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Review

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Contribution of Professor Charles W. Rees to the development of the chemistry of disulfur dichloride

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With gratitude to Professor Charles W. Rees from his students and co-workers

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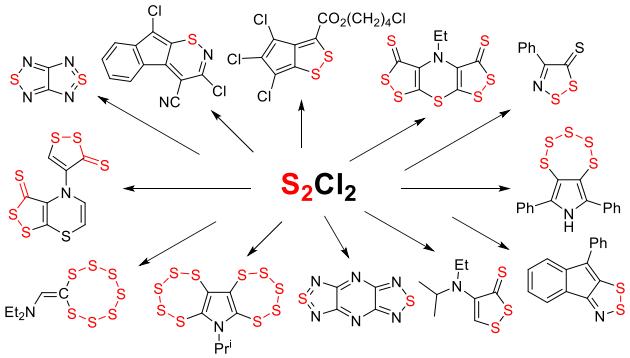
Abstract

Sulfur transfer reagents play an important role in organic synthesis, and sulfur chlorides, especially disulfur dichloride, are exceptional examples. Professor Charles W. Rees proposed novel strategies for preparing sulfur-nitrogen heterocycles from readily available organic substrates using disulfur dichloride. Together with his coworkers, he developed cascade transformations for synthesizing a wide range of heterocyclic systems, including 1,2-dithioles, 1,2,3,4,5-pentathiepins, 1,2,3-dithiazoles, 1,2,5-thiadiazoles, 1,4-thiazines, and 1,2,3,4,5,6,7-heptathiocanes. This review highlights Professor Rees's contributions to the chemistry of disulfur dichloride.



Keywords: Disulfur dichloride, heterocycles, one-pot synthesis, 1,2-dithioles, 1,2,3-dithiazoles, 1,2,3,4,5-pentathiepins, tertiary amines, chalcogen exchange

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1. Introduction

Sulfur-nitrogen heterocycles are of considerable interest to both chemists and materials scientists, and interest in them has been growing for decades. The presence of heteroatoms leads to significant changes in cyclic molecular structures due to the lone pairs of electrons and the difference in electronegativity between sulfur and nitrogen and carbon. As a result, these unique heterocycles have a number of features in contrast to all-carbon-containing compounds, and have promising material properties in both the pharmaceuticals and agrochemical fields, as well as compounds with interesting physical properties in optoelectronics, magnetism, and electrical conductivity (see Section 6.6).

In a paper published in 1992, Professor Charles W. Rees (Imperial College, London, UK) recognized the importance and the great potential of sulfur-nitrogen heterocyclic chemistry for the development of new drugs and materials.[1] One of the most common routes for the synthesis of sulfur-nitrogen-containing heterocycles is the reaction of nitrogen-containing compounds with sulfur-containing reagents. One of the most effective and inexpensive such reagents is disulfur dichloride (S_2Cl_2). Professor Rees was one of the first to realize the key role of this reagent, and he introduced it into wide practice. It took Rees and his colleagues many years to understand the main advantages and disadvantages of this reagent.

In the course of this research, Rees and his colleagues found that disulfur dichloride is highly reactive to a variety of functional groups in organic compounds. This is because reactions with S_2Cl_2 formally lead to products of various chemical reactions, which have been reviewed in many publications.[2-10] For example, S_2Cl_2 has been used for the perchlorination of aromatic compounds.[11-12] Disulfur dichloride is also considered to be a reactive electrophile and an oxidizing agent.[3,4,10] However, its sulfurizing ability is the most pronounced. All these reactivities of disulfur dichloride typically manifest themselves simultaneously, which reduces its value as a selective sulfur agent on the one hand but leads to complex cascade transformations with the formation of unusual heterocyclic compounds on the other hand.

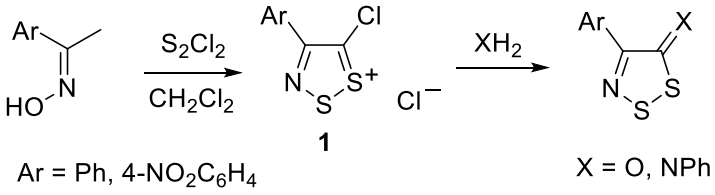
Prior to Rees's work, disulfur dichloride was typically used in reactions with organic compounds alone, without the addition of activating reagents. Rees's contribution was to use bases, mainly organic, to activate

transformations, which led to the discovery of a new theme in organic chemistry: the reaction of disulfur dichloride with nitrogen-containing bases.

2. Reaction of Disulfur Dichloride with Oximes and Related Compounds

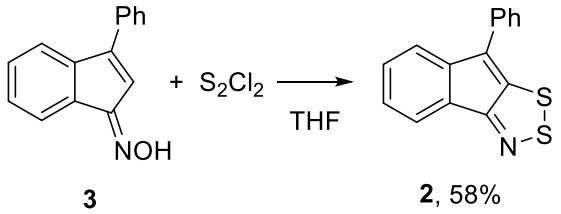
1,2,3-Dithiazoles are one of the most interesting classes among five-membered sulfur-nitrogen heterocycles because of their important physical and biological properties and versatile chemical composition.[13,14] The abundance of monocyclic 1,2,3-dithiazoles can be explained by the easy availability and high and varied reactivity of 4,5-dichloro-1,2,3-dithiazolium chloride, also known as Appel salt.[15] Remarkably, apart from Appel salt, only a few 4-substituted 1,2,3-dithiazolium chlorides have been isolated in free form (see Section 6.3).

