Tertiary amine–S_2Cl_2 chemistry: interception of reaction intermediates

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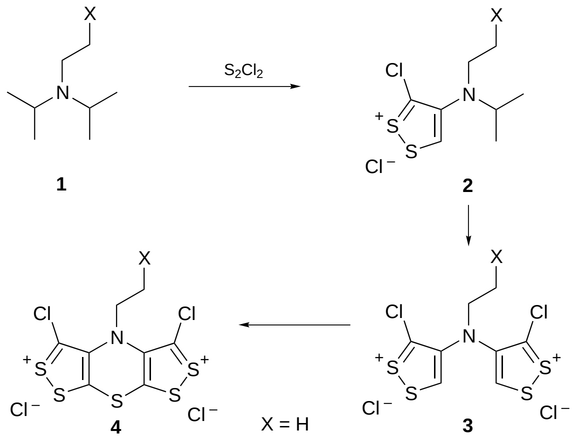
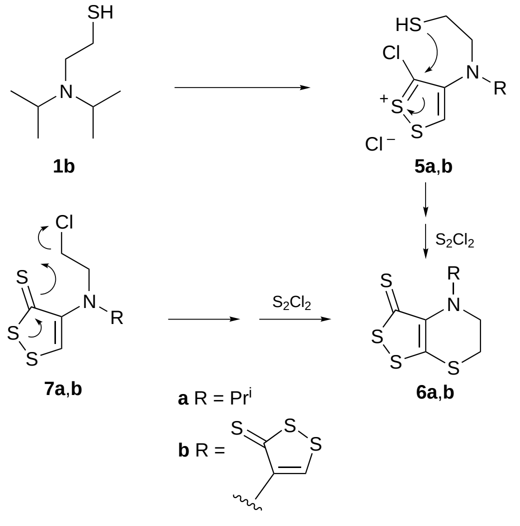
The reaction of *N*-(2-chloroethyl)diisopropylamine 1a with S_2Cl_2 allows the selective one-pot preparation of the tricyclic 4-(2-chloroethyl)bisdithiolothiazines 8 and 9 or, by addition of phosphorus pentasulfide at a late stage of the reaction, of the dithiolothiazine 6b characterised by X-ray crystallography; the chloroethyl derivative 8 is also obtained from (2-diisopropylamino)ethanethiol 1b and its disulfide 1c and S_2Cl_2, in a rare conversion of a thiol or disulfide into the corresponding chloro compound.

We have shown that Hünig's base, a simple saturated tertiary amine, is converted in a one-pot reaction by disulfur dichloride S_2Cl_2 into the fully unsaturated tricyclic bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*][1,4]thiazine ring system[1] or, at a higher temperature, into the bis[1,2]dithiolo[4,3-*b*:3′,4′-*d*]pyrrole system[2] by selective sulfur extrusion from the thiazine.

Only the isopropyl groups of Hünig's base reacted with S_2Cl_2, the ethyl group being untouched. This led us to consider the reactivity of functionalised ethyl groups, both to broaden the reaction scope and hopefully to intercept proposed intermediates on the long reaction pathway, by cyclisations involving the ethyl group substituents. The key intermediates in our earlier proposals[6] were considered to be **2**, **3** and **4** (Scheme 1) when X = H, with **4** finally reacting with sulfur and oxygen nucleophiles to give the observed products. If X is a sufficiently nucleophilic group such as SH, the intermediates **2** and **3** could be diverted (arrows in **5**), to give the bicyclic compounds **6a**, or **6b** (Scheme 2). If X is a leaving group such as Cl then, at a later stage in the reaction when the dithiolium salt has been converted into the thione **7**, nucleophilic displacement could lead to the same bicyclic intermediates **6** (Scheme 2).



