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Selective synthesis of bis[1,2]dithiolo[1,4]thiazines from 4-isopropylamino-5-chloro-1,2-dithiole-3-ones

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Abstract—Reaction of 4-isopropylamino-5-chloro-1,2-dithiole-3-ones **3** and S_2Cl_2 in acetonitrile gave selectively 3-oxo-bis[1,2]dithiolo[1,4]thiazine-5-thiones **1** by the addition of triethylamine and bis[1,2]dithiolo[1,4]thiazine-3,5-diones **5** under the action of formic acid. 3,5-Diones **5** were also obtained by intramolecular cyclization of *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines **6** with S_2Cl_2 in the presence of Et_3N.

Compounds containing 3*H*-1,2-dithiole-3-thione and 3-one fragments are of current interest since they have a broad spectrum of biological activity and may be useful synthons for many sulfur heterocycles. Oltipraz (4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione) has been clinically tested as a preventive agent against various types of cancer.[1] Anethole dithiolethione (Sulfarlem, 5-(4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione), a clinically available pluripotent antioxidant, has been recently proposed as a neuroprotectant for Parkinson's disease. Also, it has various applications in human therapy for its choleretic and sialogogic properties and as a cytoprotective agent in lung precancerous lesions prevention in smokers.[2] 1,2-Dithiole-3-thiones were considered as potent bacterial inhibitors of enzyme Fabh from *Escherichia coli* and *Staphylococcus aureus*.[3] Apart from their biological activities, dithiolethiones have been intensively investigated in 1,3-dipolar cycloaddition reactions with dipolarophiles.[4]

With a view to discovering new materials we have described the new polycyclic dithiole derivatives, bis[1,2]dithiolo[1,4]thiazines,[5] bis[1,2]dithiolopyrroles,[6] and [1,2]dithiolo[1,4]thiazine.[7] Bisdithiolothiazine ketothione (**1**, R = Et) bearing reactive thione and activating and chemically inert keto groups in one molecule was found to be the most useful compound from a synthetic point of view.[8] Ketothiones **1** could also be of interest as biologically active substances containing potentially biologically active 1,2-dithiole-3-thione and 3-one moieties in one molecule.

Unfortunately, ketothiones **1** are less accessible from other bisdithiolothiazines; only an *N*-ethyl derivative can be prepared from *N*-ethyldiisopropylamine, S_2Cl_2 and cyclopenten-1-yl-acetic acid, selectively, and in moderate yield.[5] Other ketothiones **1** were synthesized from non-commercial N-substituted diisopropylamines, as a rule, in low yields and in mixtures with other bisdithiolothiazines. Monocyclic 5-mercapto-1,2-dithiole-3-thiones **2**, which we have recently obtained,[9] show high promise as synthons for the preparation of bisdithiolothiazine ketothiones **1**. Yet, on reaction with a mixture of S_2Cl_2 and DABCO under the conditions employed for preparing tricyclic bis(dithiolo)thiazines from substituted diisopropylamines,[5] 5-chlorodithiol-3-ones **3** were generated in high yields.[9] In this Letter we report a selective synthesis of bisdithiolothiazine ketothiones and diones from 5-chloro-1,2-dithiole-3-ones; the unique feature of these transformations is electrophilic substitution of chlorine attached to the dithiole ring by sulfur upon treatment with sulfur monochloride.

We have found that 5-chloro-1,2-dithiol-3-ones **3** could be synthesized directly from the corresponding diisopropylamines, S_2Cl_2 and DABCO in moderate to high yields using a modified method[9] at low temperature (−15 °C) and further treatment with formic acid