The possibility of synthesizing 4-substituted 5-chloro-1,2,3-dithiazolium chlorides **1** was demonstrated by reactions of acetophenone oxime and its 4-nitro derivative with S_2Cl_2 in the absence of any base (Scheme 1). The existence of these salts has been proven by reactions with aniline and water to form the corresponding imines and ketones.[16,17]



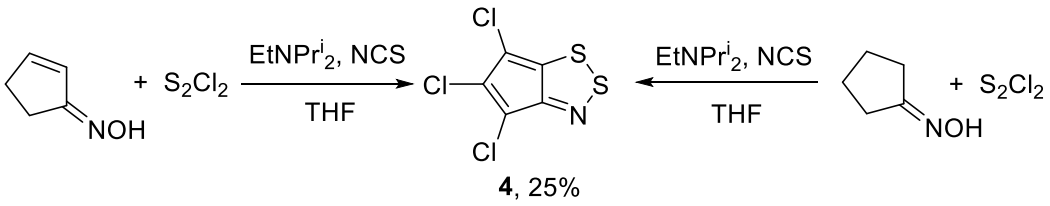
Scheme 1. Reaction of acetophenone oximes with S_2Cl_2.

Similarly, 8-phenylindenodithiazole **2** was obtained by the reaction of a cyclic oxime **3** with disulfur dichloride in THF in 58% yield (Scheme 2).



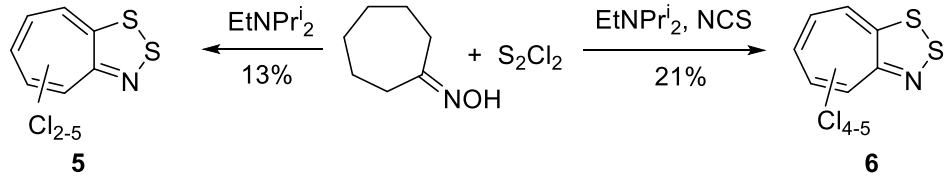
Scheme 2. Reaction of 3-phenyl-1*H*-inden-1-one oxime **3** with S_2Cl_2.

Significantly, when this reaction was extended to the oximes of cyclopentenone and cyclopentanone, no dithiazole ring was formed. The most important condition for the formation of the dithiazole ring was the use of *N*-ethyldiisopropylamine (Hünig's base) as a reagent, resulting in the highest yields of dithiazoles **2** (90%) and **4** (25%) (Scheme 3).[1,18] The yield of the final product of this complex multistage transformation strongly depends on the smallest changes in the reaction conditions, because the mechanism includes numerous reactions of chlorination, dehydrochlorination, and oxidation (according to the authors). If the carbocyclic ring is protected by a phenyl substituent (see formation of compound **2**), chlorination of this ring does not occur.



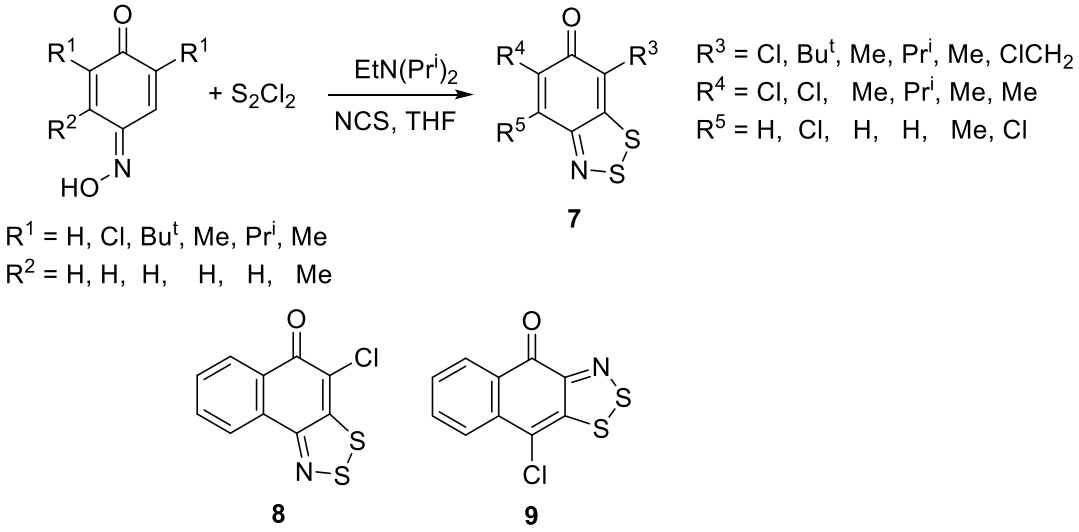
Scheme 3. Synthesis of 4,5,6-trichlorocyclopenta[*d*][1,2,3]dithiazole.

The reaction proceeds similarly for the oxime of a seven-membered cyclic ketone, forming a mixture of chlorinated cyclohepta-1,2,3-dithiazoles **5** and **6** (Scheme 4). A 15-fold excess of disulfur dichloride is used for chlorination, and polychlorination occurs in higher yields with *N*-chlorosuccinimide (NCS).[18]



Scheme 4. Reaction of cycloheptanone oxime with S_2Cl_2.

