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Synthesis of 1,4-Dithiins from Pentathiepins

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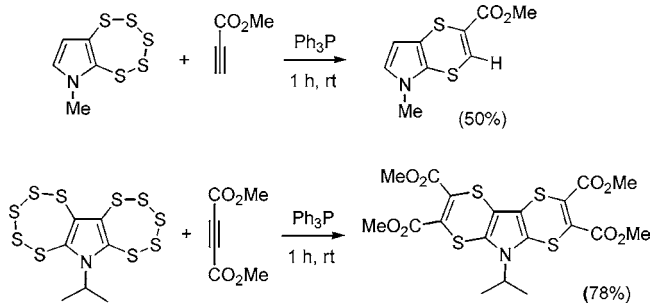
ABSTRACT



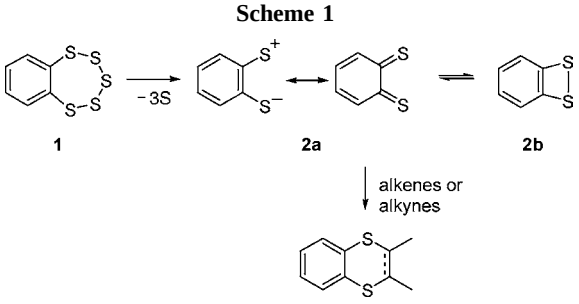
Fused aromatic and heterocyclic 1,2,3,4,5-pentathiepins react with triphenylphosphine and alkynes bearing electron-withdrawing groups to give the corresponding 1,4-dithiins in high yields. Unsymmetrical alkynes add regioselectively to afford products in agreement with the electron distribution in a proposed reaction intermediate. A mechanism for these reactions is proposed.

1,2,3,4,5-Pentathiepins are of particular interest among polysulfur heterocycles because of their unusual stability, stereochemistry, occurrence in nature, and significant biological activity.[1] Many benzopentathiepins, including natural products, possess strong anticancer, antimicrobial, and antifungal activity resulting from the polysulfur moiety.[1] Furthermore the use of pentathiepins in technical devices as cathodic material in battery systems has recently been proposed.[2]

The chemistry of pentathiepins has been investigated mainly for the benzo fused system **1**.[3] Its reactions are often associated with the loss of from one to all five sulfur atoms. Most frequently three sulfurs are extruded, possibly via intermediates such as **2a,b** (Scheme 1), which may add alkenes or alkynes to give 1,4-dithianes or 1,4-dithiins, respectively.[4] 1,4-Dithiins have attracted considerable attention because of their biological activity, particularly as fungicides and antibacterials.[5]

Given our ready one-pot preparation of heterofused pentathiepins by treatment of nucleophilic heterocycles with

Scheme 1



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[‡] Imperial College London.

(1) Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W. *Chem. Rev.* **2004**, *104*, 2617.
(2) Tsutsumi, H.; Higashiyama, H.; Onimura, K.; Oishi, T. *J. Power Sci.* **2005**, *146*, 345.
(3) Chenard, B. L.; Harlow, R. L.; Johnson, A. L.; Vladuchick, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 3871.

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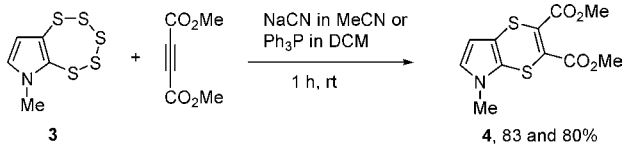
disulfur dichloride,[6] we wished to extend this work to the mild formation of fused 1,4-dithiins generally, to develop their chemistry and biological activity further.

6-Methyl-6*H*-[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole **3**, readily prepared from *N*-methylpyrrole or *N*-methylpyrrolidine with S_2Cl_2 and Dabco in dichloromethane,[6] was treated with DMAD with reagents to remove sulfur atoms from the penathiepin ring. Compound **3** was shown not to react with DMAD (5 equiv) alone on heating under reflux for 10 h in dichloromethane or chloroform.