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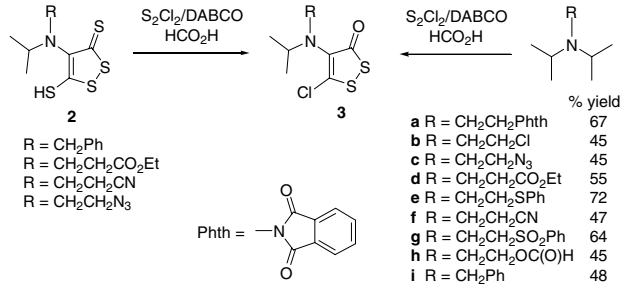
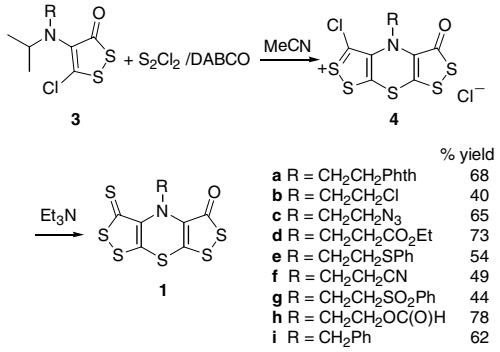


Scheme 1. Synthesis of 4-isopropylamino-5-chloro-1,2-dithiole-3-ones **3**.

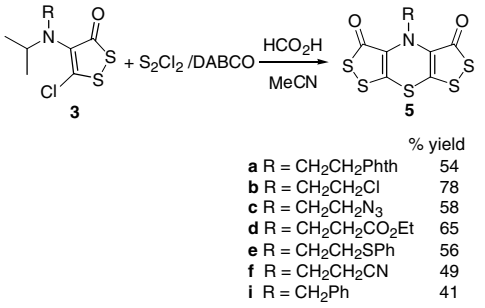
(Scheme 1). Thus we decided to use dithioles **3** as starting materials for the synthesis of bisdithiolothiazines.

The reaction of dithiolone **3a** with S_2Cl_2 and DABCO was investigated in detail; the nature of the solvent used appeared crucial for a successful reaction. If the reaction was carried out in inert solvents such as chloroform, dichloromethane or 1,2-dichloroethane, the starting dithiolone **3a** was isolated in practically quantitative yield. Attempts to employ other solvents recently used in reactions with sulfur monochloride (THF[10] or DMF[11]) failed. Treatment of S_2Cl_2 and DABCO in acetonitrile—a solvent, which is rarely used in S_2Cl_2 reactions—gave bisdithiolothiazine ketothione **1a** after treatment with triethylamine as a base (Scheme 2).

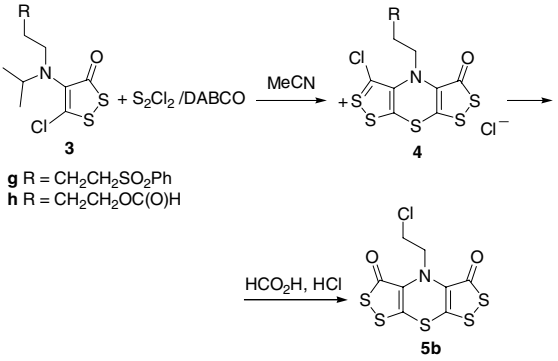
We then extended this reaction to other N-substituted 4-isopropylamino-5-chloro-1,2-dithiole-3-ones **3**. Bisdithioloketothiones **1** were obtained selectively in all reactions in moderate to high yields (Scheme 2).[12] We believe this to be the first case where a chloro substituent is replaced by sulfur under the eletrophilic action of sulfur monochloride and a base. Presumably the key intermediate in the reaction is 3-chlorodithiolium salt **4**, which gave thiones **1** with sulfur nucleophiles generated from a base (e.g., triethylamine) and sulfur formed in the ongoing reaction.[5] It was envisaged that an oxygen nucleophile (the most frequently used being formic acid) on reaction with **3** could give diketones **5**. We checked this possibility by replacing Et_3N with formic acid at the last step and found that diketones **5** were prepared selectively in moderate yields (Scheme 3).



Scheme 2. Synthesis of 3-oxo-bis[1,2]dithiolo[1,4]thiazine-5-thiones **1**.



