A sample of **19** was obtained by repeating the reaction for 16 h. Concentration of the organic layer during workup was carried out at atmospheric pressure and the crude product was purified by preparative GC: IR ($CHCl_3$) 1630 (C=C) and 2200 cm^{-1} (CN); NMR 2.3–2.8 (m, 4 H), 1.99 (s) on 1.75–2.2 (m, total 5 H).

The reaction was repeated for 40 min to obtain a 56:42:02 mixture of **15** (67:33 **15a**/**15b**), **18**, and **19**, respectively. Preparative TLC (CH_2Cl_2–MeOH, 99:1) of the crude products gave in low yield a fraction enriched in **15b** (27:73 **15a**/**15b**) as the lower third of the alcohol band: IR (film) 3450 (OH) and 2240 cm^{-1} (CN); NMR δ 1.55 (s, 70%) and 1.49 (s, 30%) on 1.3–2.9 (m). This enriched material was subjected to refluxing benzene–5% aqueous NaOH for 25 min and at that time the isomer ratio was measured by GC: (67:33 **15a**/**15b**).

β-Hydroxy nitrile **15a** (40 mg), benzene (2.5 mL), and aqueous 5% NaOH (2.5 mL) were mixed and stirred at room temperature for 24 h. Workup as in the above procedure gave 30 mg (75% recovery) of an oil which by GC and NMR was a mixture of diastereomers (65:35 **15a**/**15b**); no **19** could be detected and only a trace (<5%) of **18** was apparent.

Registry No. **2**, 70367-26-9; **3**, 108470-80-0; **4**, 108470-81-1; **5**, 70367-30-5; **6**, 70367-29-2; **7a**, 108470-82-2; **8a**, 85355-68-6; **9**, 85355-67-5; **10**, 15166-77-5; **11**, 70367-35-0; *trans*-**11**, 63301-31-5; **12**, 70367-34-9; **13**, 70367-36-1; **14**, 17190-29-3; **15a**, 108470-83-3; **15b**, 108470-86-6; **16**, 71312-66-8; **17**, 71312-73-7; **18**, 18458-15-6; **19**, 765-76-4; **22**, 70367-23-6; $PhSO_2CH_2NO_2$, 21272-85-5; $PhSO_2CHBrNO_2$, 108470-84-4; $PhSO_2CBr_2NO_2$, 108470-85-5; $CH_3CO(CH_2)_2CH{=}CH_2$, 109-49-9; $PhCH{=}CH_2$, 100-45-2; Na–Hg, 11146-94-4; $PhCH_2CN$, 140-29-4; $PhCH_2OH$, 100-51-6; PhCHO, 100-52-7; norbornylene, 498-66-8; cyclohexene, 110-83-8; 1-methylcyclopentene, 693-89-0; cyclohexene oxide, 286-20-4.

A New Synthesis of 4- and 5-Imidazolethiols

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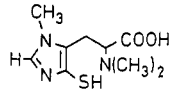
Several examples of a new, mild, and regiocontrolled multistep synthesis of multiply substituted 4- and 5-imidazolethiols are reported. The key step involves a dehydration/cyclization promoted by trimethylsilyl triflate and triethylamine.

The discovery in marine invertebrate oocytes of multiply alkylated histidinethiols[1] (of which **1**, ovothiol C, is exemplary), which appear to be important during embryogenesis,[2] prompted us to study methods for the synthesis of 4-histidinethiols. In the course of this study, we devised a new method for the preparation of substituted 4-imidazolethiols. This procedure made possible the synthesis of L-ovothiol A[3] and, furthermore, appears to be general. Additional examples and details of this process are described herein. Furthermore, a variant of this process has been used for the synthesis of 5-imidazolethiols.



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Although 4(5)-imidazolethiols are a relatively little studied class, a few methods for their construction have appeared. Introduction of a sulfur substituent onto a preformed imidazole ring has been achieved by direct deprotonation and subsequent thiation of the resulting C-lithioimidazole.[4] Alternatively, a halide at C-4(5) activated by an electron-withdrawing substituent at C-5(4) may be displaced by a sulfur nucleophile.[5] Direct construction of an imidazole ring bearing a 4-thiol group has been accomplished by the condensation of imines with α-oxo thionoamides.[6,7] Given the substitution pattern and functionality of the ovothiols, it was not obvious that any of these methods were directly applicable to ovothiol synthesis. Accordingly, we devised an alternate approach.

