New pyridine dithiols: synthesis and structures of complexes with acids

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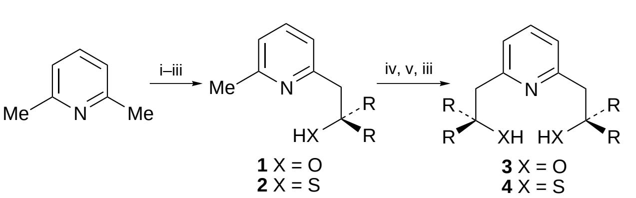
Pyridine dithiols have been synthesized by base-induced addition of 2,6-lutidine to (non-enolisable) thioketones, and have been found to encapsulate various acids.

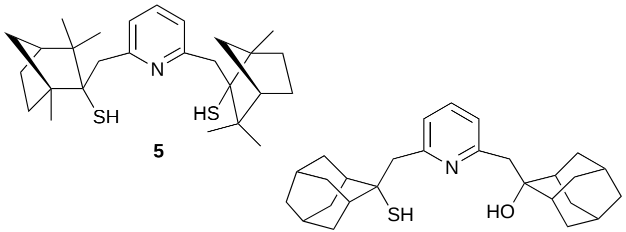
The addition products (‘pyridine diols’ **3**, Scheme 1) of 2 equiv. of ketone with 2,6-dimethylpyridine (2,6-lutidine) are tridentate ligands capable of encapsulating metal ions or acids.[1] Extensive structural variation is possible: benzophenone, fluorenone, acetone, acetophenone, adamantanone, fenchone and camphor are examples of ketones that have been used.[1d,2] Replacement of 2,6-lutidine by 2,9-dimethylphenanthroline leads to tetradentate ligands.[3] As an example of the opportunities for encapsulation of acids, we have described the crystal structure of the HCl complex of **3** whereby adamantanone was used as ketone.[3] The host organizes itself so that the acid is perfectly enclosed in a cavity wherein Cl is hydrogen bonded to the two hydroxy groups and the proton of HCl is directed towards the pyridine nitrogen.

We find that the approach of Scheme 1 can be extended to the preparation of certain ‘pyridine dithiols’ **4**. This method is more straightforward and efficient (overall yields 65–70%) than the multi-step synthesis of pyridine dithiols that has been reported previously and which is limited to thiols with relatively acidic α-protons.[1a–d] No products derived from addition of the carbanion to the sulfur of the thioketone have been isolated.[4] The two step addition shown leads to far better yields than either a single step approach involving direct deprotonation of 2,6-lutidine with 2 equiv. Bu^nLi followed by addition of 2 equiv. thioketone or a two step, one pot approach in which the mono-adduct is not isolated. An additional advantage of this approach is that the ‘single-armed’ derivative **2** (or **1**) can be obtained and studied separately. The bis-lithium salt of **4a** ($–CR_2–$ = adamantane-2,2-diyl) is remarkably stable, as was confirmed by means of ^7Li NMR spectroscopy, and is completely converted to the dithiol only after stirring for several hours with 5 M HCl. The pyridine dithiols can be handled without special precautions except that exposure to air should be limited to prevent oxidation.

The C_2 symmetrical double condensation product **5** obtained from optically pure (*R*)-thiofenchone can also be prepared; the crystal structure (not shown) confirms addition from the *exo* side of thiofenchone. Thiocamphor fails to undergo addition owing to formation of the thioenolate; competitive enolate formation appears to be a limitation to the direct approach of Scheme 1 when thioketones are used. The mixed adduct **6** can be prepared by lithiation of the ‘single-armed’ derivative **1** followed by a quench with 1 equiv. of thioadamantanone.