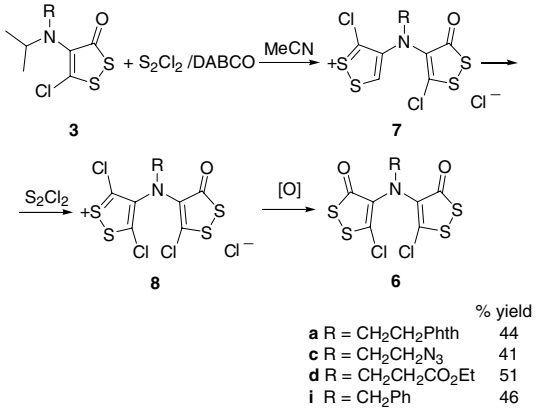
Scheme 3. Synthesis of bis[1,2]dithiolo[1,4]thiazine-3,5-diones **5**.



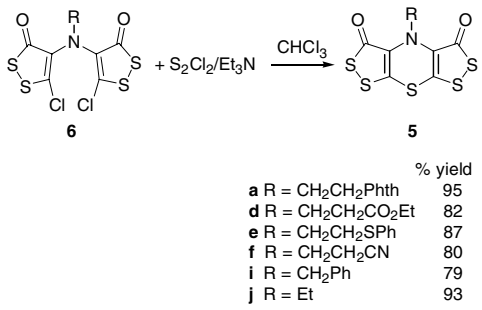
Scheme 4. Reaction of chloroketones **3g** and **3h** with S_2Cl_2 and DABCO.

Treatment of chloroketones **3g** and **3h** with S_2Cl_2 and DABCO in acetonitrile followed by addition of formic acid resulted in chloroethyl derivative **5b** isolated in low yields (15–20%). Presumably, the phenylsulfonyl and formyloxy groups are sensitive to attack of hydrochloric acid formed from S_2Cl_2 and HCO_2H to give chloroethyl bisdithiolothiazine **5b** (Scheme 4).

Interesting results were obtained when chloroketones were treated with a mixture of S_2Cl_2 and DABCO where DABCO is in deficiency relative to S_2Cl_2 (S_2Cl_2/DABCO ratio = 2:1). In the cases examined bis(dithiolyl)amines **6** were isolated in moderate yields (Scheme 5). Apparently the reaction with this ratio of reagents,



Scheme 5. Synthesis of *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines **6**.



Scheme 6. Cyclization of *N*,*N*-bis(5-chloro-3-oxox[1,2]dithiol-4-yl)-amines **6** into bis[1,2]dithiolo[1,4]thiazine-3-5-diones **5**.

instead of undergoing ring closure to tricycles **1** or **5**, led to the formation of intermediate salt **7**, which was further chlorinated by excess S_2Cl_2 to give salt **8**, the latter then being converted to bis(dithiolyl)amines **6** with oxygen donors. Although bisdithiolylamines **6** were obtained in moderate yields, they were formed selectively, but not in mixtures with bisdithiolothiazines as described previously.[13]

In an attempt to extend the S_2Cl_2 sulfurating ability in reactions with 5-chloro-1,2-dithioles, we investigated the reaction *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)-amines **6** with sulfur monochloride and a base. DABCO was found to be inert in this reaction, which was not surprising bearing in mind that bicyclic compounds **6** were formed in the presence of DABCO (see Scheme 5 and data in Ref. 13). Treatment of **6** with S_2Cl_2 and triethylamine in chloroform for 3 d at room temperature followed by heating under reflux for 3 h gave bisdithiolothiazines **5** in high yields (Scheme 6). The best results were obtained when Et_3N was present in threefold excess with respect to S_2Cl_2.

All new compounds were fully characterized by elemental analysis, ^1H and ^{13}C NMR, IR spectroscopy and mass spectrometry, and some by HMRS.

