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A FACILE SYNTHETIC ROUTE TO HIGHLY FUNCTIONALIZED 2,4-PYRROLIDINEDIONES: A NEW BASE-CATALYZED CYCLIZATION

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Abstract - 2,4-Pyrrolidinedione derivatives were synthesized in 67-85% yield in one-pot reaction *via* base-catalyzed cyclization of α -(arylvinylcarbonyl)- α' -(*N*-arylamino-carbonyl)ketene dithioacetals formed *in situ* by the reaction of α -acetyl- α' -(*N*-arylamino-carbonyl)ketene dithioacetals with pyridinecarboxaldehydes or benzaldehydes containing electron-withdrawing substituents.

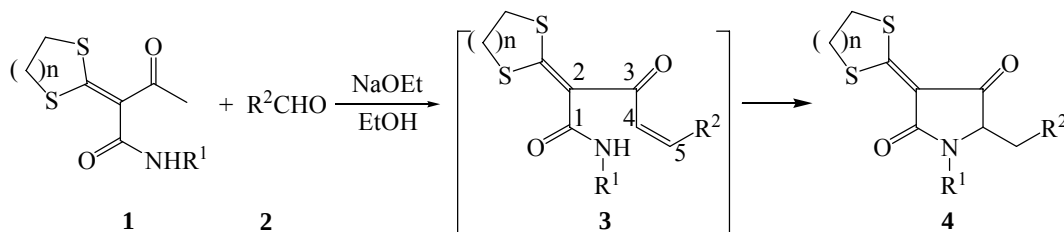
INTRODUCTION

2,4-Pyrrolidinedione is a tautomer of tetramic acid.¹ A number of 2,4-pyrrolidinedione derivatives have attracted an attention over the years as a result of their biological activities and synthetic challenges.²⁻⁵ It has been reported that the biological activities of the naturally occurring tetramic acid derivatives are essentially due to the presence of the 2,4-pyrrolidinedione ring, the carbonyl group on C-3, and the stereocenter on C-5, together with the ability to form complexes with metallic ions.³ Herein, we report a new route to 2,4-pyrrolidinedione derivatives, as shown in Scheme 1. A base-catalyzed reaction of α -acetyl- α' -(*N*-arylamino-carbonyl)ketene dithioacetal (**1**) with arylaldehyde (**2**), formed α -(arylvinylcarbonyl)- α' -(*N*-arylamino-carbonyl)ketene dithioacetal (**3**) which underwent cyclization *in situ* to give highly functionalized 2,4-pyrrolidinedione (**4**). α -Acetyl- α' -(*N*-arylamino-carbonyl)ketene dithioacetal (**1**), a well-known class of α -oxoketene dithioacetals for organic syntheses,⁶ can be synthesized from *N*-aryl-3-oxobutanamide^{6b} or ethyl 3-oxobutanoate.⁷

RESULTS AND DISCUSSION

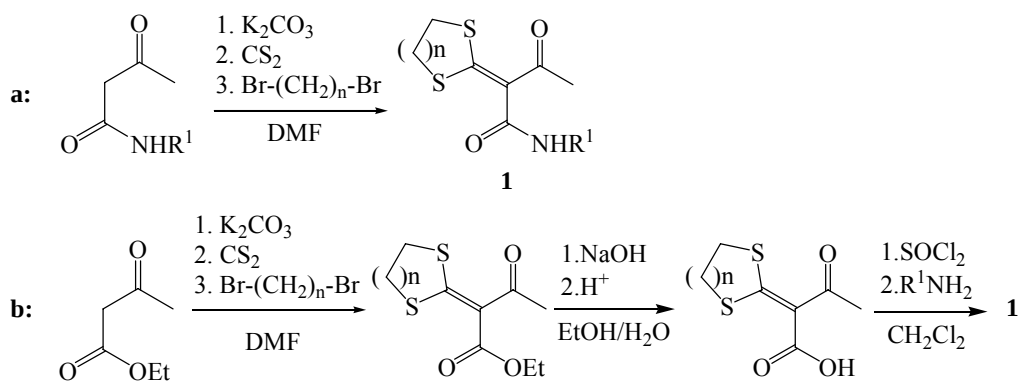
As shown in Scheme 1, the synthetic strategy in this paper was designed by considering that compound (**3**) (aldol condensation product), formed from compounds (**1** and **2**) in the presence of base, may undergo

cyclization to produce compound (**4**) *in situ*, since the nitrogen atom of amido group in compound (**3**) may readily attack carbon 4 rather than carbon 5 according to the Baldwin's rule.⁸



Scheme 1. Synthetic route to highly functionalized 2,4-pyrrolidinedione (**4**) from dithioacetals (**1**) and arylaldehydes (**2**).

α -Acetyl- α' -(*N*-arylamino-carbonyl)ketene dithioacetals (**1**) were prepared in high yields (85-97%) from commercial *N*-aryl-3-oxobutanamides, carbon disulfide and 1,2-dibromoethane or 1,3-dibromopropane under basic conditions, according to the known procedure (Scheme 2a).^{6b, 7} They were also synthesized from ethyl 3-oxobutanoate (Scheme 2b).⁷



Scheme 2. Synthetic route to dithioacetal (**1**) from (a) *N*-aryl-3-oxobutanamide and (b) ethyl 3-oxobutanoate.

During the first attempt, compound (**4a**) was successfully synthesized, simply by reacting **1a** (1.0 equiv.) with **2a** (1.1 equiv.) in the presence of $NaOEt$ (0.5 equiv.) in ethanol at room temperature (Table 1) *via* additional cyclization of α -(arylvinylcarbonyl)- α' -(*N*-arylamino-carbonyl)ketene dithioacetal (**3**). Based on this preliminary result, we attempted to apply the route for the synthesis of a variety of 2,4-pyrrolidinediones.