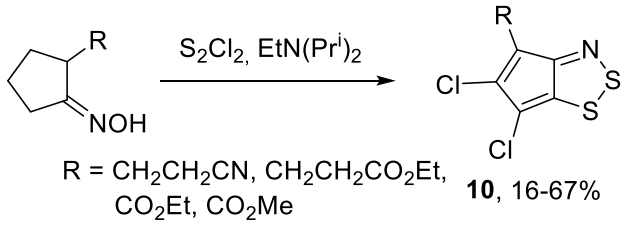
6*H*-1,2,3-Benzodithiazol-6-ones **7** were similarly synthesized from benzoquinone-4-oximes, S_2Cl_2, *N*-ethyldiisopropylamine, and NCS (Scheme 5). The formation of the dithiazole ring from the oxime is accompanied by chlorination, as usual. The substituents at positions-2 and -6 of the benzoquinone ring remain unchanged in the reaction products, except for the *tert*-butyl group, which is replaced by a chlorine atom. 1,4-Naphthoquinone-4-oxime and 1,2-naphthoquinone-2-oxime form dithiazoles **8** and **9** under the same conditions.[19]



Scheme 5. Reaction of benzoquinone-4-oximes with S_2Cl_2.

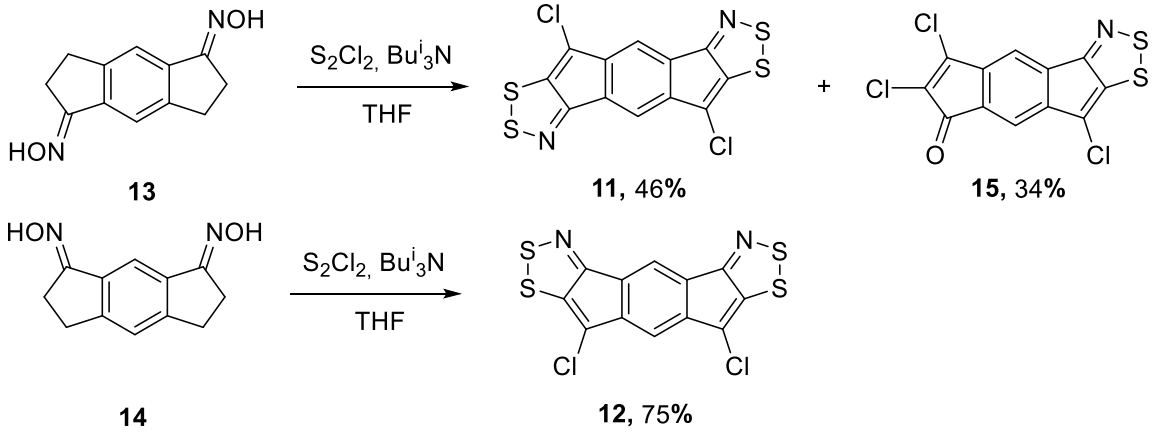
Cyclopenta-1,2,3-dithiazolium system **10** is formed by reacting 2-substituted oximes of cyclopentanone and disulfur dichloride and Hünig's base (Scheme 6).[20] This reaction is accompanied by exhaustive

chlorination, as is the case with other cyclopentadithiazoles (see above). In selected examples, tri-isobutylamine can successfully replace the Hünig's base.[21]



Scheme 6. Synthesis of cyclopent-1,2,3-dithiazoles **10**.

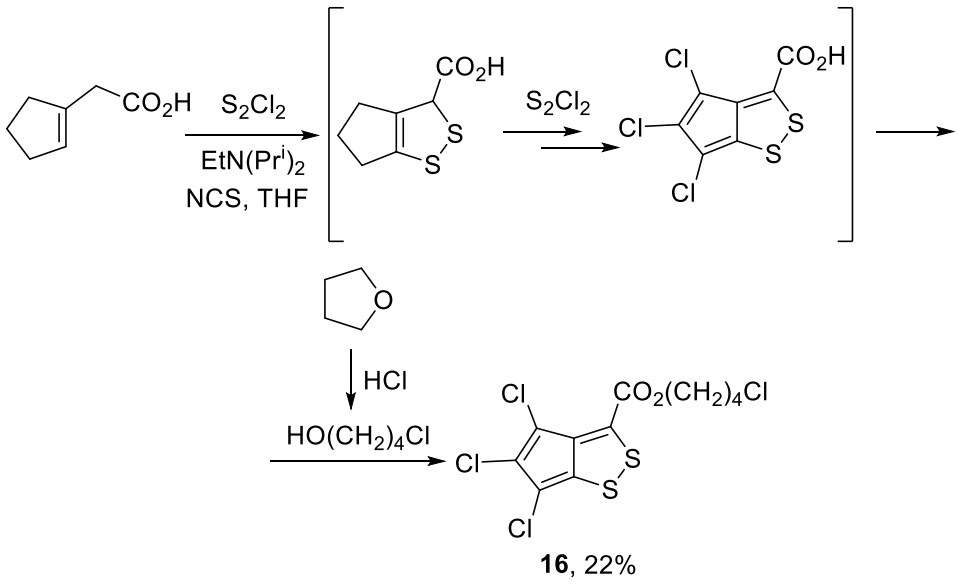
The same approach was also used to prepare pentacyclic bis[1,2,3]dithiazolo-*s*-indacenes **11** and **12** from dioximes of 1,5- and 1,7-hydrindacenediones **13** and **14** in 46 and 75% yields, respectively (Scheme 7).[21] In the preparation of **11**, the reaction is complicated by the hydrolysis of one oxime group, which leads to the formation of monodithiazole **15**.



