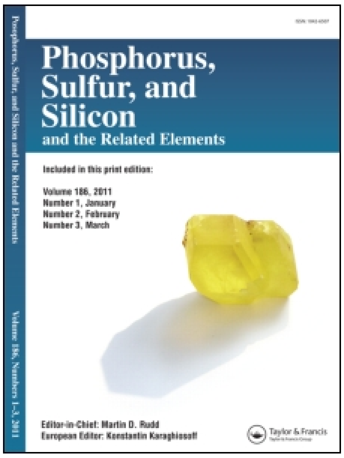

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Heterocyclic *o*-Chloroaldehydes as Synthons in Organic and Inorganic Sulfur Chemistry

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HETEROCYCLIC *o*-CHLOROALDEHYDES AS SYNTHONS IN ORGANIC AND INORGANIC SULFUR CHEMISTRY

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Abstract

Many heterocyclic *o*-chloroaldehydes are easy to prepare, for example *via* the Vilsmeier chloroformylation reaction. Due to the electron withdrawing effect of the formyl group, the halogen atom is normally a nucleofuge. This can be used to prepare a range of *o*-substituted heterocyclic aldehydes showing interesting rearrangement reactions. Such types of compounds are also useful as starting materials for the preparation of annelated heterocyclic systems.

We have demonstrated that heterocyclic mercapto groups can be protected as *t*-butylthioethers. Furthermore, we have found that thiolation of heterocyclic systems containing reactive halogen substituents can conveniently be carried out *via* the easily prepared *t*-butylsulfides.

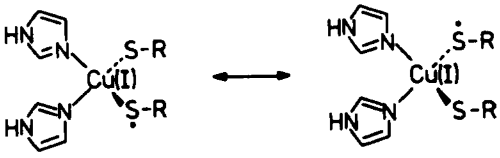
This method has been used in the preparation of a number of N_2S_2-ligands. The resulting transition metal N_2S_2-complexes have been used in the study of model systems for one of the active sites in cytochrome c oxidase. The method also gives access to polymeric heterocyclic multisulfur transition metal complexes with high electrical conductivity.

CYTOCHROME C OXIDASE MODELS

Over the past several years we have been interested in the syntheses of N_2S_2-ligands to be used in the preparation of transition metal N_2S_2-complexes for the study of model systems for one of the active sites in cytochrome c oxidase.

The structure of cytochrome c oxidase has received considerable attention as a result of its importance in cellular respiration and energy utilization. This metalloenzyme is found in the mitocondria of the cells of all aerobic organisms, and it is the terminal enzyme in the respiratory electron transfer system effecting the reduction of oxygen to water. Cytochrome c oxidase contains two heme a's and two copper-sites, of which the Cu_A-site participate in the electron transfer.

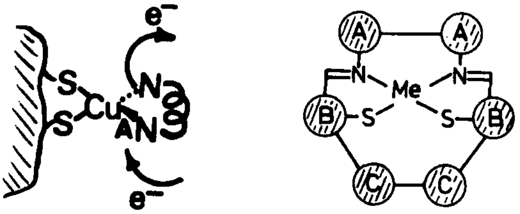
The description of the electronic ground state of the oxidized Cu_A is incomplete, and better model systems are therefore required. Chan et al.[1] have suggested that the Cu_A-site consists of a pseudo-tetrahedral $CuN_2(His)S_2(Cys)$ unit, with considerable Cu(I)-thiyl radical character or, alternatively, a rather unusually covalent Cu(II)-thiolate character.



Scheme 1

The active Cu_A in cytochrome c oxidase

The Cu_A-site in cytochrome c oxidase consists of two imidazole lone pairs from histidine and two thiolates from cysteine, in this site the Cu_A central atom aquires an unusual pseudo tetrahedral geometry, and until recently no model system which reproduced the geometry of this structure was known.



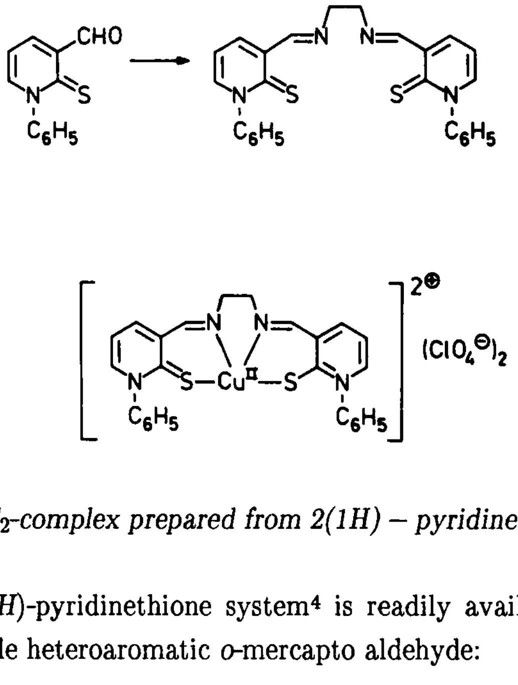
Scheme 2

The Cu_A-center in c oxidase and a synthetic model of this site.