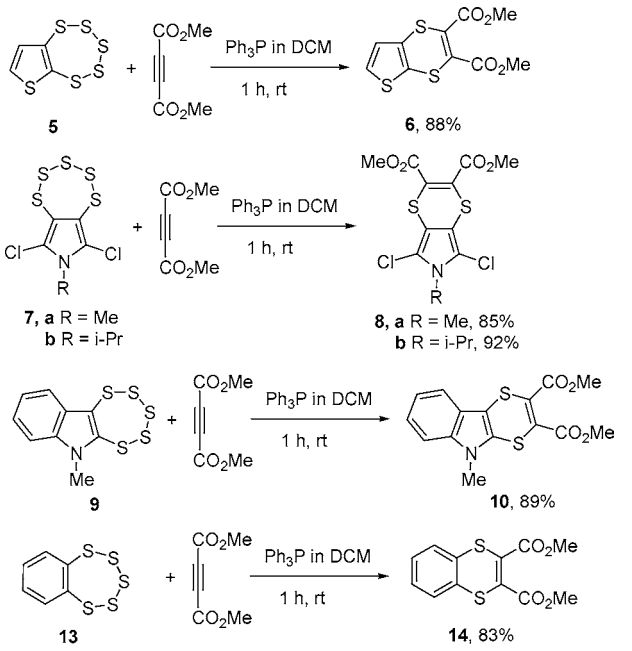
In the presence of DMAD, sodium phenylsulfinate ($PhSO_2Na$), sodium cyanide, and triphenylphosphine each removed three atoms of sulfur from pentathiepin **3** to form sodium phenylthiosulfinate ($PhSO_2SNa$), sodium thiocyanate (NaSCN), and triphenylphosphine sulfide in high yield (94−99%). With $PhSO_2Na$, dithiin **4** was not formed, and only oligomeric products (NMR and mass spectra) were isolated from the reaction mixture. DMAD reacted smoothly with pentathiepin **3** and NaCN or Ph_3P to give **4** in 83 and 80% yields, respectively, after 1 h at room temperature (Scheme 2).

Scheme 2



Although both reagents gave high yields of the dithiin,we chose triphenylphosphine as our standard because it is less toxic and required much less organic solvent than NaCN. Triphenylphosphine alone does react smoothly with **3** in DCM at room temperature to remove three atoms of sulfur; more than 3 equiv of triphenylphosphine leaves the excess of reagent unchanged and isolable by column chromatography, together with 3 equiv of $Ph_3P{=}S$. The best conditions for conversion of **3** into dithiin **4** (yield 86%) were stirring **3** in DCM with Ph_3P (4 equiv) and DMAD (3 equiv) at room temperature for 1 h. These conditions were employed for the heterofused pentathiepins **5**, **7**, **9**, and **11** recently prepared[6,7] and for benzopentathiepin **13**;[8] all of the corresponding fused mono- and bis-1,4-dithiins **6**, **8**, **10**, **12**, and **14** were isolated in the high yields shown (Schemes 3 and 4).[9]

