HETEROCYCLES, Vol. 68, No. 2, 2006, pp. 357 – 368. © The Japan Institute of Heterocyclic Chemistry
Received, 7th November, 2005, Accepted, 22nd December, 2005, Published online, 27th December, 2005. COM-05-10618

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

Yu-Zi Jin,[a, b] Bing Zhu Yin,[a]* and Youn-Sik Lee[b]*

[a]Department of Chemistry, College of Science, Yanbian University, Yanji, 133-002, P. R. China, and [b]Division of Environmental and Chemical Engineering, Nanomaterials Research Center, Chonbuk National University, Chonju 561-756, Korea, Tel.: +82 652 270 2312, e-mail: yosklear@chonbuk.ac.kr

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

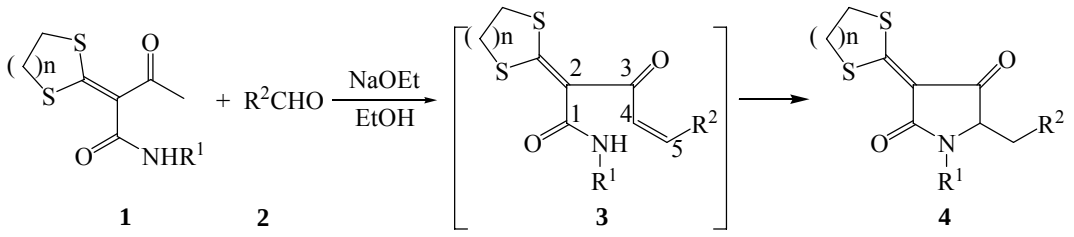
INTRODUCTION

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 based-catalyzed reaction of α-acetyl-α′-(*N*-arylaminocarbonyl)ketene dithioacetal (**1**) with arylaldehyde (**2**), formed α-(arylvinyl-carbonyl)-α′-(*N*-arylaminocarbonyl)ketene dithioacetal (**3**) which underwent cyclization *in situ* to give highly functionalyzed 2,4-pyrrolidinedione (**4**). α-Acetyl-α′-(*N*-arylaminocarbonyl)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

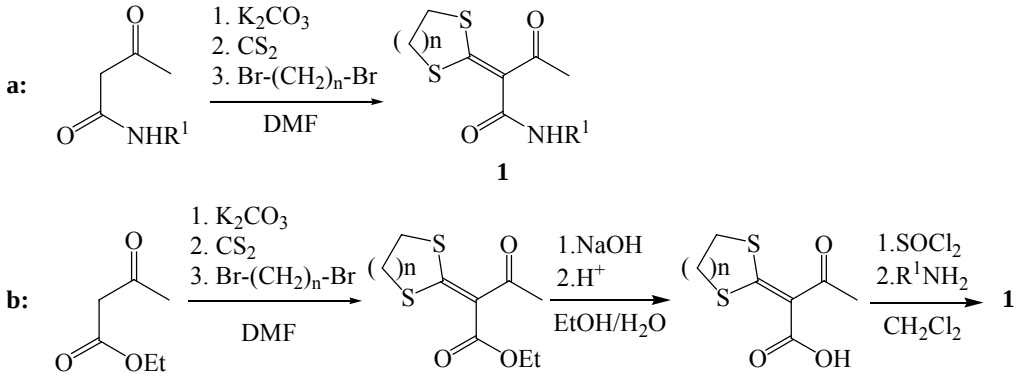
As shown in Scheme 1, the synthetic strategy in this paper was designed by considering that compound (**3**) (aldol condensation product), formed from compounds (**1** and **2**) in the presence of base, may undergo

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*-arylaminocarbonyl)ketene dithioacetals (**1**) were prepared in high yields (85-97%) from commercial *N*-aryl-3-oxobutyramides, 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*-arylaminocarbonyl)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 CH_3 and $NHCOCH_3$ 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.