Scheme 7. Reaction of dioximes of 1,5- and 1,7-hydrindacenediones **13** and **14** with S_2Cl_2.

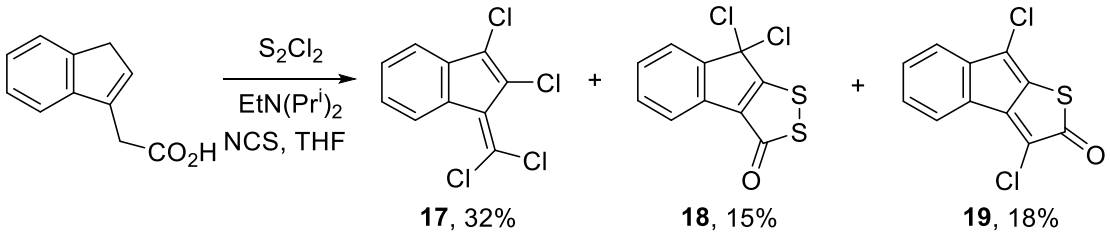
3. Synthesis of Other Sulfur Containing Heterocycles

Disulfur dichloride, in the presence of a chlorinating agent (NCS) and Hünig's base, proved to be an effective sulfuration system for obtaining other heterocycles by reaction with various classes of compounds. The reactions of S_2Cl_2 with NCS and Hünig's base in THF with 1-cyclopentenylacetic acid, 3-indenylacetic acid, its nitrile, and 1-(dicyanomethylene)indane[22] sometimes gave completely different types of heterocyclic and polychlorinated derivatives. The cyclopentenylacetic acid yielded trichlorocyclopenta-1,2-dithiole ester **16**, the product of heterocyclic ring formation, chlorination, and dehydrochlorination, furthermore unexpectedly, conversion of the acid into its 4-chlorobutyl ester also occurred (Scheme 8).



Scheme 8. Reaction of cyclopentenylacetic acid with S_2Cl_2.

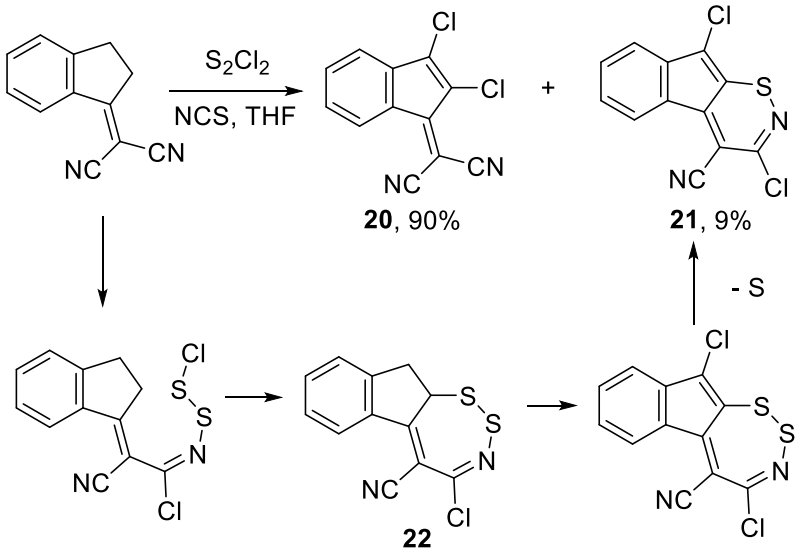
Treatment of 3-indenylacetic acid with S_2Cl_2, Hünig's base, and NCS in various solvents yielded three crystalline products (Scheme 9). The main reaction product (yield 32%) was polychlorinated methyleneindene **17**, which did not contain sulfur atoms. It was likely formed as a result of intense chlorination and dehydrochlorination of indenylacetic acid, which is common in S_2Cl_2 reactions, as well as chlorine decarboxylation. The other two products, **18** and **19**, were heterocyclic compounds containing sulfur atoms in the ring. The formation of heterocycle **18** is based on the ability of the S_2Cl_2 system, NCS, and Hünig's base, discovered by Professor Rees, to form 1,2-dithiole rings with activated allyl systems followed by extensive chlorination-dehydrochlorination to form completely unsaturated and chlorinated products. It is hypothesized that the acid group is lost by decarboxylation to form 3-chloro-1,2-dithiolium chloride, which then reacts with some external source of oxygen, as has been suggested in similar reactions. The formation of a condensed thiophenone **19** is rare in S_2Cl_2 reactions. It has been suggested that S_2Cl_2 converts carboxylic acids to acid chlorides, which can then be cyclized to a 1,2-dithiine derivative in this conversion. This derivative can eventually be converted into a thiophene by extrusion of the sulfur atom.



