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[A0001]

New heterocyclic materials

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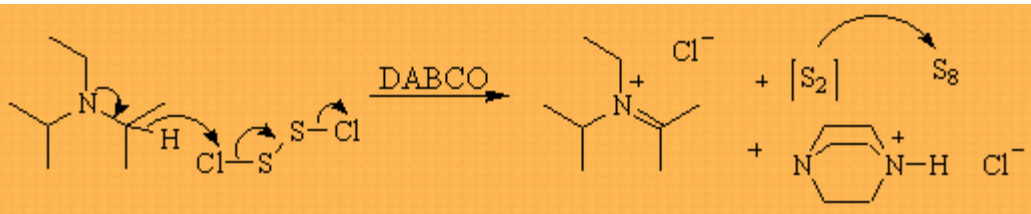
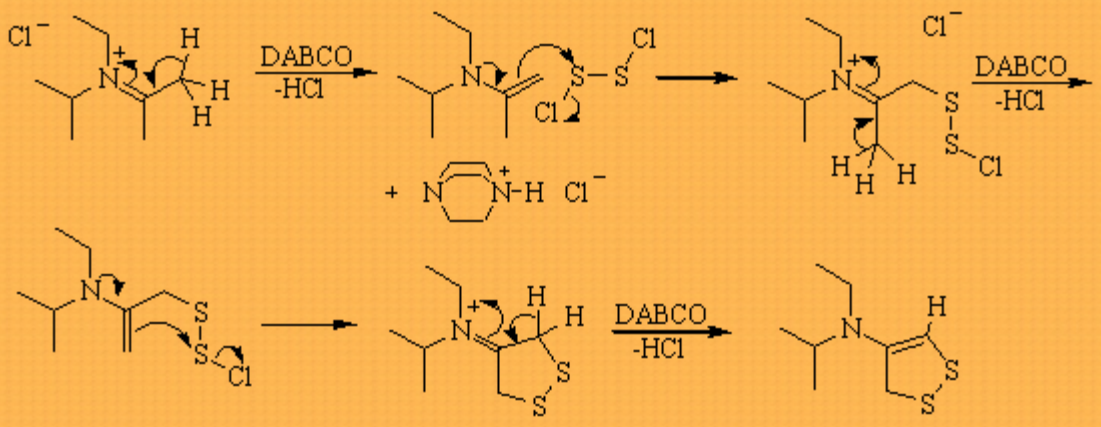
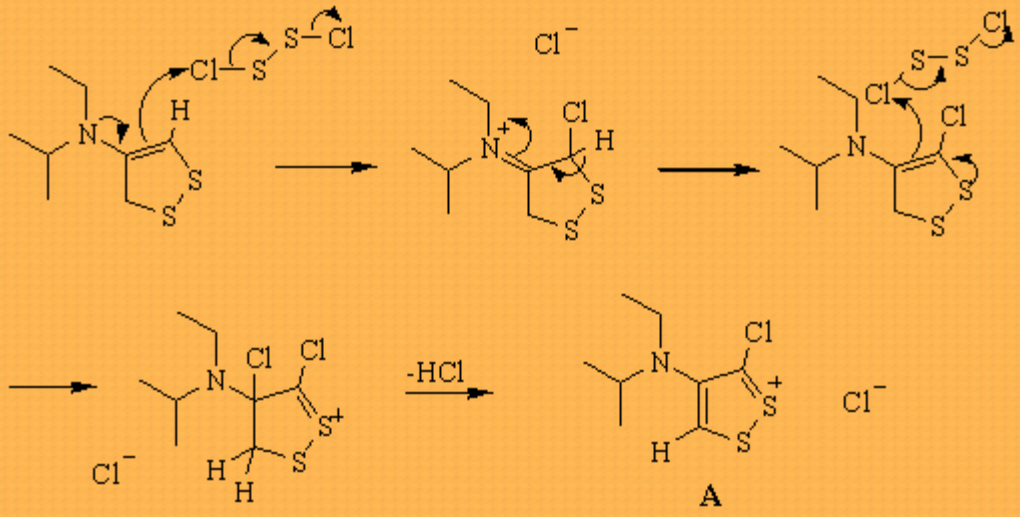
The preparation of new heterocyclic systems by conventional ways is normally a hard work that implies many synthetic steps and expensive starting materials. Even more, many heterocyclic systems, being predictably stable, are impossible to be prepared because the synthetic approach simply does not exist. There is a very different approach to get new heterocyclic systems that uses simple organic starting materials (tertiary amines, alicyclic oximes) bearing a nucleophilic nitrogen which generates reactive intermediates, subsequently trapped by a inorganic reagent, disulfur dichloride (S_2Cl_2). In general, trapping of intermediates is followed by extensive dehydrogenation and chlorination to give new intermediates that can be trapped by selected nucleophiles on the way to stable final products.[1-2] A good combination of reagents and reaction sequences permits the preparation of heterocycles that imply up to fifteen different steps all working sequentially in a one-pot reaction. The best example of this chemistry is the reaction of *N*-ethyldiisopropylamine (Hünig's base), with disulfur dichloride.[3-4] The first step is a slow oxidation of the amine to an immonium salt by a combination of disulfur dichloride and DABCO (diazabicyclo[2.2.2]octane).



The imonium salt can subsequently be converted into a reactive enamine trapped by another molecule of S_2Cl_2. Deprotonation of the imonium ion gives a new enamine that cyclizes to a dithiole ring.



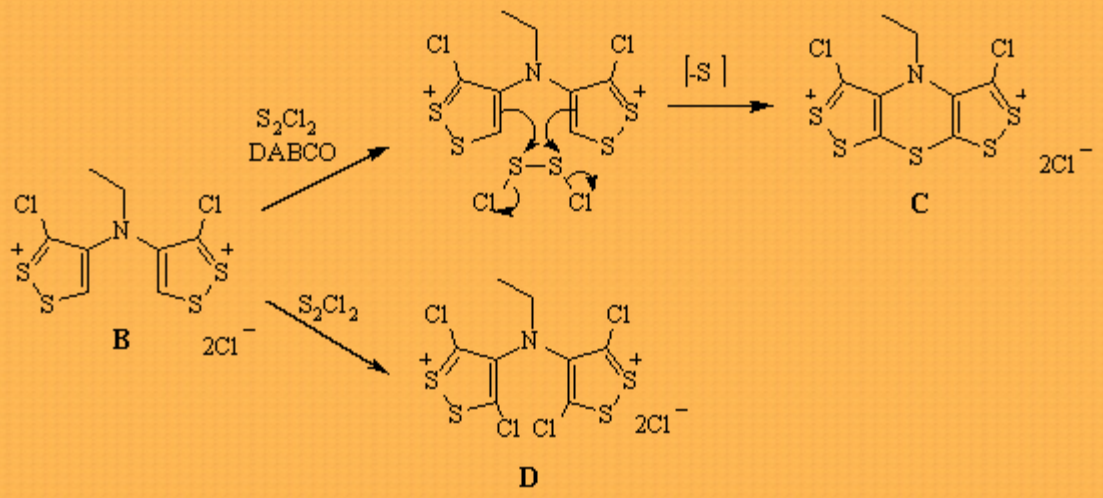
Then the chlorination and dehydrogenation of the dithiole ring affords a stable salt **A**.