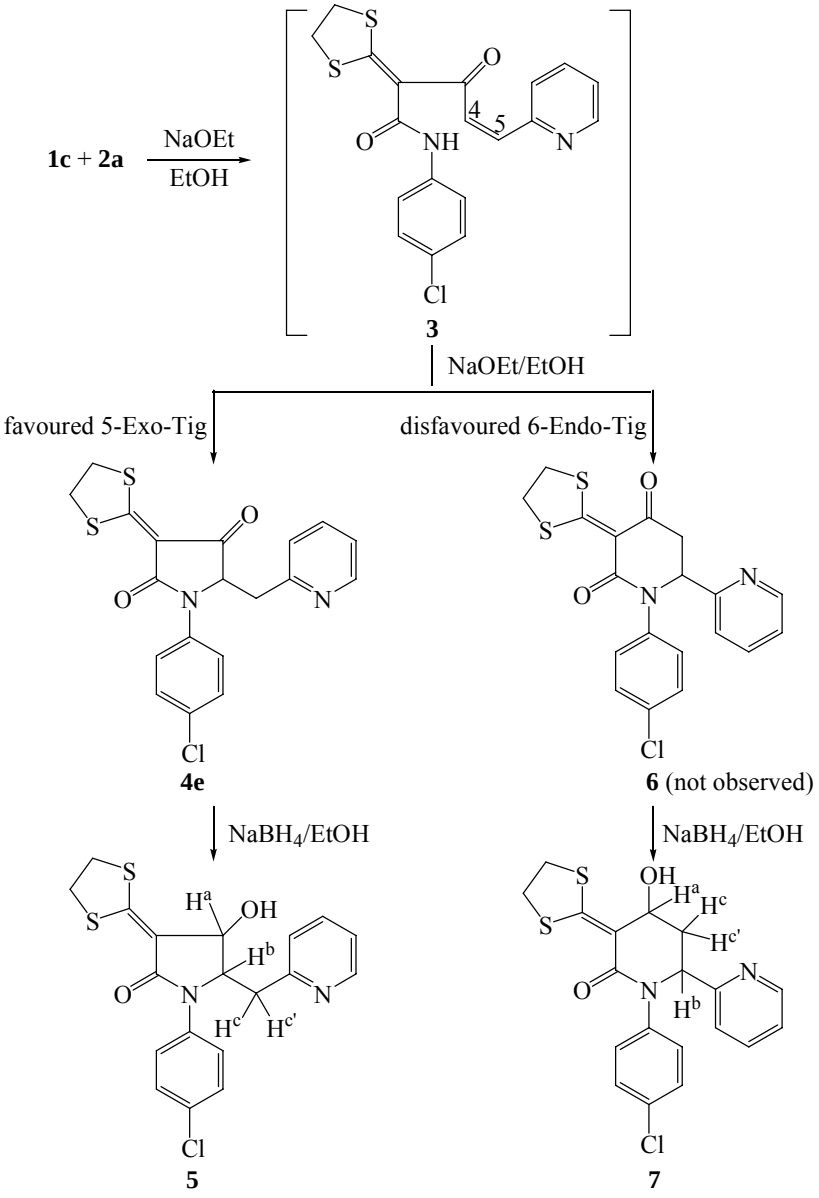
Table 1. Synthesis of 2,4-pyrrolidinediones (**4**) from dithioacetals (**1**) and arylaldehydes (**2**).

Dithioacetal		n	Aldehyde		Product	Time (h)	Yield (%)	mp (℃)
	R^1			R^2				
1a	2,4-$Me_2C_6H_3$	1	**2a**	2-pyridyl	**4a**	2	83	198-200
1a	2,4-$Me_2C_6H_3$	1	**2b**	4-pyridyl	**4b**	2	75	196-198
1b	2-MeC_6H_4	1	**2a**	2-pyridyl	**4c**	5	78	155-157
1b	2-MeC_6H_4	1	**2b**	4-pyridyl	**4d**	2	73	162-164
1c	4-ClC_6H_4	1	**2a**	2-pyridyl	**4e**	2	77	168-170
1c	4-ClC_6H_4	1	**2b**	4-pyridyl	**4f**	3	72	168-170
1d	C_6H_5	1	**2a**	2-pyridyl	**4g**	6	70	169-170
1e	4-$O_2NC_6H_4$	1	**2b**	2-pyridyl	**4h**	6	75	128-130
1f	4-MeC_6H_4	1	**2a**	2-pyridyl	**4i**	3	72	210-212
1a	2,4-$Me_2C_6H_3$	1	**2c**	3-$O_2NC_6H_4$	**4j**	2	85	206-207
1a	2,4-$Me_2C_6H_3$	1	**2d**	2-$HOCC_6H_4$	**4k**	5	67	140-142
1a	2,4-$Me_2C_6H_3$	1	**2e**	2-MeC_6H_4	**4l**	6	~20[B]	176-178
1a	2,4-$Me_2C_6H_3$	1	**2f**	4- CH_3CONH-C_6H_4	**4m**	7	~30[B]	183-187
1a	2,4-$Me_2C_6H_3$	1	**2g**	4-OHC_6H_4	**4n**	7	--	--
1b	2-MeC_6H_4	2	**2a**	2-pyridyl	**4o**	2	80	200-202
1g	2-$MeOC_6H_4$	2	**2h**	4-$O_2NC_6H_4$	**4p**	2	76	190-192

