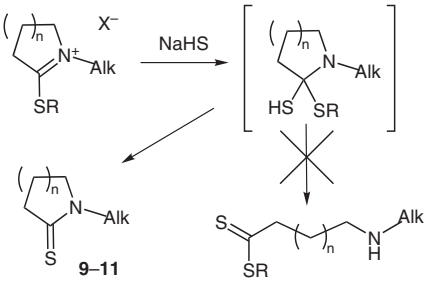
The tested thionolactams were prepared according to Scheme 4. The commercially available β-lactam was N-alkylated with benzhydryl bromide and reacted with Lawesson's reagent to furnish 1-benzhydrylazetidin-2-thione (**9**) (Equation 1 in Scheme 4). The commercially available *N*-alkyl and *N*-aryl pyrrolidin-2-ones (γ-lactams) could be directly transformed into pyrrolidin-2-thiones **10**–**12** with Lawesson's reagent (Equation 2 in Scheme 4). For the preparation of 1-benzoyl thionolactams, the corresponding β- to ε-lactams were first treated with Lawesson's reagent (**13**, **15**, **17**, **19**), then N-acylated with benzoyl chloride (Equation 3 in Scheme 4); the γ-, δ- and ε-thionolactams (**16**, **18**, **20**) were recovered in good yields but not the β-thionolactam **14** due to extensive polymerization during the thionation step.

We started the study with the *N*-benzhydryl β-thionolactam **9**, and tried to apply the protocol successfully developed for the corresponding bisfluorinated precursor **3**. The 2-thiomethylazetidinium salt (Scheme 5; R = Me, n = 0, X = OTf) could be obtained by treatment with methyl triflate [^{1}H NMR: δ = 2.79 ppm (CH_3S)], but this salt was unreactive towards hydrogen sulfide, even in polar solvents. With the more nucleophilic sodium hydrosulfide (NaHS), reaction occurred but the tetrahedral intermediate decomposed with expulsion of methylthiolate instead of C2–N1 ring cleavage. Thus β-thionolactam **9** was recovered (Table 1, entry 2). The same disappointing results were observed in the case of *N*-methyl and *N*-benzyl



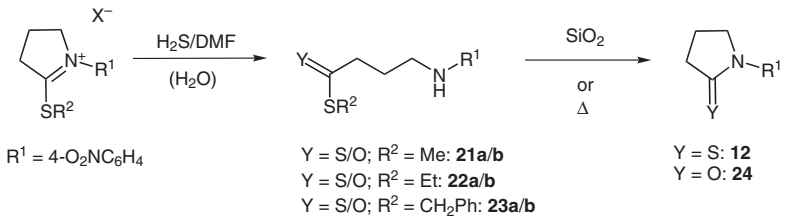
Scheme 4 *Reagents and conditions*: (i) KOH, Ph_2CHBr, benzene (see note); (ii) Lawesson's reagent, THF, reflux; (iii) Benzoyl chloride, pyridine, CH_2Cl_2.

γ-thionolactams **10** and **11**, irrespective of the alkylating agent used (methyl or ethyl triflate, benzyl bromide, benzhydryl bromide; Table 1, entries 3–7). The formation of the intermediate salts was proven by ^{1}H and/or ^{13}C NMR analysis of the crude reaction mixtures. Treatment with hydrogen sulfide in pyridine or with NaHS gave **10** and **11** again (Scheme 5).



Scheme 5

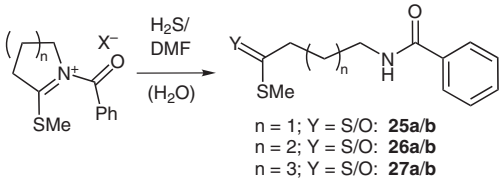
At this stage, we speculated that an electron-withdrawing group on the N1 position should enhance the ability of the C2–N1 bond to cleave during the decomposition of the tetrahedral intermediate. This was first verified with the *N*-*p*-nitrophenyl precursor **12** (Table 1, entry 8; Scheme 6). S-Methylation was performed with methyl triflate in dichloromethane, followed by thiolysis with hydrogen sulfide in DMF during 15 minutes. After work-up, three products were identified: the γ-aminodithioester **21a** (major product), the γ-aminothiolester **21b** (minor product) and the γ-lactam **24** (very minor product). By carefully controlling the experimental conditions (to avoid moisture), we could determine that the side compounds **21b** and **24** arose from competitive hydrolysis. Moreover, **21b** was the precursor of **24** (intramolecular cyclization by standing at temperature 25 °C). During the chromatographic purification of **21a** on silica gel column, we observed extensive cyclization of **21b** into **24** and partial cyclization of **21a** into the starting material **12**.



Scheme 6

However, a pure sample of **21a** was obtained, without chromatography, by taking extra care to avoid moisture during the thiolysis (< 5% of **21b** were present, as determined by ^{1}H NMR). The dithioester **22a** (R^2 = Et; Table 1, entry 9 and Scheme 6) was similarly prepared by using ethyl triflate as alkylating agent, and with the same problems due to the occurrence of side-products **22b**, **24**, and **12**. The synthesis of the benzyl dithioester **23a** made use of benzyl bromide and silver triflate for the alkylation step (R^2 = CH_2Ph; Table 1, entry 10 and Scheme 6), the protocol for thiolysis being identical to **21a** and **22a**. Unfortunately, although **23a** was identified by ^{13}C NMR and mass spectrometry of the crude reaction mixture, we were not able to isolate an analytical sample.