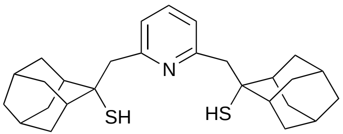
Scheme 1 *Reagents and conditions*: i, Bu^nLi (1.1 equiv.), THF, −80°C; ii, −80 °C → −40 °C; iii, $R_2C=X$; iv, Bu^nLi (1.2 equiv.), THF, −80 °C; v, −80 °C → −50 °C



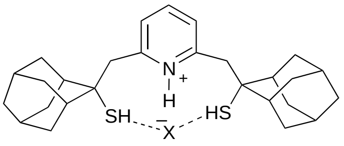
5

6

The complexation behaviour of **4a** has been studied extensively; other pyridine dithiols appear to behave in a related fashion. Treatment of **4a** with 1 equiv. HCl or HBr (titrated saturated CH_2Cl_2 solutions) leads to the air- and moisture-stable complexes **4a**·HCl and **4a**·HBr in quantitative yields. On addition of 1 equiv. of aqueous HNO_3 to **4a** in $CHCl_3$ at 0 °C, **4a**·HNO_3 is obtained; on complexation at ambient temperature, however, the thiol groups are partly oxidized. Attempted encapsulation of phosphonic acids failed.



4a



4a•HX

X = Cl, Br, ONO_2

Complexation with $ZnCl_2$ in MeOH provides the dimer [**4a**·$ZnCl_2$·MeOH]$_2$, whereas complexation of $Zn(NO_3)_2$·$4H_2O$ affords a monomeric and unstable **4a**·$Zn(NO_3)_2$ complex

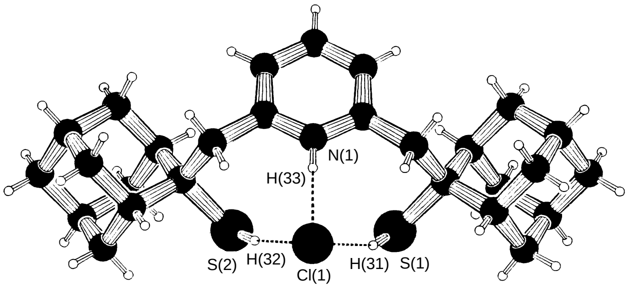


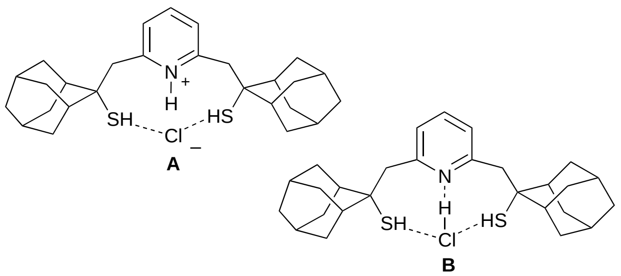
Fig. 1 The molecular structure of **4a**·HCl. Selected distances (Å) and angles (°): H(31)–Cl 2.58(3), H(32)–Cl 2.45(5), H(33)–Cl 2.19(3), N–H(33) 0.86(3), N–Cl 3.056(2), S(1)–H(31)–Cl 162(3), S(2)–H(32)–Cl 168(3), N–H(33)–Cl 178(3).

(characterized spectroscopically), which in MeOH or MeCN is slowly converted to the **4a**·HNO_3 complex.‡ These structures are not shown for reasons of space.

Crystal structures of all complexes except those with HBr and $Zn(NO_3)_2$ have been determined. Those of **4a**·HCl§ (Fig. 1) and **4a**·HNO_3 (Fig. 2)§ are shown, and for purposes of illustration some salient features of the former are briefly mentioned.

Monomeric HCl is firmly embedded in a cavity and held in place by bonding to pyridine nitrogen and the two thiols. The free pyridine dithiol **4a** (structure not illustrated) is not preorganized in this arrangement. In the complex the thiol groups are clearly hydrogen bonded to the chloride, although the bonds are of unequal length [H(31)··Cl(1) 2.58(3), H(32)··Cl(1) 2.45(5) Å], probably as a result of crystal packing effects. The thiol groups bond from the same face (roughly a plane of symmetry in the complex) whereas in the corresponding pyridine diol complex, the hydroxy groups hydrogen bond to chloride from opposite faces (approximate C_2 molecular symmetry, an analogous arrangement is seen in the structure of **4a**·HNO_3 shown in Fig. 2).[3a] The H··Cl bond distance in **4a**·HCl is 2.19 Å, which is 0.92 Å longer than the covalent HCl bond length in the gas phase (1.27 Å).[5] A search of the Cambridge Database for pyridine··HCl complexes revealed an average bond length for the H··Cl bond distance of 2.20 Å with a deviation of 0.17 Å for 39 hits. For this screening a minimum N··H··Cl bond angle of 120° was included.