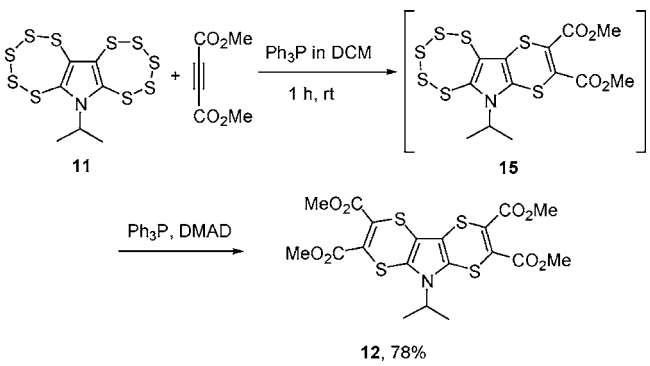
Scheme 3



Treatment of *N*-isopropylpyrrolidine with S_2Cl_2 and Dabco gave the only characterized bis-pentathiepin **11**;[6] with DMAD/Ph_3P this could give a bis-dithiin, **12**, possibly via the monopentathiepin **15**. When bis-pentathiepin **11** (1 equiv) was treated with DMAD (10 equiv) and Ph_3P (6 equiv) in DCM at room temperature for 1 h it gave only the red bis-dithiin **12** in 78% yield. With **11** (1 equiv), DMAD (1 equiv), and Ph_3P (3 equiv), we isolated a lower yield (54%) of the same bis-dithiin **12**, together with recovered **11** (18%). The unsymmetrical product **15** was not obtained nor detected, suggesting that attack by Ph_3P and DMAD on the second pentathiepin ring of **11** started before that on the first was complete (see reaction mechanism).

Another alkyne with two electron-withdrawing groups, dibenzoylacetylene, reacted in the same way as DMAD, under the same conditions, to give the dibenzoyldithiins **16**−**19** from **5**, **7a**, **9,** and **13**, respectively, in the yields shown in Figure 1.

Scheme 4



(4) Sato, R.; Chino, K.; Saito, M. *Sulfur Lett.* **1990**, *10*, 233.
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(9) **Typical Experimental Procedure.** A solution of triphenylphosphine (4 mmol) in dichloromethane (3 mL) was added dropwise to a stirred solution of appropriate pentathiepin (1 mmol) and appropriate alkyne (3 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred for 1 h, solvent was evaporated under reduced pressure, and the corresponding dithiin was separated by column chromatography (silica gel Merck 60).

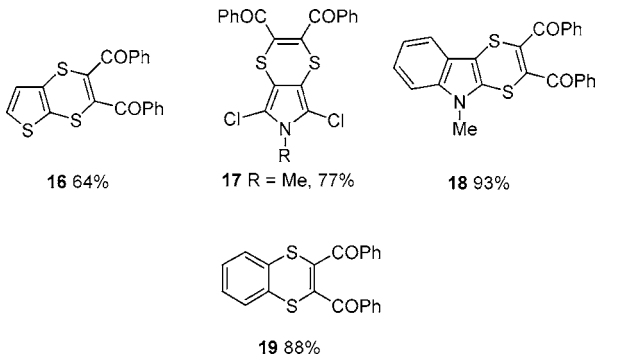
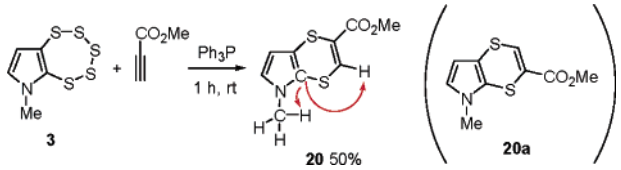


Figure 1. Dibenzoyldithiins **16**−**19** obtained.

Alkynes with only one electron-withdrawing group are of particular interest because, with unsymmetrical pentathiepins, they could lead to a pair of regioisomers. We therefore examined the above reactions but with DMAD replaced by methyl propiolate. This reacted under the same conditions with pentathiepinopyrrole **3** and triphenylphosphine to give dithiin **20**, accompanied by baseline material from **3** and triphenylphosphine also observed (TLC) in the absence of methyl propiolate. No evidence for regioisomer **20a** was observed in the ^{1}H and ^{13}C NMR spectra (Scheme 5).

Scheme 5



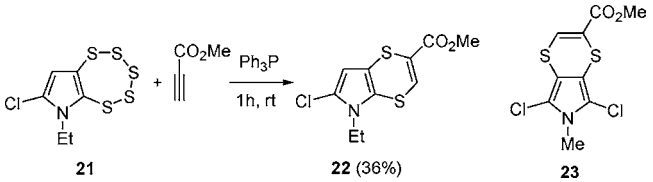
The molecular formula of **20** was based on elemental analysis and mass spectra. According to ^{1}H and ^{13}C NMR spectra, only one isomer is formed in this reaction. The exact structure of **20** was determined by an HMBC experiment[10] elucidating long-range hydrogen−carbon correlations (see Supporting Information). There are two strong correlations between pyrrole C(2) atom (δ = 115.0 ppm) and 1,4-dithiin C−H proton (δ = 7.4 ppm) and protons of the *N*-methyl group (δ = 3.5 ppm) through three bonds, confirming the structure **20**; these interactions would not be observed with **20a** (Scheme 5).