Scheme 9. Reaction of 3-indenylacetic acid with S_2Cl_2.

Dicyanomethyleneindane forms dichloroindene **20** and red thermochromic indeno-1,2-thiazine **21** under similar conditions (Scheme 10).[23] The most probable pathway for the conversion of dicyanide to thiazine is shown in Scheme 10. The addition of S_2Cl_2 to the nitrile bond, followed by cyclization to the activated allyl

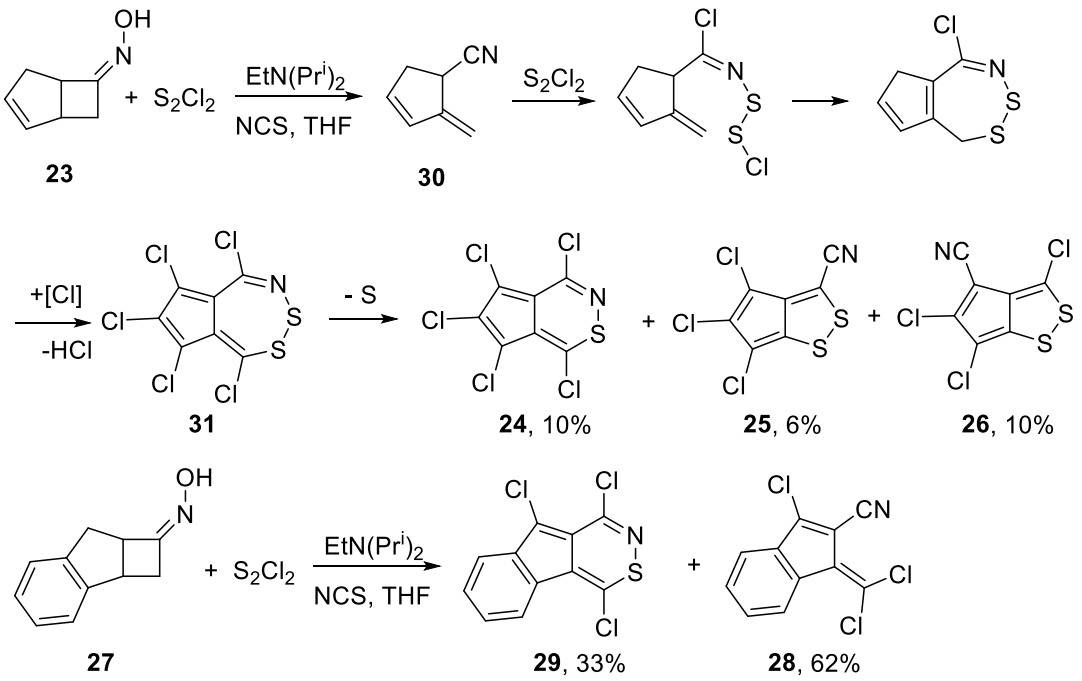
position, leads to dithiazepine **22**. Standard chlorination-dehydrochlorination, followed by extrusion of sulfur, leads to a planar and formally aromatic product **21**.



Scheme 10. Reaction of dicyanomethylene indane with S_2Cl_2.

Many of these products, when heated in a hot stage polarizing microscope, showed birefringence, indicating their liquid crystal behavior. This opens up a new class of discotic liquid crystals in which the molecular order of the mesophases is maintained by intermolecular interactions.[24]

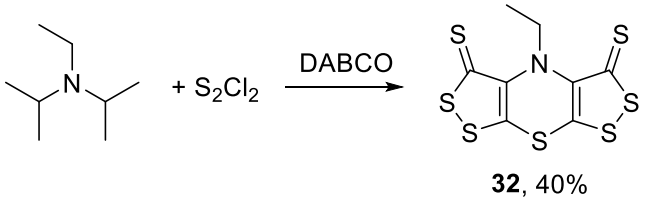
Cyclobutanone oxime **23**, unlike other cyclic oximes, reacted with a mixture of S_2Cl_2, NCS and Hünig's base to form cyclopenta-1,2-thiazine **24**. It also formed two other unexpected 10π pseudoazelenes, **25** and **26** (Scheme 11).[25] Treatment of oxime of the **27** also results in a mixture of products, mainly methylenoindene **28** and also the similar benzo product **29**.[26] The simplest mechanism for the conversion of oxime **23** to 1,2-thiazine **24** may be an abnormal fragmentation of ketoxime (second order) according to Beckmann, induced by disulfur dichloride. This opens the cyclobutane ring to form nitrile **30**, which adds S_2Cl_2 to form a 7-membered dithiazepine ring. A sequence of dehydrogenation and chlorination then gives completely chlorinated product **31**. This is formally a 12π system, which subsequently loses sulfur to form a more stable 10π thiazine **24** (Scheme 11).



Scheme 11. Reaction of cyclobutanone oximes with S_2Cl_2.