In general, few Cu(II)–N_2S_2-complexes of this type were known[2], one reason being that the use of aliphatic thiolates in the preparation of a Cu(II)-N_2S_2-complex will often give rise to formation of disulfides:

$$2RS^- + 2Cu^{2+} \longrightarrow 2Cu^+ + R\text{-}S\text{-}S\text{-}R$$

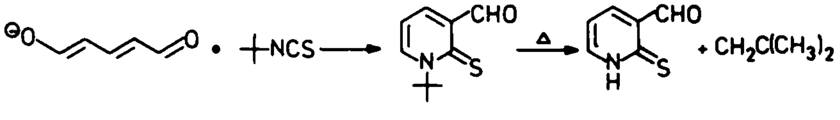
However, at the start of this project we already[3] had one workable N_2S_2-ligand derived from the readily available[4] 3-formyl-2(1*H*)-pyridinethione which gave stable Cu(II)-complexes with square planar geometry:



Scheme 3

Planar Cu(II)N₂S₂-complex prepared from 2(1H) – pyridinethione units

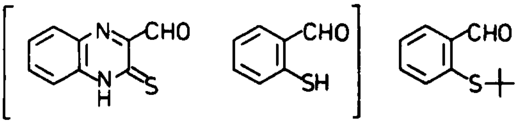
The 3-formyl-2(1*H*)-pyridinethione system[4] is readily available and it is an example of a stable heteroaromatic o-mercapto aldehyde:



Scheme 4

Preparation of the parent 3-formyl-2(1H)-pyridinethione

Other aldehydes of this type such as the parent *o*-mercaptobenzaldehyde and its quinoxaline equivalent[5] are unstable and therefore difficult to prepare and use (Scheme 5):

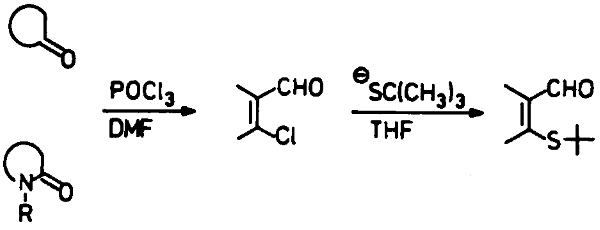


Scheme 5
Examples of relative unstable o-mercaptoaldehydes and a stable synthon for o-mercaptobenzaldehyde.

Dimerization to bicyclic bridged dithiocines[6] often takes place under acidic reaction conditions, similar dimers are formed from 2-mercaptoketones[7]. We, therefore, found it more convenient to work with starting materials containing protected mercapto groups. Meth-Cohn[8] had described the 2-(*t*-butylthio)-benzaldehyde as a stable synthon for 2-mercaptobenzaldehyde in which the *t*-butyl group could be eliminated as isobutene under acidic reaction conditions. As this protective group also had been used in cystein derivatives[9] we decided to look at its use in the heterocyclic series.

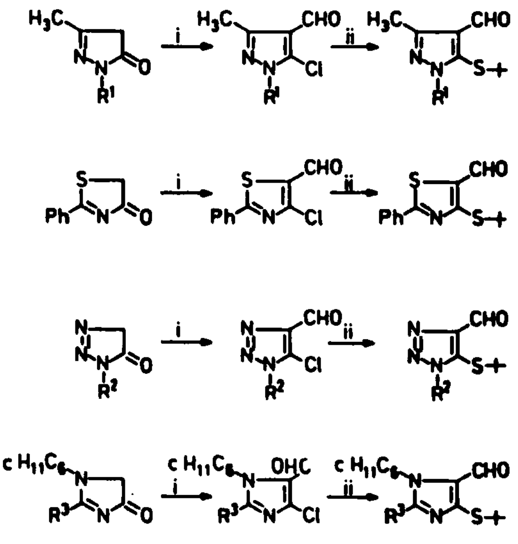
The number of heteroaromatic systems containing nitrogen, oxygen or sulfur is almost limitless, and heterocycles show an enormous variation with respect to chemical reactivity and electronic properties. We desided to take advantage of this versatility and use heteroaromatic compounds as building blocks in the construction of N_2S_2-ligands (see figure in Scheme 2).