[A] Isolation yield

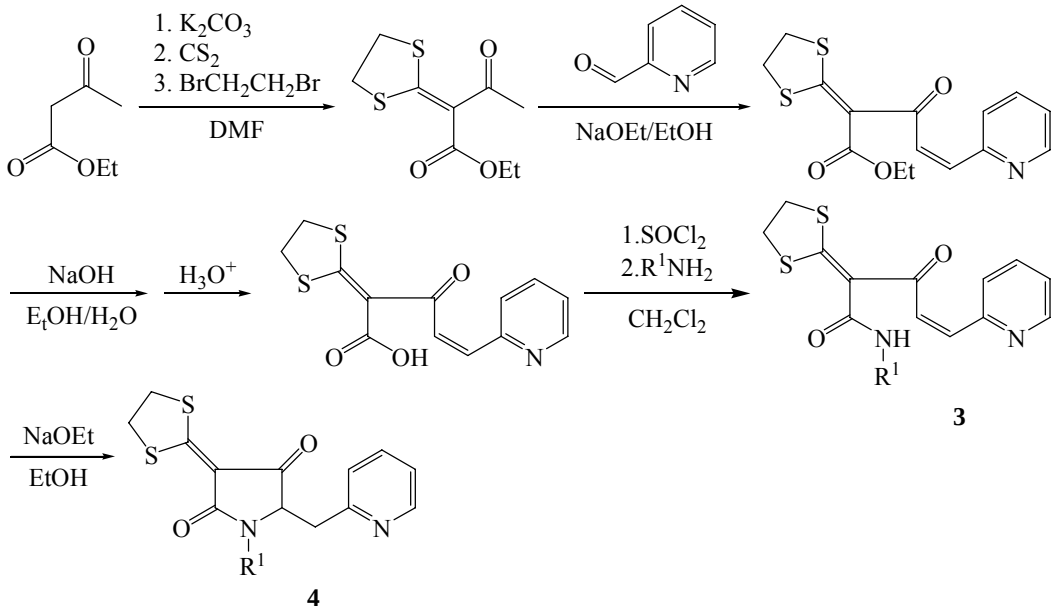
[B] Calculated based on ^1H NMR

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-memberd 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′-(*N*-arylaminocarbonyl)ketene dithioacetal		Product	Time (h)	Yield (%)
	R_1			
3a	C_6H_5	**4g**	2	76
3b	4-$O_2NC_6H_4$	**4h**	2	77
3c	4-MeC_6H_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*-arylaminocarbonyl)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*-arylaminocarbonyl)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.

^{1}H 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 ^{1}H 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*-arylaminocarbonyl)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 ℃, ^{1}H 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 (CH_2), 37.8 (CH_2), 37.4 (CH_2), 20.9 (CH_3), 18.2 (CH_3); IR (KBr) ν (cm^{-1}) 1661, 1497, 1437, 1385, 1285, 1237, 833 cm^{-1}. *Anal*. Calcd for $C_{21}H_{20}N_2O_2S_2$: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.62; H, 5.11; N, 7.19.