Scheme I summarizes the new 4-imidazolethiol synthesis. Conversion, under standard conditions, of an aldehyde and primary amine to the corresponding cyano amine **2** followed by acylation[8] gave the nitrile amide **3**. Addition of hydrogen sulfide[9] to the nitrile took place under mild conditions to afford cyclization substrate **4**. Cyclization of **4** was accomplished with trimethylsilyl triflate[10,11] and triethylamine in methylene chloride to yield **5**. The imi-

Scheme I

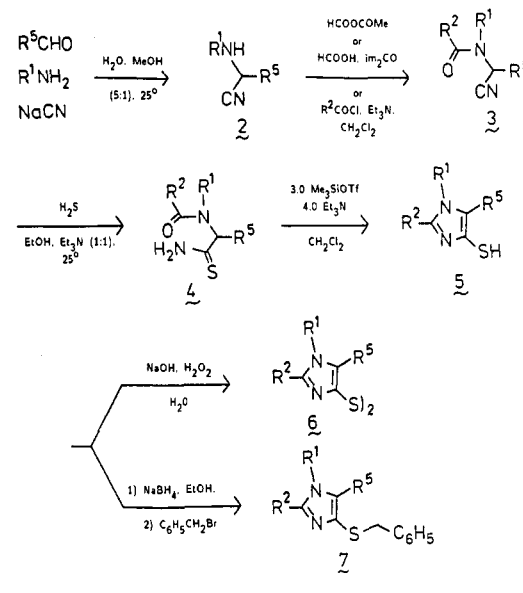

Table I. Yields for the Synthesis of 4-Imidazolethiols

entry	substituents R^1	R^2	R^5	4, % (overall)	heterocycle,[a] % (formula)
1	CH_3	H	H	36	60 (**6a**)
2	n-C_4H_9	i-C_3H_7	i-C_3H_7	... (70)[b]	57 (**6b**)
3	n-C_4H_9	C_6H_5	i-C_3H_7	... (86)[b]	46 (**6c**)
4	CH_3	H	CH_2OTHP	52 (30)[b]	69 (**7a**)
5	CH_3	H	$CH_2OCH_2C_6H_5$	64 (52)[b]	42[c] (**5a**)
6	CH_3	H	$CH_2CH_2OCH_2C_6H_5$	50 (35)[b]	84 (**7b**)
7	CH_3	H	$CH_2CH{=}C(CH_3)_2$	26	84 (**7c**)

[a] Yield from **4**. [b] Reflects yield of **4** without intermediate purification of **2** or **3**. [c] *tert*-Butyldimethylsilyl triflate substituted for trimethylsilyl triflate.

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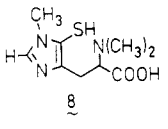
0022-3263/87/1952-2977$01.50/0

dazolethiol **5** may be isolated by a hydrolytic and extractive workup, followed by chromatography of the crude product on silica gel, but purification of the product is, in general, facilitated by masking of the thiol function. Thus, the disulfides **6** and sulfides **7** were more commonly isolated. Specifically, oxidation[6] of **5** to the disulfide **6** or alkylation of **5** to the sulfide **7** were effected as shown.

Table I illustrates the yields[12] and structures of substituted 4-imidazolethiols prepared by this method. Several observations are noteworthy. Although the overall yield is somewhat compromised, the sequence of steps from aldehyde and amine through final products **5–7** can be successfully conducted without purification of intermediates. In the latter mode, the process is rapid (1–2 days from start to finish), inexpensive, and amenable to large-scale synthesis (multigram).

Some details of the cyclization step are worthy of remark. The cyclizations that produce a 2-unsubstituted heterocycle occur at −78 °C in 5 min; the presence of a 2-substituent slows the cyclization remarkably, entries 2 and 3 (Table I) being examples requiring 25 °C to achieve a useful reaction rate. The use of trialkylsilyl triflate/triethylamine was successful in all cyclizations attempted; formic acid could be successfully employed in place of the silicon reagent/trialkylamine in cyclizations that produce relatively robust, unfunctionalized 4-imidazolethiols but was less successful or failed completely in more sensitive (and useful) functionalized cases. For example, the entries 5 and 7 (Table I) could not be formed by formic acid promoted cyclization.[13]