First, the ring size effect of the ketene dithioacetal moiety (i.e., $n = 1, 2$) was examined, along with the

position effect of pyridyl (Py) group (i.e., 2-Py-CHO or 4-Py-CHO) and the substituent effect of benzaldehydes. The isolation yields of the corresponding 2,4-pyrrolidinedione derivatives (**4**) were moderate to high (67-85%, except **4l** and **4m**), irrespective of the ring size of the ketene dithioacetal moiety and the position of Py group (**4a-i**, **4o**). However, when benzaldehydes containing an electron-releasing substituent such as CH₃ and NHCOCH₃ were employed as starting materials, the corresponding 2,4-pyrrolidinediones (**4l** and **4m**) were produced in very low yields (calc. 20-30%). Furthermore, when 4-hydroxybenzaldehyde (**2g**) was reacted with **1a**, the corresponding 2,4-pyrrolidinedione (**4n**) was not detected from the reaction mixture. The yield of **4k** was relatively low (67%), due to the alkali-sensitive CHO group. Thus this method was applicable to only benzaldehydes containing an electron-withdrawing substituent.

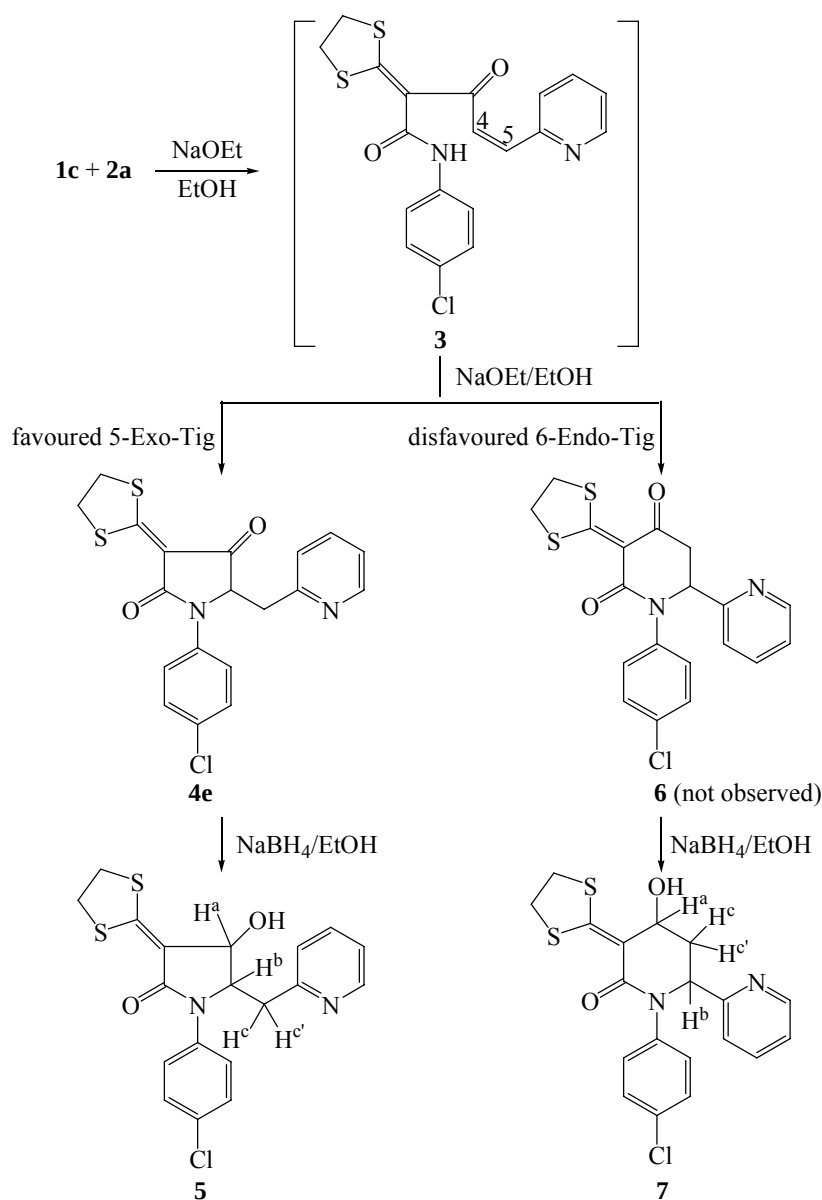
Table 1. Synthesis of 2,4-pyrrolidinediones (**4**) from dithioacetals (**1**) and arylaldehydes (**2**).

	Dithioacetal	n		Aldehyde	Product	Time (h)	Yield (%)	mp (°C)
	R ¹			R ²				
1a	2,4-Me ₂ C ₆ H ₃	1	2a	2-pyridyl	4a	2	83	198-200
1a	2,4-Me ₂ C ₆ H ₃	1	2b	4-pyridyl	4b	2	75	196-198
1b	2-MeC ₆ H ₄	1	2a	2-pyridyl	4c	5	78	155-157
1b	2-MeC ₆ H ₄	1	2b	4-pyridyl	4d	2	73	162-164
1c	4-ClC ₆ H ₄	1	2a	2-pyridyl	4e	2	77	168-170
1c	4-ClC ₆ H ₄	1	2b	4-pyridyl	4f	3	72	168-170
1d	C ₆ H ₅	1	2a	2-pyridyl	4g	6	70	169-170
1e	4-O ₂ NC ₆ H ₄	1	2b	2-pyridyl	4h	6	75	128-130
1f	4-MeC ₆ H ₄	1	2a	2-pyridyl	4i	3	72	210-212
1a	2,4-Me ₂ C ₆ H ₃	1	2c	3-O ₂ NC ₆ H ₄	4j	2	85	206-207
1a	2,4-Me ₂ C ₆ H ₃	1	2d	2-HOCC ₆ H ₄	4k	5	67	140-142
1a	2,4-Me ₂ C ₆ H ₃	1	2e	2-MeC ₆ H ₄	4l	6	~20 ^B	176-178
1a	2,4-Me ₂ C ₆ H ₃	1	2f	4-CH ₃ CONH-C ₆ H ₄	4m	7	~30 ^B	183-187
1a	2,4-Me ₂ C ₆ H ₃	1	2g	4-OHC ₆ H ₄	4n	7	--	--
1b	2-MeC ₆ H ₄	2	2a	2-pyridyl	4o	2	80	200-202
1g	2-MeOC ₆ H ₄	2	2h	4-O ₂ NC ₆ H ₄	4p	2	76	190-192