With these examples, we proved the validity of the strategy outlined in Scheme 3, but the method was handicapped by the recyclization of the target compounds into starting materials under purification conditions. Accordingly, we considered further the *N*-benzoyl motif as activating group for the thiolysis step and protecting group for masking the amine nucleophilicity. Thus *N*-benzoyl-γ-thionolactam (**16**) was treated with methyl triflate and then with hydrogen sulfide in DMF to furnish the γ-aminodithioester **25a** as main product; this was stable and did not cyclize under purification conditions (Table 1, entry 11 and Scheme 7). The same protocol allowed us to obtain δ- and ε-aminodithioesters **26a** and **27a** from the corresponding *N*-benzoylthionolactams **18** and **20** (Table 1, entries 12 and 13, Scheme 7). We tried to apply the benzyl bromide/silver triflate strategy to **16** (in situ formation of benzyl triflate), but we only recovered γ-thionolactam **15**. N-Deprotection most probably occurred through Lewis acid catalysis by the silver salt.



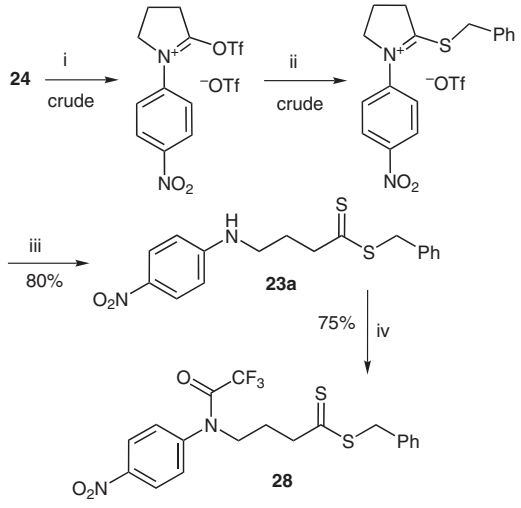
Scheme 7

Table 1 Reactions of Thionolactams

Entry	Starting material	Intermediate salt			Products with H_2S (or NaHS)
		R^1	R^2	X	
1	**3**	$CHPh_2$	Me	OTf	**5a** + **5b** (80:20) (Scheme 2)
2	**9**	$CHPh_2$	Me	OTf	No reaction (or **9**) (Scheme 5)
3	**10**	Me	Et	OTf	No reaction (or **10**) (Scheme 5)
4	**10**	Me	CH_2Ph	Br	No reaction (or **10**) (Scheme 5)
5	**10**	Me	$CHPh_2$	Br	No reaction (or **10**) (Scheme 5)
6	**11**	CH_2Ph	Me	OTf	No reaction (or **11**) (Scheme 5)
7	**11**	CH_2Ph	CH_2Ph	Br	No reaction (or **11**) (Scheme 5)
8	**12**	4-$O_2NC_6H_4$	Me	OTf	**21a** + **21b** (95:5) (Scheme 6)
9	**12**	4-$O_2NC_6H_4$	Et	OTf	**22a** + **22b** (95:5) (Scheme 6)
10	**12**	4-$O_2NC_6H_4$	CH_2Ph	OTf	**23a** + **23b** + **24** (25:25:50) (Scheme 6)
11	**16**	COPh	Me	OTf	**25a** + **25b** (80:20) (Scheme 7)
12	**18**	COPh	Me	OTf	**26a** + **26b** (80:20) (Scheme 7)
13	**20**	COPh	Me	OTf	**27a** + **27b**(80:20) (Scheme 7)

Finally, we found that the in situ production of benzyl triflate could be bypassed and that the *S*-benzyl iminium intermediate was also accessible from the lactam precursor treated with triflic anhydride followed by benzyl thiol. This alternative protocol has been illustrated with the preparation of benzyl-4-(*p*-nitrophenyl)aminobutanedithioate (**23a**) in 80% yield from **24** (Scheme 8). We also found that compound **23a** could be protected against intramolecular cyclization by direct treatment with trifluoroacetic anhydride to yield the trifluoroacetamide **28**.

In conclusion, we have disclosed a novel and practical route for preparing ω-amino dithioesters, protected as *N*-benzoyl or *N*-*p*-nitrophenyl and trifluoroacetyl derivatives, starting from γ-, δ-, and ε-lactams. The key intermediate was a *S*-alkyl thioamidinium triflate, which suffers thiolysis with ring opening. β-Lactam could not be used in this strategy because the starting material (**14**, see Scheme 4) was not readily available. On the other hand, α,α′-difluoro-β-thionolactam (**3**) represents a particular case where ring opening did not require the presence of a N1-electronwithdrawing group.



Scheme 8 *Reagents and conditions*: (i) Tf_2O, 30 min; (ii) benzylthiol, 2,6-di-*tert*-butylpyridine, 30 min; (iii) H_2S/DMF, 15 min; (iv) Et_3N, $(CF_3CO)_2O$, 2 h.

The novel compounds prepared in this article were characterized by the usual spectroscopies, but ^{13}C NMR was the most indicative method. The C=X chemical shifts of thionolactams, dithioesters and thiolesters are 202–209 ppm (NC=S), 236–240 ppm (SC=S) and 198–200 ppm (SC=O), respectively, for the non-fluorinated compounds. The presence of a CF_2 motif in α position provokes a shielding effect: 192 ppm (NC=S of **3**), 225 ppm (SC=S of **5a**) and 193 ppm (OC=S of **5b**)