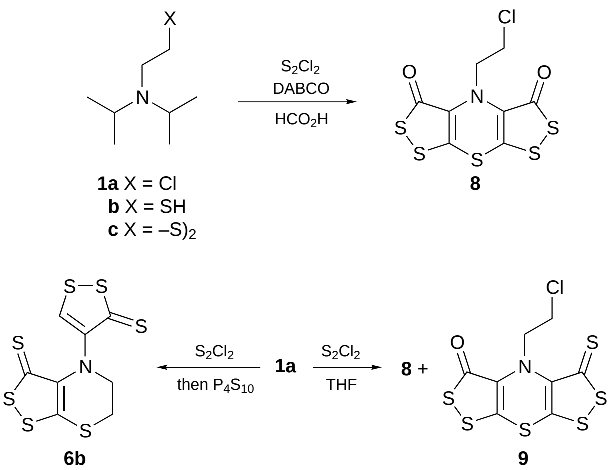
Scheme 1



Scheme 2

We therefore selected the commercially available *N*-(2-chloroethyl)diisopropylamine **1a**, which was readily converted into the thiol **1b** and its disulfide **1c**.[3] These compounds (1 equiv.) were each treated with S_2Cl_2 (10 equiv.) and DABCO (10 equiv.) in 1,2-dichloroethane for 3 d at room temperature. Formic acid (20 equiv.) was then added and the mixture heated under reflux for 1 h, since we find that this treatment gives clean reactions by converting the 3-chlorodithiolium salts into dithiol-3-ones. To our surprise all three starting materials **1a–c** gave exactly the same product **8** as a yellow solid, mp 175–177 °C (16–25%) after chromatography (Scheme 3). When the reaction of **1a** (1 equiv.) with S_2Cl_2 (1 equiv.) was performed in THF without addition of DABCO or formic acid, the oxo thione **9** was obtained as an orange solid, mp 256–258 °C (10%),† together with **8** (30%)† (Scheme 3). The structures of **8** and **9** were fully supported by all their spectroscopic properties.

In these reactions the chloroethylamine **1a**, the mercaptoethylamine **1b** and the disulfide **1c** reacted with S_2Cl_2 in the same way as Hünig's base itself, without detectable diversion of



Scheme 3

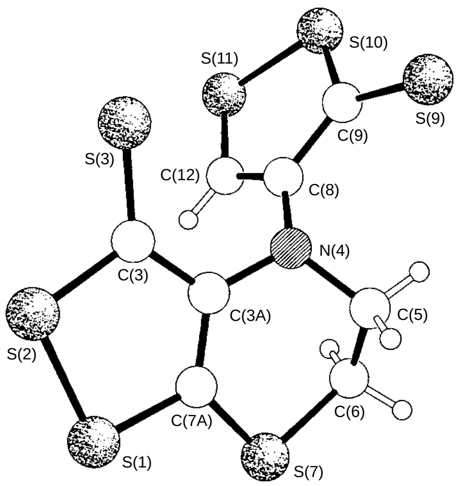


Fig. 1 The molecular structure of **6b**. Selected bond lengths (Å), S(1)–S(2) 2.057(1), S(2)–C(3) 1.731(3), C(3)–C(3A) 1.431(3), C(3A)–C(7A) 1.371(4), C(7A)–S(1) 1.729(3). C(3A)–N(4) 1.410(3), N(4)–C(8) 1.418(4), C(8)–C(9) 1.437(4), C(9)–S(10) 1.729(3), S(10)–S(11) 2.055(1), S(11)–C(12) 1.705(3) and C(12)–C(8) 1.348(4).

the reaction pathway, but with the additional conversion at some stage of the thiol and disulfide into the corresponding chloro compound. This last transformation is surprisingly rare, but has been achieved with sulfuryl chloride, followed by treatment with triphenylphosphine.[4]

These results suggest that S_2Cl_2 reacted with the sulfur groups faster than with the isopropyl groups; we therefore decided to try to regenerate a thiol derivative from the chloro compound by addition of a sulfur nucleophile at a late stage in the reaction. Treatment of the 2-chloroethylamine **1a** (1 equiv.) and S_2Cl_2 (1 equiv.) in THF for 3 d at room temperature was followed by addition of phosphorus pentasulfide (P_4S_{10}, 0.3 mol) and heating under reflux for 5.5 h. Chromatography gave new compound **6b** ($C_8H_5NS_7$) as shining orange needles, mp 240–241 °C (40%)† (Scheme 3). This did not contain chlorine (mass spectrum), although two different methylene groups were still present, together with an aromatic methyne group (^1H and ^{13}C NMR spectra) and a thiocarbonyl but not a carbonyl group (IR). The presence of an aromatic proton indicated that the fully fused tricyclic system of **8** and **9** had not been reached, and suggested the presence of a 1,2-dithiole with one ring hydrogen; structure **6b** was confirmed by X-ray crystallography (Fig. 1).‡ The partially saturated 1,4-thiazine ring has an 'envelope' conformation with C(5) lying 0.7 Å out of the plane of the remaining five atoms (which are co-planar to within 0.07 Å). There is a noticeable pyramidalization at N(4), the nitrogen atom lying 0.28 Å out of the plane of its substituents. The two dithiole rings are oriented approximately orthogonally (*ca.* 80°) thereby minimising interactions between them.