In the ^1H NMR spectrum of **4a**·HCl (in $CDCl_3$) downfield shifts are seen at the 3- and 4-positions of the pyridine ring comparable in magnitude to those observed for the complex of 2,6-lutidine with HCl. We concluded that the NMR and bond length data are consistent with the tight ion pair (formulation **A**) rather than the covalent formulation **B**.¶



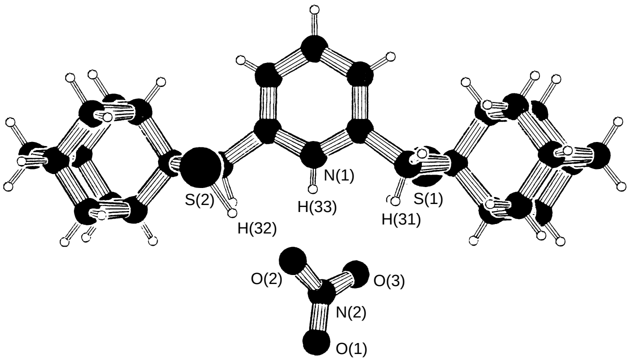


Fig. 2 The molecular structure of **4a**·HNO_3. Selected distances (Å) and angles (°): H(31)–O(3) 2.21(5), H(32)–O(2) 2.26(5), H(33)–O(2) 1.92(5), H(33)–O(3) 2.58(5), H(33)–N(1) 0.87(5), N(1)–O(2) 2.762(6), S(1)–H(31)–O(3) 160(3), S(2)–H(32)–O(2) 156(3), N(1)–H(33)–O(2) 162(5), N(1)–H(33)–O(3) 143(4).

In summary, pyridine dithiols can be obtained from direct addition of 2,6-lutidine to (non-enolisable) thioketones in the presence of a strong base. These pyridine dithiols provide a well-defined cavity, perhaps even better than the pyridine diols, in which various acids are encapsulated by three point bonding. We are examining methods to transfer these complexed acids from chiral nonracemic pyridine dithiols such as **5** to suitable acceptors such as prochiral epoxides.

Footnotes

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‡ Unless otherwise mentioned, satisfactory elemental analyses and/or X-ray structure analyses were obtained for all new compounds. ^1H NMR and infrared (IR) spectra were in accord with expectations for all compounds.

§ Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/449.

¶ Formulation **B** is mentioned because of puzzling physical properties and observations in the infrared (IR) spectra. Upon exposure of the solid to low pressure we observed that the HCl evaporates. This is not observed for other complexes, for example 2,6-lutidine·HCl. IR spectra of **4a**·HCl in KBr are complicated by the fact that the HCl absorptions are hidden under the strong adamantyl C–H bands. This led us to the study of the DCl complex. In some cases the **4a**·DCl complex shows a sharp absorption at 2211 cm^{-1}, which is partially masked by a broad pyridine–D^+ absorption in the region 2212–1850 cm^{-1}. The 2211 cm^{-1} absorption is close to that expected for *covalent* D–Cl. For example, values of 2091 and 2090 cm^{-1} for monomeric DCl in, respectively, the gas phase[6a] and in an Ar matrix[6b] are given in the recent literature. The ^1H NMR spectra as well as the IR spectra indicate clearly that D–Cl has not exchanged with S–H (attempts to prepare the S–D derivative of **4a** have been unsuccessful owing to the failure of the S–H groups to exchange with D at a measurable rate either in free **4a** or in the D–Cl complex). The 2211 cm^{-1} absorption is not observed in the D–Cl complex with 2,6-lutidine.

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