Melting points were determined with an electrothermal microscope and are uncorrected. IR spectra were taken with a Bio-Rad FTS 135 instrument and were calibrated with polystyrene. The ^1H and ^{19}F NMR spectra were recorded on a Varian Gemini 300 spectrometer (300 MHz for ^1H, and 282 MHz for ^{19}F). ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer at 125 MHz and on a Bruker AC 250 spectrometer at 75 MHz. References for the NMR spectra were $CDCl_3$ for ^1H and ^{13}C NMR and $CFCl_3$ for ^{19}F NMR. Multiplicities are indicated as follows: (br) s: (broad) singlet; d: doublet; t: triplet; q: quadruplet; qt: quintuplet; m: multiplet; dt: doubled triplet. NMR attributions were made at 125 MHz by using correlations spectroscopies (COSY, HMBC). Mass spectra were obtained on a Finnigan-MAT TSQ-70 instrument at 70 eV (chemical ionization mode). Microanalyses were performed at the Christopher Ingold Laboratories, University College, London, UK. HRMS were recorded at the University of Mons, Belgium (Prof. R. Flammang). TLC analyses were carried out on silica gel 60 plates F254 (Merck, 0.1 mm thickness); visualization was effected with UV light and/or iodine. Column chromatography (under medium pressure) was carried out with Merck silica gel 60 of 230–240 mesh ASTM.

Synthesis of Thionolactams from Lactams; General Procedure

Lawesson's reagent (1.2 equiv) was added to a THF solution (5 mL/mmol) of the amide (1 equiv). The stirred mixture was then brought to reflux overnight (unless specified below). After evaporation of the solvent under vacuum, the resulting oil was submitted to column chromatography.

1-Benzhydryl-3,3-difluoroazetidin-2-thione (3)

β-Thionolactam **3** was obtained from azetidinone **2** (1.8 g, 6.6 mmol, 1 equiv) after 3 h of reflux, according to the general procedure. Column chromatography (SiO_2; hexane–EtOAc, 7:3; R_f = 0.95) afforded **3** (1.9 g; 97% yield) as a pale yellow solid. Analytical sample was obtained by recrystallization from *i*-PrOH; mp 76–78 °C.

IR (NaCl): 1593, 1273, 1198 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.16–7.41 (m, 10 H_{arom}), 6.73 (s, 1 H, Ph_2CH), 4.11 (t, $^3J_{HF}$ = 6.3 Hz, 2 H, CH_2CF_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4 (t, $^2J_{CF}$ = 31 Hz, C=S), 136.0, 129.3, 128.8, 128.2, 112.3 (t, $^1J_{CF}$ = 282 Hz, CF_2), 61.4 ($CHPh_2$), 61.2 (t, $^2J_{CF}$ = 31 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.53 (t, $^2J_{CF}$ = 31 Hz).

MS (CI^+, CH_4N_2O): *m*/*z* (%) = 292.1 (1) $[M + 2 + H]^+$, 290.0 (20) $[M + H]^+$, 167.0 (100) $[CHPh_2 + H^+]$.

HRMS: *m*/*z* calcd for $C_{16}H_{13}NSF_2$: 289.07364; found: 289.07368

Anal. Calcd for $C_{16}H_{13}NSF_2$: C, 66.42; H, 4.53; N, 4.84. Found: C, 66.43; H, 4.50; N, 4.84.

1-Benzhydrylazetidin-2-thione (9)

To a stirred solution of azetidin-2-one (200 mg, 2.8 mmol, 1 equiv) in benzene (25 mL; **caution: see note**) were successively added at r.t., benzhydryl bromide (1.25 g, 4.6 mmol, 2 equiv), powdered KOH (190 mg, 3.4 mmol, 1.2 equiv), and 18-crown-6 (897 mg, 3.4 mmol, 1.2 equiv). After 4 h of stirring, the reaction mixture was filtered and the solvent was evaporated under vacuum. After column chromatography (hexane–EtOAc, 8:2; R_f = 0.85), **8** (60 mg, 0.3 mmol; 11% yield) was recovered as a white solid.

IR (NaCl): 1738 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 10 H_{arom}), 6.16 (s, 1 H, Ph_2CH), 3.16 (t, ^3J = 4 Hz, 2 H), 2.91 (t, ^3J = 4 Hz, 2 H).

N-Benzhydrylazetidinone (**8**; 120 mg, 0.5 mmol, 1 equiv) was treated according to the general procedure. Column chromatography (SiO_2; hexane–EtOAc, 7:3, R_f = 0.85) afforded **9** (82 mg; 65% yield) as a pale yellow solid.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.38 (m, 10 H_{arom}), 6.66 (s, 1 H, Ph_2CH), 3.75 (t, ^3J = 3.6 Hz, 2 H, CH_2N), 3.06 (t, ^3J = 3.6 Hz, 2 H, CH_2C=S).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.7 (C=S), 133.4, 130.0, 128.9, 128.4, 61.3 (*C*HPh$_2$), 46.8 (CN), 39.5 (*C*C=S).

MS (CI$^+$, CH_4N_2O): *m*/*z* (%) = 255 (4) [M + 2 + H]$^+$, 253 (30) [M + H]$^+$, 167.0 (100) [CHPh$_2$ + H$^+$].

_N_-Methyl Pyrrolidin-2-thione (10)[33]

Compound **10** was obtained from *N*-methyl pyrrolidin-2-one (1 g, 11 mmol) according to the general procedure. Column chromatography (SiO_2; hexane–EtOAc, 5:5; R_f = 0.5) afforded **10** (1.06 g; 84% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (t, ^3J = 8 Hz, 2 H, CH_2N), 3.27 (s, 3 H, NCH_3), 3.05 (t, ^3J = 8 Hz, 2 H, CH_2C=S), 2.08 (qt, ^3J = 8 Hz, 2 H, CCH_2C).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.1 (C=S), 59.6 (NCH_3), 56.9 (CH_2N), 44.5 (*C*C=S), 19.3 (C*C*C).