The Vilsmeier chloroformylation is a mild method which will formylate a wide variety of heterocycles. When a heterocyclic system with an amide or oxo function is treated with dimethylformamide/phosphorus oxychloride it is often possible to obtain fair yields of the corresponding *o*-chloroaldehydes according to the general scheme (Scheme 6):



Scheme 6
Preparation of protected o-mercaptoaldehydes

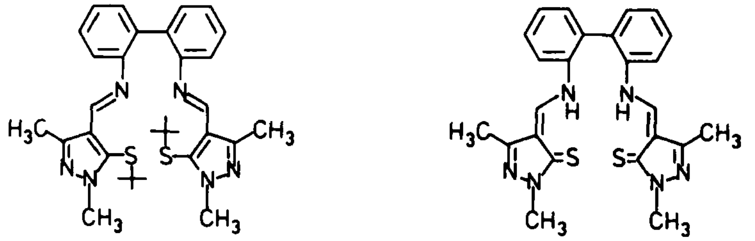
The formyl group is an electron withdrawing group and, therefore, the halogen atom in the o-chloroaldehydes is activated towards attack by nucleophilic reagents. Scheme 7 gives examples[10] of the types of protected o-mercaptoaldehydes which we have obtained using sodium t-butylthiolate in dry THF or DMF:



i: POCl3/DMF; NaSC(CH3)3

Scheme 7
Examples of protected heterocyclic o-mercaptoaldehydes

Reaction of such heterocyclic aldehydes with diamines results in formation of the bis-imines, often in excellent yields. An added advantage of this method is the relatively moderate melting points and high solubility of the resulting bis-imines in nonpolar solvents. Normally compounds of such relatively high molecular weight can be expected to have high melting points and be insoluble, etc. and therefore difficult to work with, Scheme 8 gives an idea of the difference:

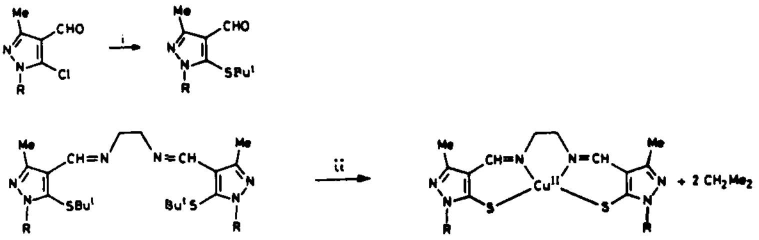


mp. 191–192°C (ethanol)
(Yield 88%)

mp. 299–301°C (2-methoxyethanol)
(Yield 75%)

Scheme 8

Strong acids as well as Lewis-acids will cleave *t*-butyl sulfides with elimination of isobutene. Metal ions such as copper(II) can also function as Lewis-acids, and consequently, when the bis-imines derived from ethylediamine shown in Scheme 9 was heated with copper(II) acetate, two moles of isobutene have evolved giving the corresponding N_2S_2-copper(II)-complexes in high yield[11] directly without any redox side-reactions. We believe that in some cases this may be due to a stepvise elimination reaction:

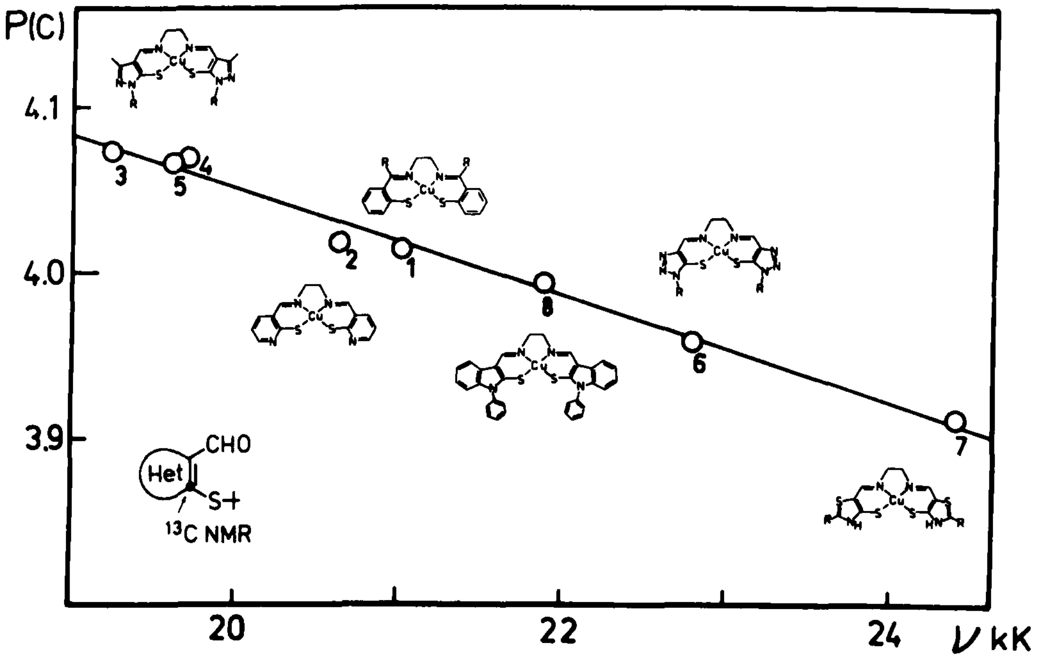


i: $NaSCMe_3$. ii: Cu^{2+}

Scheme 9

Planar Cu(II) N_2S_2 complexes based on pyrazoles

With a series of ligands it was now possible to correlate[2] the Cu^{II} <—— LMCT (ligand to metal charge transfer) energies with the electron density at the thiolate sulfur, assuming they all have identical square planar geometry. The charge density P(c) was derived from the ^{13}C-NMR shift values of the C-S ring-carbon in the starting *t*-butylthioaldehydes, the result is shown in Scheme 10:



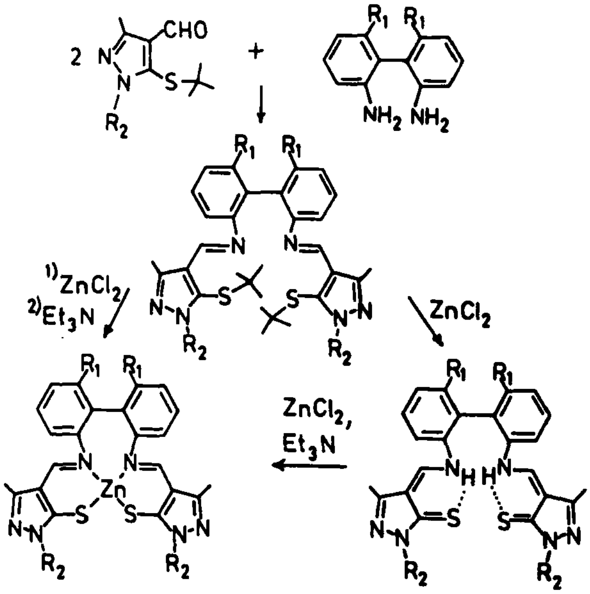
Scheme 10

Correlation scheme for the square planar N_2S_2 Cu-complexes.

Scheme 10 clearly demonstrates the versatility of using heterocyclic systems as building blocks, as the corresponding use of aliphatic or simple aryl units never would have given rise to such a large variation in the electronic proporties of the complexes.

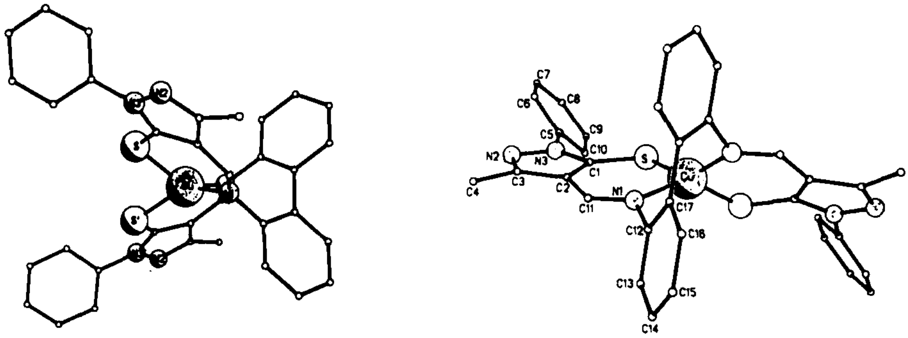
In order to prepare complexes with distorted tetrahedral geometry around the central metal atom we have chosen to use 2,2'-diaminobiphenyls as the backbone in the ligands. The rationale behind this choice is the large distance between the two donor nitrogens giving rise to an opening of the NCuN angle and hence favouring a more tetrahedral geometry when compared, for example, to the ethylenediamine backbone which was used in Scheme 9.

In some cases the reaction with copper(II) salts only gave low yields of N_2S_2-complexes. An alternative route can[12] be used in such cases, as zinc chloride gives the stable orange crystalline bis-thiones in high yields (Scheme 11):



Scheme 11
Preparation of N_2S_2 Zn-complex and the free ligand.