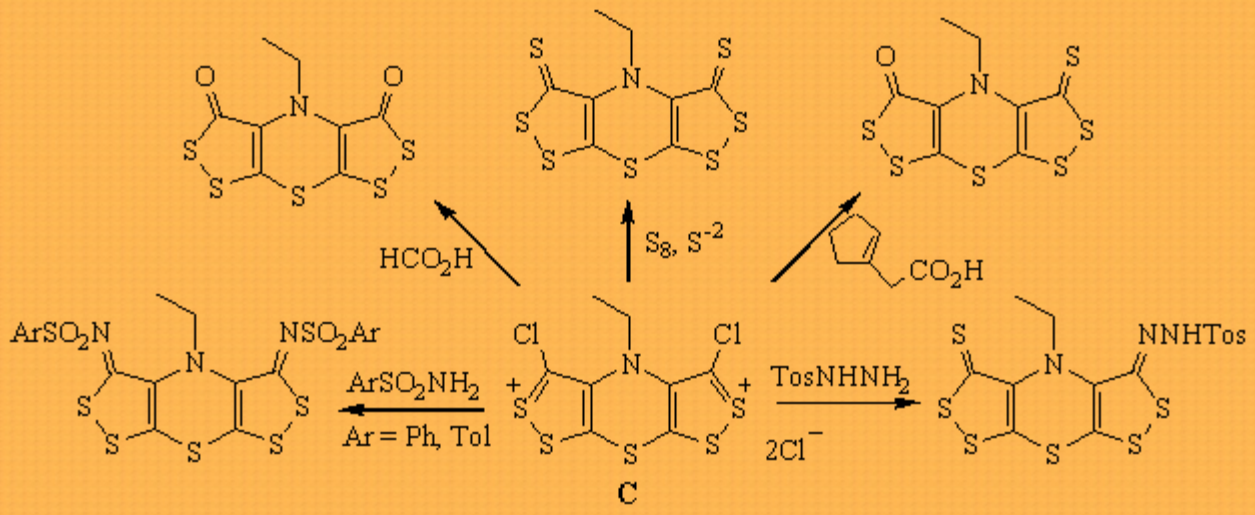
Repeating the reaction on the other isopropyl group successfully converts the starting material into the crucial intermediate disalt **B**.

The disalt **B** is very sensitive to the reaction conditions. In the presence of S_2Cl_2 and DABCO in equimolecular amounts, a new cyclization step, followed by extrusion of sulfur, gives rise to a new disalt **C**, but in the presence of excess disulfur dichloride only, chlorination is favored, affording

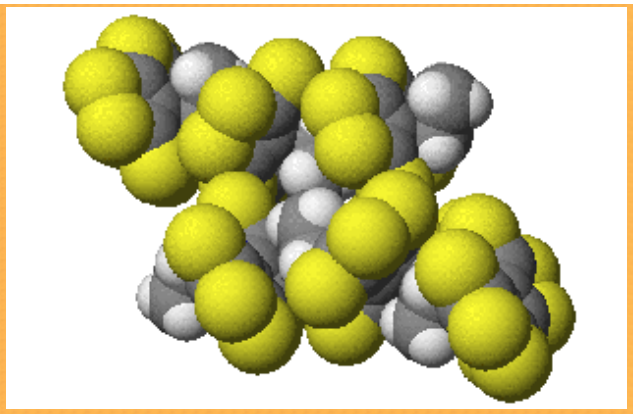
chlorinated disalt **D**.

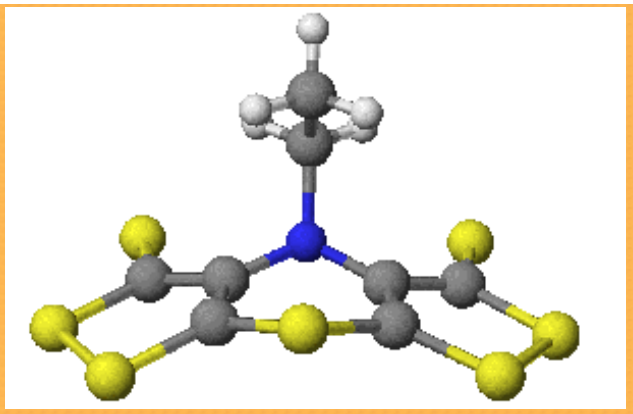


These reactive disalts **C**-**D** (even **A**) undergo reaction with nucleophiles that can be already present in the reaction environment or added during the last period of the reaction. To make the reaction more selective, the insoluble salts are filtered from the reaction mixture and then subjected to reaction with the appropriate nucleophile. This is useful with nitrogen nucleophiles, but in general, the multicomponent mixture works with a high efficiency, permitting the selective preparation of every final product. From salt **C** a complete range of bis[1,2]dithiolo[1,4]thiazine derivatives are obtained.

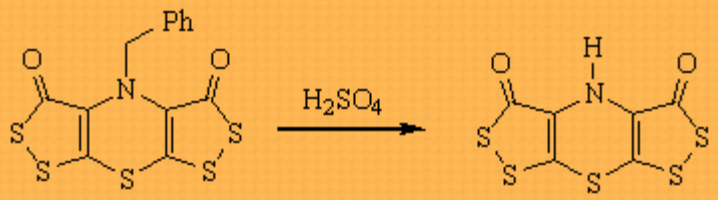


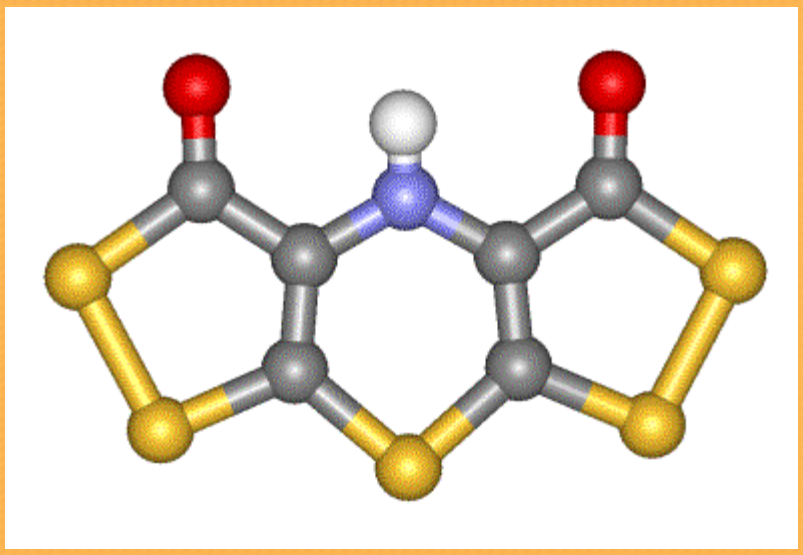
All [1,2]dithiolo[1,4]thiazine derivatives adopt a bent conformation in the solid state, with the 1,4-thiazine ring having a boat conformation with the *N*-alkyl group standing on the thiazine sulfur atom.