^A Isolation yield

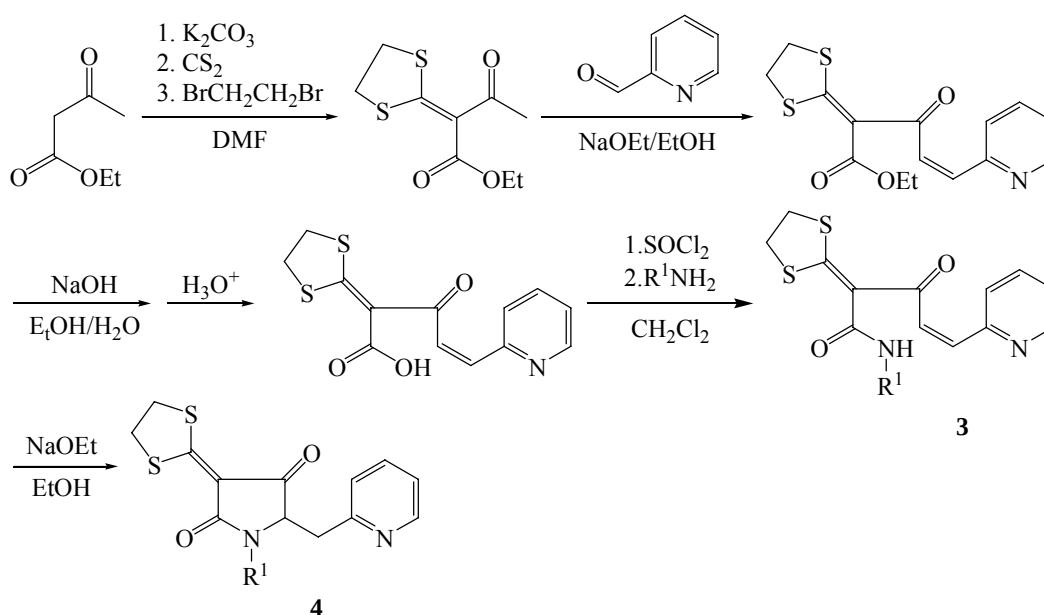
^B Calculated based on ¹H NMR

We proposed a mechanism for the cyclization, as shown in Scheme 3, where **4e** was chosen as a typical example. According to the Baldwin's rule,⁸ the attack of the amido nitrogen on carbon 4 to form 5-membered ring (5-Exo-Trig closure), is more favorable than that on carbon 5 to form 6-membered ring (6-Endo-Trig closure). Furthermore, the attack on carbon 4 results in the formation of a more stable carbanion intermediate (5-membered ring), due to more resonance structures. The previous observation, where compounds (**4l** and **4m**) were obtained in very low yields, also supports the above mechanism, since the electron-releasing substituents in benzaldehydes destabilize the resulting carbanion intermediates. This indicates that only pyridinecarboxaldehyde or benzaldehydes containing an electron-withdrawing substituent can be successfully employed for the synthesis of 2,4-pyrrolidinediones through our synthetic route.



Scheme 3. Proposed mechanism for the formation of **4e** and chemical structure of its reduction product (**5**).

To prove the above mechanism, compound (**4e**) was reduced with NaBH_4 to obtain compound (**5**) (Scheme 3). If the cyclization reaction formed **6**, the corresponding reduction product should be **7**. According to the ^1H - ^1H COSY spectrum of the reduction product, proton resonance *b* was correlated with three protons *a*, *c* and *c'*, which is possible only for compound (**5**). On the other hand, we expect that in the case of compound (**7**), proton resonance *b* should be correlated with only two protons *c* and *c'*. This result clearly supports the proposed mechanism for the formation of 5-membered ring products.



Scheme 4. Synthesis of **4g-i** from isolated **3a-3c**.

Table 2 . Synthesis of **4g-i** from isolated **3a-c**.

α -(2-Pyridylvinylcarbonyl)- α' -(<i>N</i> -arylaminocarbonyl)ketene dithioacetal		Product	Time (h)	Yield (%)
R_1				
3a	C_6H_5	4g	2	76
3b	$4\text{-O}_2\text{NC}_6\text{H}_4$	4h	2	77
3c	$4\text{-MeC}_6\text{H}_4$	4i	2	81

In order to confirm that the aldol condensation product (**3**) is the intermediate undergoing the subsequent *in situ* cyclization, to form the corresponding 2,4-pyrrolidinedione (**4**), compounds (**3a-c**) were synthesized, as shown in Scheme 4.⁹ The isolated compounds (**3a-c**) were then treated with NaOEt in ethanol, to give the corresponding products (**4g-i**), respectively. The isolation yields of the final products

were 76-81% (Table 2). This result supports that the above reactions between α -acetyl- α' -(*N*-arylamino-carbonyl)ketene dithioacetal (**1**) and arylaldehyde (**2**) undergo the base-catalyzed cyclization to afford the corresponding 2,4-pyrrolidinedione (**4**).