MS (CI$^+$, CH_4N_2O): *m*/*z* (%) = 255 (4) [M + 2 + H]$^+$, 253 (30) [M + H]$^+$, 167.0 (100) [CHPh$_2$ + H$^+$].

_N_-Benzyl Pyrrolidin-2-thione (11)[34]

Compound **11** was obtained from *N*-benzyl pyrrolidin-2-one (1 g, 6 mmol) according to the general procedure. Column chromatography (SiO_2; hexane–EtOAc, 7:3; R_f = 0.65) afforded **11** (910 mg; 83% yield) as a pale yellow oil.

IR (NaCl): 1509, 1265 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.34 (m, 5 H$_{arom}$), 4.99 (s, 2 H, CH_2Ph), 3.59 (t, ^3J = 7.4 Hz, 2 H, CH_2N), 3.11 (t, ^3J = 7.4 Hz, 2 H, CH_2N), 2.02 (qt, ^3J = 7.4 Hz, 2 H, CCH_2C).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.9 (C=S), 135.3, 129.0, 128.5, 128.2, 54.2, 51.7, 45.1, 19.6.

MS (CI$^+$, CH_4N_2O): *m*/*z* (%) = 194.0 (5) [M + 2 + H]$^+$, 192.0 (100) [M + H]$^+$, 90.9 (100) [CH_2Ph^+].

1-(4-Nitrophenyl)pyrrolidin-2-thione (12)[35]

Compound **12** was obtained from 1-(4′-nitrophenyl)pyrrolidine-2-one (2 g, 10 mmol) after 24 h of reflux, according to the general procedure. Column chromatography (SiO_2; hexane–EtOAc, 7:3; R_f = 0.2) afforded **12** (2.09 g; 97% yield) as a yellow powder. Recrystallization from *i*-PrOH produced yellow needles for elemental analysis; mp 148–150 °C.

IR (NaCl): 1597, 1266, 1145 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30–8.32 (m, 2 H$_{arom}$, $CHCNO_2$), 7.88–7.90 (m, 2 H$_{arom}$, CHCN), 4.21 (t, $^3J_{CH}$ = 7.3 Hz, 2 H, CH_2N), 3.26 (t, $^3J_{CH}$ = 7.8 Hz, 2 H, CH_2C=S), 2.28 (qt, $^3J_{CH}$ = 7.8 Hz, 2 H, CCH_2C).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.5 (C=S), 145.9 (CHN), 145.8 (CHN), 124.9 (*C*HCN), 124.6 (*C*HCNO_2), 58.0 (CH_2N), 47.0 (CH_2C=S), 20.9 (C*C*H$_2$C).

MS (APCI$^+$): *m*/*z* (%) = 225.7 (4) [M + 2 + H]$^+$, 223.7 (100) [M + H]$^+$.

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60; S, 14.43. Found: C, 53.69; H, 4.50; N, 12.42; S, 14.59.

Pyrrolidin-2-thione (15)[36]

Compound **15** was obtained from pyrrolidin-2-one (5 g, 58 mmol) according to the general procedure. After column chromatography (SiO_2; hexane–EtOAc, 4:6; R_f = 0.4) **15** (4.5 g; 77% yield) was obtained as a white powder. Recrystallization from *i*-PrOH produced analytically pure white needles; mp 120–122 °C.

IR (NaCl): 3158 1540, 1294, 1115 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (br s, 1 H, NH), 3.67 (t, ^3J = 7.2 Hz, 2 H, CH_2N), 2.92 (t, ^3J = 7.2 Hz, 2 H, CH_2C=S), 2.26 (qt, ^3J = 7.2 Hz, 2 H, CCH_2C).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6 (C=S), 49.9 (CN), 43.6 (*C*C=S), 23.0 (C*C*C).

MS (CI$^+$, CH_4N_2O): *m*/*z* (%) = 103.99 (4) [M + 2 + H]$^+$, 101.99 (100) [M + H]$^+$.

Anal. Calcd for C_4H_7NS: C, 47.49; H, 6.97; N, 13.84; S, 31.69. Found: C, 47.87; H, 7.15; N, 13.87; S, 31.81.

Piperidin-2-thione (δ-Thiovalerolactam) (17)[34]

Compound **17** was obtained from piperidin-2-one (2 g, 20 mmol) according to the general procedure. Column chromatography (SiO_2; hexane–EtOAc, 5:5; R_f = 0.45) afforded **17** (4.5 g; 75% yield) as a white powder. Recrystallization from *i*-PrOH produced analytically pure white needles; mp 110–113 °C.

IR (NaCl): 3186, 1561, 1261, 1111 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.90 (br s, 1 H, NH), 3.35 (dt, $^3J_{HCH}$ = 6.2 Hz, 2 H, CH_2N), 2.89 (t, ^3J = 6.3 Hz, 2 H, CH_2C=S), 1.79–1.84 (m, 2 H, $NCCH_2C$), 1.74–1.77 (m, 2 H, CCH_2CC=S).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.9 (C=S), 44.9 (CN), 39.2 (*C*C=S), 20.9 (*C*CN), 20.3 (*C*CC=S).

MS (CI$^+$, CH_4N_2O): *m*/*z* (%) = 117.9 (4) [M + 2 + H]$^+$, 116.1 (100) [M + H]$^+$.

Anal. Calcd for C_5H_9NS: C, 52.13; H, 7.87; N, 12.16. Found: C, 51.96; H, 7.91; N, 11.96.

Azepan-2-thione (ε-Thiocaprolactam) (19)[37]

Compound **19** was obtained from ε-caprolactam (2.5 g, 22 mmol) according to the general procedure. Column chromatography (SiO_2; hexane–EtOAc, 5:5; R_f = 0.45) afforded **19** (2.32 g; 88% yield) as a white powder. Recrystallization from *i*-PrOH produced analytically pure white needles; mp 113–115 °C.