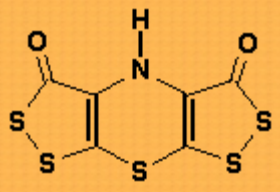


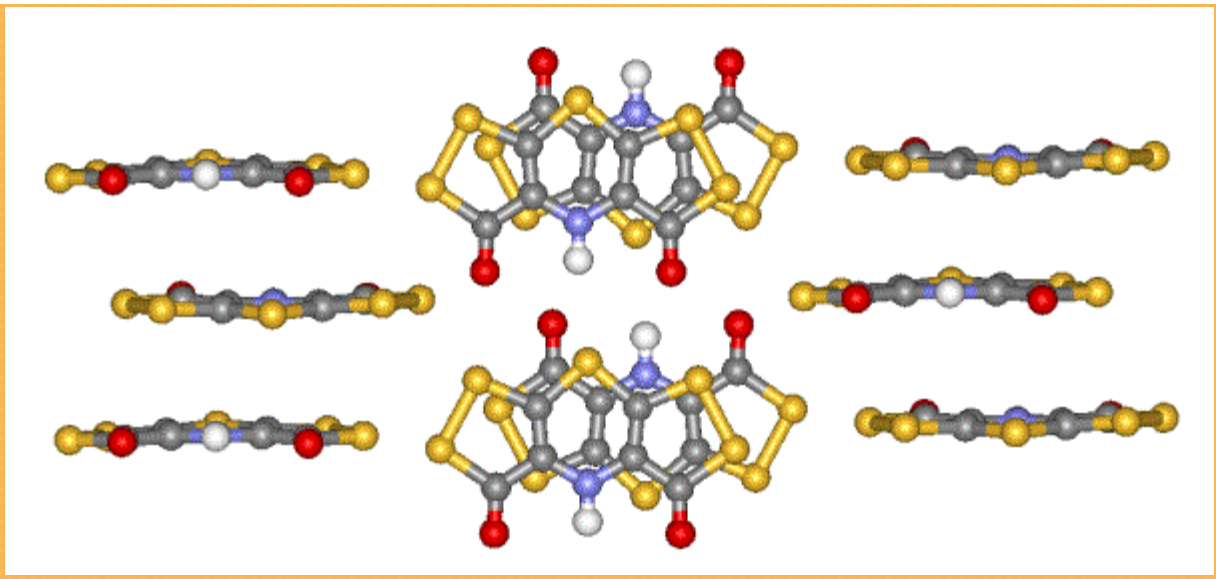


There is one exception to this molecular habit. Thus, the parent ring, having a unique hydrogen on the nitrogen, is a planar compound in the solid state.[5] The unsubstituted ring system has shown complete inhibitory activity against some tumor strains at low concentration (10^{-4} M) in the preliminary *in vitro* screenings. This compound is obtained by debenzylation of the *N*-benzyl substituted bis[1,2]dithiolo[1,4]thiazine derivative.

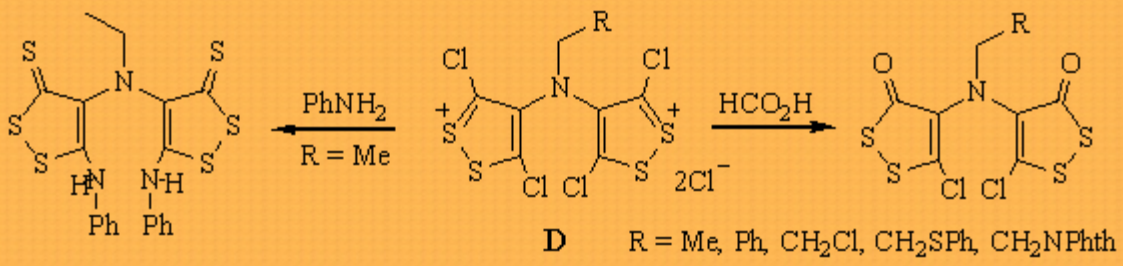






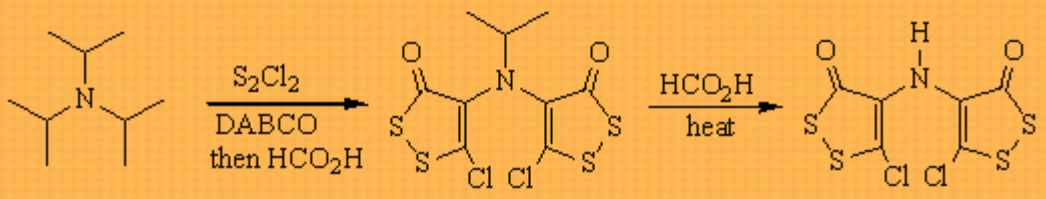


From salt **D** many derivatives of the *N,N*-bis[1,2]dithiol-4-ylamine are obtained.[6]

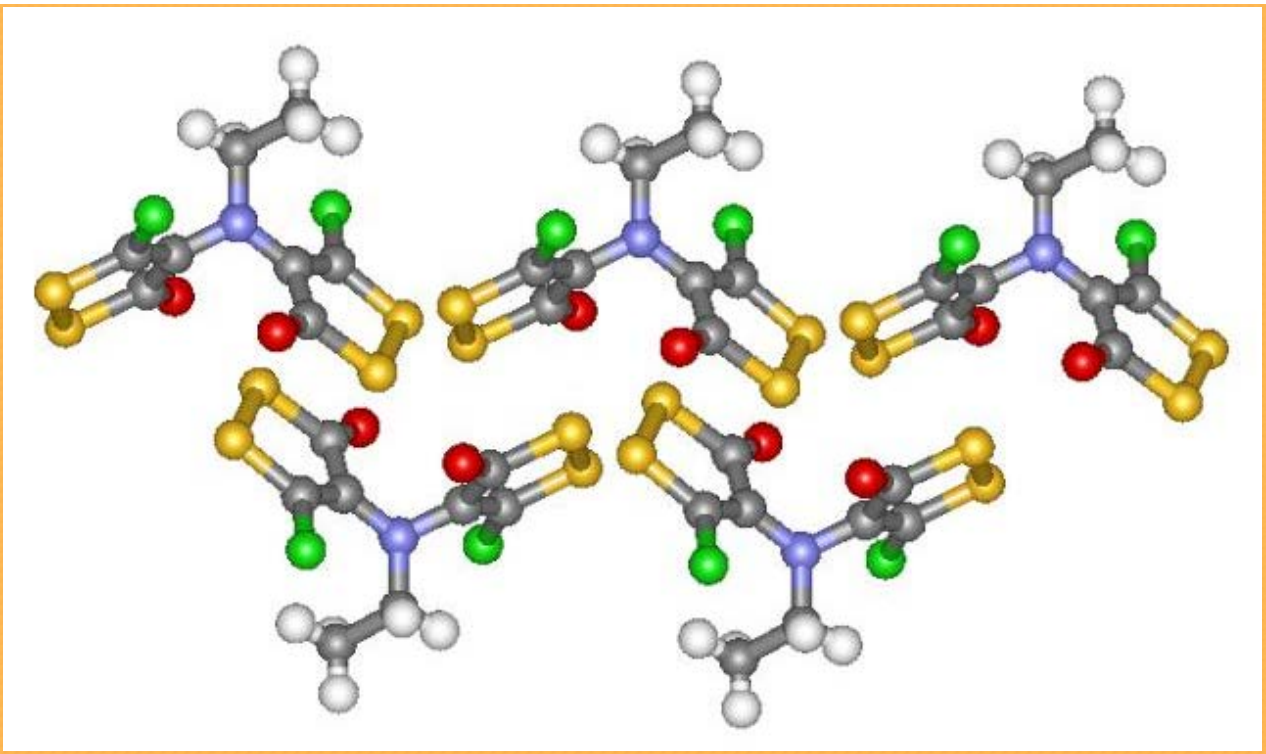


D R = Me, Ph, CH_2Cl, CH_2SPh, CH_2NPhth

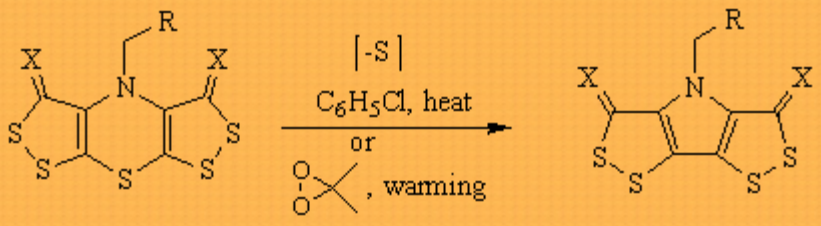
The triisopropylamine, a very hindered amine, affords uniquely the intermediate salt **D** type, from which the *N,N*-bis[1,2]dithiol-4-ylisopropylamine is obtained. Prolonged heating with formic acid gives the unsubstituted *N,N*-bis[1,2]dithiol-4-ylamine, which has shown complete inhibitory activity against leukemia tumor at very low concentration (10^{-5} M) in the preliminary *in vitro* screenings.



