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Abnormally Mild Synthesis of Bis(dithiolo)pyrroles from 2,5-Dimethylpyrroles

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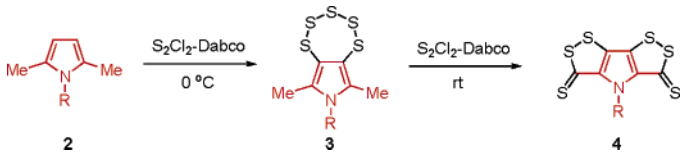
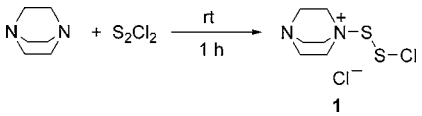
ABSTRACT



Treatment of *N*-substituted 2,5-dimethylpyrroles 2 with an equilibrated mixture of disulfur dichloride and DABCO in chloroform at 0 °C gives pentathiepinopyrroles 3 in moderate yields; further reaction of 3 with the same mixture at room temperature leads, in an extensive reaction cascade, to bis(dithiolo)pyrroles 4 in high yield; 2 can be converted into 4 in a one-pot operation under unusually mild conditions.

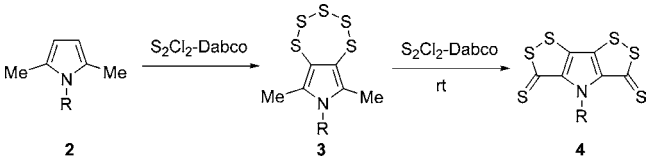
The relatively well-known benzopentathiepins display a varied chemistry and have important biological activity.[1] Similar pentathiepins fused to heterocyclic rings are rarer and much less well investigated. Recently, we have shown that equilibrated equimolecular mixtures of disulfur dichloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) in chloroform converted *N*-alkylpyrroles into *N*-alkylpentathiepinopyrroles; the S_2Cl_2−DABCO complex **1** was assumed to be the major reactive intermediate (Scheme 1).[2]

Scheme 1



If the pyrrole α-positions are chlorinated, the pentathiepin ring is fused across the 3,4-pyrrole bond to give pentathiepinopyrroles **3** (Cl for Me) in high yield.[3] We have now investigated (Scheme 2) the synthesis of pentathiepino[6,7-*c*]pyrroles **3** from 2,5-dimethylpyrroles, which are very readily available from acetonylacetone and amines.[4]

Scheme 2



The reaction of *N*-benzyl-2,5-dimethylpyrrole **2a** with an excess of S_2Cl_2 and DABCO (not preequilibrated) led unexpectedly to *N*-benzylbis(dithiolo)pyrrole **4a** (Scheme 3)

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(2) Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W.; Amelichev, S. A. *Mendeleev Commun.* **2004**, 91.
(3) Amelichev, S. A.; Konstantinova, L. S.; Lyssenko, K. A.; Rakitin, O. A.; Rees, C. W. *Org. Biomol. Chem.* **2005**, *3*, 3496.
(4) Leonard, N. J.; Curry J. W.; Sagura, J. J. *J. Am. Chem. Soc.* **1953**, *75*, 6249.

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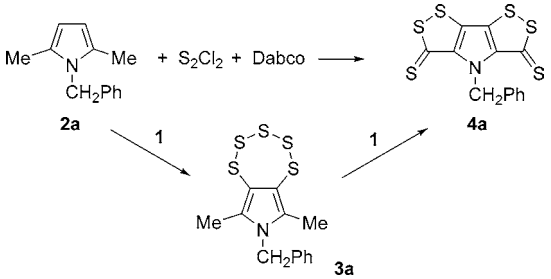
Scheme 3



in low yield (10%). Compound **4a** was identical with that prepared from *N*-benzyldiisopropylamine, S_2Cl_2, and DABCO in refluxing chlorobenzene (see Scheme 6 below).[5]

This formation of bis(dithiolo)pyrrole **4** provides a new and surprisingly mild route to the 1,2-dithiolo-3-thione ring system; the *C*-methyl carbons have become incorporated into thiocarbonyl groups in the course of an extensive reaction cascade. Attempts to increase the yield of **4a** by changing the quantity and ratio of the reagents, and the reaction temperature, were unrewarding. However, the reaction of pyrrole **2a** with preformed complex **1** gave a different product, the pentathiepin **3a**, whose yield did vary with the reaction conditions; an excess of S_2Cl_2 or increase in reaction temperature led to the decomposition of pentathiepin **3a**, with partial transformation to **4a**. When **2a** (5 mmol) in chloroform (50 mL) at 0 °C was treated with complex **1** for 48 h the best yield (60%) of **3a** was obtained with 2.5 equiv of the complex. Lower yields were obtained with less (2 equiv gave 22%) and with more complex (3 equiv gave 35%; 4 equiv gave 23%); at 20 °C, 2.5 equiv gave 34% of **3a**. It appears from NMR spectroscopy that the methyl groups in **2a**, which are transformed by the reagents, are also involved in intermolecular reactions to give (unstable) oligomeric products.

