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A one-pot, three-component synthesis of thiazolidine-2-thiones

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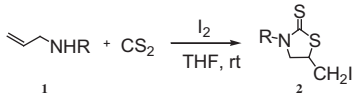
ABSTRACT

An efficient method for the synthesis of thiazolidine-2-thiones is described via regiospecific iodocyclization of an allyl amine, carbon disulfide, and iodine. Dehydrohalogenation of the iodo-derivatives gives thiazole-2(3*H*)-thiones. In addition, nucleophilic substitution of the iodine in the products is accomplished using NaN_3, thiophenol, or dithiocarbamate.

Oxazolidinones and thiazolidinethiones are the main building blocks in the structure of linezolid and its thia analogue, which have attracted attention as a new class of orally active synthetic antibiotics.[1–4] Optically active oxazolidinethiones and thiazolidinethiones have been used extensively as chiral auxiliaries for asymmetric C–C bond formation.[5] Thiazolidinethione chiral auxiliaries also exhibit several advantages over their oxazolidinone analogues. They can be directly reduced to aldehydes and displaced by several nucleophiles.[6] Also, 3-acylthiazolidine-2-thiones have been used as selective acylating agents for alcohols.[7] Furthermore, thiazolidine-2-thiones have found wide application in coordination chemistry.[8]

Iodocyclization of unsaturated C–C bonds with a wide variety of nucleophiles, including N, O, Se, and S, has been studied extensively and represents a powerful tool for the construction of various heterocycles.[9]

Thiazolidine-2-thione has commonly been synthesized by heating an alkaline solution of a β-amino alcohol and carbon disulfide.[10] This simple procedure has several disadvantages such as the use of a strong basic medium, an excess of carbon disulfide, long reaction times, and high temperature. Therefore, methods which overcome these drawbacks are required. In continuation of our interest in developing efficient methods for the synthesis of novel dithiocarbamates and the use of these intermediates in organic transformations,[11] we describe a simple, new, and efficient procedure for the synthesis of 5-iodomethyl thiazolidine-2-thiones **2** by iodocyclization of an allyl amine **1**, carbon disulfide, and iodine at room temperature (Scheme 1).



Scheme 1. Synthesis of 5-iodomethyl thiazolidine-2-thiones **2**.

The allyl amines used in this project were synthesized by Michael addition of allyl amine to activated olefins or by reductive amination of aldehydes with allyl amine. Cinnamyl amine was synthesized by reduction of the corresponding azide using $SnCl_2$ in methanol. We optimized the reaction conditions for the key iodocyclization by varying the number of equivalents of amine, carbon disulfide, I_2, and the solvent. The reactions of various allyl amines were studied and the results are summarized in Table 1. The reaction is regiospecific toward the synthesis of thiazolidine-2-thiones via a 5-*exo*-trig mechanism; 6-*endo*-trig cyclization was not observed. The products were stable for several months. The structures of the products were confirmed by IR, ^1H, and ^{13}C NMR spectroscopy, and mass spectrometry. According to the literature,[12] the CH_2I group in five-membered heterocyclic compounds is observed at 4–10 ppm in ^{13}C NMR spectra, while the –CHI group in a six-membered heterocycle appears above 14 ppm. The reaction of dithiocarbamate salts with iodine normally gives thiuram disulfides,[13] but reaction of dithiocarbamates prepared with allyl amine derivatives and iodine affords thiazolidine-2-thiones as the sole products.[14] We performed the reaction in basic medium (using $NaHCO_3$) and the yield was low when run in neutral conditions. The reaction of cinnamyl amine with carbon disulfide and iodine was not successful.

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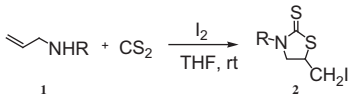
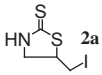
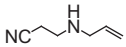
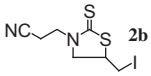
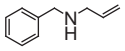
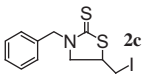
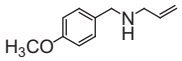
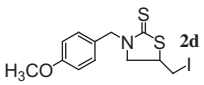
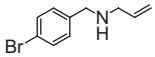
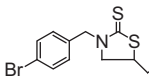
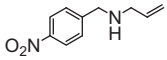
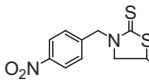
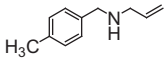
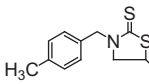
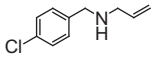
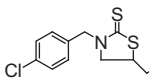
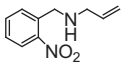
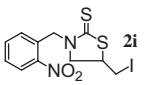
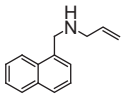
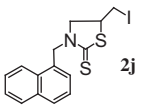
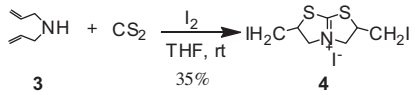
Table 1
Synthesis of thiazolidine-2-thiones via iodocyclization[a]