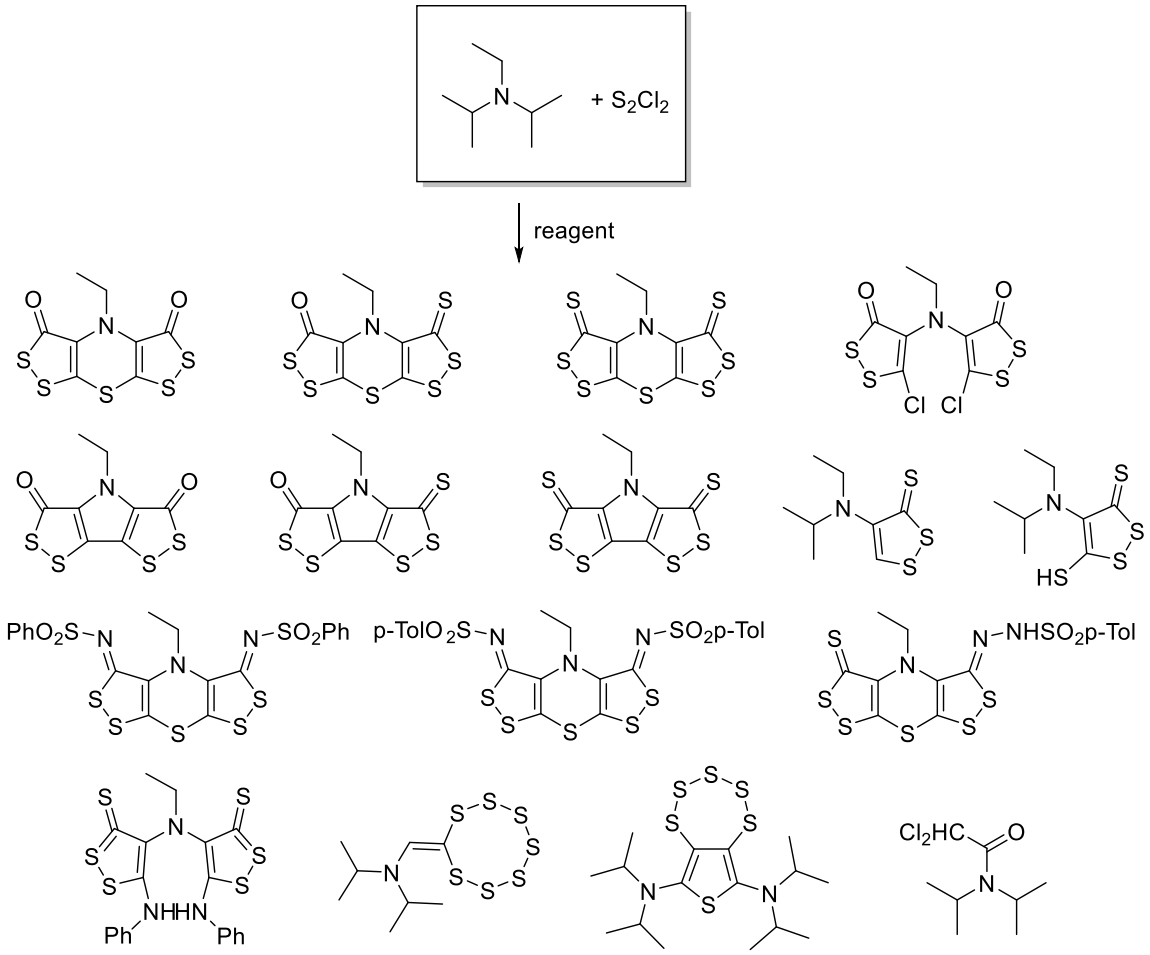
4. Reaction of Disulfur Dichloride with Tertiary Amines

In the late 1990s, Charles Rees and co-workers unexpectedly found that disulfur dichloride reacted with practically all trialkylamines investigated. These studies began after the discovery that *N*-ethyldiisopropylamine (Hünig's base), previously used as an "inert" base, reacts with disulfur dichloride and 1,4-diazabicyclo[2.2.2]octane (DABCO), unexpectedly forming a new multisulfur-nitrogen system, bis[1,2]dithiolo[1,4]thiazine **32**.[27] Remarkably, in this unique one-pot conversion of the Hünig's base to tricycle **32**, the 14 isopropyl CH bonds are replaced by 10 C-S bonds and two C=C double bonds, while the ethyl group remains intact. This reaction is a striking example of high selectivity between primary and secondary *N*-alkyl groups in a competitive reaction (Scheme 12).



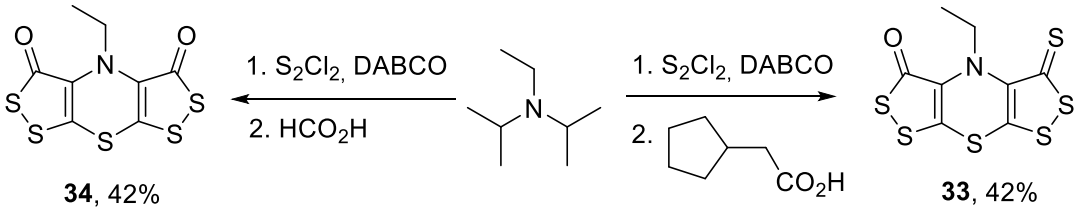
Scheme 12. Synthesis of bis[1,2]dithiolo[1,4]thiazine **32**.