In conclusion, 2,4-pyrrolidinediones were successfully synthesized from readily available α -acetyl- α' -(*N*-arylamino-carbonyl)ketene dithioacetals and aryl aldehydes in the presence of NaOEt in one-pot under mild reaction conditions. This route allows both *N*-aryl (R^1) and pyridylmethylene ($PyCH_2$) or benzyl groups containing electron-withdrawing substituents (R^2CH_2) to be incorporated into the 2,4-pyrrolidinedione derivatives as substituents. The 2,4-pyrrolidinediones contain both α -oxoketene dithioacetal moiety and two carbonyl groups, and thus can be employed as new intermediates for the synthesis of more complicated 2,4-pyrrolidinedione derivatives.

EXPERIMENTAL

General: All reagents were purchased from the Aldrich Chemical Co. and used without further treatment unless otherwise noted. A fresh solution (0.1N) of NaOEt in EtOH was used. The products were purified by column chromatography over silica gel purchased from Qingdao Ocean Chemical Co.

1H NMR spectra were recorded on a Bruker Avance 600 NMR spectrometer (600 MHz) and a Varian Unity-Inova 400 NMR spectrometer (400 MHz) in $CDCl_3$ or $DMSO-d_6$. ^{13}C NMR spectra were obtained on a Varian Mercury 300 NMR spectrometer (75 MHz) in $CDCl_3$ unless otherwise stated. Chemical shifts were expressed relative to TMS for 1H and ^{13}C NMR spectra. IR spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer in the range of 400-4000 cm^{-1} . Elemental analyses were measured on a PE-2400 analyzer (Perkin-Elmer).

General procedure for the preparation of 2,4-pyrrolidinedione derivatives (4): To a stirred suspension of α -acetyl- α' -(*N*-arylamino-carbonyl)ketene dithioacetal (**1**) (2.0 mmol) in ethanol (15 mL) was added compound (**2**) (2.2 mmol) and 0.1N solution of NaOEt in EtOH (0.5 equiv.). The reaction mixture was stirred at rt until the starting material (**1**) disappeared (checked by TLC), and then the reaction solvent was removed under reduced pressure. The residue was washed with water (3 x 15 mL) and then dried. The crude product was column chromatographed on silica gel with hexane-EtOAc (4/3) as eluent, and recrystallized from hexane-EtOAc (3/1) to provide the 2,4-pyrrolidinedione (**4**) (see Table 1).

Product (**4a**): $R^1 = 2,4-Me_2C_6H_3$, $n = 1$, $R^2 = 2-Py$, yellowish crystal, mp 198-200 °C, 1H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, 1H, $J = 4.2$ Hz, ArH), 7.41 (m, 1H, ArH), 6.99 (m, 1H, ArH), 6.87-6.94 (m, 4H, ArH), 4.71-5.10 (br, 1H, NCH), 3.48-3.58 (m, 4H, 2 x SCH_2), 3.16 (m, 2H, CH_2), 2.25 (s, 3H, *p*-MeAr), 1.90-2.17 (br, 3H, *o*-MeAr); ^{13}C NMR δ 192.8 (C=O), 175.5 (C= on the adjacent S atoms), 156.5 (C=O on the adjacent N atom), 149.0 (Ar C), 137.1 (Ar C), 135.9 (Ar C), 132.3 (Ar C), 131.57 (Ar C), 129.9 (Ar C), 127.0 (Ar C), 126.4 (Ar C), 125.4 (Ar C), 123.7 (Ar C), 121.23 (Ar C), 113.4 (C= in the ring of

pyrrolidinedione), 66.2 (CH), 38.57 (CH₂), 37.8 (CH₂), 37.4 (CH₂), 20.9 (CH₃), 18.2 (CH₃); IR (KBr) ν (cm⁻¹) 1661, 1497, 1437, 1385, 1285, 1237, 833 cm⁻¹. *Anal.* Calcd for C₂₁H₂₀N₂O₂S₂: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.62; H, 5.11; N, 7.19.

(**4b**): R¹ = 2,4-Me₂C₆H₃, n = 1, R² = 4-Py, yellowish crystal, mp 196-198 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.50 (d, 2H, J = 5.7 Hz, ArH), 7.45 (m, 2H, ArH), 7.06 (s, 1H, ArH), 6.97 (m, 2H, ArH), 4.45-4.80 (br, 1H, NCH), 3.59 (m, 4H, 2 x SCH₂), 3.23 (m, 2H, CH₂), 2.32 (s, 3H, CH₃), 2.09 (s, 3H, CH₃); ¹³C NMR δ 195.1 (C=O), 179.1 (C= on the adjacent S atoms), 160.5 (C=O on the adjacent N atom), 148.2 (2Ar C), 147.1 (Ar C), 134.3 (Ar C), 131.6 (Ar C), 126.9 (Ar C), 126.0 (Ar C), 125.6 (2Ar C), 124.4 (Ar C), 121.7 (Ar C), 121.3 (Ar C), 110.4 (C= in the ring of pyrrolidinedione), 68.8 (CH), 33.6 (CH₂), 38.1 (2 x SCH₂), 23.6 (CH₃), 18.1 (CH₃); IR (KBr) ν (cm⁻¹) 1653, 1482, 1412, 1383, 1227, 835 cm⁻¹; *Anal.* Calcd for C₂₁H₂₀N₂O₂S₂: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.77; H, 5.15; N, 7.00.

