Regioselective synthesis of pentathiepino-fused pyrroles and indoles

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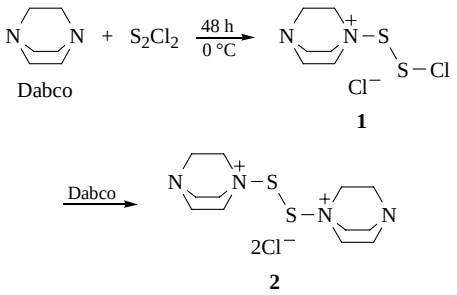
DOI: 10.1070/MC2004v014n03ABEH001912

Treatment of simple pyrroles, pyrrolidines and indoles with S_2Cl_2 and Dabco in chloroform at room temperature gives their fused pentathiepino derivatives 4, 6 and 8 in extensive cascade reactions; the reaction profile is changed and the regioselectivity enhanced when the S_2Cl_2 and Dabco are premixed and equilibrated before the heterocycle is added.

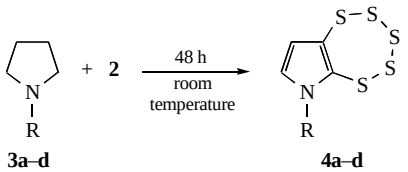
In spite of much recent activity, few different syntheses of pentathiepins are available.[1] Most methods require 1,2-dithiols; thus, pentathiepins fused to other heterocyclic rings are rare.[2–6] We found that the treatment of nucleophilic heterocycles like pyrroles and thiophenes and their tetrahydro derivatives with disulfur dichloride (S_2Cl_2) and a base in chloroform at room temperature provides a simple and direct one-pot synthesis of fused mono- and (previously unknown) bis(pentathiepins).[5] However, when there is more than one site for fusion of the new polysulfur ring, these reactions are not regioselective and are sensitive to the nature of the nucleophilic heterocycle and the reaction conditions.[5]



Scheme 1

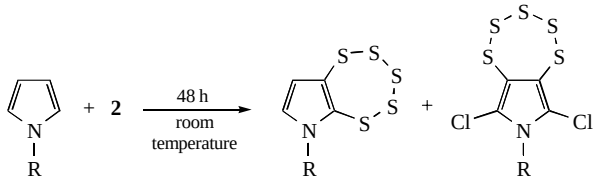
Recently, we found that a mixture of equimolar amounts of S_2Cl_2 and Dabco in chloroform, stored for 48 h at 0 °C before use, gave different products to those formed when the heterocycle, S_2Cl_2 and Dabco were all mixed together at the beginning.[6] We assume that a complex is formed between S_2Cl_2 and Dabco in the slow reaction in chloroform at 0 °C, and we studied this solution by IR spectroscopy. The S–Cl absorption bands of S_2Cl_2 (436 and 452 cm^{-1}) are present in the 1:1 mixture of S_2Cl_2 and Dabco, but they disappear when a second mole of Dabco is added. We assume that the 1:1 mixture contains complex **1** predominantly, and the 1:2 mixture, complex **2** predominantly (Scheme 1). These complexes could well display different reactivities since **1** is a potential source of Cl^+ and $^+$S–SCl and could be an electrophilic chlorinating and sulfurating agent whilst **2** should react only as the latter. Complex **2** in the 1:2 mixture is also fully formed in about 1 h at 20 °C and then decomposes slowly with the formation of S_8 and, in the presence of a reacting substrate, Dabco hydrochloride.

Treatment of *N*-alkylpyrrolidines **3** with a fivefold excess of complex **2** in chloroform for 48 h at room temperature gave selectively *N*-alkyl-1,2,3,4,5-pentathiepino[6,7-*b*]pyrroles **4** in low to moderate yields (Scheme 2).



a R = Me, 29%
b R = Et, 31%
c R = Pr^i, 30%
d R = Bu^t, 61%

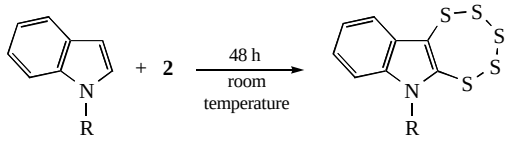
Scheme 2



a R = Me, 23% 6%
d R = Bu^t, 14% 17%

Scheme 3

Treatment of two analogous *N*-alkylpyrroles **5a**,**d** under the same conditions gave products **4a**,**d** in lower yields (23 and 14%) together with dichlorinated pentathiepino[6,7-*c*]pyrroles **6a**,**d** (Scheme 3). S_2Cl_2 chlorinated **4a** with concomitant rearrangement of the pentasulfur ring to give **6a**,[5] and this is probably happening here under the influence of the excess of S_2Cl_2 and adventitious moisture.† The higher yield (61%) of **4d** above may result from steric protection of this product by the *tert*-butyl group.