IR (NaCl): 3185, 1563, 1262, 1116 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50 (br s, 1 H, NH), 3.37–3.42 (m, 2 H, CH_2N), 2.99–3.27 (m, 2 H, CH_2C=S), 1.66–1.81 (m, 2 H, $NCCH_2C$), 1.74–1.77 (m, 6 H, $CCH_2CH_2CH_2C$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.4 (C=S), 47.2 (CN), 44.95 (*C*C=S), 30.4 (*C*CN), 28.1 (*C*CC=S), 24.5 (CC*C*CC).

MS (CI$^+$, CH_4N_2O): *m*/*z* (%) = 131 (4) [M + 2]$^+$, 129 (100) [M]$^+$.

HRMS (EI): *m*/*z* calcd for $C_6H_{11}NS$: 129.06083; found: 129.06122.

Anal. Calcd for $C_6H_{11}NS$: C, 55.77; H, 8.58; N, 10.84. Found: C, 55.76; H, 8.69; N, 10.72.

Synthesis of _N_-Benzoylthionolactams; General Procedure

To a CH_2Cl_2 solution (3 mL/mmol) of the NH-thionolactam (1 equiv) were successively added benzoyl chloride (1.1 equiv) and pyridine (1.1 equiv). The mixture was stirred at r.t. overnight. The reaction mixture was then washed with 0.1 N HCl solution (3 × 30 mL). The organic phase was dried over $MgSO_4$. After evaporation, the residue was submitted to column chromatography on silica gel.

_N_-Benzoylpyrrolidin-2-thione (16)

Compound **16** was obtained from thionolactam **15** (1 g, 10 mmol) according to the general procedure. After chromatography (cyclohexane–EtOAc, 7:3; R_f = 0.7), **16** was recovered as an orange oil (1.43 g; 70% yield).

IR (NaCl): 1711, 1599, 1191 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.72 (m, 5 H$_{arom}$), 4.19 (t, ^3J = 7.1 Hz, 2 H, CH_2N), 3.15 (t, ^3J = 7.7 Hz, 2 H, CH_2C=S), 2.23 (qt, ^3J = 7.5 Hz, 2 H, CCH_2C).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.8 (C=S), 172.7 (Ph*C*=O), 133.9, 132.8, 129.5, 128.5, 54.2 (CN), 48.4 (*C*C=S), 27.1 (*C*CN), 20.9 (*C*CC=S).

MS (CI$^+$, CH_4N_2O): *m/z* (%) = 208.0 (4) [M + 2 + H]$^+$, 206.0 (100) [M + H]$^+$, 105.1 [PhCO]$^+$.

HRMS (EI$^+$): *m/z* calcd for $C_{11}H_{11}NOS$: 205.0561; found: 205.0563.

N-Benzoylpiperidin-2-thione (18)

Compound **18** was obtained from thionolactam **17** (0.9 g, 8 mmol) according to the general procedure. After chromatography (hexane–EtOAc, 6:4; R_f = 0.6), **18** was recovered as an orange oil (1.22 g; 70% yield).

IR (NaCl): 1715, 1597, 1241, 1152 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.86 (m, 5 H_{arom}), 3.72 (t, ^3J = 6.3 Hz, 2 H, CH_2N), 3.06 (t, ^3J = 6.3 Hz, 2 H, CH_2C=S), 2.04–2.12 (m, 2 H, $NCCH_2C$), 1.91–1.99 (m, 2 H, CCH_2CC=S).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2 (C=S), 175.4 (Ph*C*=O), 133.7, 132.2, 129.7, 129.2, 49.05 (CN), 42.4 (*C*C=S), 21.9 (*C*CN), 21.1 (*C*CC=S).

MS (APCI$^+$): *m/z* (%) = 222.1 (5) [M + 2 + H]$^+$, 220.1 (100) [M + H]$^+$, 105.1 (6) [PhCO]$^+$.

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; S, 14.62. Found: C, 66.09; H, 6.50; N, 5.96; S, 14.29.

N-Benzoylazepan-2-thione (20)

Compound **20** was obtained from thionocaprolactam **19** (0.95 g, 7.4 mmol) according to the general procedure. After chromatography (hexane–EtOAc, 6:4; R_f = 0.6), **20** was recovered as a yellow powder (1.38 g; 80% yield); mp 87–88 °C.

IR (NaCl): 1709, 1597, 1258, 1192 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.89 (m, 5 H_{arom}), 3.9 (m, 2 H, CH_2N), 3.23 (m, 2 H, CH_2C=S), 1.91 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.4 (C=S), 175.9 (C=O), 133.4, 132.8, 129.7, 129.1, 51.85 (CN), 48.4 (*C*C=S), 29.9 (*C*CN), 28.2 (*C*CC=S), 25.3 (CC*C*CC).

MS (IC$^+$, CH_4N_2O): *m/z* (%) = 236.1 (6) [M + 2 + H]$^+$, 234.1 (100) [M + H]$^+$.

HRMS (EI$^+$): *m/z* calcd for $C_{13}H_{15}NOS$: 233.0874; found: 233.0869.

Synthesis of Dithioesters from Thionolactams; General Procedure

To a solution of thionolactam (1 equiv, in flame-dried glassware, under Ar) in anhyd CH_2Cl_2 (3 mL/mmol), was added methyl (or ethyl) triflate (2 equiv) at r.t. The mixture was stirred for 15–30 min (see particular cases below). Afterwards a H_2S-sat. anhyd DMF solution was added (5 mL/mmol). Care should be taken to avoid moisture. After 15 min or more (see particular cases below), the mixture was diluted with Et_2O (20 mL) and washed 3–4 times with brine. The Et_2O phase was dried ($MgSO_4$) and evaporated under vacuum. The crude product could be purified by column chromatography if necessary (see below).