It turned out that this unprecedented reaction between two reagents, Hünig's base and disulfur dichloride, can lead to 16 compounds in one-pot transformations when various substances are added. Some of these compounds are formed selectively and with high yields (Scheme 13).[27-37]



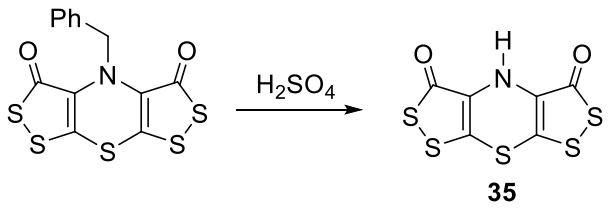
Scheme 13. Compounds obtained from the reaction of S_2Cl_2 and *N*-ethyldiisopropylamine.

Other bis[1,2]dithiolo[1,4]thiazines **33** and **34** were also selectively prepared by the reaction of Hünig's base with disulfur dichloride in the presence of oxygen donors, cyclopentadienylacetic or formic acids (Scheme 14).[28]



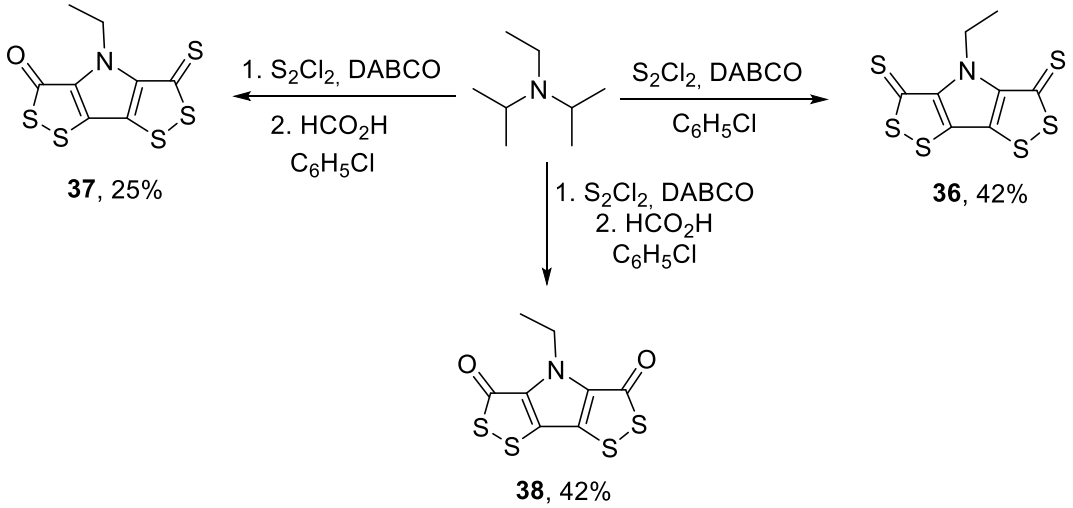
Scheme 14. Synthesis of bis[1,2]dithiolo[1,4]thiazines **33** and **34**.

All tricyclic *N*-substituted bis-dithiolothiazines adopt a bent conformation but there is one exception to this molecular habit. The parent ring, having hydrogen on nitrogen, is a planar compound in the solid state. This compound **35** was obtained by debenzylation of the *N*-benzyl-substituted derivative of bis[1,2]dithiolo[1,4]thiazine (Scheme 15).[29-30]



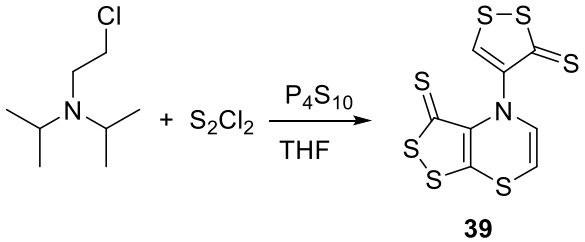
Scheme 15. Synthesis of unsubstituted bis[1,2]dithiolo[1,4]thiazine **35**.

The reaction of Hünig's base with disulfur dichloride in refluxing chlorobenzene gave the corresponding bis[1,2]dithiolopyrroles **36**–**38** by the extrusion of a sulfur atom from thiazines **32**–**34** (Scheme 16).[31]



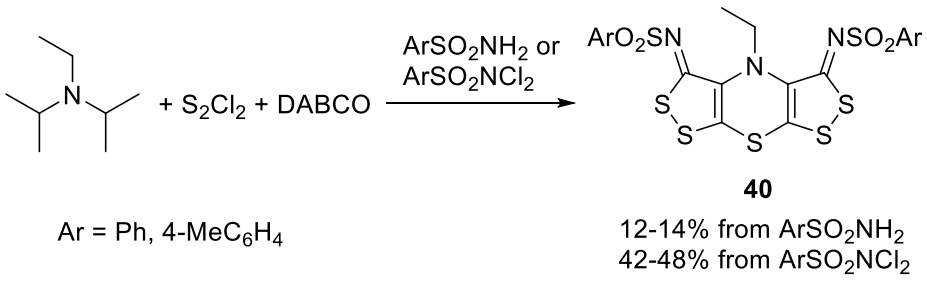
Scheme 16. Synthesis of bis[1,2]dithiolopyrroles **36**–**38**.