The reactions described provide new and efficient routes to bis(dithiolo)thiazines and bis(dithiolyl)amines, some of which have marked activity against various cancer lines.[14] The conversion of chlorodithiolones **3** into unsymmetrical bisdithiazolothiazine ketothiones **1** in acetonitrile surpasses their synthesis from diisopropylamines in selectivity and yields.[8] The novelty of these transformations is in replacing chlorines by sulfur in the reaction with electrophilic sulfur monochloride and its mixtures with tertiary amines. The key steps may be explained by the addition of sulfur monochloride into C–H or C–Cl bonds with further extrusion of SCl_2 from intermediates **9** or **10** (Scheme 7), as explained for polysulfur chain extension in the formation of pentathiepins.[15] The described experimental procedures may serve as an efficient basis for new syntheses of sulfur compounds from readily available chloro derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.071.

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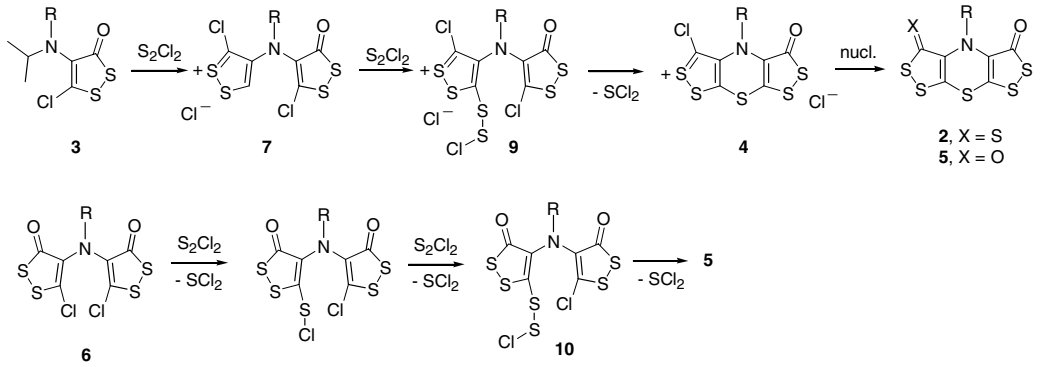

Scheme 7. A plausible mechanism for the formation of bisdithiolothiazines **2** and **5**.