We then extended these reactions to other *N*-substituted 2,5-dimethylpyrroles **2**. The bis(dithiolo)thiones **4** were obtained directly in all reactions with a (nonequilibrated) mixture of S_2Cl_2 and DABCO, but in low yields (R = Me, 8%, R = Et, 9%, R = ^{n}Pr, 12%, R = ^{i}Pr, 17%). The best conditions for the formation of **3a** (2.5 equiv of complex **1**) were also best for the analogous pentathiepins **3**, formed in better yield; R = Me, 36%, R = Et, 40%, R = ^{n}Pr, 38%, R = ^{i}Pr, 37%.

Surprisingly the isolated and purified pentathiepins **3** were found to react further with complex **1** quite rapidly at a slightly higher temperature (20 °C) to give the bis(dithiolo)-pyrroles **4** in high yield (Scheme 4).[6] The reactions are almost complete after 1 h but heating the mixture briefly under reflux improved the work up procedure. Although pentathiepin rings and methyl groups are normally unreactive toward S_2Cl_2−DABCO at room temperature, the pyrroles **3** react in an extensive cascade sequence. Presumably the electron releasing pyrrole nitrogen activates **3** to attack by the

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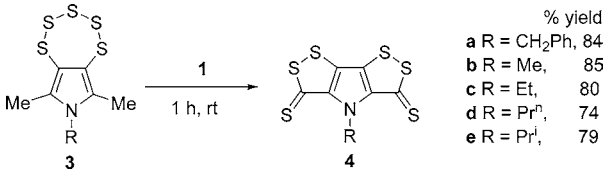
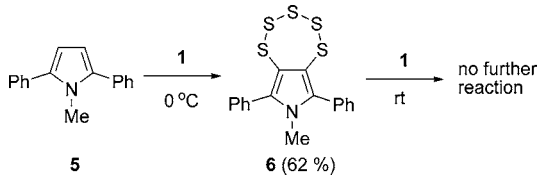
Scheme 4

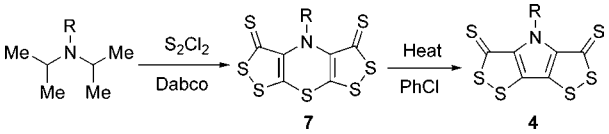


electrophilic reagent, either at the pentathiepin ring or at a methyl group. When *N*-methyl-2,5-diphenylpyrrole[7] **5** was treated with complex **1** under the same conditions the yellow pentathiepinopyrrole **6** was obtained in good yield (62%), but treatment of this with complex **1** gave no further reaction even on heating for 3 h, the pentathiepin ring remaining intact (Scheme 5). Thus, it is likely that attack of the pentathiepinopyrroles **3** occurs first at the *C*-methyl groups, which are activated by electron release from both heterocyclic rings. A possible mechanism for this reaction is proposed below (Scheme 7).

Scheme 5



Scheme 6



We have previously prepared *N*-benzyl- **4a** and *N*-ethylbis-(dithiolo)pyrrole **4c** from *N*-benzyl- and *N*-ethyldiisopropyl-amine by treatment with S_2Cl_2−DABCO to give the corre-

(6) **General Procedure for the Preparation of 3 and 6.** Disulfur dichloride (12.5 mmol) was added dropwise at −25 to −35 °C to a stirred solution of DABCO (12.5 mmol) in chloroform (40 mL) under argon. The mixture was stirred at rt for 1 h. The corresponding substituted 2,5-dimethylpyrrole (5 mmol) in chloroform (10 mL) was added, the mixture was stirred at 0 °C for 48 h under argon and filtered, and solvents were evaporated. The residue was separated by column chromatography (silica gel, Merck 60, light petroleum and then light petroleum−CH_2Cl_2 mixtures). Yields are given in the text. **General Procedure for the Preparation of 4 from 3.** Disulfur dichloride (3.6 mmol) was added dropwise at −25 to −35 °C to a stirred solution of DABCO (3.6 mmol) in chloroform (10 mL) under argon. The mixture was stirred at rt for 1 h. The corresponding pentathiepin **3** (0.7 mmol) in chloroform (5 mL) was added, the mixture was stirred at rt for 1 h and then refluxed for 15 min and filtered, and solvents were evaporated. The residue was separated by column chromatography (silica gel, Merck 60, light petroleum and then light petroleum−CH_2Cl_2 mixtures). Yields are given in Scheme 4.

