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A one-step synthesis of fused pentathiepins†

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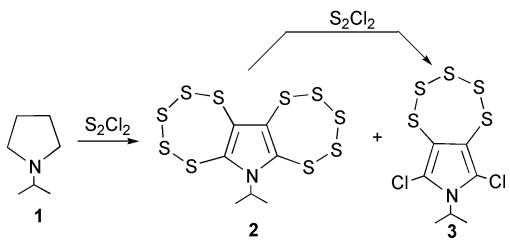
Treatment of nucleophilic heterocycles like pyrroles and thiophene, and their tetrahydro derivatives, with S_2Cl_2 and a base in chloroform at room temperature provides a simple one-pot synthesis of heterocyclic fused mono and bis pentathiepins such as 2, 3, 4, 5, 9, and 11.

Fused pentathiepins have attracted attention recently because of their stability, biological activity and high energy barrier for inversion of the chair-like pentathiepin ring.[1] The first naturally occurring examples varacin,[2] lissoclinotoxin A,[3,4] and *N,N*-dimethyl-7-(methylthio)varacin[5] have strong antimicrobial and antifungal activity, selectively inhibit protein kinase C,[5] and varacin is highly toxic towards human colon cancer HCT116.[2] The polysulfur ring of these benzopentathiepin antibiotics is crucial for the biological activity.[4,5] Several benzopentathiepins are known but heterocyclic fused systems are limited to isothiazolo,[6] pyrazolo,[7] 1,3-dithiolo,[8] trithiolobenzo[9] and 1,2,3-dithiazolocyclopenta[10] derivatives.

Methods for the synthesis of pentathiepins which are very limited involve treatment of the preformed *o*-dithiols and their salts with disulfur dichloride, S_2Cl_2,[6] S_3Cl_2[11] or S_8 in liquid ammonia.[12] *o*-Disubstituted starting materials are not always readily available, especially for heterocycles. We now describe a very simple and direct route to pentathiepins from electron rich heterocycles such as pyrroles, indoles and thiophene, and their tetrahydro derivatives.

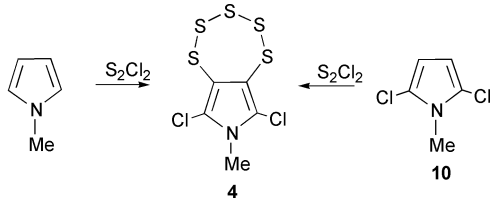
We have shown that *N*-isopropyl groups can be converted by S_2Cl_2 into *N*-(1,2-dithiole-3-thiones).[13] However treatment of *N*-isopropylpyrrolidine **1** with S_2Cl_2 (5 equiv) and DABCO (5 equiv) in chloroform under argon at RT for 3 d gave two unexpected products **2** and **3** (Scheme 1). In each of these the isopropyl group was unchanged but the pyrrolidine ring had been extensively transformed to give the fused bispentathiepine **2** as a yellow oil, $C_7H_7NS_{10}$ (31%) and monopentathiepin **3** as yellow crystals, $C_7H_7Cl_2NS_5$ (16%). Since the precise stoichiometry of these and the other reactions reported here are not yet known, all yields are based on the assumption that the S_2Cl_2 is in excess, and are thus minimum values based on the organic substrate. Both **2** and **3** are symmetrical, showing *N*-isopropyl groups in the ^1H and ^{13}C NMR spectra in addition to two different sp^2 carbons; the mass spectra showed major loss of S_4 and S_2 respectively, presumably for conversion of the pentathiepins into 1,2,3-trithioles. Based on this and their molecular formulae the pentathiepin structures **2**, the first bispentathiepin reported, and **3** were assigned and the latter was confirmed by X-ray structure determination.[14] When an excess of S_2Cl_2 (10 equiv) was used with **1**, only the monopentathiepin **3** was isolated; possibly any bispentathiepin **2** formed was converted into **3**. A separate experiment showed that **2** was indeed converted into **3** by S_2Cl_2–DABCO in high yield.



Scheme 1

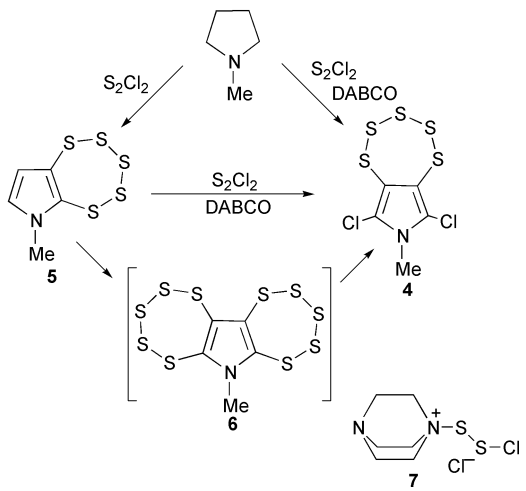
Thus the pyrrolidine ring in **1** is more reactive than the isopropyl group towards S_2Cl_2, and the subsequent transformations provide a very simple synthesis of fused pentathiepins. To explore this further we studied the analogous reactions of *N*-methyl derivatives of pyrrolidine, pyrrole, 2,5-dichloropyrrole and indole, and some related reactions.

N-Methylpyrrole gave the dichloropentathiepinopyrrole **4**, analogous to **3**, as the major product (Scheme 2), and the effect of reaction time and temperature and reactant ratio were investigated. Our standard procedure was to mix the reactants at −35 °C and to stir the mixture for 2 d at RT, followed by column chromatography. Without added base the yields were very low even though the starting pyrrole was consumed, but with pyridine, triethylamine or DABCO the yields were 30–50%, the best being obtained with 5 equiv each of S_2Cl_2 and DABCO.