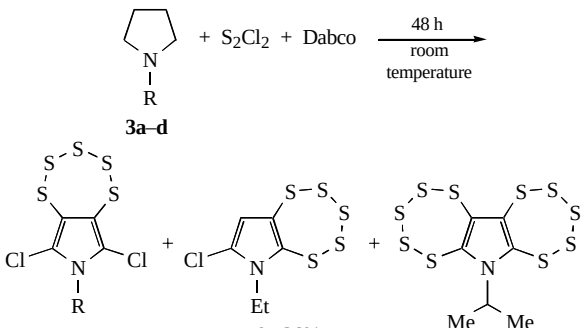


a R = Me, 51%
d R = Et, 62%

Scheme 4

If this migration of the intact pentasulfur ring in **4**→**6** is prevented by substitution as in *N*-alkylindoles **7**, initially formed *b*-fused products **8** are isolated in relatively high yields (Scheme 4).

For comparison with these reactions of complex **2**, we treated some of the same heterocycles with S_2Cl_2 and Dabco



6a R = Me, 18%
b R = Et, 14%
c R = Pr^i, 16%
d R = Bu^t, 23%

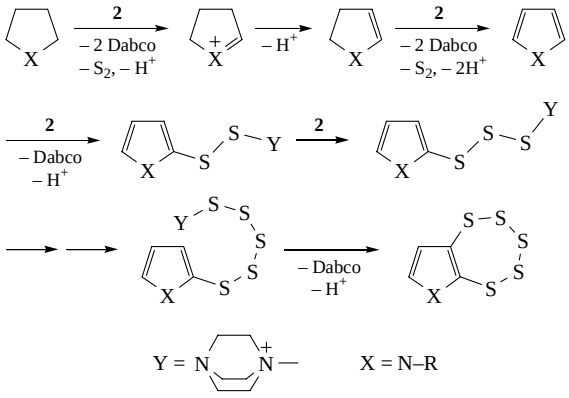
9, 36%

10, 31%

Scheme 5

(1:1) under the earlier conditions,[5] *i.e.*, without premixing the reagents. With *N*-alkylpyrrolidines **3a–d**, the latter reactions were a little more complex in that they all gave dichloro[*c*]fused pentathiepin **6** in lower yields shown together with monochloro[*b*] fused pentathiepin **9** when R = Et and bisfused pentathiepin **10** when R = Pr^i (Scheme 5). Previously,[5] we suggested that these last two products are intermediates on the way to the ultimate formation of **6**. With *N*-methylpyrrole **5a** and *N*-methylindole **7a** the earlier reaction conditions gave products formed largely or exclusively by chlorination, *i.e.*, **6a** (50%) and 2,3-dichloro-*N*-methylindole (78%), respectively.

It is clear that preformed complex **2**, whilst not entirely regioselective, has a significantly different reaction profile with greater selectivity than a mixture of S_2Cl_2 and Dabco without premixing. A tentative reaction sequence for this unique formation of the thermodynamically stable[1] pentathiepins is shown in Scheme 6.



Scheme 6

† Dabco is very hygroscopic.

General procedure for the formation and reactions of complex **2**. Disulfur dichloride (25 mmol) was added dropwise at –15 to –20 °C to a stirred solution of anhydrous Dabco (50 mmol) in chloroform (100 ml). The mixture was stirred at 0 °C for 48 h. The corresponding heterocycle (5 mmol) was added, the mixture was stirred for another 48 h at room temperature and filtered, and the solvent was 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.

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

*6-Methyl-6*H-*[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole* **4a**: yellow solid, mp 99–101 °C. ^{1}H NMR ($CDCl_3$) δ: 6.58 (d, 1H, CH, *J* 2.6 Hz), 6.48 (d, 1H, CH, *J* 2.6 Hz), 3.80 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 132.60 and 128.55 (2*sp*^{2} tertiary C), 123.86 and 115.31 (2CH), 35.80 (Me). MS, *m*/*z* (%): 239 (M^+, 47), 207 (2), 175 (M – S_2, 100), 142 (53), 128 (3), 111 (49). Found M^+, 238.9016; $C_5H_5NS_5$ requires M, 238.9026.