Reaction of the new bis-iminothiones with the copper reagent $(Cu(MeCN_4))(BF_4)$ under nitrogen followed by air oxidation gave a new N_2S_2-copper(II) complex as violet crystals which were recrystallized from 2-methoxyethanol in 55% yield. The X-ray diffraction result for this complex is shown in Scheme 12:



Scheme 12
X-ray structure of the Cu(II)-complex

From the structure in Scheme 12 it is obvious that in this case we have obtained a copper(II)-complex of the required type with a Cu-S distance of 2.245 Å which compares well with the average value 2.27 Å determined[13] by EXAFS measurements in cytochrome c oxidase. It is also seen that the S-S distance 3.105 Å for sulfur is relatively short, suggesting partial disulfide bond formation.

Continued investigation of related ligands as well as preparation of the corresponding zinc and nickel N_2S_2-complexes have given interesting results, for example, with 2,2'-diamino-6,6'-dimethylbiphenyl as the backbone in the ligand, a complex with an even greater twist around the central metal atom[14] is obtained.

Table 1 compiles some of the relevant data for this and a related copper complex recently reported[15] which are compared with some metalloenzymes:

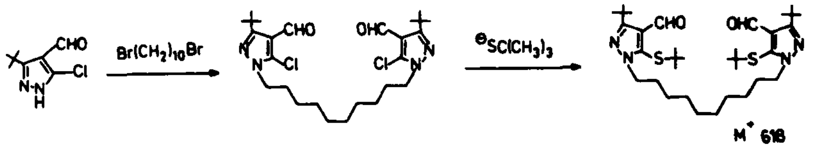
Table 1

Complex	Metal–S Å	Metal–N Å	S–S (distance) Å	Reference
from Scheme 12				
Cu–pyrazol	2.25	1.98	3.11	13
Cytochrome c				
oxidase EXAFS	2.27	1.97		17
Plastocyanin				
X–ray	2.13	2.04–2.10		16
EXAFS	2.08–2.10			
A stable Cu(II)–aliphatic dithiolate complex prepared by				
Schugar *et al*	2.23	2.00	3.41	15

From the results we have obtained it can be concluded that our methodology allows a systematic variation of electron density at the thiolate sulfurs along with a variation of the geometry at the central metal atom, which have given rise to the preparation of a number of unusual new N_2S_2-transition metal complexes. Furthermore, the π-system in the heterocyclic building blocks in the ligands does not seem to interfere with the electron system of the central metal atom, as one might have expected.

We are convinced that ligands in which heterocyclic systems are used as building blocks offer many advantages in comparison to the use of more traditional ligands with aliphatic carbon chains linking the donor groups.

We are currently using this approach both in the preparation of unsymmetrical ligands and in the construction of macrocyclic ligands via bis-alkylation of the 3-*t*-butylpyrazoles as shown in Scheme 13:



Scheme 13

Preparation of a macrocyclic ligand half unit.

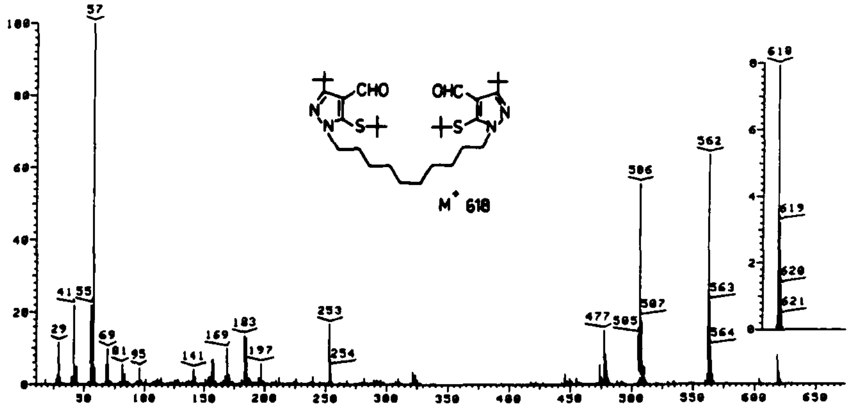


Figure 1

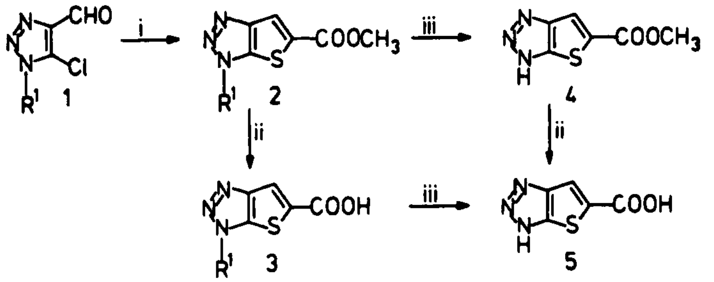
MS of the bis-pyrazole system

Only one main alkylation product[16] was obtained due to the steric contraint from the 3-*t*-butyl group we have therefore tentatively assigned the structure shown in Scheme 13, thiolation of this bis-pyrazole system using sodium *t*-butylthiolate yielded the bis-(*t*-butylthioaldehyde). It is expected that a copper(II)-complex derived from this and related ligands will show stabilization of a sulfur radical as molecular models show that the two sulfurs in the resulting complex will be relatively protected by the alkane chain.