(**4c**): R¹ = 2-MeC₆H₄, n = 1, R² = 2-Py, yellowish crystal, mp 200-202 °C, ¹H NMR (600 MHz, CDCl₃) δ 8.37 (d, 1H, J = 6.0 Hz, ArH), 7.38 (m, 1H, ArH), 7.06–7.11 (m, 4H, ArH), 6.96 (m, 1H, ArH), 6.83 (d, 1H, J = 6.0 Hz, ArH), 4.75-5.20 (br, 1H, NCH), 3.54 (m, 4H, 2 x SCH₂), 3.20 (br, 2H, CH₂), 1.98-2.18 (br, 3H, CH₃); ¹³C NMR δ 194.7 (C=O), 180.5 (C= on the adjacent S atoms), 159.4 (C=O on the adjacent N atom), 158.8 (Ar C), 149.1 (Ar C), 136.1 (Ar C), 134.0 (Ar C), 128.8 (Ar C), 126.9 (Ar C), 124.9 (Ar C), 125.3 (Ar C), 123.4 (Ar C), 122.7 (Ar C), 121.2 (Ar C), 110.4 (C= in the ring of pyrrolidinedione), 68.3 (CH), 38.57 (2 x SCH₂), 30.4 (CH₂), 16.2 (CH₃); IR (KBr) ν (cm⁻¹) 1653, 1482, 1412, 1383, 1227, 835 cm⁻¹; *Anal.* Calcd for C₂₀H₁₈N₂O₂S₂: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.94; H, 4.81; N, 7.29.

(**4d**): R¹ = 2-MeC₆H₄, n = 1, R² = 4-Py, yellowish crystal, mp 162-164 °C, ¹H NMR (600 MHz, CDCl₃) δ 8.35 (d, 1H, J = 4.0 Hz, ArH), 7.38 (m, 1H, ArH), 7.21 (m, 3H, ArH), 7.16 (m, 1H, ArH), 6.92 (m, 2H, ArH), 4.75 (br, 1H, CH), 3.54 (m, 4H, SCH₂), 3.07 (m, 2H, CH₂), 2.09 (s, 3H, CH₃); ¹³C NMR δ 195.7 (C=O), 180.6 (C= on the adjacent S atoms), 162.4 (C=O on the adjacent N atom), 148.8 (2 x Ar C), 148.1 (Ar C), 136.0 (Ar C), 129.5 (Ar C), 126.8 (Ar C), 124.3 (Ar C), 123.9 (Ar C), 123.3 (2 x Ar C), 122.1 (Ar C), 110.0 (C= in the ring of pyrrolidinedione), 70.3 (CH), 37.7 (2 x SCH₂), 32.4 (CH₂), 15.2 (CH₃); IR (KBr) ν (cm⁻¹) 1658, 1509, 1423, 1384, 1274, 1214 cm⁻¹; *Anal.* Calcd for C₂₀H₁₈N₂O₂S₂: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.90; H, 4.78; N, 7.27.

(**4e**): R¹ = 4-ClC₆H₄, n = 1, R² = 2-Py, yellowish crystal, mp 168-170 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.47 (d, 1H, J = 4.23 Hz, ArH), 7.55 (d, 2H, J = 7.7 Hz, ArH), 7.45 (m, 2H, ArH), 7.25 (d, 2H, J = 7.7 Hz, ArH), 6.83 (d, 1H, J = 7.7 Hz, ArH), 4.85 (br, 1H, CH), 3.52-3.60 (m, 4H, 2 x SCH₂), 3.19 (dd, 1H, J₁ = 18.0 Hz, J₂ = 6.0 Hz, CH-H), 3.39 (m, 1H, CH-H); ¹³C NMR δ 190.3 (C=O), 179.0 (C= on the adjacent S atoms), 165.6 (C=O on the adjacent N atom), 153.7 (Ar C), 149.56 (Ar C), 143.7 (Ar C), 135.09 (Ar C), 130.5 (Ar C), 133.08 (Ar C), 131.5 (Ar C), 129.3 (Ar C), 125.8 (Ar C), 124.9 (Ar C), 123.3 (Ar C), 118.3

(=C in the ring of pyrrolidinedione), 63.5 (CH), 37.9 (2 x SCH₂), 33.8 (CH₂); IR (KBr) ν (cm⁻¹) 1660, 1514, 1489, 1376, 1286, 832 cm⁻¹; *Anal.* Calcd for C₁₉H₁₅N₂O₂ClS₂: C, 56.64; H, 3.75; N, 6.95. Found: C, 56.62; H, 3.75; N, 6.87.

(**4f**): R¹ = 4-ClC₆H₄, n = 1, R² = 4-Py, yellowish crystal, mp 194-196 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, 2H, J = 4.8 Hz, ArH), 7.46 (d, 2H, J = 9.0 Hz, ArH), 7.41 (d, 2H, J = 9.0 Hz, ArH), 6.76 (d, 2H, J = 6.3 Hz, ArH), 4.78 (dd, 1H, J = 5.1 Hz, J = 3.3 Hz, NCH), 3.40-3.60 (m, 4H, 2 x SCH₂), 3.24 (dd, 1H, J = 14.8 Hz, J = 3.3 Hz, CH-H), 3.14 (dd, 1H, J = 14.8 Hz, J = 5.1 Hz, CH-H); ¹³C NMR δ 190.3 (C=O), 179.0 (C= on the adjacent S atoms), 165.6 (C=O on the adjacent N atom), 153.7 (Ar C), 149.56 (Ar C), 143.7 (Ar C), 135.09 (Ar C), 130.5 (2 x Ar C), 129.3 (Ar C), 125.8 (Ar C), 124.9 (2 x Ar C), 123.3 (Ar C), 118.3 (=C in the ring of pyrrolidinedione), 63.5 (CH), 37.9 (2 x SCH₂), 33.8 (CH₂); IR (KBr) ν (cm⁻¹) 1657, 1511, 1486, 1376, 1283, 1214, 836 cm⁻¹; *Anal.* Calcd for C₁₉H₁₅N₂O₂ClS₂: C, 56.64; H, 3.75; N, 6.95. Found: C, 56.77; H, 3.82; N, 6.91.