Methyl 3-(Benzhydrylamino)-2,2-difluoropropanedithioate (5a)

Compound **5a** was obtained from β-thionolactam **3** (580 mg, 2 mmol) according to the general procedure. The mixture was stirred for 30 min after methyl triflate (450 μL, 4mmol) addition and for 15 min after DMF–H_2S addition. After chromatography on silica gel (cyclohexane–EtOAc, 5:5; R_f = 0.5), **5a** was recovered as an orange oil (540 mg; 80% yield).

IR (NaCl): 3338, 1203, 1099 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.42 (m, 10 H_{arom}), 4.97 (s, 1 H, Ph_2CH), 3.36 (t, $^3J_{HF}$ = 13.5 Hz, 2 H, CH_2CF_2), 2.68 (s, 3 H, SCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 225.35 (t, $^2J_{CF}$ = 27 Hz, C=S), 143.23, 128.68, 127.47, 127.43, 121.49 (t, $^1J_{CF}$ = 252 Hz, CF_2), 66.55 ($CHPh_2$), 52.32 (t, $^2J_{CF}$ = 27 Hz, CH_2CF_2), 19.51 (SCH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –96.41 (t, *J* = 14 Hz).

MS (APCI$^+$): *m/z* (%) = 338 (3) [M + H]$^+$, 167.0 (100) [$CHPh_2$ + H$^+$].

Anal. Calcd for $C_{17}H_{17}NS_2F_2$: C, 60.51; H, 5.68; N, 4.15. Found: C, 60.38; H, 6.01; N, 3.93.

Methyl 4-[(4′-Nitrophenyl)amino]butanedithioate (21a)

Compound **21a** was obtained from thionolactam **12** (300 mg, 1.4 mmol) according to the general procedure. The reaction mixture was stirred for 15 min after methyl triflate (320 μL, 2.8 mmol) addition and for 15 min after DMF–H_2S addition. The crude **21a** (340 mg, 1.3 mmol; 95% yield) was obtained as an orange powder. Recrystallization from *i*-PrOH–acetone (95:5) afforded an analytical sample; mp 72–74 °C.

IR (NaCl): 3368, 1600, 1275, 1112 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.11 (d, 2 H_{arom}, $CHCNO_2$), 6.52–6.55 (d, 2 H_{arom}, CHCN), 3.31 (t, $^3J_{CH}$ = 6.6 Hz, 2 H, CH_2N), 3.15 (t, $^3J_{CH}$ = 6.6 Hz, 2 H, CH_2C=S), 2.66 (s, 3 H, SCH_3), 2.23 (qt, $^3J_{CH}$ = 6.6 Hz, 2 H, CCH_2C).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 238.1 (C=S), 153.3 (CHNH), 138.1 ($CHNO_2$), 126.6 ($CHCNO_2$), 111.17 (*C*HCNH), 48.79 (CH_2C=S), 42.3 (CH_2N), 29.85 (SCH_3), 20.86 (CCH_2C).

MS (APCI$^+$): *m/z* (%) = 273.01 (8) [M + 2 + H]$^+$, 271.01 (60) [M + H]$^+$, 223.01 (100) [M – CH_3SH]$^+$.

Anal. Calcd for $C_{11}H_{14}N_2O_2S_2$: C, 48.87; H, 5.22; N, 10.36; S, 23.72. Found: C, 49.21; H, 5.43; N, 10.12; S, 23.79.

Ethyl 4-[(4′-Nitrophenyl)amino]butanedithioate (22a)

Compound **22a** was obtained from thionolactam **12** (200 mg, 0.9 mmol) according to the general procedure. The reaction mixture was stirred for 15 min after ethyl triflate addition (235 μL, 1.8 mmol) and for 15 min after DMF–H_2S addition. Crude **22a** (240 mg, 0.8 mmol; 95% yield) were obtained as an orange powder. Recrystallization from *i*-PrOH–acetone (95:5) afforded an analytical sample; mp 78–80 °C.

IR (NaCl): 3346, 1603, 1273, 1108 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06–8.11 (d, 2 H_{arom}, $CHCNO_2$), 6.50–6.54 (d, 2 H_{arom}, CHCN), 4.55 (br s, 1 H, NH), 3.30 (t, $^3J_{CH}$ = 7.1 Hz, 2 H, CH_2N), 3.22 (q, $^3J_{CH}$ = 7.1 Hz, 2 H, SCH_2CH_3), 3.14 (t, $^3J_{CH}$ = 7.4 Hz, 2 H, CH_2C=S), 2.15 (qt, $^3J_{CH}$ = 7.1 Hz, 2 H, CCH_2C), 1.31 (t, $^3J_{CH}$ = 7.4 Hz, 3 H, SCH_2CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 237.4 (C=S), 153.3 (CHNH), 138.1 ($CHNO_2$), 126.6 ($CHCNO_2$), 111.16 (*C*HCNH), 48.8 (CH_2C=S), 42.3 (CH_2N), 29.85 (SCH_2), 29.7 (CCH_2C), 12.28 (CH_2CH_3).

MS (APCI$^+$,): *m/z* (%) = 273.01 (8) [M + 2 + H]$^+$, 271.01 (60) [M + H]$^+$, 223.01 (100) [M – CH_3SH]$^+$.