The *N,N*-bis[1,2]dithiolylamines show a conformation in which the two dithiole rings are inclined almost orthogonally.



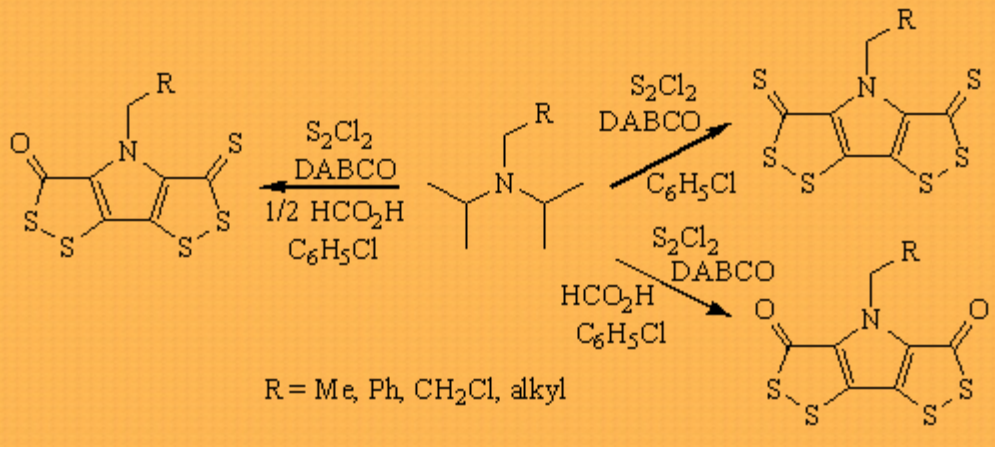
The sulfur atom from the 1,4-thiazine ring is easily extruded in all the N-substituted bis[1,2]dithiolo[1,4]thiazine derivatives (except the *N*-unsubstituted one) by heating the compound in high boiling point solvents.[7] Alternatively, selective oxidation with dimethyldioxyrane and gentle warming also promotes extrusion of the 1,4-thiazine sulfur atom.[8] In this way, one carbon-carbon bond is obtained between two carbon atoms that initially belonged to two different isopropyl groups in the starting tertiary amine.



R = Me, Ph, CH_2Cl, CH_2SPh, CH_2NPhth

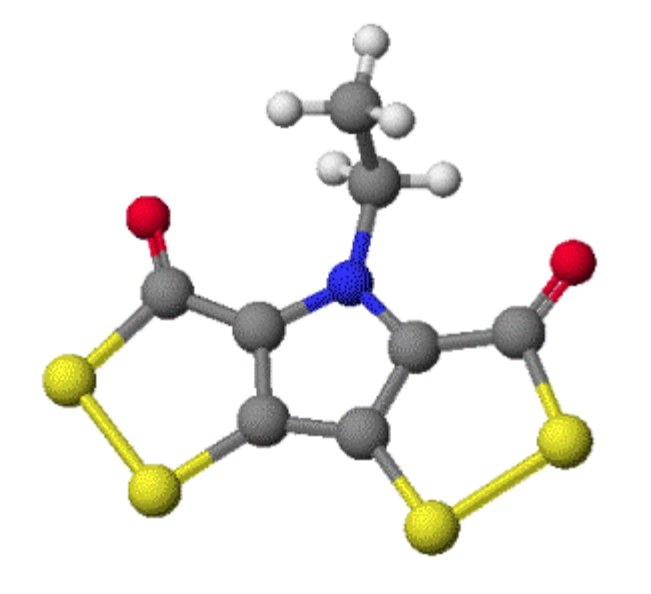
X = O, S

Of course, it is not necessary to isolate the dithiolothiazine for the sulfur extrusion, so the reaction is effectively performed in one-pot.[7]

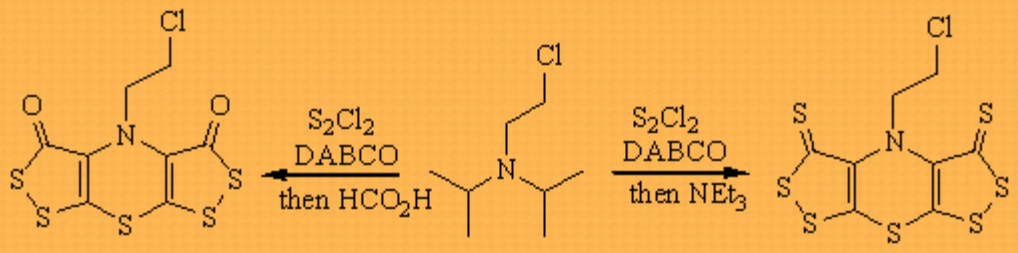


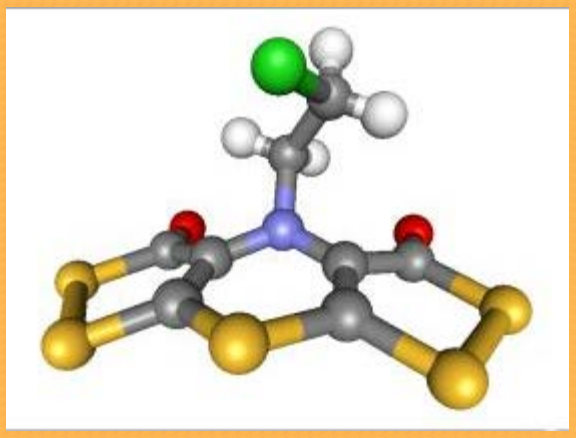
R = Me, Ph, CH_2Cl, alkyl

The new ring system is of course planar because of the aromatic pyrrole ring formed by the sulfur extrusion.



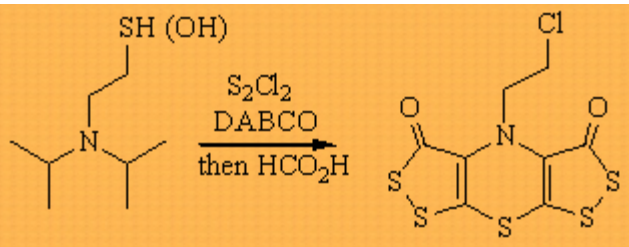
The *N*-(2-chloroethyl)diisopropylamine constitutes a very special case. Its reaction with disulfur dichloride, whether or not in the presence of formic acid, gives the tricyclic bis[1,2]dithiolo[1,4]thiazine derivatives.[9-10]