*6-Ethyl-6*H-*[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole* **4b**: yellow oil. ^{1}H NMR ($CDCl_3$) δ: 6.58 (d, 1H, CH, *J* 3.0 Hz), 6.45 (d, 1H, CH, *J* 3.0 Hz), 4.11 (m, 2H, CH_2), 1.42 (t, 3H, Me, *J* 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 131.72 and 128.22 (2*sp*^{2} tertiary C), 122.22 and 115.47 (2CH), 43.87 (CH_2), 17.31 (Me). MS, *m*/*z* (%): 253 (M^+, 13), 221 (2), 189 (M – S_2, 100), 156 (26), 128 (26). Found M^+, 252.9181; $C_6H_7NS_5$ requires M, 252.9182.

*6-Isopropyl-6*H-*[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole* **4c**: yellow oil. ^{1}H NMR ($CDCl_3$) δ: 6.65 (d, 1H, CH, *J* 2.8 Hz), 6.48 (d, 1H, CH, *J* 2.8 Hz), 4.80 (m, 1H, CH), 1.50 (d, 3H, Me, *J* 6.8 Hz), 1.40 (d, 3H, Me, *J* 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 131.80 and 127.74 (2*sp*^{2} tertiary C), 118.80 and 115.67 (2CH), 49.74 (CH), 24.00 and 23.85 (2Me). MS, *m*/*z* (%): 267 (M^+, 15), 235 (2), 203 (M – S_2, 75), 161 (95), 138 (24), 128 (74). Found M^+, 266.9331; $C_7H_9NS_5$ requires M, 266.9338.

*6-*tert*-Butyl-6*H-*[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole* **4d**: yellow oil. ^{1}H NMR ($CDCl_3$) δ: 6.71 (d, 1H, CH, *J* 2.9 Hz), 6.39 (d, 1H, CH, *J* 2.9 Hz), 1.71 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$) δ: 131.84 and 130.88 (2*sp*^{2} tertiary C), 121.03 and 114.18 (2×CH), 59.43 (*C*Me$_3$), 31.31 (Me). MS, *m*/*z* (%): 281 (M^+, 21), 253 (7), 217 (M – S_2, 93), 161 (100). Found M^+, 280.9490; $C_8H_{11}NS_5$ requires M, 280.9495.

*6,8-Dichloro-7-*tert*-butyl-7*H-*[1,2,3,4,5]pentathiepino[6,7-*c*]pyrrole* **6d**: yellow solid, mp 102–104 °C. ^{1}H NMR ($CDCl_3$) δ: 1.87 (s, 9H, Me). ^{13}C NMR ($CDCl_3$) δ: 124.06 and 123.55 (2*sp*^{2} tertiary C), 65.84 (*C*Me), 31.43 (Me). MS, *m*/*z* (%): 297 (M^+ + 4, 16), 295 (M^+ + 2, 40), 293 (M^+, 45), 233 (M^+ + 4 – S_2, 34), 231 (M^+ + 2 – S_2, 84), 229 (M – S_2, 88). Found M^+, 348.8698; $C_8H_9Cl_2NS_5$ requires M, 348.8716.

*6-Ethyl-6*H-*[1,2,3,4,5]pentathiepino[6,7-*b*]indole* **8b**: yellow solid, mp 95–97 °C. ^{1}H NMR ($CDCl_3$) δ: 7.73 (m, 1H, ArH), 7.29 (m, 3H, ArH), 4.40 (10-tet, 2H, CH_2, *J* 7.0 and 7.5 Hz), 1.42 (t, 3H, Me, *J* 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 140.37, 135.29, 129.07 and 119.05 (4*sp*^{2} tertiary C), 124.47, 121.92, 120.60 and 110.31 (4CH), 39.94 (CH_2), 16.10 (Me). MS, *m*/*z* (%): 303 (M^+, 28), 239 (M – S_2, 100), 206 (42), 64 (46). Found M^+, 302.9352; $C_{10}H_9NS_5$ requires M, 302.9339.

*7-Chloro-6-ethyl-6*H-*[1,2,3,4,5]pentathiepino[6,7-*b*]pyrrole* **9**: yellow solid, mp 62–63 °C. ^{1}H NMR ($CDCl_3$) δ: 6.42 (s, 1H, CH), 4.18 (septet, 2H, CH_2, *J* 6.9 and 7.3 Hz), 1.32 (t, 3H, Me, *J* 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 131.14, 117.58 and 105.14 (3*sp*^{2} tertiary C), 113.82 (CH). 41.61 (CH_2), 16.59 (Me). MS, *m*/*z* (%): 289 (M^+ + 2, 15), 287 (M^+, 28), 225 (M^+ + 2 – S_2, 44), 223 (M^+ – S_2, 100). Found M^+, 286.8797; $C_6H_6ClNS_5$ requires M, 286.8792.

This work was supported by the Royal Society, MDL Information Systems (UK) Ltd. O. A. R. acknowledges the support of the RSC Research Fund. We thank the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.

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Received: 1st March 2004; Com. 04/2238