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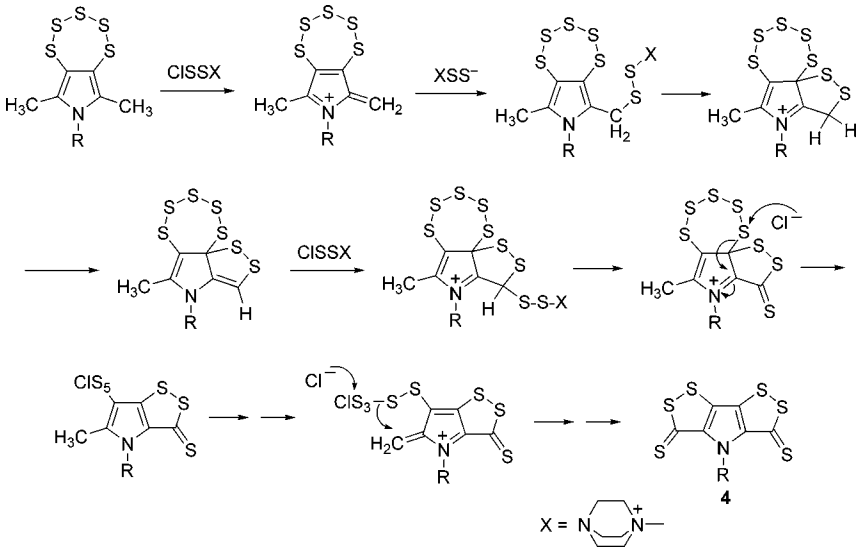
Scheme 7



sponding bis[1,2]dithiolo[5,4-*b*][4′,5′-*e*][1,4]thiazine-3,5-dithiones **7**, followed by thermal extrusion of the [1,4]thiazine sulfur (Scheme 6).[5,8] However, this procedure does not give the analogous dithiolopyrroles **4b**, **4d** and **4e** from the corresponding diisopropylamines, and it appears to be less general than the present route (Scheme 4). The latter is equally simple and can be performed in one pot from the dimethylpyrroles **2** by adding complex **1** (2.5 equiv) in chloroform and stirring the mixture for 48 h at 0 °C and then heating under reflux with more complex **1** (5 equiv) without isolation of the pentathiepin **3**.

This reaction cascade (Scheme 3) provides a new and unusual route from 2,5-dimethylpyrroles to bis(dithiolo)-pyrroles, some of which have marked activity against various cancer lines.[9] The procedure is better yielding and very much milder than the classical, high temperature (ca. 200 °C) reactions between sulfur and a variety of three-carbon components such as arylalkanes, arylalkenes, alkynes, and their chloro derivatives, largely used hitherto to form the 1,2-dithiolo-3-thione ring system.[10]

The conversion of pentathiepinopyrroles **3** into dithiolo-pyrroles **4** (Scheme 4) is reminiscent of the similar conversion of diisopropylamines into dithiolothiazines **7** (Scheme 6) and is probably mechanistically related. We now propose (Scheme 7) a working hypothesis for the cascade of **3** into **4** which further illustrates the manifold oxidizing, chlorinating, and sulfurating properties of S_2Cl_2,[7,11] and involves the breaking and making of at least eight old and eight new bonds in high overall yield (74−85%). A reasonable sequence could be as follows: (i) oxidation and sulfuration of the activated C-methyl group; (ii) *ipso*-cyclization of the CH_2SSX group onto the pyrrole β-position; (iii) oxidation and sulfuration of the activated methyl group to the thiocarbonyl group of the dithiolthione; (iv) opening and fragmentation of the pentathiepin ring, and cyclization onto the second methyl group; and (v) conversion of the second methylene group to thiocarbonyl.

The actual sequence of these steps is not known, and there may be some equilibration/disproportionation of the polysulfur chain.

This unusual reaction cascade is under further investigation and extension, but it is already clear that it provides a very short and unusually mild route to potentially antitumor 1,2-dithiole-3-thiones.

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Supporting Information Available: Experimental procedures and full characterization for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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