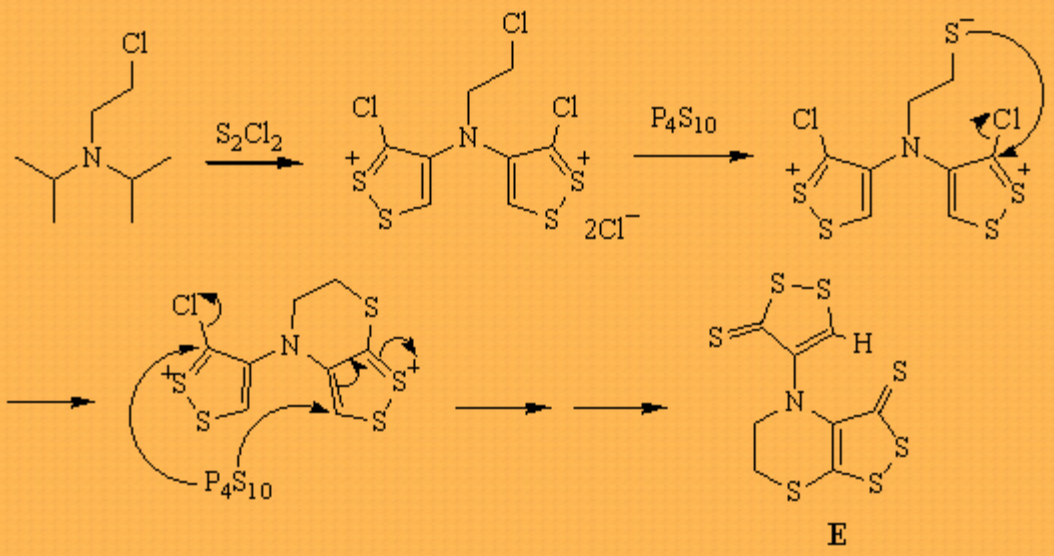


In the solid state, the molecule adopts a conformation in which the chlorine atom lies on the thiazine sulfur ring. The crystal packing in this molecule is dominated by interactions between the chlorine atoms and the dithiole sulfur atoms.

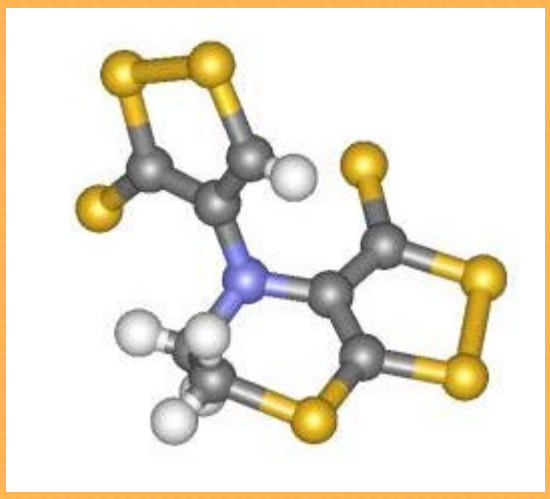
The inertness of the chlorine atom is only apparent. In fact, *N,N*-diisopropylamino-mercaptoethanol (or -ethanol) affords the same chloroethyl derivative of the heterocycle, so there is a effective chlorination on the lateral chain of the ring.



The course of the reaction is completely changed by addition of phosphorus pentasulfide at the last stage of the reaction. In this case, the chlorine atom is replaced by sulfur both in the lateral chain or in the intermediate salt, thus giving a new [1,2]ditiolo[1,4]thiazine ring system.[9-10]

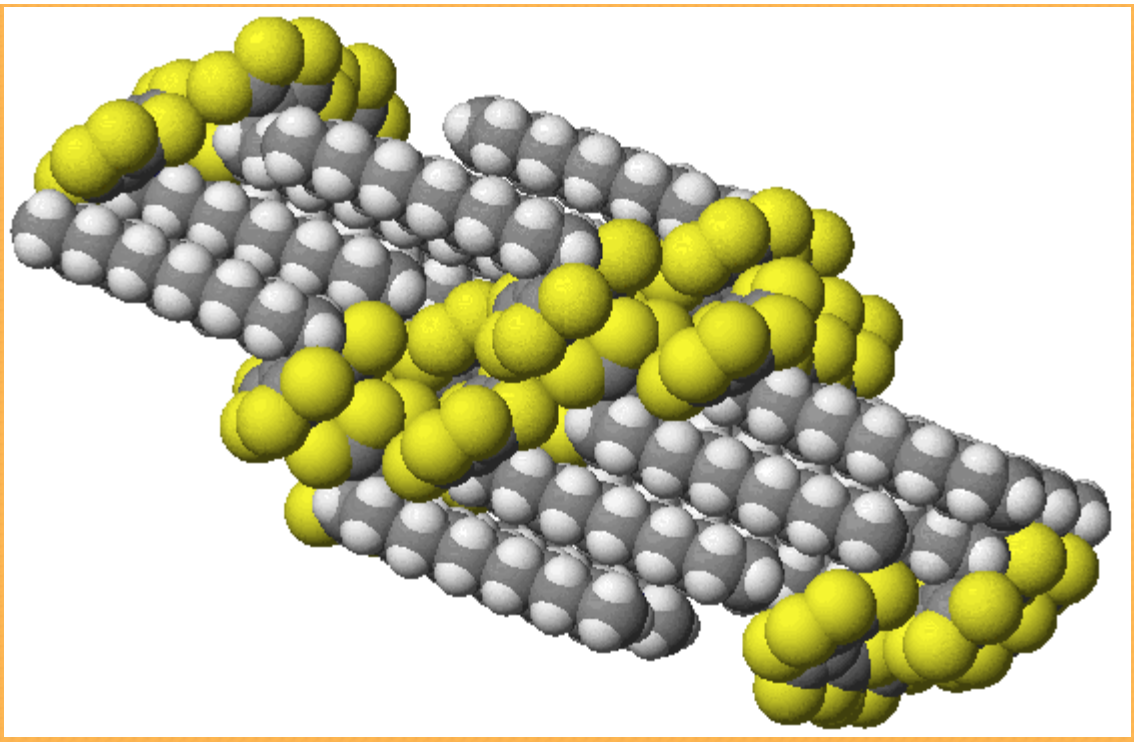


E

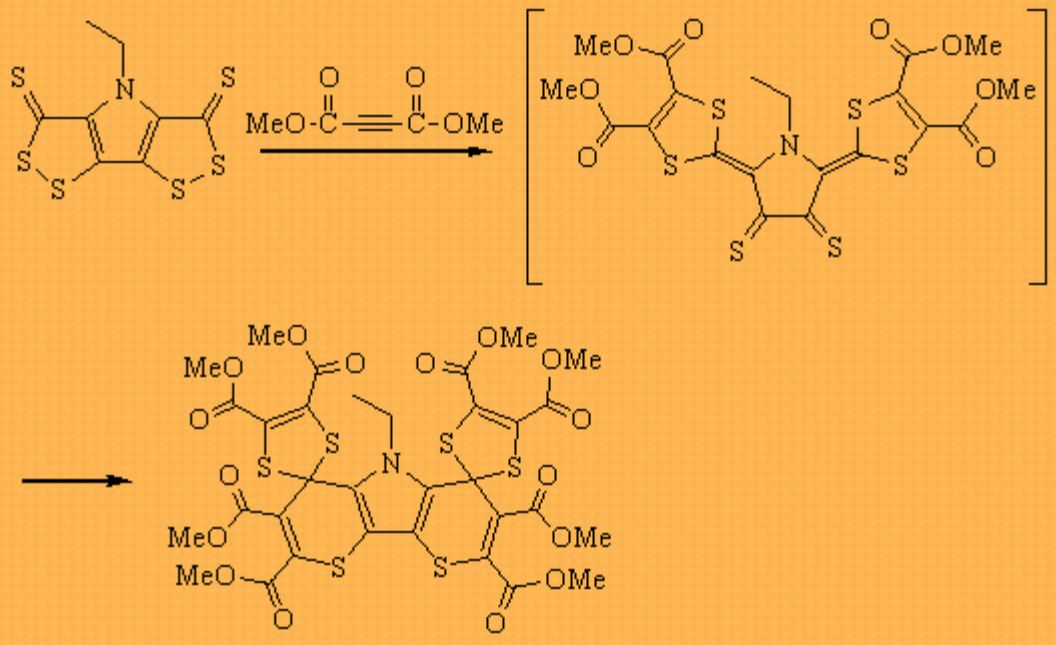


This new compound **E** has shown a notable antitumor activity against breast cancer cells at low concentration (10^{-4} M). The compound **E** adopts a half-chair conformation in the solid state. The crystal packing in this molecule is dominated by sulfur-sulfur interactions between the electron-donor dithiole sulfur atoms and the electron-acceptor thione groups