(**4b**): R^1 = 2,4-$Me_2C_6H_3$, n = 1, R^2 = 4-Py, yellowish crystal, mp 196-198 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 3.23 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.09 (s, 3H, CH_3); ^{13}C 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 (CH_2), 38.1 (2 x SCH_2), 23.6 (CH_3), 18.1 (CH_3); IR (KBr) ν (cm^{-1}) 1653, 1482, 1412, 1383, 1227, 835 cm^{-1}; *Anal*. Calcd for $C_{21}H_{20}N_2O_2S_2$: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.77; H, 5.15; N, 7.00.

(**4c**): R^1 = 2-MeC_6H_4, n = 1, R^2 = 2-Py, yellowish crystal, mp 200-202 ℃, ^{1}H NMR (600 MHz, $CDCl_3$) 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 SCH_2), 3.20 (br, 2H, CH_2), 1.98-2.18 (br, 3H, CH_3); ^{13}C 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 SCH_2), 30.4 (CH_2), 16.2 (CH_3); IR (KBr) ν (cm^{-1}) 1653, 1482, 1412, 1383, 1227, 835 cm^{-1}; *Anal.* Calcd for $C_{20}H_{18}N_2O_2S_2$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.94; H, 4.81; N, 7.29.

(**4d**): R^1 = 2-MeC_6H_4, n = 1, R^2 = 4-Py, yellowish crystal, mp 162-164 ℃, ^{1}H NMR (600 MHz, $CDCl_3$) 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, SCH_2), 3.07 (m, 2H, CH_2), 2.09 (s, 3H, CH_3); ^{13}C 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 SCH_2), 32.4 (CH_2), 15.2 (CH_3); IR (KBr) ν (cm^{-1}) 1658, 1509, 1423, 1384, 1274, 1214 cm^{-1}; *Anal*. Calcd for $C_{20}H_{18}N_2O_2S_2$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.90; H, 4.78; N, 7.27.

(**4e**): R^1 = 4-ClC_6H_4, n = 1, R^2 = 2-Py, yellowish crystal, mp 168-170 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 3.19 (dd, 1H, J_1 = 18.0 Hz, J_2 = 6.0 Hz, CH-H), 3.39 (m, 1H, CH-H); ^{13}C 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 SCH_2), 33.8 (CH_2); IR (KBr) ν (cm^{-1}) 1660, 1514, 1489, 1376, 1286, 832 cm^{-1}; *Anal*. Calcd for $C_{19}H_{15}N_2O_2ClS_2$: C, 56.64; H, 3.75; N, 6.95. Found: C, 56.62; H, 3.75; N, 6.87.

(**4f**): R^1 = 4-ClC_6H_4, n = 1, R^2 = 4-Py, yellowish crystal, mp 194-196 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 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); ^{13}C 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 SCH_2), 33.8 (CH_2); IR (KBr) ν (cm^{-1}) 1657, 1511, 1486, 1376, 1283, 1214, 836 cm^{-1}; *Anal*. Calcd for $C_{19}H_{15}N_2O_2ClS_2$: C, 56.64; H, 3.75; N, 6.95. Found: C, 56.77; H, 3.82; N, 6.91.

(**4g**): R^1 = C_6H_5, n = 1, R^2 = 2-Py, yellowish crystal, mp 230 ℃ (decomp.), ^{1}H NMR (600 MHz, $CDCl_3$) 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 SCH_2), 3.36 (m, 1H, CH-H), 3.20 (dd, 1H, J_1 = 14.4 Hz, J_2 = 6.6 Hz, CH-H); ^{13}C 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 SCH_2), 32.84 (CH_2); IR (KBr) ν (cm^{-1}) 1660, 1516, 1493, 1376, 1281 cm^{-1}; *Anal*. Calcd for $C_{19}H_{16}N_2O_2S_2$: C, 61.93; H, 4.38; N, 7.60. Found: C, 62.01; H, 4.30; N, 7.53.

(**4h**): R^1 = 4-$NO_2C_6H_4$, n = 1, R^2 = 2-Py, yellowish crystal, mp 178-180 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 3.37 (m, 1H, CH-H), 3.24 (dd, 1H, J_1 = 14.4 Hz, J_2 = 6.6 Hz, CH-H); ^{13}C 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 (CH_2),, 37.64 (CH_2), 33.84 (CH_2); IR (KBr) ν (cm^{-1}) 1659, 1512, 1334, 1281 cm^{-1}; *Anal*. Calcd for $C_{19}H_{15}N_3O_4S_2$: C, 55.19; H, 3.66; N, 10.16. Found: C, 54.11; H, 4.21; N, 11.03.