We also note a single example of a variant of this process that affords 5-imidazolethiols, substances of potential use in the synthesis of a family of histidinethiol derivatives (e.g., **8**) isolated from marine sources and reported by Prota,[14] which are isomeric with the ovothiols. The thionoamide **9** (prepared from *t*-BOC-L-alanine methyl ester by the sequence (1) $CH_3NH_2/H_2O/CH_3OH$; (2) $(p\text{-}CH_3OC_6H_4PS_2)_2/C_6H_6$, 70 °C, 1 h;[15] (3) CF_3CO_2H, 25 °C, 2 h; and (4) $(C_3H_3N_2)_2C{=}O/HCOOH/THF$ was cyclized with trimethylsilyl triflate and alkylated as described above to yield the protected imidazole-5-thiol **10** in 75% yield. Interestingly, when excess formic acetic anhydride at 100 °C was substituted for carbonyldiimidazole and formic acid in the above formylation, both formylation and cyclization occurred, but the thiazole derivative **11**, rather than the imidazolethiol, was isolated in 74% yield.



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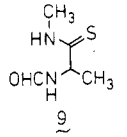

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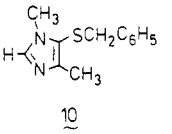

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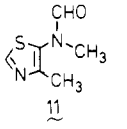

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Experimental Section[16]

Cyano Amine 2 ($R^1 = CH_3$, $R^5 = CH_2OTHP$), 2-(Methylamino)-3-[(2-tetrahydropyranyl)oxy]propionitrile. 2-[(2-Tetrahydropyranyl)oxy]ethanal (0.80 g, 5.5 mmol) in 2.0 mL of methanol was added dropwise to a solution of 1.0 g (15 mmol) of methylamine hydrochloride and 0.75 g (15 mmol) of sodium cyanide in 10 mL of water at 25 °C. The solution was stirred for 10 min and extracted with dichloromethane. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (40% ethyl acetate–petroleum ether) to afford the title compound (0.70 g, 69%) as a colorless oil: ^1H NMR (500 MHz) δ 1.4–1.9 (7 H, m, THP ether and NH), 2.58 (3 H, s, CH_3), 3.50–4.00 (5 H, m, 2 CH_2O, CHN), 4.70 (1 H, br s, OCHO); IR (neat) 3340 (NH), 2235 cm^{-1} (CN); LRMS (EI), *m/e* 185 (M^+ +

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(2) Turner, E.; Somers, C. E.; Shapiro, B. M. *J. Biol. Chem.* **1985**, *260*, 13163.

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(6) (a) Asinger, F.; Saus, A.; Offermanns, H.; Krings, P.; Andree, H. *Justus Liebigs Ann. Chem.* **1971**, *744*, 51. (b) Offermanns, H.; Krings, P.; Asinger, F. *Tetrahedron Lett.* **1968**, 1809.

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(9) Olin, J. F.; Johnson, T. B. *Recl. Trav. Chim. Pays-Bas* **1931**, *50*, 72.

(10) For a review, see: Simchen. G.; et al. *Synthesis*, **1982**, 1.

(11) For a dehydration/cyclization approach to furans using $(Me_3Si)OTf$, see: Duhamel, L.; Chaurin, J. *Chem. Lett.* **1985**, 693. For reaction of $(Me_3Si)OTf$ with amides, see: Bassindale, A.; Stout, T. *J. Organomet. Chem.* **1982**, *238*, C41.

(12) Yields (%) of purified intermediates **2–4**, respectively, are as follows for each entry in Table I [(entry) yield **2**, yield **3**, yield **4**]: (1) 79, 53, 87; (4) 69, 84, 90; (5) 83, 89, 86; (6) 75, 78, 86; (7) 36, 87, 83.

(13) Subsequent to the completion of this study, we found that, in a single example, chlorotrimethylsilane (5 equiv) and triethylamine (6 equiv) at 25 °C (5 h) may substitute for trimethylsilyl triflate and triethylamine at −78 °C in the cyclization. This modification may afford an economic advantage in large-scale work.