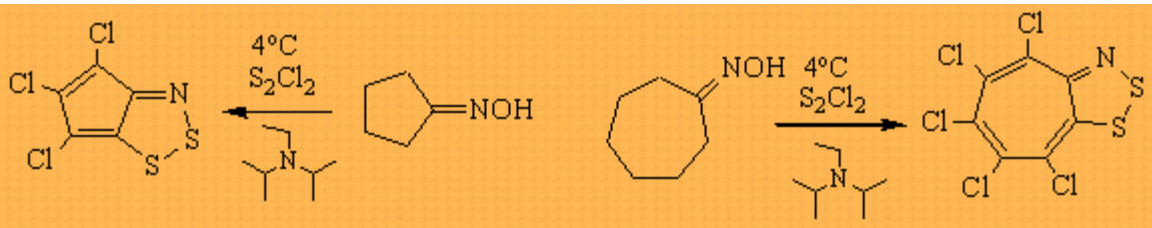
In general, the crystal packing in all the obtained 1,4-thiazine derivatives is dominated by sulfur-sulfur interactions between the electron-donor dithiole sulfur atoms and the electron-acceptor ketone or thione groups, giving highly ordered crystalline materials. When there is a long alkyl chain, the alkyl groups pack themselves in the crystal.[8]



Searching for applications as new materials, we have studied the reactivity of all these compounds by 1,3-dipolar cycloadditions, founding a very high reactivity in the starting materials and good stability in the obtained products. For example, dithiolopyrrole ketothiones are good substrates for cycloaddition reactions. In this case, the initial 1,3-dipolar cycloaddition gives a diene that is more reactive than the starting material, thus adding a second molecule of the dienophile to re-establish the aromaticity of the pyrrole ring. Dithiolopyrrole dithiones cycloadd in both sides of the molecule, giving branched molecules with a planar pyrrole as the central core.[7]

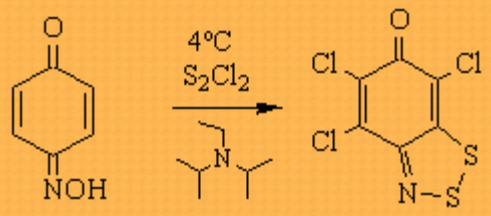


Simple 5- or 7-members saturated cyclic oximes react with disulfur dichloride to give complete dehydrogenated and chlorinated cyclopenta- or cycloheptadithiazole derivatives of pseudoazulene structure.11-12

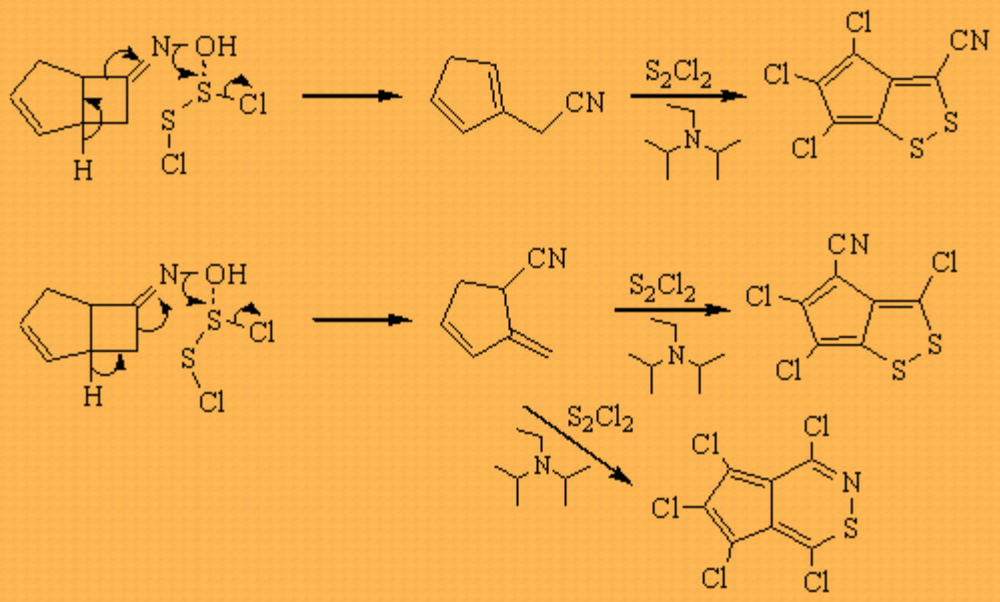


These reactions imply, first, the addition of S_2Cl_2 to the oxime, then cyclization onto a methylene activated by the oxime, then dehydrogenation, chlorination by S_2Cl_2, dehydrogenation by the Hünig's base, and new chlorination by S_2Cl_2 or, in the case of the 7-members ring, by S_2Cl_2 and N-chlorosuccinimide, involving a very high number of mechanistic steps. Both sulfur and nitrogen atoms activate the ring carbon atoms, in a curious example of long-distance activation.

Quinone monoximes are also able to react, giving chlorinated fused 1,2,3-dithiazoles.[13]