A characteristic feature of heterocyclic *t*-butylthioaldehydes is the relatively low abundance of their molecular ions in the mass spectra due to the easy loss of isobutene. The mass spectrum seen in Fig. 1 is typical with the small molecular ion and peaks at $m/z = M^{+}\text{-}56$ as well as at $m/z = M^{+}\text{-}(2 \times 56)$.

o-CHLOROALDEHYDES IN HETEROCYCLIC SYNTHESES

The series of heterocyclic *o*-chloroaldehydes used in the ligand syntheses described above have allowed us[17] to prepare derivatives of the hitherto unknown thieno[2,3-*d*]triazole system. Thus reaction of the 5-chloro-4-formyltriazoles 1 with methyl mercaptoacetate gave the thieno[2,3-*d*]triazoles, whereupon hydrolyses and debenzylation gave the expected thieno[2,3-*d*]triazoles 3 and 4. However, all attempts to prepare the parent unsubstituted system have failed so far, apparently because this fused thiophene-system is unstable under the reaction conditions used. Brian Iddon[18] has confirmed this observation independently.

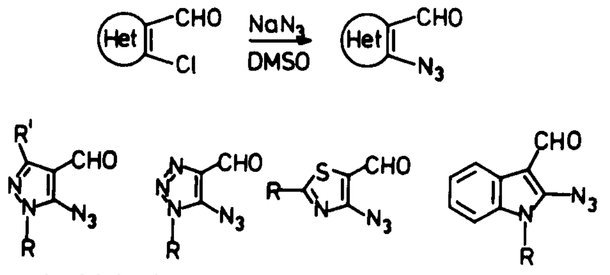


i: mercaptoacetic acid methylester, sodium carbonate. ii: sodium hydroxide(2M). iii: trifluoro acetic acid, 65° C.

Scheme 14

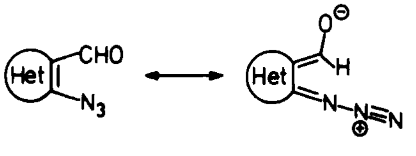
Preparation of thieno(2,3-d)triazoles

As we had easy access to the heterocyclic *o*-chloroaldehydes we have recently investigated the chemistry of a series of stable heterocyclic *o*-azidoaldehydes, all prepared from the corresponding *o*-chloroaldehydes in excellent yields; some examples are shown in Scheme 15:



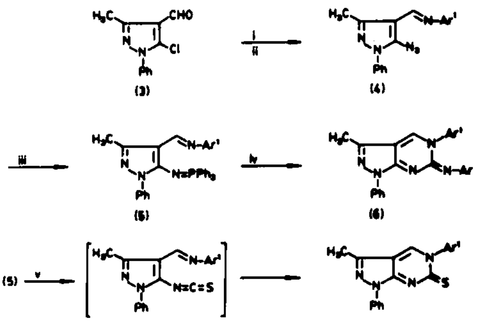
Scheme 15
Heterocyclic o-azidoaldehydes

The high thermal stability found in these o-azidoformyl-azoles may be due to the type of delocalization shown in Scheme 16:



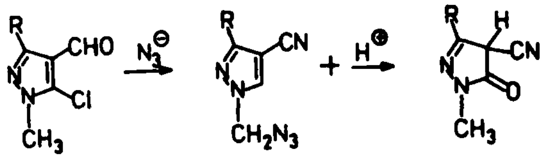
Scheme 16

Molina *et al.*[20] have shown that such o-azidoaldehydes are excellent starting materials for the preparation of new fused pyrimidines. The iminophosphoranes which can be prepared in high yields *via* the Staudinger reaction easily undergoes electrocyclization as exemplified in Scheme 17:



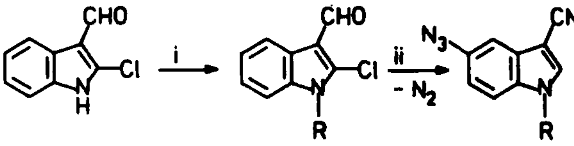
Reagents: i) NaN_3/DMSO: ii) Ar^1-NH_2: ii) Ph_3P; iv) Ar^2-NCO; v) CS_2
Scheme 17

We have also found that the o-azidoaldehydes undergo a new interesting ring opening-ring closure reaction[21] which seems to be general as we have confirmed so far that it takes place in the pyrazole, pyrrole and indole series. Thus, reaction of a 2-chloro-3-formyl-1-methylpyrazole with an excess of sodium azide in DMSO at 90-100° C leads to elimination of one mole of nitrogen, the overall reaction is seen in Scheme 18:



Scheme 18
Ring opening-ring closure of a 5-azido-4-formyl-1-methylpyrazole.