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(16) Air- or water-sensitive reactions were conducted under a positive argon atmosphere. Commercial reagents were used as received, except tetrahydrofuran, which was distilled from benzophenone ketyl, and methylene chloride, which was distilled from calcium hydride. The aldehydes R^5CHO (see scheme and table) either were commercially available or were obtained by ozonolysis (dimethyl sulfide reduction) of appropriate olefins [table: entry 4 from 1,4-bis(2-tetrahydropyranyl)-oxy]-*cis*-2-butene; entry 5 from 1,4-bis(benzyloxy)-*cis*-2-butene; entry 6 from 5-(benzyloxy)-2-methyl-2-pentene] or by PCC oxidation of the corresponding alcohol (table: entry 7 from 4-methyl-3-penten-1-ol, in low yield). Thin-layer chromatography was performed on Merck precoated silica gel 60 plates (0.25 mm); column chromatography was performed under a slight positive pressure on Merck silica gel 60 (230–400 mesh). Infrared spectra (IR) were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^1H NMR) were determined on a Varian CFT-20 (80-MHz) or Bruker WM 500 (500-MHz) spectrometer and, unless otherwise noted, are in $CDCl_3$ and reported in parts per million (δ) downfield from internal tetramethylsilane (δ 0.00). Coupling constants (*J*) are reported in hertz. Low-resolution mass spectra (LRMS) were measured on a Hewlett-Packard 5985 mass spectrometer; high-resolution mass spectra (HRMS) were measured on a VG 7070H double-focusing mass spectrometer. Ultraviolet (UV) spectra were measured on a Hewlett-Packard Model 8450A UV/vis spectrometer and are reported as wavelength (extinction coefficient).

1), 158 (M^+ – CN), 101 (THP – O^+), 85 (100%, THP^+).

Cyano Amide 3 ($R^1 = CH_3$, $R^2 = H$, $R^5 = CH_2OTHP$), *N*-Methyl-*N*-[1-cyano-2-[(2-tetrahydropyranyl)oxy]ethyl]-methanamide. A solution of 0.97 g (6.0 mmol) of 1,1'-carbonyldiimidazole in 10 mL of tetrahydrofuran at 25 °C was treated with 0.245 g (5.3 mmol) of 97% formic acid. The solution was stirred 15 min and then treated sequentially with 0.61 g (6.0 mmol) of triethylamine and 0.50 g (2.7 mmol) of 2-(methylamino)-3-[(2-tetrahydropyranyl)oxy]propionitrile (**2**; $R^1 = CH_3$, $R^5 = CH_2OTHP$). After 0.5 h at 25 °C, the mixture was diluted with diethyl ether and washed with water. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel (40% ethyl acetate–petroleum ether) to afford the title compound (0.48 g, 84%; two diastereoisomers each as two rotamers) as a colorless oil: ^1H NMR (500 MHz) δ 1.45–1.85 (6 H, m, THP ether), 3.00, 3.01, 3.16, 3.17 (3 H, 4 s, ratio 1:1:2:2, CH_3), 3.5–4.0 (4 H, m, 2 CH_2O), 4.69 (1 H, br s, OCHO), 5.58, 5.62 (1 H, 2 dd, J = 6, 7 Hz, ratio 1:1, CHCN), 8.10, 8.12 (1 H, 2 s, ratio 2:1, CHO); IR (neat) 2226 (CN), 1690, 1675 cm^{-1} (C=O); LRMS (EI), m/e 213 ($M^+ + 1$), 111 (M^+ – THP – O), 85 (100%, THP^+).

Thionoamide 4 ($R^1 = CH_3$, $R^2 = H$, $R^5 = CH_2OTHP$). Hydrogen sulfide was bubbled through a solution of the cyano amide **3** ($R^1 = CH_3$, $R^2 = H$, $R^5 = CH_2OTHP$) [*N*-methyl-*N*-[1-cyano-2-[(2-tetrahydropyranyl)oxy]ethyl]methanamide; 0.135 g, 0.64 mmol] in 5 mL of ethanol and 5 mL of triethylamine at 25 °C for 10 min. The volatiles were removed in vacuo, and the residue was chromatographed on silica gel (40% ethyl acetate–petroleum ether) to yield 0.14 g (90%, mixture of two diastereoisomers each as two rotamers) of the thionoamide 4 ($R^1 = CH_3$, $R^2 = H$, $R^5 = CH_2OTHP$) as a colorless oil: ^1H NMR (500 MHz) δ 1.40–1.85 (6 H, m, THP ether), 2.82, 2.85, 3.08, 3.09 (3 H, 4 s, ratio 2:2:3:3, CH_3), 3.57–4.70 (5 H, m, 2 CH_2O, OCHO), 5.17, 5.20 (1 H, 2 dd, J = 6, 7 Hz, ratio 1:1, CHCS), 8.14, 8.18 (1 H, 2 s, ratio 3:2 CHO), 7.8–8.3 (2 H, br, NH_2); IR (neat) 3310, 3200 (NH_2), 1665 cm^{-1} (C=O); LRMS (EI), m/e 246 (M^+), 187 ($M^+ - CSNH_2$), 85 (100%, THP^+).