(**4g**): R¹ = C₆H₅, n = 1, R² = 2-Py, yellowish crystal, mp 230 °C (decomp.), ¹H NMR (600 MHz, CDCl₃) δ 8.42 (d, 1H, J = 4.8 Hz, ArH), 7.43 (m, 3H, ArH), 7.32 (m, 2H, ArH), 7.13 (m, 2H, ArH), 6.90 (m, 1H, ArH), 5.13 (m, 1H, NCH), 3.50 (m, 4H, 2 x SCH₂), 3.36 (m, 1H, CH-H), 3.20 (dd, 1H, J₁ = 14.4 Hz, J₂ = 6.6 Hz, CH-H); ¹³C NMR δ 193.19 (C=O), 181.30 (C= on the adjacent S atoms), 161.11 (C=O on the adjacent N atom), 155.89 (Ar C), 147.36 (Ar C), 138.34 (Ar C), 143.00 (Ar C), 136.21 (Ar C), 124.92 (2 x Ar C), 123.98 (Ar C), 121.87 (Ar C), 121.29 (2 x Ar C), 118.26 (C= in the ring of pyrrolidinedione), 67.54 (CH), 37.64 (2 x SCH₂), 32.84 (CH₂); IR (KBr) ν (cm⁻¹) 1660, 1516, 1493, 1376, 1281 cm⁻¹; *Anal.* Calcd for C₁₉H₁₆N₂O₂S₂: C, 61.93; H, 4.38; N, 7.60. Found: C, 62.01; H, 4.30; N, 7.53.

(**4h**): R¹ = 4-NO₂C₆H₄, n = 1, R² = 2-Py, yellowish crystal, mp 178-180 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.46 (d, 1H, J = 5.1 Hz, ArH), 8.19 (d, 2H, J = 7.5 Hz, ArH), 7.77 (d, 2H, J = 7.5 Hz, ArH), 7.45 (m, 1H, ArH), 7.08 (m, 1H, ArH), 7.87 (m, 1H, ArH), 5.11 (m, 1H, NCH), 3.56 (m, 4H, 2 x SCH₂), 3.37 (m, 1H, CH-H), 3.24 (dd, 1H, J₁ = 14.4 Hz, J₂ = 6.6 Hz, CH-H); ¹³C NMR δ 190.69 (C=O), 179.40 (C= on the adjacent S atoms), 166.06 (C=O on the adjacent N atom), 155.69 (Ar C), 149.36 (Ar C), 143.54 (Ar C), 134.54 (Ar C), 129.12 (2 x Ar C), 123.98 (Ar C), 122.87 (Ar C), 121.39 (2 x Ar C), 121.08 (Ar C), 118.26 (C= in the ring of pyrrolidinedione), 69.84 (CH), 37.98 (CH₂), 37.64 (CH₂), 33.84 (CH₂); IR (KBr) ν (cm⁻¹) 1659, 1512, 1334, 1281 cm⁻¹; *Anal.* Calcd for C₁₉H₁₅N₃O₄S₂: C, 55.19; H, 3.66; N, 10.16. Found: C, 54.11; H, 4.21; N, 11.03.

(**4i**): R¹ = 4-MeC₆H₄, n = 1, R² = 2-Py, yellowish crystal, mp 198-201 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.46 (d, 1H, J = 4.5 Hz, ArH), 7.49 (m, 1H, ArH), 7.32 (d, 2H, J = 7.8 Hz, 2 x ArH), 7.21 (m, 1H, ArH), 7.11 (d, 2H, J = 7.8 Hz, 2 x ArH), 6.62 (d, 1H, J = 7.5 Hz, ArH), 5.04 (m, 1H, NCH), 3.45 (m, 4H, 2 x SCH₂), 3.17 (m, 2H, CH₂), 2.30 (s, 3H, CH₃); ¹³C NMR δ 194.59 (C=O), 180.48 (C= on the adjacent S

atoms), 163.16 (C=O on the adjacent N atom), 161.09 (Ar C), 149.36 (Ar C), 138.34 (Ar C), 135.36 (Ar C), 135.34 (Ar C), 129.22 (2 x Ar C), 123.98 (Ar C), 121.87 (Ar C), 121.49 (2 x Ar C), 110.26 (C= in the ring of pyrrolidinedione), 70.04 (CH), 37.88 (2 x SCH₂), 30.84 (CH₂); 24.24 (CH₃); IR (KBr) ν (cm⁻¹) 1661, 1490, 1385, 1284, 1208, 740 cm⁻¹; *Anal.* Calcd for C₂₀H₁₈N₂O₂S₂: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.94; H, 4.81; N, 7.29.

(**4j**): R¹ = 2,4-Me₂C₆H₃, n = 1, R² = 3-O₂NC₆H₄, yellowish crystal, mp 206-207 °C, ¹H NMR (600 MHz, CDCl₃) δ 7.97 (d, 1H, J = 7.2 Hz, ArH), 7.68 (s, 1H, ArH), 7.31 (m, 2H, ArH), 7.00 (s, 1H, ArH), 6.90 (br, 2H, ArH), 4.45-4.83 (br, 1H, NCH), 3.50-3.61 (m, 4H, 2 x SCH₂), 3.13 (m, 2H, CH₂), 2.28 (s, 3H, CH₃), 2.05 (s, 3H, CH₃); ¹³C NMR δ 206.84 (C=O), 191.79 (C= on the adjacent S atoms), 177.4 (C=O on the adjacent N atom), 155.69 (Ar C), 149.36 (Ar C), 143.54 (Ar C), 129.12 (Ar C), 123.98 (Ar C), 123.54 (Ar C), 122.92 (Ar C), 122.91 (Ar C), 122.87 (Ar C), 121.39 (Ar C), 121.08 (Ar C), 120.08 (Ar C), 118.26 (C= in the ring of pyrrolidinedione), 69.84 (CH), 37.98 (CH₂), 37.64 (CH₂), 33.84 (CH₂), 23.98 (CH₃), 16.64 (CH₃); IR (KBr) ν (cm⁻¹) 1658, 1523, 1498, 1382, 1350, 1234, 822 cm⁻¹; *Anal.* Calcd for C₂₂H₂₀N₂O₄S₂: C, 59.98; H, 4.58; N, 6.36. Found: C, 60.11; H, 4.63; N, 6.20.