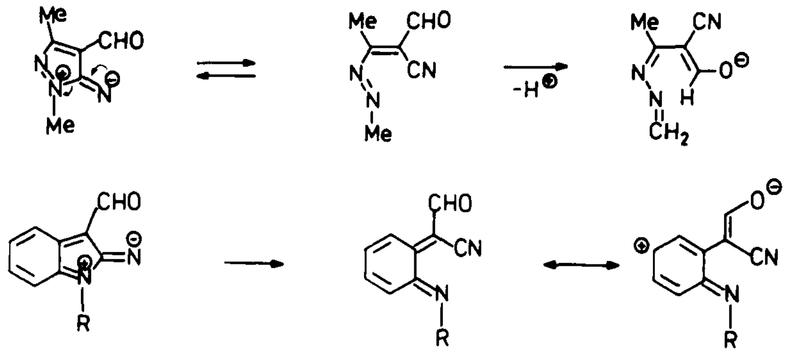
A similar rearrangement takes place in the indole series, but this time the reaction also leads to a nucleophilic tele-substitution at the 5-position in the indole ring, (Scheme 19):



	R
a	$-CH_3$
b	$-C_6H_5$
c	$CH_2(CH_2)_3CH=CH_2$
d	$CH_2C_6H_5$

Scheme 19

Scheme 20 shows the ring-opened intermediates which accounts for the products in these two examples:

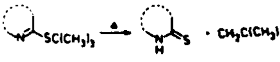


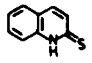
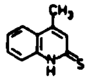
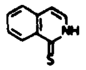
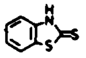
Scheme 20

Proposed intermediates for the rearrangement of azides in the pyrazole and indole series.

THIOLATION REACTIONS IN OTHER HETEROCYCLIC SYSTEMS

I have already explained how the t-butylthiolate can be used as a convenient thiolation reagent in o-chloroaldehydes, but any heterocycle with a sufficiently nucleofuge halogen will react. Scheme 21 shows some examples in which the corresponding thioamides were obtained[22] either by simple pyrolyses or by heating in a solvent with catalytic amounts of aluminum chloride or p-toluene sulfonic acid.

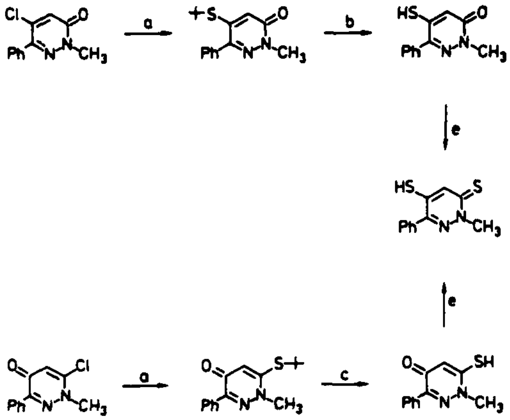


	m p °C		Method
Product	found	(reported)	and yield
	210–215°d	(218–219°d)	95%
	174–176°	(178–179°)	57%
	261–263°	(266°)	95%
	169–170°	(171°)	65%
	176–178°	(178–181°)	91%

Scheme 21

Pyrolyses of S-t-butylthioethers.

We have recently used[23] this method for the regioselective introduction of mercapto groups into 6-phenylpyridazine derivatives. These mercaptopyridazines would have been difficult to obtain with standard thiolation reactions. Scheme 22 shows a typical example.

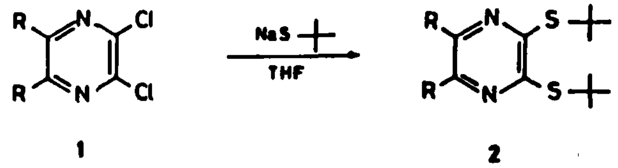


a: $(CH_3)_3CSNa$ in 2-propanol, b: $AlCl_3$ in toluene, c: conc. HCl, e: P_2S_5 in toluene.