(**4i**): R^1 = 4-MeC_6H_4, n = 1, R^2 = 2-Py, yellowish crystal, mp 198-201 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 3.17 (m, 2H, CH_2), 2.30 (s, 3H, CH_3); ^{13}C 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 SCH_2), 30.84 (CH_2); 24.24 (CH_3); IR (KBr) ν (cm^{-1}) 1661, 1490, 1385, 1284, 1208, 740 cm^{-1}; *Anal*. Calcd for $C_{20}H_{18}N_2O_2S_2$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.94; H, 4.81; N, 7.29.

(**4j**): R^1 = 2,4-$Me_2C_6H_3$, n = 1, R^2 = 3-$O_2NC_6H_4$, yellowish crystal, mp 206-207 ℃, ^{1}H NMR (600 MHz, $CDCl_3$) 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 SCH_2), 3.13 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); ^{13}C 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 (CH_2), 37.64 (CH_2), 33.84 (CH_2), 23.98 (CH_3), 16.64 (CH_3),; IR (KBr) ν (cm^{-1}) 1658, 1523, 1498, 1382, 1350, 1234, 822 cm^{-1}; *Anal*. Calcd for $C_{22}H_{20}N_2O_4S_2$: C, 59.98; H, 4.58; N, 6.36. Found: C, 60.11; H, 4.63; N, 6.20.

(**4k**): R^1 = 2,4-$Me_2C_6H_3$, n = 1, R^2 = 2-$HOCC_6H_4$, yellowish crystal, mp 140-142 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 3.13 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); ^{13}C 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 SCH_2), 25.68 (CH_2), 23.88 (CH_3); 15.87 (CH_3); IR (KBr) ν (cm^{-1}) 1646, 1517, 1455, 1293, 812 cm^{-1}; *Anal*. Calcd for $C_{23}H_{21}NO_3S_2$: C, 65.22; H, 5.00; N, 3.31. Found: C, 64.12; H, 5.33; N, 3.20.

(**4l**): R^1 = 2,4-$Me_2C_6H_3$, n = 1, R^2 = 2-MeC_6H_4, yellowish crystal, mp 176-178 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 3.13 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); ^{13}C 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 SCH_2), 27.68 (CH_2), 23.88 (CH_3); 15.87 (CH_3); 16.87 (CH_3); IR (KBr) ν (cm^{-1}) 1655, 1545, 1435, 1283, 822 cm^{-1}.

(**4m**): R^1 = 2,4-$Me_2C_6H_3$, n = 1, R^2 = 4-$CH_3CONHC_6H_4$, yellowish crystal, mp 183-187 ℃, ^{1}H 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 SCH_2), 2.98 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); ^{13}C 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 SCH_2), 30.68 (CH_2), 23.98 (CH_3); 22.87 (CH_3); 22.12 (CH_3); IR (KBr) ν (cm^{-1}) 1655, 1545, 1435, 1283, 822 cm^{-1}.

(**4o**): R^1 = 2-MeC_6H_4, n = 2, R^2 = 2-Py, yellowish crystal, mp 155-157 ℃, ^{1}H NMR (400 MHz, $CDCl_3$) 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 SCH_2), 2.87 (m, 2H, CH_2 in sulfur ring), 2.33 (m, 2H, CH_2), 2.07 (s, 3H, CH_3); ^{13}C 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 SCH_2), 29.89 (CH_2), 29.68 (CH_2), 16.88 (CH_3). IR (KBr) ν (cm^{-1}) 1654, 1516, 1472, 1302, 1202, 861, 698; *Anal*. Calcd for $C_{21}H_{20}N_2O_2S_2$: C, 63.61; H, 5.08; N, 7.06. Found: C, 63.67; H, 5.12; N, 7.00.

