A novel oxime to pentathiepin cascade reaction

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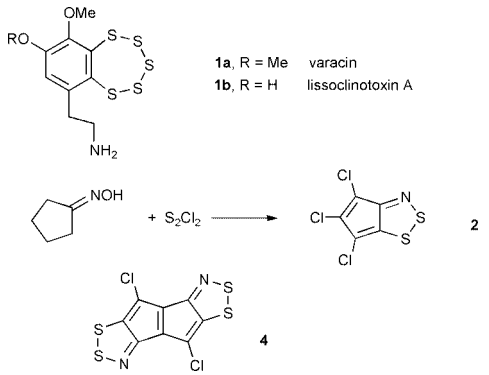
An extensive domino sequence, including a vinylogous sulfur-assisted Beckmann fragmentation, is involved in the one-pot conversion of a dioxime 3 by S_2Cl_2 into a cyanoethyl-1,2,3-dithiazole 5 and a novel tricyclic pentathiepin 6; the yield of 6 is increased by added lithium sulfide, and both 5 and 6 are formed in higher yield from 2-(cyanoethyl)cyclopentanone oxime 7; reaction mechanisms are proposed for these cascade reactions.

Benzopentathiepins have attracted much attention recently because of their remarkable stability, the very high barrier (up to *ca*. 30 kcal mol^{-1}) for inversion of the chair-like heterocyclic ring[1] and their potent biological activity. The first naturally occurring examples varacin **1a**[1] and lissoclinotoxin A **1b**,[1,2] and



related dopamine-like structures, have strong antimicrobial and antifungal activity, selectively inhibit protein kinase C,[3] and varacin is highly toxic towards human colon cancer HCT 116.[1] Furthermore 7-methylbenzopentathiepin, lacking the aminoethyl group, is a potent thiol-dependent DNA cleaving agent.[4] The pentasulfur ring appears to be essential for biological activity. However, with the notable exceptions of Chenard's isothiazolo and pyrazolo pentathiepins[5] and Sato's trithiolobenzopentathiepins,[6] very little is known about heterocyclic fused pentathiepins. We now describe an unusual and unexpected one-pot synthesis of a new polyheteroatom pentathiepin **6**.

The reaction of simple saturated ketoximes with disulfur dichloride, S_2Cl_2, in the presence of tertiary amines provides an effective one-pot route to 1,2,3-dithiazoles; the initial cyclocondensation is followed by extensive dehydrogenation and chlorination to yield fully unsaturated heteroaromatic products.[7] A typical example is the conversion of cyclopentanone oxime into the deep violet 10 π pseudoazulene **2**.[8]

In an extension of this work we treated the dioxime **3** of tricyclo[3.3.0]octan-2,6-dione[9] (Scheme 1) with S_2Cl_2 and Et_3N hoping to produce the tetracyclic 18 π bis-dithiazole **4**, but instead we isolated two mono-dithiazoles **5** and **6**.

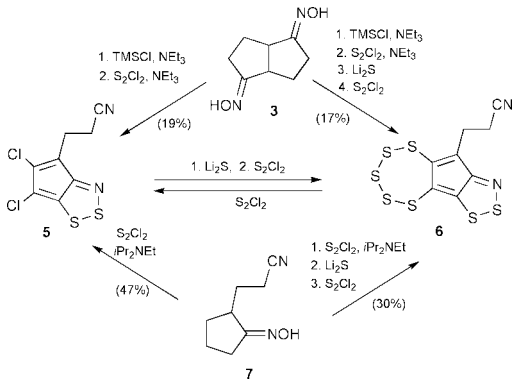
Better yields of products were obtained from silylated oximes, so we first treated dioxime **3** with TMSCl and Et_3N in boiling THF for 1 h. Then the mixture was cooled (−20 °C) and Et_3N (20 equiv.) and S_2Cl_2 (20 equiv.) were added and the mixture stirred for 3 d at 4 °C. Chromatography gave a purple product **5**, $C_8H_4Cl_2N_2S_2$ (19%) and, in some reactions, a very minor mauve product **6**, $C_8H_4N_2S_7$ (1–3%). The purple product was similar to cyclopentadithiazole **2** but had a nitrile and two methylene groups in addition to the five sp^2 carbons. Based on this, and mechanistic considerations, structure **5** was assigned to this compound. One cyclopenta-1,2,3-dithiazole has been formed but the second carbocyclic ring has been opened, together with dehydrogenation and chlorination, as before.[7]

The mauve product with five extra sulfur atoms in place of the two chlorines in **5** also showed a cyanoethyl group, but now one of the methylenes gave a complex signal in the ^{1}H NMR compounded of two quintets; each quintet was the sum of two overlapping triplets, suggesting the presence of conformational isomers. This information supported the (chiral[10]) structure **6** with a slowly inverting chair-like pentathiepin ring fused to a cyclopentadithiazole, a new ring system.