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12. *General procedure for the preparation of* **1** *and* **5** *from* **3**. Disulfur dichloride (2 mmol) was added dropwise at −25 to −35 °C to a stirred solution of DABCO (2 mmol) in acetonitrile (20 ml) under argon. The corresponding N-substituted 4-isopropylamino-5-chloro-1,2-dithiole-3-one **3** (0.2 mmol) in acetonitrile (2 ml) was added and the mixture was stirred at rt for 2 h. Then Et_3N (2 mmol) for the synthesis of **1** or HCO_2H (40 mmol) for the synthesis of **5** was added, the mixture was refluxed for 3 h, filtered and the solvents were evaporated. The residue was separated by column chromatography (Silica gel Merck 60, light petroleum and then light petroleum–CH_2Cl_2 mixtures). Bisdithioloketothiones **1b** (yield 40%), **1d** (yield 73%), **1i** (yield 62%) and bisdithioloketothiones **5a** (yield 54%), **5b** (yield 78%), **5d** (yield 65%), **5e** (yield 56%) and **5i** (yield 41%) are identical with the known compounds.
2-[2-(3-Oxo-5-thioxo-3H,4H,5H-bis[1,2]dithiolo[3,4-b:4′,3′-e][1,4]thiazin-4-yl)ethyl]-1H-isoindole-1,3(2H)-dione **1a**, yield 68%. Red crystals, mp 216–217 °C. Anal. Calcd for $C_{16}H_8N_2O_3S_6$: C, 41.01; H, 1.72; N, 5.98. Found: C, 41.24; H, 1.50; N, 5.90. $C_{16}H_8N_2O_3S_6$ requires M, 467.8859. Found M^+, 467.8859. ^1H NMR (250 MHz, Py-d_5) δ: 3.96 (2H, t, *J* 6.6, CH_2), 4.77 (2H, br s, CH_2), 7.42 (2H, m, Ar), 7.65 (2H, m, Ar). ^{13}C NMR (75.5 MHz, Py-d_5) δ: 38.1 and 43.8 ($2CH_2$), 132.5, 136.6, 147.2, 149.4 and 157.8 (6 sp^2 tertiary C), 123.1 and 134.3 (4CH, Ar), 168.3 (2C=O, Ar), 183.3 (C=O), 202.4 (C=S). MS (EI, 70 eV), *m*/*z* (%): 468 (M^+, 5), 436 (10), 308 (21).
4-(2-Azidoethyl)-5-thioxo-3H,4H,5H-bis[1,2]dithiolo[3,4-b:4′,3′-e][1,4]thiazin-3-one **1c**, yield 65%. Red crystals, mp 187–189 °C. Anal. Calcd for $C_8H_4N_4OS_6$: C, 26.36; H, 1.11; N, 15.37. Found: C, 26.09; H, 1.19; N, 15.17. $C_8H_4N_4OS_6$ requires M, 363.8709. Found M^+, 363.8709. ^1H NMR (250 MHz, Py-d_5) δ: 3.29 (2H, t, *J* 5.3, CH_2), 4.09 (2H, t, *J* 5.3, CH_2). ^{13}C NMR (75.5 MHz, Py-d_5) δ: 45.7 and 51.3 ($2CH_2$), 136.8, 147.8, 150.3 and 158.3 (4 sp^2 tertiary C), 183.4 (C=O), 202.6 (C=S). MS (EI, 70 eV), *m*/*z* (%): 364 (M^+, 19), 308 (30), 262 (59).
4-[2-(Phenylthio)ethyl]-5-thioxo-3H,4H,5H-bis[1,2]dithiolo[3,4-b:4′,3′-e][1,4]thiazin-3-one **1e**, yield 54%. Red crystals, mp 159–160 °C. Anal. Calcd for $C_{14}H_9NOS_7$: C, 38.95; H, 2.10; N, 3.24. Found: C, 38.76; H, 2.05; N, 3.43. ^1H NMR (250 MHz, Py-d_5) δ: 3.43 (2H, t, *J* 6.7, CH_2), 4.58 (2H, t, *J* 6.6, CH_2), 7.21 (3H, m, Ph), 7.45 (2H, m, Ph). ^{13}C NMR (75.5 MHz, Py-d_5) δ: 33.1 and 45.9 ($2CH_2$), 126.5 (CH, Ph), 129.3 (2CH, Ph), 129.6 (2CH, Ph), 135.9, 136.8, 147.7, 158.3 and 163.1 (5 sp^2 tertiary C), 183.3 (C=O), 202.6 (C=S). MS (EI, 70 eV), *m*/*z* (%): 431 (M^+, 15), 399 (31), 263 (57).