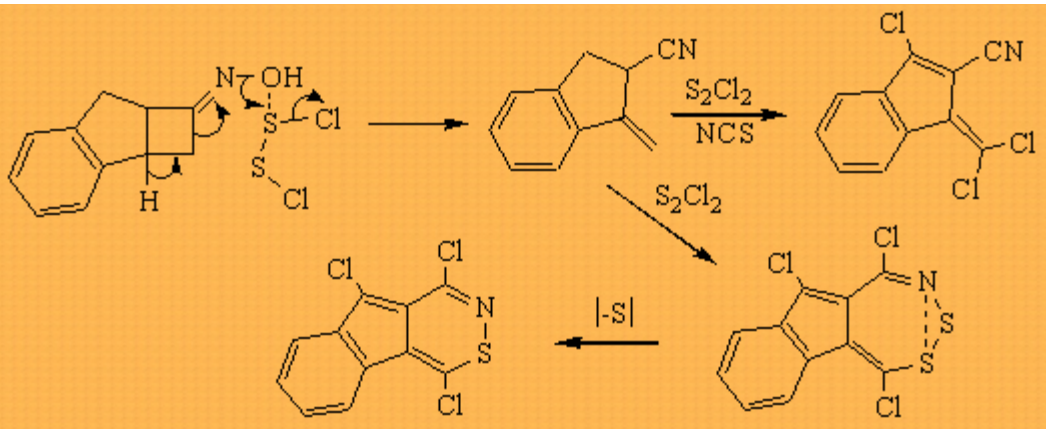


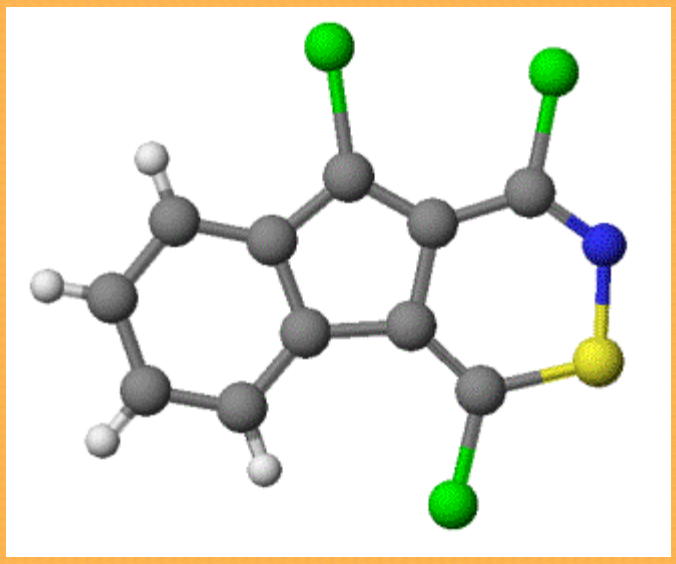
The sequence of ring closing, dehydrogenation and chlorination is extraordinarily well suited to be combined with second-order Beckmann rearrangements that give rise to very reactive intermediates trapped in the reaction environment by S_2Cl_2.[14-15]



Thus, very fast routes to cyclopenta-1,2-dithioles and cyclopenta-1,2-thiazines, obtained in one-pot reactions, have been developed.

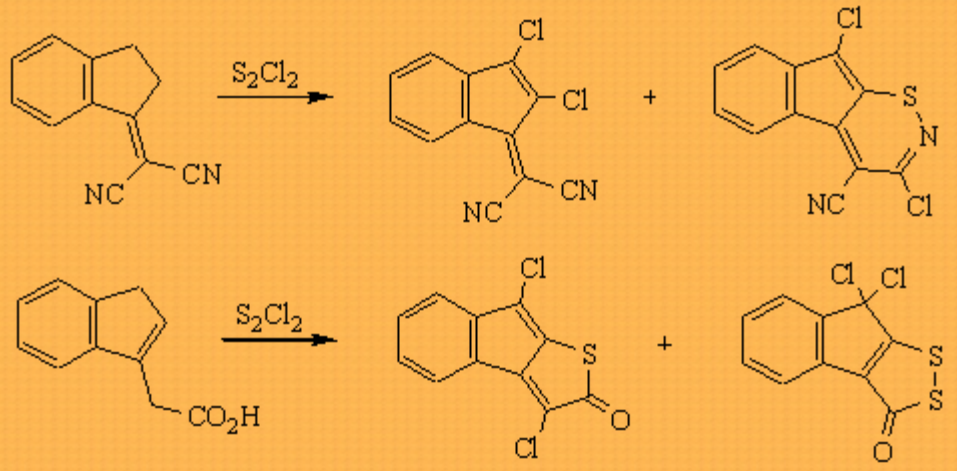
The indenecyclobutanone oxime only gives a single pathway of its abnormal Beckmann rearrangement, affording a unique intermediate that is captured in two different ways. In one way, trapping the intermediate by disulfur dichloride, a tricyclic 1,2-thiazine is produced. In the other way, simple chlorination by S_2Cl_2 and *N*-chlorosuccinimide of the same intermediate gives a dichloromethylenoindene derivative.

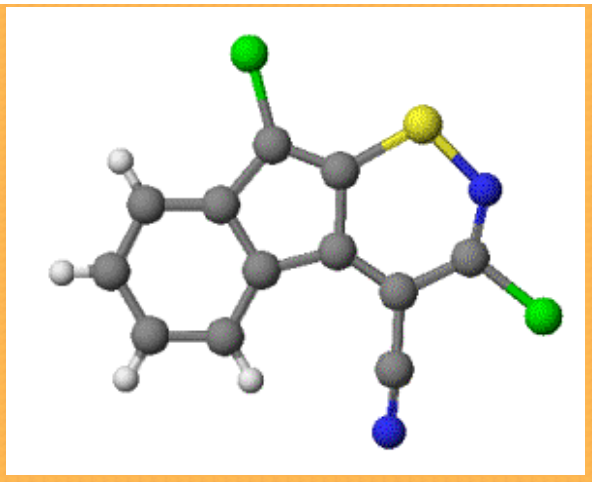


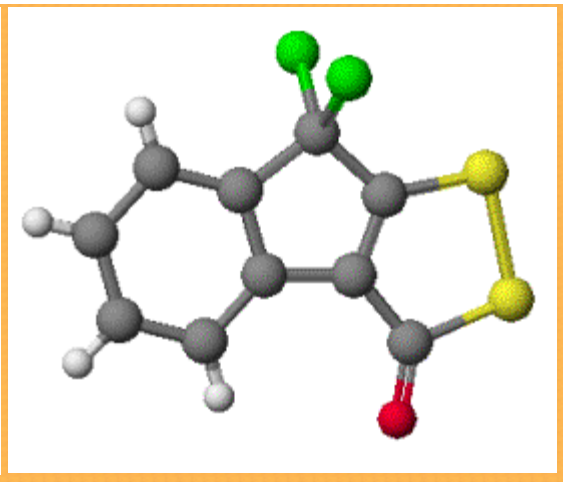


In this reaction, the addition of *N*-chlorosuccinimide leads the reaction to the production of the indene derivative as the main product, but the presence of only S_2Cl_2 (and a base for trapping hydrochloric acid after the dehydrochlorination) affords mainly the 1,2-thiazine derivative.

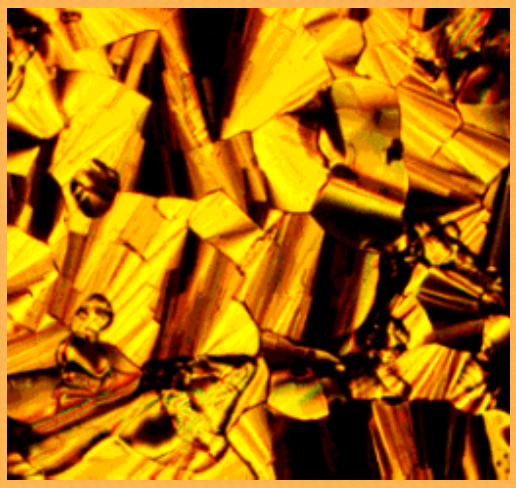
Production of new heterocycles and chlorinated indene derivatives is not restricted to cyclobutanone oximes. In fact, indene acetonitrile or indene acetic acid derivatives also give chlorinated compounds as well as new heterocyclic systems.[16-17]