Scheme 22
Preparation of mercaptopyridazines

In these series we found that *t*-butylthio groups at different positions do not show identical reactivity, this was therefore used in selective *S*-dealkylation reactions, and it can be concluded that thiolation using the *t*-butylthioethers can be expected to be of general value in related heterocyclic systems as well.

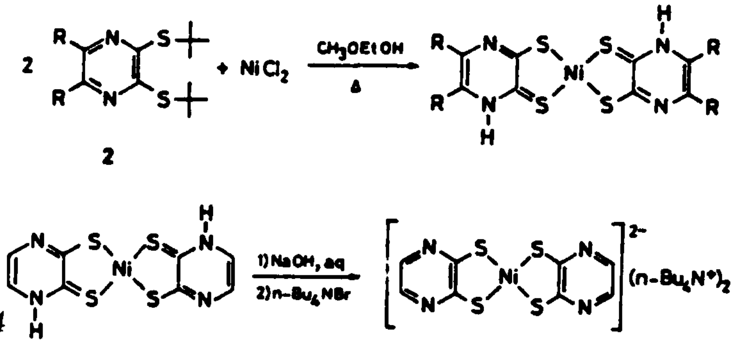
The *t*-butylthio method may also be used for the preparation of multisulfur ligands as the following examples show. There is currently much interest in the preparation of multisulfur-containing compounds since the discovery of superconductivity in mixed valence perchlorates of tetrathiafulvalenes (TTF) and related compounds[24]. Metal complexes such as bis-(4,5-dimercapto-1,3-dithiole-2-thion)-nickel(II)[25] generate salts with TTF which show high conductivity while superconductivity has been reported[26] in the compound TTF-$(Ni(dmit)_2)_2$. Using the methodology described above we have prepared[26] a number of 2,3-bis-(*t*-butylthio)-pyridazines in high yields (Scheme 23):



1	R	2	R
a	H	a	H
b	C_6H_5	b	C_6H_5
c	$-(CH)_4-$	c	$-(CH)_4-$
d	Cl	d	$SC(CH_3)_3$

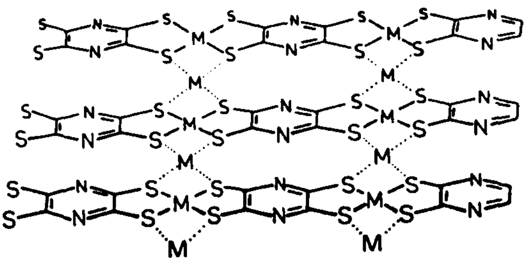
Scheme 23

Again it is important to note that the *t*-butylthio substituted pyrazines all are good crystalline compounds which are readily soluble in non polar solvents. Therefore, such compounds are easy to purify, for example *via* chromatography or crystallization. Formation of transition metal complexes from the *t*-buthylthiopyrazines in Scheme 23 is straightforward; for example when 2,3-bis(*t*-butylthio)-pyrazine was refluxed with nickel(II) chloride in 2-methoxyethanol, containing traces of hydrogen chloride, isobutene was readily eliminated and a dark blue nickel(II) complex precipitated[26] (Scheme 24):



Scheme 24
Formation of nickel complexes.

The 2,3,5,6-tetrakis(*t*-butylthio)-pyrazine (Scheme 24, R=$(CH_3)_3C$) gave rise to a black polymeric nickel complex[27] with nickel(II)-chloride, for which we suggest a structure which has strong metal-metal and sulfur-sulfur contacts as shown in Scheme 25:



Scheme 25
Proposed structure for $M_2(ttp)$ polymers.

The electrical conductivities at room temperature of the nickel and copper polymers shown in Scheme 25 are approximately 1 and 0.07 S cm^{-1}. These values are approximately 10^6 higher than those for the corresponding monomeric complexes, and are indicative of the facile electron transport that results from polymeric ligands with extensive delocalized π-systems. The conductivity process must occur mainly along the polymer chains since the monomeric complexes conduct to a much lesser extent.

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NOTE

t-Butylmercaptane is a mobile liquid (bp.$_{760}$ 64°C) which has an extremely low olfactory threshold value with a heavy skunk odor. It is a cheap chemical (Aldrich 1000ml, 45.10 DM) and it can be used as a tracer for natural gas and extremely small traces in the air therefore, resembles a gas leak. All operations with this compound must be carried out in a well ventilated hood and glasware must be treated with sodium hypochlorite solution prior to normal cleaning. Mother liquors and possible by-products must be treated with hypochlorite as well. It is recommended that reaction mixtures are being kept at the basic side and the use of any excess of *t*-butylmercaptane be avoided. When these precautions are followed it is possible to work with this compound without too much resentment from other people in the laboratory.

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