Entry	Amine	Product	Yield[b] (%)
1		 **2a**	55
2		 **2b**	46
3		 **2c**	60
4		 **2d**	59
5		 **2e**	62
6		 **2f**	68
7		 **2g**	75
8		 **2h**	60
9		 **2i**	62
10		 **2j**	65

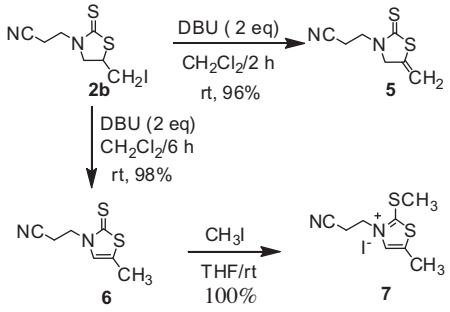
[a] Reaction conditions: amine (3 mmol), CS_2 (5 mmol), I_2 (3.3 mmol), 24 h.
[b] Isolated yield.



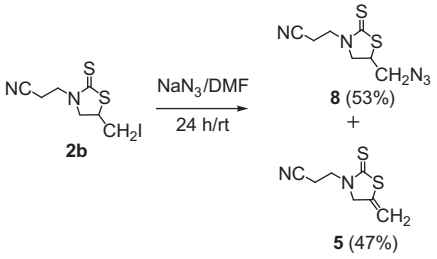
Scheme 2. Synthesis of 2,6-bis(iodomethyl)-2,3,5,6-tetrahydrothiazolo[2,3-*b*]thiazol-4-ium iodide **4**.

The reaction of diallyl amine **3** with carbon disulfide and iodine gave 2,6-bis(iodomethyl)-2,3,5,6-tetrahydrothiazolo[2,3-*b*]thiazol-4-ium iodide **4** as the only product. The pure product was obtained from the reaction mixture by simple filtration and was characterized using ^1H and ^{13}C NMR spectroscopy and CHN analysis (Scheme 2).[14]

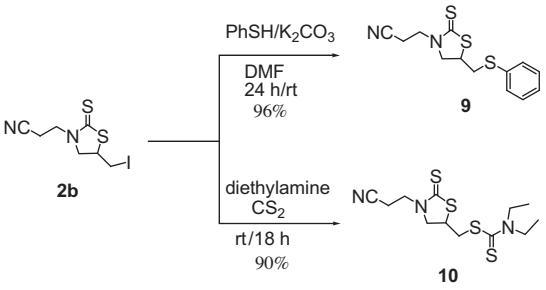
The presence of the iodo group in the products allowed further structural elaboration. Dehydrohalogenation of compound **2b** using DBU was examined as a model reaction. When the reaction was carried out over a short time (1–2 h), only the exocyclic double bond containing product **5** was obtained as the kinetic product, while over a longer reaction time (more than 6 h), the endocyclic double bond containing product **6** was obtained as the thermodynamic product in an excellent yield.[15] In addition, we have shown that the thiazole-2(3*H*)-thione **6** could be converted simply into the substituted 2-methylthio-thiazolium iodide **7** by reaction with methyl iodide. (Scheme 3). Compound **7** is an example member of an important family of ionic liquids.[16]



Scheme 3. Dehydrohalogenation of compound **2b**.



Scheme 4. Nucleophilic substitution of compound **2b** with NaN_3.



Scheme 5. Nucleophilic substitutions of compound **2b**.

Also, nucleophilic substitution of iodo products is an effective method for the synthesis of various valuable molecules. For this purpose, the reaction of **2b** with NaN_3 was investigated. We observed that the azide product **8** and kinetic dehydrohalogenation product **5** were obtained in a 53:47 ratio (Scheme 4).[17] In addition, reaction of thiophenol with **2b** was carried out in the presence of K_2CO_3 in DMF and the corresponding thioether **9** was obtained in excellent yield (Scheme 5).[18] Furthermore, the one-pot, three-component reaction of diethylamine, carbon disulfide, and compound **2b** was carried out under neat conditions to afford the corresponding dithiocarbamate **10** in an excellent yield (Scheme 5).[19] Substitution of the iodide with amines was not successful.