(**4p**): R^1 = 2-$MeOC_6H_4$, n = 2, R^2 = 4-$O_2NC_6H_4$, yellowish crystal, mp 190-192 ℃, 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, OCH_3), 3.55 (m, 4H, 2 x SCH_2), 3.01 (m, 2H, CH_2 in sulfur ring), 2.07 (m, 2H, CH_2); ^{13}C 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 (OCH_3), 28.58 (2 x SCH_2), 28.48 (CH_2), 27.58 (CH_2). IR (KBr) ν (cm^{-1}) 1614, 1516, 1346, 1223, 755.04; *Anal*. Calcd for $C_{22}H_{20}N_2O_5S_2$: C, 57.88; H, 4.42; N, 6.14. Found: C, 60.07; H, 4.32; N, 6.12.

ACKNOWLEDGMENTS

Financial support of this research was provided by the NNSFC (29862004) in P. R. China and the BK-21 project in 2003 in Korea.

REFERENCES

1. R. Anschüz and R. Boecker, *Ann. Chem.*, 1909, **368**, 53.

2. B. J. L. Royles, *Chem. Rev.*, 1995, **95**, 1981.

3. (a) O. Markopoulou, J. Markopoulos, and D. Nicholls, *J. Inorg. Biochem.*, 1990, **39**, 307. (b) B. T.

Heaton, C. Jacob, J. Markopoulos, O. Markopoulou, J. Nähring, C.-K. Skylaris, and A. K. Smith, *J. Chem. Soc.*, *Dalton Trans*., 1996, 1701.

4. (a) A. Nowak and B. Steffan, *Angew. Chem., Int. Ed. Eagl.*, 1998, **37**, 3139. (b) R. J. Capon, C. Skene, E. Lacey, J. H. Gill, D. Wadsworth, and T. Friedel, *J. Nat. Prod.*, 1999, **62**, 1256. (c) N. U. Sata, S. Wada, S. Matsunaga, S. Watabe, R. W. M. van Soest, and N. Fusetani, *J. Org. Chem.*, 1999, **64**, 2331. (d) D. Wolf, F. J. Schmitz, F. Qiu, and M. Kelly-Borges, *J. Nat. Prod.*, 1999, **62**, 170. (e) C. Osterhage, R. Kaminsky, G. M. Konig, and A. D. Wright, *J. Org. Chem.*, 2000, **65**, 6412, and references therein.
5. (a) S. Fustero, M. García de la Torre, J. F. Sanz-Cervera, C. Ramírez de Arellano, J. Piera, and A. Simón, *Org. Lett.*, 2002, **4**, 3651. (b) J. Matthews and R. A. Rivero, *J. Org. Chem.*, 1998, **63**, 4808. (c) Z. Liu, X. Ruan, and X. Huang, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2505. (d) Jörg Wuckelt, M. Döring, P. Langer, H. Görls and R. Beckert, *Tetrahedron Lett.*, 1998, **39**, 1135. (e) B. A. Kulkarni and A. Ganesan, *Tetrahedron Lett.*, 1998, **39**, 4369. (f) M. Petroliagi and O. Igglessi-Markopoulou, *Tetrahedron*: *Asymmetry*, 1999, **10**, 1873. (g) T. T. Romoff, L. Ma, Y. Wang, and D. A. Campbell, *Synlett*, 1998, 1341.
6. (a) R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029. (b) H. Junjappa, H. Ila, and C. V. Asokan, *Tetrahedron*, 1990, **46**, 5423. (c) H. Ila, H. Junjappa, and O. Barun, *J. Organomet. Chem.*, 2001, **624**, 34. (d) P. K. Mahata, U. K. Syam Kumar, V. Sriram, H. Ila, and H. Junjappa, *Tetrahedron*, 2003, **59**, 2631.
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 $SOCl_2$ (100 mmol, 11.90 g), and reacted with R^1NH_2 (20 mmol) to yield **1**. **1a**: colorless crystal (recrystallized from hexane/EtOAc = 5/1), mp 196-198 ℃, ^{1}H NMR (600 MHz, $CDCl_3$) 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, SCH_2), 3.38 (m, 2H, SCH_2), 2.46 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.30 (s, 3H, CH_3).
8. (a) J. E. Baldwin, *J. C. S. Chem. Comm*., 1976, **98**, 734. (b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *J. C. S. Chem. Comm*., 1976, **98**, 736.
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^2CHO) (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^1NH_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 ℃, ^{1}H 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).