Anal. Calcd for $C_{12}H_{16}N_2O_2S_2$: C, 50.68; H, 5.67; N, 9.85; S, 22.55. Found: C, 50.40; H, 5.67; N, 9.74; S, 22.76.

Methyl 4-(Benzoylamino)butanedithioate (25a)

Compound **25a** was obtained from thionolactam **16** (225 mg, 1.1 mmol) according to the general procedure. The reaction mixture was stirred for 30 min after methyl triflate (248 μL, 2.2 mmol) addition and for 6 h after DMF–H_2S addition [addition of anhyd pyridine (1 mL) reduced this time to 20 min). After chromatography on

silica gel (hexane–EtOAc, 7:3; R_f = 0.5), **25a** was recovered as an orange oil (178 mg; 64% yield).

IR (NaCl): 3308, 1634, 1539, 1308, 1163 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.78–7.75 (m, 2 H_{arom}), 7.48–7.38 (m, 3 H_{arom}), 6.45 (br s, 1 H, NH), 3.5 (qdt, ^3J = 6.6 Hz, 2 H, CH_2N), 2.62 (s, 3 H, SCH_3), 3.13 (t, ^3J = 7.2 Hz, 2 H, CH_2C=S), 2.17 (qt, ^3J = 6.6 Hz, 2 H, CCH_2C).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 236.7 (C=S), 167.7 (C=O), 133.3, 131.6, 126.6, 127.1, 48.9 (CC=S), 39.9 (CN), 30.6 (C*C*C), 20.18 (SC).

MS (APCI$^+$): *m*/*z* (%) = 258 (1) [M + 4 + H]$^+$, 256.0 (9) [M + 2 + H]$^+$, 254.0 (100) [M + H]$^+$, 105.1 (95) [PhCO]$^+$.

Methyl 5-(Benzoylamino)pentanedithioate (26a)

Compound **26a** was obtained from thionolactam **18** (150 mg, 0.7 mmol) according to the general procedure. The reaction mixture was stirred for 30 min after methyl triflate (160 μL, 1.4 mmol) addition and for 6 h after DMF–H_2S addition [addition of anhyd pyridine (1 mL) reduced this time to 20 min]. After chromatography on silica gel (hexane–EtOAc, 6:4; R_f = 0.6), **26a** was recovered as an orange oil (125 mg; 67% yield).

IR (NaCl): 3315, 1638, 1540, 1161 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.79–7.70 (m, 2 H_{arom}), 7.49–7.40 (m, 3 H_{arom}), 6.18 (br s, 1 H, NH), 3.48 (qdt, ^3J = 7.2 Hz, 2 H, CH_2N), 3.09 (t, ^3J = 7.5 Hz, 2 H, CH_2C=S), 2.62 (s, 3 H, SCH_3), 1.90–2.02 (m, 2 H, $NCCH_2$), 1.63–1.75 (m, 2 H, CH_2CC=S).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 239.4 (C=S), 167.7 (C=O), 133.1, 131.5, 128.7, 126.9, 51.1(*C*C=S), 39.7 (CN), 28.6 (*C*CN), 28.3 (*C*CC=S), 20.18 (SC).

MS (APCI$^+$): *m*/*z* (%) = 272 (1) [M +4 + H]$^+$, 270 (21) [M + 2 + H]$^+$, 268 (100) [M + H]$^+$, 106 [PhCO]$^+$.

Methyl 6-(Benzoylamino)hexanedithioate (27a)

Compound **27a** was obtained from thionolactam **20** (100 mg, 0.4 mmol) according to the general procedure. The reaction mixture was stirred for 30 min after methyl triflate (91 μL, 0.8 mmol) addition and for 6 h after DMF–H_2S addition [addition of anhyd pyridine (1 mL) reduced this time to 20 min]. After chromatography on silica gel (hexane–EtOAc, 5:5; R_f = 0.45), **27a** was recovered as an orange oil (92 mg; 82% yield).

IR (NaCl): 3337, 1647, 1273, 1108 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.69 (m, 2 H_{arom}), 7.19–7.44 (m, 3 H_{arom}), 6.06 (br s, 1 H, NH), 3.39 (qdt, ^3J = 7.0 Hz, 2 H, CH_2N), 2.99 (t, ^3J = 7.4 Hz, 2 H, CH_2C=S), 2.54 (s, 3 H, SCH_3), 1.84 (qt, ^3J = 7.4 Hz, 2 H, CH_2CC=S), 1.59 (qt, ^3J = 7.4 Hz, 2 H, $NCCH_2$), 1.38 (qt, ^3J = 7.5 Hz, 2 H, $CCCH_2CC$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 239.8 (C=S), 167.7 (C=O), 134.9, 131.5, 128.7, 127.0, 51.6 (*C*C=S), 40.0 (CN), 30.8 (*C*CC=S), 29.5 (*C*CN), 26.1 (CC*C*CC), 20.1 (SC).

MS (APCI$^+$): *m*/*z* (%) = 286 (1) [M + 4 + H]$^+$, 284 (10) [M + 2 + H]$^+$, 282 (100) [M + H]$^+$, 106 (25) [PhCO]$^+$.