A similar result was obtained in the reaction of pyrrolopentathiepin **21** with the same mixture of methyl propiolate and triphenylphosphine. Again one dithiin **22** was isolated, and its structure was proved, as for **20**, by spectra and an HMBC experiment (Scheme 6).

The symmetrical pyrrolopentathiepin **7a** gave 1,4-dithiin **23** (40%); indolopentathiepin **9** did not react with methyl propiolate but was decomposed by the action of triphenylphosphine.

(10) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

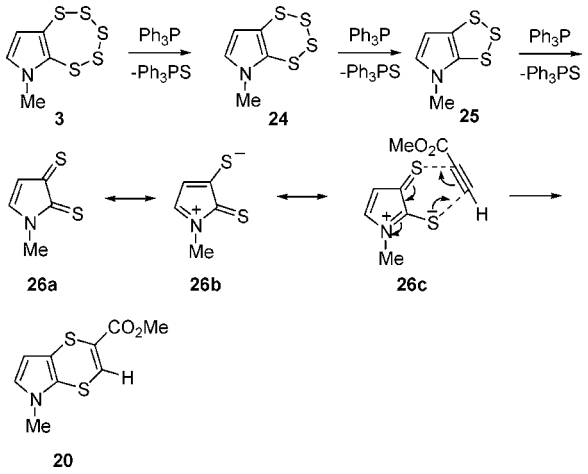
Scheme 6



The much less reactive phenylacetylene did not react with Ph_3P and pentathiepins **3**, **7a**, or **9** to give dithiins; the pentathiepins were decomposed in the same way (TLC) as by Ph_3P alone.

To gain some insight into the mechanism for the formation of 1,4-dithiins from the pentathiepins (see Scheme 7), we

Scheme 7



investigated the reaction of *N*-methylindolopentathiepin **9**, which is less reactive than other pentathiepins toward Ph_3P and DMAD. When Ph_3P (1 equiv) was added to **9** (1 equiv), the reaction mixture still contains a substantial amount of **9**; another 1 equiv of Ph_3P caused the complete disappearance of **9**. If DMAD is added to this mixture, there is no reaction. Possibly the sequential removal of sulfur atoms from the pentathiepin does not stop at the tetrathiin (e.g., **24**) but proceeds to the trithiole (e.g., **25**); Ph_3P═S is formed immediately after the addition of Ph_3P. Addition of a third equivalent of Ph_3P led to complete removal of the pentathiepin, but no products were isolated from it; however, if DMAD was added to the reaction mixture before adding the third equivalent of Ph_3P, or immediately after, dithiin **10** was formed in high yields (80−90%). No products were observed from the breaking of any carbon−sulfur bonds by Ph_3P. The preliminary observations above with methyl propiolate suggest that unsymmetrical pentathiepinopyrroles react with this alkyne regioselectively. This can also be accommodated by a proposed mechanism (Scheme 7) shown for the reaction of the pentathiepinopyrrole **3**.

It is likely that in the 1,2-dithione intermediate **26a** the thioamide electronic contribution **26c** will be greater than

26b; thus S-2 will be more nucleophilic than S-3 and addition to methyl propiolate would occur as shown to give the observed regioisomer **20**. It is also possible, in a slightly more complex mechanism, that once the polysulfur rings are opened by Ph_3P to give dipolar intermediates, their terminal sulfide anions could add to the triple bond before loss of Ph_3PS, but the same overall electronic considerations should apply.

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

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