In conclusion, we have reported a new route toward the synthesis of 5-(iodomethyl)-thiazolidine-2-thiones via the one-pot, three-component reaction of allyl amine, carbon disulfide, and iodine. The reaction is simple, efficient, regiospecific, and gives good to high yields of products. Dehydrohalogenation of product **2b** gave the corresponding thiazole-2(3*H*) thione in high yield. In addition nucleophilic substitution of the iodine group of **2b** was accomplished with NaN_3, thiophenol, and diethylamine/CS_2.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.129.

References and notes

1. Cohen, M. L. *Nature* **2000**, *406*, 762–767.
2. Brickner, S. J. *Curr. Pharm. Design* **1996**, *2*, 175–194.
3. (a) Barbachyn, M. R.; Brickner, S. J.; Cleek, G. J.; Gadwood, R. C.; Grega, K. C.; Hendges, S. K.; Hutchinson, D. K.; Manninen, P. R.; Munesada, K.; Thomas, R. C.; Thomasco, L. M.; Toops, D. S.; Ulanowicz, D. A. In *Antiinfectives: Recent Advances in Chemistry and Structure Activity Relationships*; Bentley, P. H., O'Hanlon, P. J., Eds.; The Royal Society of Chemistry; Hartnolls Limited: Bodmin, Cornwall, 1997; pp 15–26; (b) Barbachyn, M. R.; Brickner, S. J.; Gadwood, R. C.; Garmon, S. A.; Grega, K. C.; Hutchinson, D. K.; Munesada, K.; Reischer, R. J.; Taniguchi, M.; Thomasco, L. M.; Toops, D. S.; Yamada, H.; Ford, C. W.; Zurenko, G. E. In *Resolving the Antibiotics Paradox*; Rosen, B. P., Mobashery, S., Eds.; Kluwer Academic, Plenum Publishers: New York, 1998; pp 219–240.
4. Shinabarger, D. A. *Exp. Opin. Invest. Drugs* **1999**, *8*, 1195–1202
5. (a) González, A.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949–8952; (b) Crimmins, M. T.; She, J. *Synlett* **2004**, 1371–1374; (c) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393; (d) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127–1130; (e) Crimmins, M. T.; DeBaillie, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 4936; (f) Hodge, M. B.; Olivo, H. F. *Tetrahedron* **2004**, *69*, 9397; (g) Barragan, E.; Olivo, H. F.; Romero-Ortega, M.; Sarduy, S. *J. Org. Chem.* **2005**, *70*, 4214–4217.
6. For a review on chiral thiazolidine thiones and oxazolidine thiones, see: (a) Velázquez, F.; Olivo, H. F. *Curr. Org. Chem.* **2002**, *6*, 303–340; (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775–777; (c) Smith, T. E.; Djang, M.; Velander, A. J.; Downey, C. W.; Carroll, K. A.; van Alphen, S. *Org. Lett.* **2004**, *6*, 2317–2320.
7. Yamada, S. *Tetrahedron Lett.* **1992**, *33*, 2171–2174.
8. (a) Shi, M.; Jiang, J. K. *Chirality* **2003**, *15*, 605–608; (b) Fabretti, A. C.; Ferrari, M.; Franchini, G. C.; Preti, C.; Tassi, L.; Tosi, G. *Transition Met. Chem.* **1982**, *7*, 279–281; (c) De Filippo, D.; Devillanova, F.; Preti, C.; Trogu, E. F.; Viglino, P. *Inorg. Chim. Acta* **1972**, *6*, 23–28; (d) Atzei, D.; De Filippo, D.; Rossi, A.; Caminiti, R.; Sadun, C. *Inorg. Chim. Acta* **1996**, *248*, 203–208; (e) De Filippo, D.; Devillanova, F.; Preti, C.; Verani, G. *J. Chem. Soc. A* **1971**, 1465–1468.
9. (a) Arimitsu, S.; Jacobsen, J. M.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2886–2889; (b) Butters, M.; Elliott, M. C.; Hill-Cousins, J.; Paine, J. S.; Walker, J. K. E. *Org. Lett.* **2007**, *9*, 3635–3638; (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243–246; (d) Yao, T.; Yue, D.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985–9989; (e) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748–15749; (f) Feula, A.; Male, L.; Fossey, J. S. *Org. Lett.* **2010**, *12*, 5044–5047.
10. (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391–2393; (b) Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604–6607; (c) Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603–2606; Occasionally, thiazolidine-2-thiones are prepared from β-amino thiols, see: (d) Zhang, Y.; Sammakia, T. *Org. Lett.* **2004**, *6*, 3139–3141.