3-(3-Oxo-5-thioxo-3H,4H,5H-bis[1,2]dithiolo[3,4-b:4′,3′-e][1,4]thiazin-4-yl)propanenitrile **1f**, yield 49%. Red crystals, mp 196–197 °C. Anal. Calcd for $C_9H_4N_2OS_6$: C, 31.01; H, 1.16; N, 8.04. Found: C, 31.09; H, 1.19; N, 8.28. ^1H NMR (250 MHz, Py-d_5) δ: 3.03 (2H, t, *J* 6.2, CH_2), 4.62 (2H, t, *J* 5.9, CH_2). ^{13}C NMR (75.5 MHz, Py-d_5) δ: 17.4 and 43.2 ($2CH_2$), 118.9 (CN), 122.1, 146.6, 151.5 and 159.2 (4 sp^2 tertiary C), 183.4 (C=O), 202.6 (C=S). MS (EI, 70 eV), *m*/*z* (%): 348 (M^+, 79), 316 (11).
4-[2-(Phenylsulfonyl)ethyl]-5-thioxo-3H,4H,5H-bis[1,2]-dithiolo[3,4-b:4′,3′-e][1,4]thiazin-3-one **1g**, yield 44%. Red crystals, mp 113–115 °C. Anal. Calcd for $C_{14}H_9NO_3S_7$: C, 36.26; H, 1.96; N, 3.02. Found: C, 36.02; H, 2.06; N, 3.24. ^1H NMR (250 MHz, Py-d_5) δ: 3.92 (1H, t, *J* 5.4, CH_2), 4.44 (1H, t, *J* 5.4, CH_2), 4.56 (2H, br s, CH_2), 7.48 (3H, m, Ph), 7.83 (2H, m, Ph). ^{13}C NMR (75.5 MHz, Py-d_5) δ: 46.9 and 63.4 ($2CH_2$), 125.4 (2CH, Ph), 129.5 (2CH, Ph), 132.6 (CH, Ph), 128.4, 137.0, 145.2, 148.0 and 158.6 (5 sp^2 tertiary C), 183.6 (C=O), 202.7 (C=S). MS (EI, 70 eV), *m*/*z* (%): 431 (M^+−S, 3), 322 (M−SO_2Ph, 4), 306 (15).
2-(3-Oxo-5-thioxo-3H,4H,5H-bis[1,2]dithiolo[3,4-b:4′,3′-e][1,4]thiazin-4-yl)ethyl formate **1h**, yield 78%. Red crystals, mp 188–189 °C. Anal. Calcd for $C_9H_5NO_3S_6$: C, 29.41; H, 1.37; N, 3.81. Found: C, 29.62; H, 1.52; N, 3.87. ^1H NMR (250 MHz, Py-d_5) δ: 4.54 (2H, t, *J* 4.6, CH_2), 4.60 (2H, br s, CH_2), 8.38 (s, 1H, C(O)H). ^{13}C NMR(75.5 MHz, Py-d_5) δ: 45.8 and 63.0 ($2CH_2$), 137.1, 148.0, 150.3 and 158.4 (4 sp^2 tertiary C), 161.4 (C(O)H), 183.4 (C=O), 202.7 (C=S). MS (EI, 70 eV), *m*/*z* (%): 367 (M^+, 16), 308 (10), 295 (13).
4-(2-Azidoethyl)-3H,4H,5H-bis[1,2]dithiolo[3,4-b:4′,3′-e]-[1,4]thiazine-3,5-dione **5c**, yield 58%. Yellow crystals, mp 166–168 °C. Anal. Calcd for $C_8H_4N_4O_2S_5$: C, 27.57; H, 1.16; N, 16.08. Found: C, 27.39; H, 1.08; N, 15.97. ^1H NMR (250 MHz, Py-d_5) δ: 3.64 (2H, t, *J* 5.3, CH_2), 4.20 (2H, t, *J* 5.3, CH_2). ^{13}C NMR (75.5 MHz, Py-d_5) δ: 43.7 and 49.7 ($2CH_2$), 134.7 and 147.0 (4 sp^2 tertiary C), 181.6 (2C=O). MS (EI, 70 eV), *m*/*z* (%): 348 (M^+, 11), 292 (19).
3-(3,5-Dioxo-3H,4H,5H-bis[1,2]dithiolo[3,4-b:4′,3′-e][1,4]-thiazin-4-yl)propanenitrile **5f**, yield 49%. Yellow crystals, mp 184–186 °C. Anal. Calcd for $C_9H_4N_2O_2S_5$: C, 32.51; H, 1.21; N, 8.43. Found: C, 32.62; H, 1.29; N, 8.62. ^1H NMR (250 MHz, Py-d_5) δ: 2.99 (2H, t, *J* 6.4, CH_2), 4.32 (2H, t, *J* 6.4, CH_2). ^{13}C NMR (75.5 MHz, Py-d_5) δ: 17.6 and 43.0 ($2CH_2$), 118.7 (CN), 135.3 and 154.2 (4 sp^2 tertiary C), 183.2 (2C=O). MS (EI, 70 eV), *m*/*z* (%): 332 (M^+, 48), 292 (100).
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