Synthesis of Dithioester from Lactam (23a) (Scheme 8)

To a solution of lactam **24** (200 mg, 1 mmol, 1 equiv, in flame-dried glassware, under Ar) in anhyd CH_2Cl_2 (3 mL/mmol) was added triflic anhydride (170 μL, 1 equiv) dropwise at 0 °C. The ice bath was removed after completion of the addition. After 30 min at r.t., 2,6-di-*t*-butylpyridine (224 μL, 1 equiv) was added, followed by dropwise addition of benzyl thiol (120 μL, 1 equiv). The stirring was maintained for 30 min before DMF–H_2S addition (5 mL). After 15 min, the mixture was diluted with Et_2O (20 mL) and washed 3–4 times with brine. The Et_2O phase was dried ($MgSO_4$) and evaporated under vacuum to give crude **23a** (190 mg, 55% yield).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05–8.09 (d, 2 H_{arom}, C*H*CNO_2), 7.29 (br s, 5 H_{arom}), 6.47–6.51 (d, 2 H_{arom}, C*H*CN), 4.47 (s, 2 H, SCH_2Ph), 3.28 (q, $^3J_{CH}$ = 8.0 Hz, 2 H, CH_2N), 3.13 (t, $^3J_{CH}$ = 8.0 Hz, 2 H, CH_2C=S), 2.24 (qt, $^3J_{CH}$ = 7.7 Hz, 2 H, CCH_2C).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 236.6 (C=S), 153.6 (CHNH), 138.3 ($CHNO_2$), 131.3, 124.0, 125.9 (*C*HCNO_2), 122.8 119.5, 111.2 (*C*HCNH), 48.7 (CH_2N), 41.1 (*C*H_2C=S), 29.9 (SCH_2Ph), 17.8 (C*C*H_2C).

MS (APCI): *m*/*z* (%) = 349 (9) [M + 2 + H]$^+$, 348 (18) [M + 1 + H]$^+$, 347 (100) [M + H]$^+$.

Benzyl 4-[2,2,2-Trifluoro-*N*-(4-nitrophenyl)acetamido]butanedithioate (28)

Compound **23b** (crude mixture) was dissolved in anhyd CH_2Cl_2 (10 mL) and Et_3N (83 μL, 0.6 mmol, 1 equiv) followed by addition of trifluoroacetic anhydride (85 μL, 0.6 mmol, 1 equiv). The mixture was then stirred at 25 °C for 2 h. The solvent was then evaporated under vacuum. After column chromatography on silica gel (hexane–EtOAc, 5:5; R_f = 0.5), **28** (198 mg, 0.45 mmol; 75% yield) was recovered as a yellow oil.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.15–8.18 (d, 2 H_{arom}, $CHCNO_2$), 7.40–7.42 (d, 2 H_{arom}, CHCN), 7.21 (br s, 5 H_{arom}), 4.43 (s, 2 H, SCH_2Ph), 3.93 (t, $^3J_{CH}$ = 7.6 Hz, 2 H, CH_2N), 3.05 (t, $^3J_{CH}$ = 8.0 Hz, 2 H, CH_2C=S), 2.18 (qt, $^3J_{CH}$ = 7.7 Hz, 2 H, CCH_2C).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 235.8 (C=S), 157.3 (C=O), 150.3 (CHNH), 137.3 ($CHNO_2$), 131.2, 124.1, 125.7 (*C*HCNO_2), 122.6, 119.4, 113.9 (CF_3), 111.2 (*C*HCNH), 42.6 (CH_2N), 40.9 (*C*H_2C=S), 29.8 (SCH_2Ph), 18.6 (C*C*H_2C).

MS (ESI): *m*/*z* (%) = 443 (3) [M + 2 – H], 441 (18) [M – H], 317 (100) [M – SCH_2Ph].

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{17}O_3NS_2F_3$·Na: 465.0530; found: 465.0538.

Methyl 3-Amino-2,2-difluoropropanedithioate Hydrochloride (6)

Compound **5a** (450 mg, 1.3 mmol, 1 equiv) and DDQ (2,3-dichloro-5,6-dicyanoquinone; 295 mg, 1.3 mmol, 1 equiv) were successively added to a suspension of crushed 4 Å molecular sieve in anhyd toluene (5 mL/mmol). The reaction medium was then protected from light and brought to 60 °C for 1 h. After filtration on a short pad of basic alumina (washed with toluene), the solvent was evaporated under vacuum. The oil obtained was taken back in Et_2O (10 mL) and 0.1 N HCl (10 mL) was subsequently added. The biphasic mixture was then stirred for 8 h. To prevent formation of α,α-difluoro-β-alanine (by hydrolysis of the dithioester moiety), the aqueous phase should be collected every 2 h. 'Fresh' 0.1 N HCl (10 mL) was added and the operation was repeated until no imine intermediate could be detected in the Et_2O phase [^1H NMR: δ = 7.12–7.60 (m, 10 H_{arom}), 4.11 (t, $^3J_{CF}$ = 13 Hz, 2 H, CH_2CF_2), 2.69 (s, 3 H, SCH_3)]. Meanwhile, the aqueous phases were mixed and concentrated under vacuum. Compound **6** (228 mg, 1.1 mmol, 85% yield) was recovered as an orange powder.

^1H NMR (250 MHz, D_2O): δ = 3.91 (t, $^3J_{HF}$ = 40 Hz, 2 H, CH_2CF_2), 2.71 (s, 3 H, SCH_3).

^{13}C NMR (125 MHz, D_2O): δ = 221.4 (t, $^2J_{CF}$ = 25 Hz, C=S), 118.34 (t, $^1J_{CF}$ = 251 Hz, CF_2), 44.29 (t, $^2J_{CF}$ = 25 Hz, *C*H_2CF_2), 19.9 (SCH_3).

^{19}F NMR (282 MHz, D_2O): δ = –99.31 ppm.

MS (ESI): *m*/*z* (%) = 173.9 (9) [M + 2 – Cl]$^+$, 171.9 (100) [M – Cl]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_4H_8NS_2F_2$: 172.0062; found: 172.0066.

Note on use of benzene: Benzene is a known carcinogen, and suitable protective equipment should be used. We have tried to use toluene instead, but no reaction occurred.

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