Cyclization and Isolation as Sulfide. 1-Methyl-4-(benzylthio)-5-[(2-tetrahydropyranyl)oxy]methylimidazole (7a). The thionoamide 4 ($R^1 = CH_3$, $R^2 = H$, $R^5 = CH_2OTHP$), (0.15 g, 0.6 mmol) and 0.25 g (2.5 mmol) of triethylamine in 5 mL of dichloromethane were cooled to –78 °C, and trimethylsilyl trifluoromethanesulfonate (0.40 g, 1.8 mmol) was added dropwise along the walls of the flask. The mixture was stirred at –78 °C for 5 min, then treated with 5 mL of methanol and 0.5 g of sodium fluoride, warmed to 25 °C, and stirred for 2 h. The volatiles were removed in vacuo. The residue was dissolved in ethanol and treated sequentially with sodium borohydride (0.5 g) and benzyl bromide (0.137 g, 0.8 mmol). After being stirred for 0.5 h at 25 °C, the mixture was diluted with water and extracted with dichloromethane, and the organic extracts were dried ($MgSO_4$). Concentration in vacuo and chromatography on silica gel (8% methanol–dichloromethane) afforded **7a** (0.13 g, 69%) as a colorless oil: ^1H NMR (500 MHz) δ 1.40–1.80 (6 H, m, THP ether), 3.50 (1 H, m, CH_2O), 3.62 (3 H, s, CH_3), 3.78 (1 H, m, CH_2O), 4.00 (2 H, s, SCH_2), 4.27 (1 H, d, J = 13 Hz, OCH_2Ar), 4.41 (1 H, d, J = 13 Hz, OCH_2Ar), 4.46 (1 H, m, OCHO), 7.12–7.37 (5 H, m, Ar), 7.50 (1 H, s, CH-2); IR (neat) 3060, 3035 (Ar), 2975 (CH_3), 1602, 1501 cm^{-1} (Ar); LRMS (EI), m/e 318 (M^+), 233 (M^+ – THP), 217 (M^+ – THPO), 91 ($C_7H_7^+$); HRMS (EI), m/e calcd 318.1397, found 318.1412.

Cyclization and Isolation as Thiol. 1-Methyl-5-[(benzyloxy)methyl]imidazole-4-thiol (5a). The thionoamide 4 ($R^1 = CH_3$, $R^2 = H$, $R^5 = CH_2OCH_2C_6H_5$) (0.50 g, 2.0 mmol) was cyclized as described above for the synthesis of **7a**, with the exception that *tert*-butyldimethylsilyl triflate was substituted for trimethylsilyl triflate. Removal of the volatiles in vacuo and treatment of the reaction mixture with ethanolic borohydride and benzyl bromide was deleted; the misture was instead diluted with water and extracted with dichloromethane, and the organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica gel afforded 0.19 g (42%) of **5a** as a colorless oil, which solidified on standing: ^1H NMR (500 MHz) δ 1.75 (1 H, br s, SH), 3.51 (3 H, s, CH_3), 4.31 (2 H, s, Im CH_2), 4.38 (2 H, s, $ArCH_2$), 7.22–7.33 (5 H, m, Ar), 7.42 (1 H, s, CH-2); IR ($CHCl_3$) 3075, 3030 (Ar), 2425 cm^{-1} (w, SH); LRMS (EI), m/e 233 (M^+ – 1), 111 ($M^+ - BnOCH_2$), 91 (100%, $C_7H_7^+$); HRMS (EI), m/e calcd 234.0827, found 234.0845.