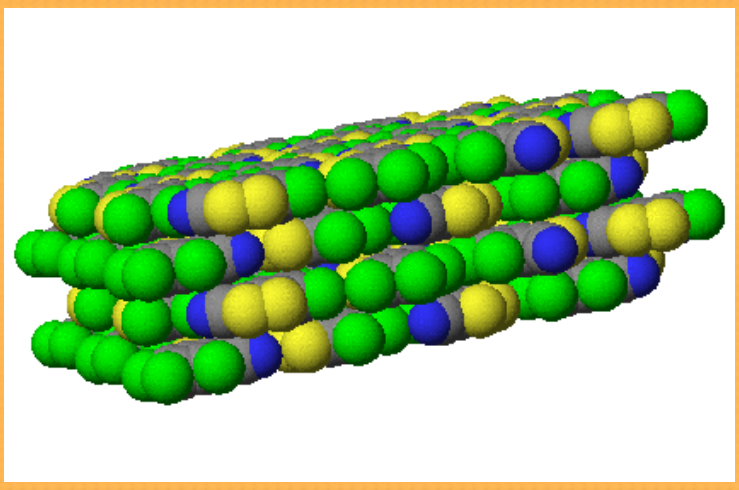


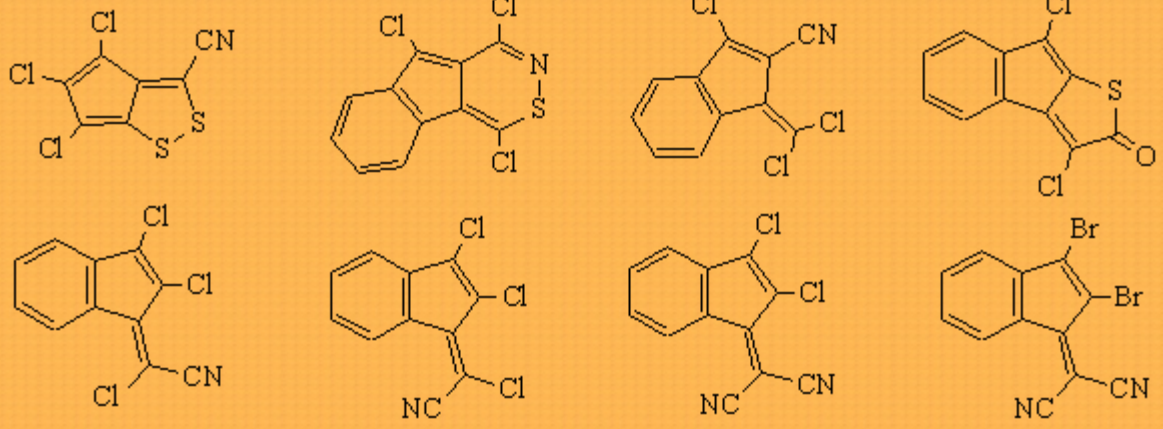




Some of these products constitute a new class of discotic liquid crystals in which the molecular order of the mesophases is supported by intermolecular interactions.[18] On heating, all compounds formed columnar mesophases of hexagonal symmetry, confirmed by differential scanning calorimetry and X-ray diffraction of the liquid crystal mesophases.

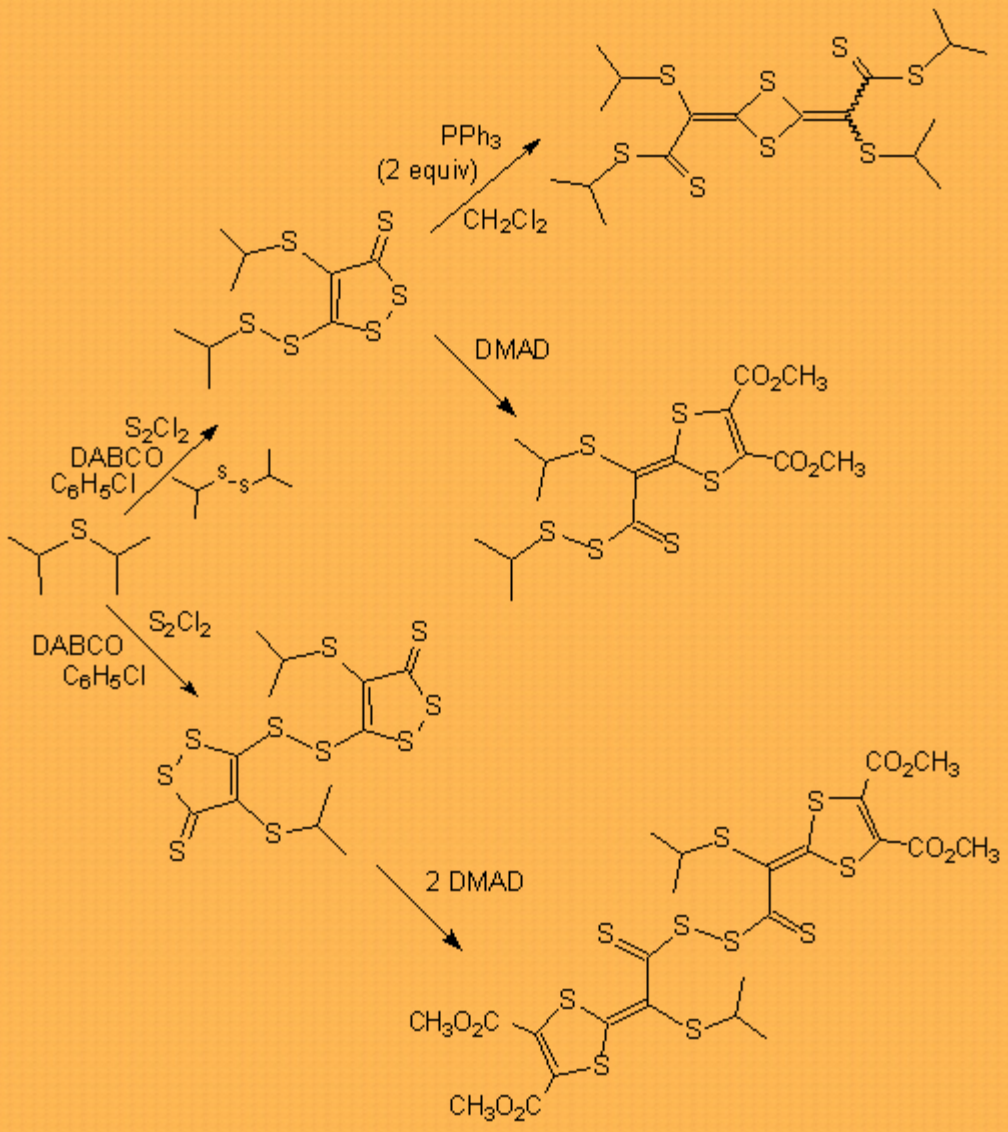






Not only nitrogen can be the center of activation of isopropyl groups, but also sulfur can play the same role. The reaction of diisopropyl sulfide and disulfur dichloride in chlorobenzene, in the presence of DABCO, gave 4-isopropylthio-5-isopropyldithio-1,2-dithiole-3-thione and the dimeric bisdithiolodisulfide.[19] When the reaction was performed in the presence of diisopropyl disulfide at the last stage of the reaction, the monomeric disulfide was selectively obtained. These compounds and diisopropyl disulfide were interconverted under UV irradiation. Treatment of these compounds with DMAD in benzene gave the 1:1 and the 1:2 adducts, respectively, which are very sulfur-rich

molecules. Treatment of the monomeric disulfide with two equivalents of triphenylphosphine afforded the thiodesaurine (*Z* + *E* isomers).



The limits of this chemistry are difficult to foresee. Some areas of this chemistry are now currently under intense research, especially those relating to new materials chemistry, liquid crystals or sulfur-rich molecules. The interesting characteristics found in many of these heterocycles, the development of rapid synthetic methods from easily available materials in multicomponent reactions, and the very wide range of products obtainable by these methods offer wide scope for the synthesis of new poly-sulfur-nitrogen heterocycles.

The new multi-component reactions described permit the preparation of new heterocyclic systems characterized by the high number of heteroatoms, sulfur and nitrogen, that are included in the structures, and constitute very fast and safe ways to get highly interesting heterocyclic systems that are very difficult to obtain by conventional ways.

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