11. (a) Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M. R. *J. Org. Chem.* **2006**, *71*, 3634–3635; (b) Ziyaei, A.; Saidi, M. R. *Can. J. Chem.* **2006**, *84*, 1515–1519; Ziyaei Halimehjani, A.; Maleki, H.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 2747–2749; Ziyaei Halimehjani, A.; Marjani, K.; Ashouri, A. *Green Chem.* **2010**, *12*, 1306–1310; (c) Aryanasab, F.; Ziyaei Halimehjani, A.; Saidi, M. R. *Tetrahedron Lett.* **2010**, *51*, 790–792; Ziyaei Halimehjani, A.; Pourshojaei, Y.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 32–34.
12. (a) Mancini, F.; Piazza, M. G.; Trombini, C. *J. Org. Chem.* **1991**, *56*, 4246–4252; (b) Sabat, M.; Liebaria, A.; Molins, E.; Miravitlles, C.; Delgado, A. *J. Org. Chem.* **2000**, *65*, 4826–4829.
13. Field, L.; Buckman, J. D. *J. Org. Chem.* **1968**, *33*, 3865–3871.
14. *General Procedure for synthesis of N-substituted-5-(iodomethyl)-thiazolidine-2-thiones*: In a test tube equipped with a magnetic stir bar, N-substituted allyl amine (3 mmol), THF (5 mL), and CS_2 (5 mmol) were added. The mixture was stirred for 20 min, I_2 (3.3 mmol) was added and the mixture stirred for 24 h at room temperature. After completion, the mixture was treated with 5 mL aqueous $NaHSO_3$ solution (2 M) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give the crude products. Purification was achieved by recrystallization from EtOH. In the case of diallyl amine (1 equivalent), I_2 (2.5 equivalents) was used and the product was obtained by simple filtration and washing the precipitate with Et_2O. *Characterization data for 3-(4-chlorobenzyl)-5-(iodomethyl)thiazolidine-2-thione (**2h**) (entry 8,* Table 1*)*: mp 62–64 °C; IR (KBr): 1490, 1316, 1158, 1014, 794, 564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.23 (1H, t, J = 10.4 Hz), 3.37 (1H, dd, J = 10.6, 4.3 Hz), 3.81–4.02 (3H, m), 4.86 (1H, d, J = 14.6 Hz), 4.99 (1H, d, J = 14.6 Hz), 7.27–7.38 (4H,m); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 7.0, 43.5, 51.9, 60.8, 129.3, 129.6, 132.4, 133.1, 196.5; MS (EI): m/z 383 (M^+), 349, 182, 167, 149, 125 (100), 89, 69, 57, 41.
15. *Synthesis of 3-[(5-methylene-2-thioxothiazolidin-3-yl)] propanenitrile (**5**) and 3-[(5-methyl-2-thioxothiazol-3(2H)-yl)] propanenitrile (**6**) by dehydrohalogenation of 3-[(5-(iodomethyl)-2-thioxothiazolidin-3-yl)]propanenitrile (**2b**)*: DBU (2 mmol) was added to a solution of **2b** (1 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was stirred for 1 to 6 h at rt. H_2O (10 mL) was added and the product was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and dried over Na_2SO_4 and evaporated in vacuo. The residue was pure enough to give satisfactory spectroscopic data. When the reaction was quenched after 1 h, compound **5** was obtained as the sole product (96% isolated yield). Increasing the reaction time to 6 h gave compound **6** as the thermodynamic product (98%). Compound **5**: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.85 (2H, t, J = 6.5 Hz), 4.02 (2H, t, J = 6.5 Hz), 4.90 (2H, t, J = 2.5 Hz), 5.12 (1H, d, J = 2.3 Hz), 5.25 (1H, d, J = 2.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 15.7, 44.8, 63.4, 106.4, 118.3, 135.9, 195.7; MS (EI): m/z 184 (M^+) (100), 131, 111, 71, 54, 41; HRMS calcd for $C_7H_8N_2NaS_2$ (M+Na^+), 207.0027; Found 207.0021; Compound **6**: mp 68–72 °C; ^1H NMR (300 MHz, acetone-d_6): δ (ppm) = 2.23 (3H, d, J = 1.2 Hz), 3.09 (2H, t, J = 6.6 Hz), 4.44 (2H, t, J = 6.6 Hz), 7.26 (1H, J = 1.2 Hz); ^{13}C NMR (75 MHz, acetone-d_6): δ (ppm) = 12.4, 16.5, 45.7, 118.0, 124.2, 129.7, 188.5; MS (EI): m/z 184 (M^+) (100), 152, 131, 98, 86, 72, 59, 41; HRMS calcd for $C_7H_8NNaS_2$ (M+Na^+), 207.0027; Found 207.0021.