Cyclization and Isolation as Disulfide. Disulfide 6b. Thionoamide 4 ($R^1 = n$-C_4H_9, $R^2 = i$-C_3H_7, $R^5 = i$-C_3H_7) (0.34 g, 1.3 mmol) was cyclized as described above for **7a**, except that the reaction mixture was warmed to 25 °C before quenching. After evaporation of the volatiles, the residue was dissolved in 10 mL of 2 N aqueous sodium hydroxide and treated with 2 mL of 15% aqueous hydrogen peroxide. Stirring at 25 °C for 1 h, extraction with dichloromethane, drying of the organic layer ($MgSO_4$), concentration in vacuo, and chromatography on silica gel (ethyl acetate) afforded the disulfide **6b** (0.18 g, 57%) as a colorless oil, which solidified on standing: ^1H NMR (500 MHz) δ 0.95 (3 H, t, J = 7 Hz, CH_3CH_2), 1.08 (6 H, d, J = 7 Hz, $(CH_3)_2CH$), 1.33 (6 H, d, J = 7 Hz, $(CH_3)_2CH$), 1.35 (2 H, m, CH_2CH_3), 1.51 (2 H, m, CH_2CH_2), 2.88 (2 H, m, 2 ArCH), 3.69 (2 H, m, CH_2N); IR ($CHCl_3$) 2980 (CH_3), 1240–1210 cm^{-1}; LRMS (EI), m/e 478 (M^+), 239 (ArS^+); HRMS (EI), m/e calcd 478.3164, found 478.3116; UV (CH_3OH) 262 nm (3700), 312 (2400).

Data for Selected Compounds in Table. Thionoamide 4 ($R^1 = CH_3$, $R^2 = R^5 = H$): ^1H NMR (80 MHz) δ 2.83, 3.05 (3 H, 2 s, ratio 5:3, CH_3), 4.34, 4.37 (2 H, 2 s, ratio 3:5, CH_2), 8.05, 8.10 (1 H, 2 s, ratio 5:3, CHO).

Thionoamide 4 ($R^1 = n$-C_4H_9, $R^2 = i$-C_3H_7, $R^5 = i$-C_3H_7): ^1H NMR (500 MHz) δ 0.86–1.34 (20 H, m, alkyl), 2.72 (1 H, m, COCH), 3.2–3.4 (3 H, m, CHCS, CH_2N), 7.5 (2 H, m, NH_2).

Thionoamide 4 ($R^1 = n$-C_4H_9, $R^2 = C_6H_5$, $R^5 = i$-C_3H_7): ^1H NMR (500 MHz) δ 0.75 (3 H, t, J = 7 Hz, CH_3CH_2), 1.06 (3 H, d, J = 6 Hz, $(CH_3)_2CH$), 1.14 (3 H, d, J = 6 Hz, $(CH_3)_2CH$), 1.0–1.8 (5 H, m, 2 CH_2, $CH(CH_3)_2$), 3.2–3.4 (2 H, m, NCH_2), 4.05 (1 H, m, CHN), 7.37–7.43 (5 H, m, Ar).

Thionoamide 4 ($R^1 = CH_3$, $R^2 = H$, $R^5 = CH_2OCH_2C_6H_5$): ^1H NMR (500 MHz) δ 2.80, 3.02 (3 H, 2 s, ratio 1:2 CH_3), 3.85–4.35 (2 H, m, OCH_2CH), 4.57 (2 H, m, $ArCH_2O$), 5.23 (1 H, m, CHCS), 7.25–7.4 (5 H, m, Ar), 8.18 (1 H, s, CHO), 7.4, 8.1 (2 H, br, NH_2).

Thionoamide 4 ($R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2CH_2OCH_2C_6H_5$): ^1H NMR (500 MHz) δ 2.21 (1 H, m, CH_2CH_2O), 2.45 (1 H, m, CH_2CHO), 2.71, 2.97 (3 H, 2 s, ratio 1:2, CH_3N), 3.49 (2 H, t, J = 5 Hz, CH_2O), 4.47 (2 H, s, OCH_2Ar), 5.16 (1 H, t, J = 7 Hz, CHCS), 7.27–7.60 (7 H, m, Ar, NH_2), 8.08, 8.12 (1 H, 2 s, ratio 2:1, CHO).

Thionoamide 4 ($R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2CH{=}C(CH_3)_2$): ^1H NMR (500 MHz) δ 1.68 (6 H, d, J = 11 Hz, CH_3), 2.72 (2 H, m, $CH_2C{=}$), 2.97 (3 H, s, CH_3N), 4.92 (1 H, t, J = 8 Hz, CHCN), 4.96 (1 H, m, =CH), 7.42, 7.99 (2 H, 2 br s, NH_2), 8.13 (1 H, s, CHO).

Disulfide 6a: HRMS (EI), m/e calcd 226.0347, found 226.0342.
Disulfide 6c: HRMS (EI), m/e calcd 546.2851, found 546.2886.
Sulfide 7c: HRMS (EI), m/e calcd 272.1347, found 272.1345.

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