The pentathiepin ring in **6** is presumably formed by substitution of the chlorines in **5** by some nucleophilic sulfur species. The 7-membered ring could then be completed by S_2Cl_2 in a reaction related to the known formation of benzopentathiepins,[2,5,11] the thermodynamically favoured products. To test this possibility we ran the reaction of dioxime **3** with S_2Cl_2 as before but after 3 days we added Li_2S (20 equiv.), stirred the mixture for 6 h at 4 °C, then added more S_2Cl_2 (20 equiv.) at −20 °C and stirred for 20 min. Chromatography gave a higher yield (17%) of **6** as the only isolable product.

We then synthesized the dithiazoles **5** and **6** in a more rational way from preformed 2-(2-cyanoethyl)cyclopentanone oxime **7**[12] to confirm their structures and improve their yields. Firstly, oxime **7** was treated with S_2Cl_2 (10 equiv.) and Hünig's base (10 equiv.) in THF for 3 d at 4 °C to give **5** (47%) and **6** (3%). Secondly, oxime **7** was treated with S_2Cl_2 (10 equiv.) and Hünig's base (10 equiv.) in THF for 3 d at 4 °C, then with Li_2S (20 equiv.) in THF for 8 h at 4 °C and then with S_2Cl_2 (10 equiv. for 18 h at 4 °C and then another 10 equiv. at RT) all in one pot to give the pentathiepin **6** (30%) as the only product. The same product was obtained in similar yield (28%) when the final aliquot of S_2Cl_2 (20 equiv.) was added in one portion and stirred for 12 min at RT.

Surprisingly, exposure of the reaction mixture to the final portion of S_2Cl_2 (20 equiv.) for longer periods resulted in the



Scheme 1

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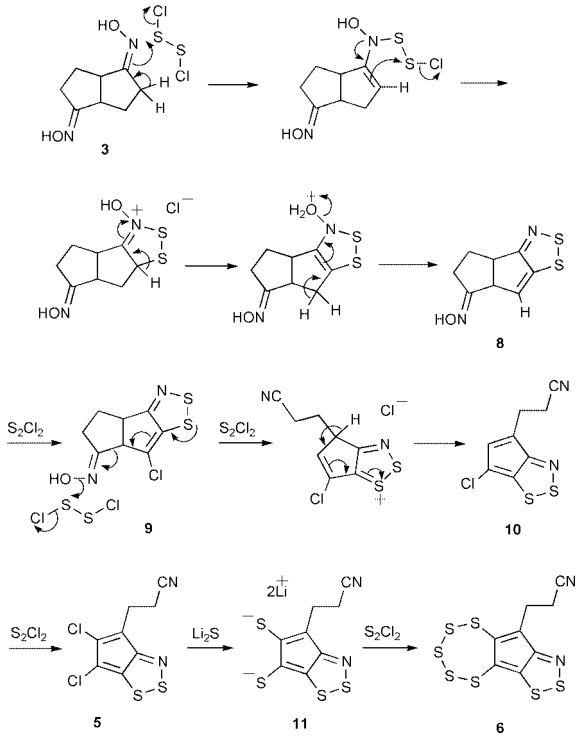

Scheme 2

formation of **5** as well as **6** and, after 1 d at 4 °C, **5** (25%) was the only product isolated. Separate experiments showed that **5** is converted into **6** by excess of sulfide anion followed by S_2Cl_2, and that **6** reverts to **5** when treated with excess of S_2Cl_2 for longer periods. These results, summarised in Scheme 1, support the structures of **5** and **6** and a pathway for the formation of **6** from **3** and from **7**.

A plausible mechanism, starting for simplicity from the free oximes, is shown in Scheme 2. Electrophilic attack by S_2Cl_2 at one oxime (or silylated oxime) group in **3** is followed by cyclisation and dehydration to give the 1,2,3-dithiazole **8**. Both sulfur atoms of **8** would activate it to chorination to give **9** in which the chlorine atom disfavours the *Z* configuration of the oxime necessary for formation of the second dithiazole ring, and the steric repulsion would be greater for the TMS derivative. Thus Beckmann fragmentation (arrows in **9**),[13] catalysed by S_2Cl_2 or by liberated acid, can supervene to give the cyanoethyl intermediate **10**. This ring fission, which is activated by both dithiazole sulfur atoms, is a vinylogous version of the long-known sulfur assisted fragmentation of oximes of β-keto-sulfides.[14] Further chlorination of **10** gives the cyclopenta-1,2,3-dithiazole **5** isolated. Nucleophilic sulfur species produced in, or added to, the reaction mixture could afford the dithiolate **11** and hence, with two equiv. of S_2Cl_2, the pentathiepin **6**, by a mechanism similar to that proposed by Toste and Still.[11]

These one-pot syntheses of the fused pentathiepin **6** from the mono-oxime **7** or the dioxime **3** provide a new and easy route to compounds related to the naturally occurring pentathiepins that are of considerable pharmaceutical and agrochemical potential.

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