16. *Synthesis of 3-[(2-cyanoethyl)-5-methyl-2-(methylthio)thiazol-3-ium] iodide (**7**) from 3-[(5-methyl-2-thioxothiazol-3(2H)-yl)] propanenitrile (**6**)*: In a test tube equipped with a magnetic stir bar were added compound **6** (1 mmol) and THF (5 mL). To this solution was added MeI (3 mmol) and the mixture was stirred for 10 h. The resulting precipitate was filtered and washed with excess THF to give the pure **7** in quantitative yield. mp 106–109 °C. ^1H NMR (500 MHz, DMSO-d_6+$CDCl_3$): δ (ppm) = 2.53 (3H, s), 2.98 (3H, s), 3.20 (2H, t, J = 6.5 Hz), 4.63 (2H, t, J = 6.5 Hz), 8.29 (1H, s) ppm; ^{13}C NMR (125 MHz, DMSO-d_6+$CDCl_3$): δ (ppm) = 12.8, 17.3, 19.3, 47.9, 116.6, 134.8, 134.9, 174.9.; MS (EI): m/z 326 (M^+), 294, 184 (100), 149, 142, 131, 123, 105, 73, 57, 41; HRMS calcd for $C_8H_{11}I_2N_2S_2$ (M+I^-), 452.8453; Found 452.8458.
17. *Synthesis of 3-[5-(azidomethyl)-2-thioxothiazolidin-3-yl] propanenitrile (**8**) from **2b***: In a test tube equipped with a magnetic stir bar, compound **2b** (2 mmol), DMF (10 mL), and NaN_3 (5 mmol) were added. The mixture was stirred overnight at room temperature, then quenched with H_2O and extracted with EtOAc (2 × 10 mL). The organic layer was washed with H_2O (4 × 20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product. NMR analysis showed that the mixture contained 53% of the azide product **8** and 47% of kinetic dehydrohalogenation product **5**. Spectroscopic data for compound **8**: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.76–2.98 (2H, m), 3.62 (2H, m), 3.79–3.91 (2H, m), 4.07–4.13 (2H, m), 4.32 (1H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 15.8, 42.8, 45.2, 54.3, 60.8, 118.3, 196.5.MS (EI): m/z 227 (M^+), 184, 170, 167, 144, 118, 111, 72 (100), 59, 54, 41.
18. *Synthesis of 3-[5-(phenylthiomethyl)-2-thioxothiazolidin-3-yl] propanenitrile (**9**) from **2b***: In a test tube equipped with a magnetic stir bar, compound **2b** (2 mmol), DMF (10 mL), thiophenol (3 mmol), and K_2CO_3 (3 mmol) were added, respectively. The mixture was stirred overnight at room temperature, then quenched with H_2O (5 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with saturated $NaHCO_3$ solution and with H_2O (4 × 20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the corresponding thioether **9** in 95% yield. The product was pure enough to give satisfactory spectroscopic data. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.76–2.84 (2H, m), 3.17–3.22 (2H, m), 3.67–3.97 (3H, m), 4.23–4.26 (2H, m) 7.25–7.38 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 15.8, 39.1, 43.4, 45.3, 61.6, 118.3, 127.9, 129.8, 131.5, 137.3, 197.1; MS (EI): m/z = 294 (M^+), 218 (100), 185, 163, 154, 141, 123, 109, 73, 65, 57, 51, 45, 41; HRMS calcd for $C_{13}H_{14}N_2NaS_3$ (M+Na^+), 317.0217; Found 317.0211.
19. *Synthesis of [3-(2-cyanoethyl)-2-thioxothiazolidin-5-yl]methyl diethylcarbamodithioate (**10**) from **2b***: In a test tube equipped with a magnetic stir bar, compound **2b** (2 mmol), CS_2 (6 mmol), and diethylamine (4 mmol) were added, respectively. The mixture was stirred overnight at room temperature, then quenched with H_2O (5 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with H_2O (2 × 20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the corresponding dithiocarbamate **10** in 90% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.29 (6H, m), 2.85–2.91 (2H, m), 3.66–3.79 (4H, m), 3.96–4.10 (5H, m) 4.23 (1H, m), 4.32 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.9, 13.0, 15.8, 40.8, 43.6, 45.5, 47.5, 50.5, 61.9, 118.4, 193.7, 197.3; MS (EI): m/z = 334 ($M+H)^+$, 185 (100), 149, 132, 116, 84, 60, 41; HRMS calcd for $C_{12}H_{19}N_3NaS_4$ (M+Na^+), 356.036; Found 356.0354.