Scheme 2

In the *N*-methylpyrrole reaction the bispentathiepin (**6**, Scheme 3) analogous to the *N*-isopropyl compound **2** was not



Scheme 3

† Electronic supplementary information (ESI) available: characterization of compounds **2**–**5**, **9**, and **11**. See http://www.rsc.org/suppdata/cc/b2/b203349f/

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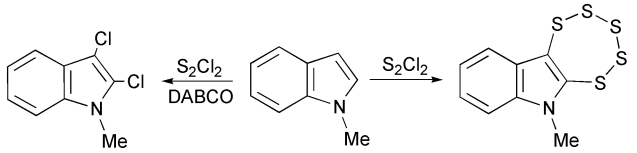
isolated, though it was probably formed since a weak TLC spot very like that for **2** was always perceptible. This component decomposed during the reaction and could not be isolated. Not unreasonably, it appears to be more reactive towards S_2Cl_2 than the bulkier derivative **2**, possibly suffering chlorination at the α-positions to give, ultimately, the dichloropentathiepin **4**.

When *N*-methylpyrrolidine was substituted for *N*-methylpyrrole (Scheme 3) the pentathiepin **4** was again formed but in lower yield (18%). However, with a deficiency of S_2Cl_2 (0.8 equiv) and with no added base the only product isolated was the simpler, unsymmetrical pentathiepin **5** in low yield (*ca*. 20%). Further treatment of **5** with S_2Cl_2–DABCO (Scheme 3) converted it into dichloropentathiepin **4**, possibly *via* the reactive bispentathiepin **6**.

The presence of DABCO in the *N*-methylpyrrolidine reaction favours chlorination which is not seen in its absence. We have observed this tendency before,[13,15] and explained it by invoking the formation of a complex **7** by attack of S_2Cl_2 at sulfur by the sterically undemanding nucleophile DABCO; **7** can then act as an electrophilic chlorinating agent. This decisive role of DABCO was also seen in the analogous reactions of *N*-methylindole (Scheme 4). Treatment of the latter with S_2Cl_2 (5 equiv) and DABCO (5 equiv) gave the 2,3-dichloroindole **8** in high yield (78%), but with a deficiency of S_2Cl_2 (0.8 equiv) in the absence of a base the only product was the unchlorinated pentathiepin **9** in 72% yield. The parent pentathiepinoindole (**9**, H for Me) is formed as a minor product (4%) when isatin is heated with P_4S_{10} in pyridine.[16]

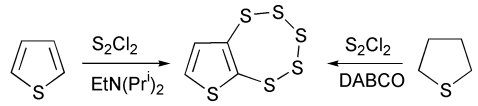


8 (78%) **9** (72%)

Scheme 4

Thus *N*-methylpyrrole and *N*-methylpyrrolidine are converted by S_2Cl_2–DABCO into the dichloropyrrolopentathiepine **4**, possibly through the intermediate bispentathiepine **6**. We therefore treated 1-methyl-2,5-dichloropyrrole **10** in exactly the same way to see if this would also give pentathiepine **4**, which it did. When the equimolar mixtures of the two reagents were in 3, 4, 5 and 6-fold excess the yields of **4** were 40, 53, 62 and 70% respectively. Thus β-substitution of the pyrrole **10** by S_2Cl_2 followed by further substitution at sulfur and cyclisation to give the stable pentathiepine ring seems entirely reasonable.

We briefly extended these S_2Cl_2 reactions to furan, thiophene and their tetrahydro derivatives. Furan and THF were extensively decomposed and gave no pure products. Thiophene and tetrahydrothiophene gave complex reactions from which the thiophenopentathiepin **11** was isolated (Scheme 5). Thiophene with 5 equiv of each reagent gave 10% of **11**; tetrahydrothiophene with 4, 5, and 6 equiv of each reagent gave



11

Scheme 5

respectively 17, 26 and 25% of **11**, based on the heterocycle. The unsymmetrical structure of **11** followed from its spectroscopic properties which are similar to those of the analogous pyrrole **5**. The symmetrical isomer of **11** has previously been prepared from 3,4-dibromothiophene by conversion into the 3,4-dithiol and treatment with S_2Cl_2 in 2% overall yield.[6]

Although the precise stoichiometry of these reactions is not yet known and mechanistic discussion would be premature, they do illustrate the versatile reactivity of S_2Cl_2 and a base. This includes the dehydrogenation of tetrahydro aromatics, chlorination of the aromatics and their conversion into –SSCl derivatives[17] (up to four times). Adjacent –SSCl groups could cyclise with loss of SCl_2 to give a fused 1,2,3-trithiole. Further attack of this by S_2Cl_2, with ring opening and closing to extrude SCl_2 would increase the ring size by one sulfur at a time, ultimately to give the thermodynamically stable[6] pentathiepin. A selection of similar reaction steps can also explain the intriguing transformations (*e.g.* **2** → **3** and **5** → **4**) of one pentathiepin into another with concomitant chlorination. Some similar processes maybe involved in the conversion of *N*-methylhexahydroazepine into 2-ethyl-1-methyl-3,4-pentathiepinopyrrole (5%) by heating with sulfur in HMPA.[18]

These reactions show how readily and uniquely pentathiepins can be fused onto certain heterocyclic rings, and suggest many possible extensions of this experimentally simple procedure.

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