(**4k**): R¹ = 2,4-Me₂C₆H₃, n = 1, R² = 2-HOCC₆H₄, yellowish crystal, mp 140-142 °C, ¹H NMR (400 MHz, CDCl₃) δ 10.27 (s, 1H, CHO), 8.07 (m, 1H, ArH), 7.77 (d, 1H, J = 7.89 Hz, ArH), 7.67 (m, 1H, ArH), 7.31 (m, 2H, ArH), 6.90 (br, 2H, 2 x ArH), 4.45-4.83 (br, 1H, NCH), 3.50-3.61 (m, 4H, 2 x SCH₂), 3.13 (m, 2H, CH₂), 2.28 (s, 3H, CH₃), 2.05 (s, 3H, CH₃); ¹³C NMR δ 198.84 (C=O), 193.64 (CH=O), 181.79 (C= on the adjacent S atoms), 177.43 (C=O on the adjacent N atom), 150.69 (Ar C), 137.54 (Ar C), 137.36 (Ar C), 134.04 (Ar C), 133.52 (Ar C), 133.44 (Ar C), 129.12 (Ar C), 128.08 (Ar C), 127.12 (Ar C), 127.11 (Ar C), 127.08 (Ar C), 122.87 (Ar C), 118.29 (C= in the ring of pyrrolidinedione), 69.04 (CH), 37.98 (2 x SCH₂), 25.68 (CH₂), 23.88 (CH₃); 15.87 (CH₃); IR (KBr) ν (cm⁻¹) 1646, 1517, 1455, 1293, 812 cm⁻¹; *Anal.* Calcd for C₂₃H₂₁NO₃S₂: C, 65.22; H, 5.00; N, 3.31. Found: C, 64.12; H, 5.33; N, 3.20.

(**4l**): R¹ = 2,4-Me₂C₆H₃, n = 1, R² = 2-MeC₆H₄, yellowish crystal, mp 176-178 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.07-7.31 (m, 5H, ArH), 6.90 (br, 2H, ArH), 4.47-4.86 (br, 1H, NCH), 3.48-3.51 (m, 4H, 2 x SCH₂), 3.13 (m, 2H, CH₂), 2.28 (s, 3H, CH₃), 2.15 (s, 3H, CH₃), 2.05 (s, 3H, CH₃); ¹³C NMR δ 199.84 (C=O), 181.26 (C= on the adjacent S atoms), 176.45 (C=O on the adjacent N atom), 138.67 (Ar C), 137.84 (Ar C), 137.33 (Ar C), 135.02 (Ar C), 132.62 (Ar C), 126.44 (Ar C), 126.12 (Ar C), 125.08 (Ar C), 124.12 (Ar C), 124.11 (Ar C), 123.08 (Ar C), 122.57 (Ar C), 118.45 (C= in the ring of pyrrolidinedione), 68.03 (CH), 38.58 (2 x SCH₂), 27.68 (CH₂), 23.88 (CH₃); 15.87 (CH₃); 16.87 (CH₃); IR (KBr) ν (cm⁻¹) 1655, 1545, 1435, 1283, 822 cm⁻¹.

(**4m**): R¹ = 2,4-Me₂C₆H₃, n = 1, R² = 4-CH₃CONHC₆H₄, yellowish crystal, mp 183-187 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.02 (s, 1H, NH), 7.98-7.21 (m, 3H, ArH), 6.84-7.10 (m, 4H, ArH), 4.86 (br, 1H,

NCH), 3.46-3.54 (m, 4H, 2 x SCH₂), 2.98 (m, 2H, CH₂), 2.35 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 2.01 (s, 3H, CH₃); ¹³C NMR δ 194.64 (C=O), 183.24 (C= on the adjacent S atoms), 168.34 (NHC=O), 167.48 (C=O on the adjacent N atom), 137.68 (Ar C), 137.64 (Ar C), 137.53(Ar C), 135.82 (Ar C), 133.64 (Ar C), 127.41 (Ar C), 127.12 (Ar C), 126.05 (Ar C), 125.17 (Ar C), 124.17 (Ar C), 124.16 (Ar C), 123.89 (Ar C), 113.45 (C= in the ring of pyrrolidinedione), 69.03 (CH), 38.67 (2 x SCH₂), 30.68 (CH₂), 23.98 (CH₃); 22.87 (CH₃); 22.12 (CH₃); IR (KBr) ν (cm⁻¹) 1655, 1545, 1435, 1283, 822 cm⁻¹.

(**4o**): R¹ = 2-MeC₆H₄, n = 2, R² = 2-Py, yellowish crystal, mp 155-157 °C, ¹H NMR (400 MHz, CDCl₃) δ 8.36 (d, 1H, J = 4.6 Hz, ArH), 7.36 (m, 1H, ArH), 7.08 (m, 2H, ArH), 6.97 (m, 3H, ArH), 6.82 (d, 1H, J = 8.2 Hz, ArH), 4.75 (br, 1H, NCH), 3.06 (m, 4H, 2 x SCH₂), 2.87 (m, 2H, CH₂ in sulfur ring), 2.33 (m, 2H, CH₂), 2.07 (s, 3H, CH₃); ¹³C NMR δ 201.64 (C=O), 180.26 (C= on the adjacent S atoms), 169.43 (C=O on the adjacent N atom), 148.64 (Ar C), 138.86 (Ar C), 137.23(Ar C), 136.02 (Ar C), 128.43 (Ar C), 127.13 (Ar C), 126.49 (Ar C), 126.55 (Ar C), 126.07 (Ar C), 125.33(Ar C), 124.89 (Ar C), 110.85 (C= in the ring of pyrrolidinedione), 70.03 (CH), 45.58 (2 x SCH₂), 29.89 (CH₂), 29.68 (CH₂), 16.88 (CH₃). IR (KBr) ν (cm⁻¹) 1654, 1516, 1472, 1302, 1202, 861, 698; *Anal.* Calcd for C₂₁H₂₀N₂O₂S₂: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.67; H, 5.12; N, 7.00.