Taken in conjunction with our previous work on the conversion of Hünig's base with S_2Cl_2 into the *N*-ethyl analogues of compounds **8** and **9**,[1] the present results can be explained by the overall mechanism outlined in Scheme 4. The basic '*N*-ethyl' reaction does extend to other *N*-substituents and an appropriate functional group can divert the proposed reaction intermediates to form, in the present case, the new [1,2]dithiolo[3,4-*b*][1,4]thiazine ring system of **6b**. These complex 1,2-dithioles, now readily available from commercial materials in one-pot reactions, may be useful in the chemistry of new materials[5] and in pharmaceutical research.[6]

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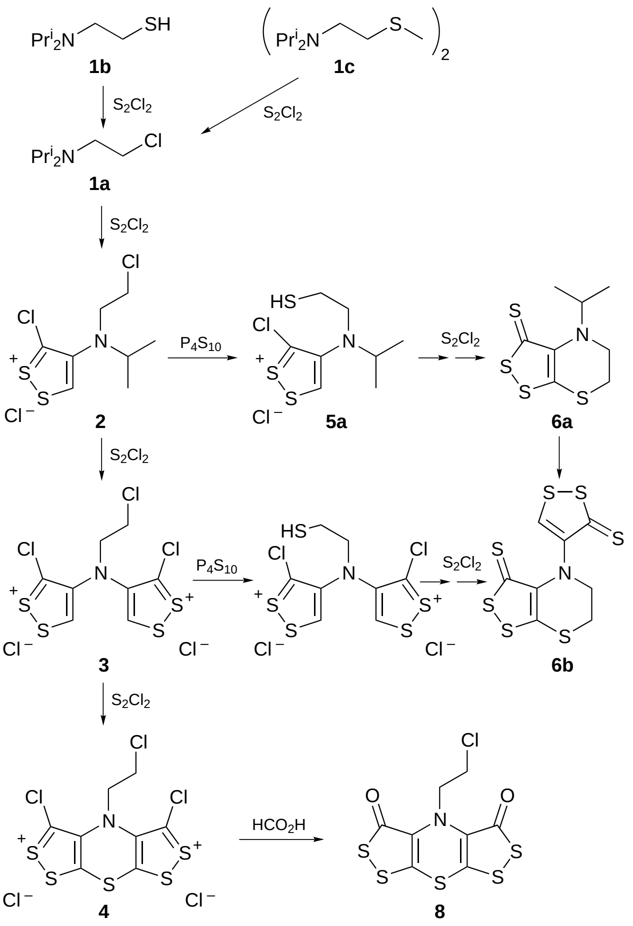

Scheme 4

Notes and References

† In the absence of DABCO, yields are calculated on the basis of 15 mol of amine **1** giving 1 mol of product and 14 mol of amine **1** hydrochloride.

‡ *Crystal data* for **6b**: $C_8H_5NS_7$, M = 339.6, orthorhombic, space group *Pbca* (no. 61), a = 14.672(1), b = 8.757(2), c = 19.626(2) Å, V = 2521.7(6) Å^3, Z = 8, D_c = 1.789 g cm^{-3}, μ(Cu-Kα) = 113.2 cm^{-1}, λ = 1.54178 Å, $F(000)$ = 1376. An orange platy needle of dimensions 0.67 × 0.22 × 0.02 mm was used. Data were measured on a Siemens P4/PC diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. 2089 Independent reflections were measured ($2\theta \leqslant 128°$) of which 1855 had $|F_0| > 4\sigma(|F_0|)$ and were considered to be observed. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on F^2 using absorption corrected data (face-indexed numerical, maximum and minimum transmission factors 0.80 and 0.16, respectively) to give R_1 = 0.036, wR_2 = 0.096 for the observed data and 146 parameters. CCDC 182/736.

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