(**4p**): R¹ = 2-MeOC₆H₄, n = 2, R² = 4-O₂NC₆H₄, yellowish crystal, mp 190-192 °C, ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 (d, 2H, 2 x ArH, J = 8.0 Hz), 7.61(m, 1H, ArH), 7.44-7.14 (m, 3H, 3 x ArH), 7.02 (d, 2H, 2 x ArH, J = 8.0 Hz), 4.70 (br, 1H, NCH), 3.65 (s, 3H, OCH₃), 3.55 (m, 4H, 2 x SCH₂), 3.01 (m, 2H, CH₂ in sulfur ring), 2.07 (m, 2H, CH₂); ¹³C NMR δ 195.64 (C=O), 181.26 (C= on the adjacent S atoms), 165.42 (C=O on the adjacent N atom), 155.02 (Ar C), 145.68 (Ar C), 145.24 (Ar C), 127.89 (Ar C), 127.22 (Ar C), 126.81 (Ar C), 126.45 (Ar C), 126.13 (Ar C), 125.48(Ar C), 125.17 (Ar C), 124.33(Ar C), 123.89 (Ar C), 113.23 (C= in the ring of pyrrolidinedione), 70.93 (CH), 56.88 (OCH₃), 28.58 (2 x SCH₂), 28.48 (CH₂), 27.58 (CH₂). IR (KBr) ν (cm⁻¹) 1614, 1516, 1346, 1223, 755.04; *Anal.* Calcd for C₂₂H₂₀N₂O₅S₂: C, 57.88; H, 4.42; N, 6.14. Found: C, 60.07; H, 4.32; N, 6.12.

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7. General procedure for the preparation of **1** and the selected analysis data for **1a**: Potassium carbonate (40 mmol, 5.52 g), ethyl 3-oxobutanoate (20 mmol, 2.6 g) and DMF (20 mL) were placed in a 50-mL round-bottomed flask, and then the whole was stirred for 10 min at rt. The reaction mixture was cooled in ice-water, followed by the addition of carbon disulfide (22 mmol, 1.3 mL). 1,2-Dibromoethane or 1,3-dibromopropane was added to the above mixture, and the resulting mixture was stirred for 8 h at rt. The reaction mixture was poured into ice-water (200 mL), and the yellow solid material was separated by filtration. The solid was washed with water and dried. Ethyl ester of 2-(1,3)-dithiolan/dithian-2-ylidene-3-oxobutyric acid in EtOH/water (5/1) was refluxed in the presence of NaOH (5 equiv.) for 3 h to obtain the corresponding hydrolyzed carboxylic acid, which was then treated with SOCl₂ (100 mmol, 11.90 g), and reacted with R¹NH₂ (20 mmol) to yield **1**. **1a**: colorless crystal (recrystallized from hexane/EtOAc = 5/1), mp 196-198 °C, ¹H NMR (600 MHz, CDCl₃) δ 7.87 (s, 1H, NH), 7.77 (d, 1H, J = 8.0 Hz, ArH), 7.05 (d, 1H, J = 8.0 Hz, ArH), 7.04 (s, 1H, ArH), 3.45 (m, 2H, SCH₂), 3.38 (m, 2H, SCH₂), 2.46 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 2.30 (s, 3H, CH₃).
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9. General procedure for the preparation of **3** and the selected analysis data for **3a**: According to general procedure for the preparation of **1**, ethyl 2-(1,3-dithiolan-2-ylidene)-3-oxobutanoate was first prepared

from ethyl 3-oxobutanoate. And then to a stirred suspension of ethyl 2-(1,3-dithiolan-2-ylidene)-3-oxobutanoate (2.0 mmol) in ethanol (20 mL) was added aldehyde ($R^2\text{CHO}$) (2.2 mmol) and a solution of NaOEt (0.5 equiv.) in EtOH (0.1N, 10 mL). The reaction mixture was stirred at rt for about 2 h (checked by TLC). The reaction solvent was removed under reduced pressure. The residue was washed with water (3 x 15 mL) and then dried. The crude product was column chromatographed on silica gel (eluant, hexane/EtOAc=85/15), and recrystallized from hexane-EtOAc (5/1) to obtain dithioacetal, which was hydrolyzed to give the corresponding carboxylic acid. The acid was then activated with SOCl_2 (50 mmol, 6 g), and reacted with $R^1\text{NH}_2$ (20 mmol) to yield crude compound (**3**). The crude product was column chromatographed on silica gel (eluant, hexane/EtOAc/MC=75/20/5), and recrystallized from hexane-EtOAc (3/2) to obtain compound (**3**). **3a**: Yellowish crystal (recrystallized from hexane/EtOAc=3/2), mp 204-206 °C, ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, 1H, $J = 4.2$ Hz, ArH), 8.10 (s, 1H, NH), 7.88 (m, 3H, 3 x ArH), 7.88 (d, 1H, $J = 15.6$ Hz, =CH), 7.87 (m, 1H, ArH), 7.45 (d, 1H, $J = 15.6$ Hz, =CH), 7.41-7.21 (m, 4H, 4 x ArH), 3.31-3.41 (m, 4H, 2 x SCH_2).