On further studying the reactions of substituted diisopropylamines with disulfur dichloride, Rees and colleagues synthesized a series of tricyclic bis-dithiolothiazines, including the parent members.[29,32,33] Treatment of *N*-(2-chloroethyl)diisopropylamine with disulfur dichloride in tetrahydrofuran, followed by the addition of phosphorus pentasulfide, led to the unexpected formation of the dithiolothiazine bicyclic system.[32] The authors suggested that the formation of partially saturated thiazine **39** occurs by sulfuration of the chloroethyl group by P_2S_5 followed by addition to the dithiole ring (Scheme 17).



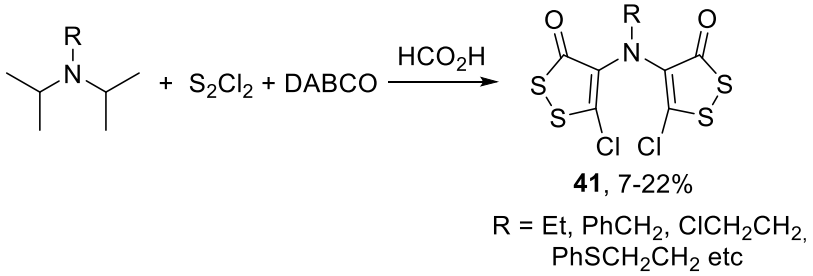
Scheme 17. Synthesis of 4-(3-thioxo-3*H*-1,2-dithiol-4-yl)-3*H*,4*H*-[1,2]dithiolo[3,4-*b*][1,4]thiazine-3-thione.

Treatment of *N*-ethyldiisopropylamine, S_2Cl_2, and DABCO in chloroform at room temperature followed by the addition of arenesulfonamides and their *N*,*N*-dichloro derivatives led to the formation of *N*,*N*′-bis(arylsulfonyl)dithiolothiazinediimines **40** in moderate yields (Scheme 18).[34]



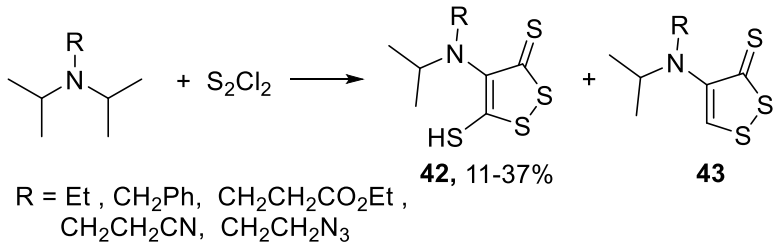
Scheme 18. Synthesis of *N*,*N*′-bis(arylsulfonyl)dithiolothiazinediimines.

The reaction of *N*-alkyldiisopropylamines with disulfur dichloride and a reduced amount of DABCO with respect to S_2Cl_2 prevented the formation of the 1,4-thiazine ring and led to the formation of *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines **41**, although in low yields, by chlorination of intermediate dithiazolium salts with excess S_2Cl_2 and then conversion into keto derivatives by treatment with formic acid (Scheme 19).[35]



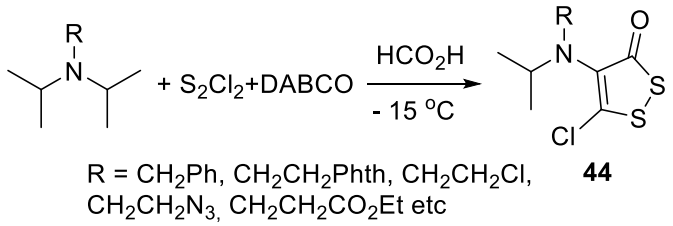
Scheme 19. Synthesis of *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines **41**.

In all the reactions discussed in this section, both isopropyl groups were converted into a 1,2-dithiole ring. When mixing *N*-alkyldiisopropylamines and disulfur dichloride in chloroform in the absence of another base, DABCO manages to carry out the reaction at one of the isopropyl groups and two monocyclic dithiole-3-thiones **42** and **43** result. In all cases considered, the main product was the 5-mercapto derivative **42** (Scheme 20).[36,37]



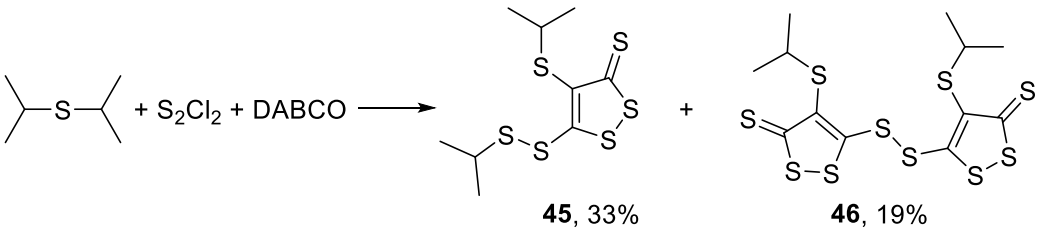
Scheme 20. Synthesis of monocyclic 1,2-dithioles from substituted diisopropylamines.

Rees and co-workers showed that the reaction of disulfur dichloride with diisopropylamines can be stopped at the stage of formation of monocyclic 1,2-dithioles.[36] The main condition for the successful synthesis of monodithioles is low temperature (-15 °C). In accordance with the previously proposed mechanism for the formation of a dithiole ring in these reactions, the combination of an excess of disulfur dichloride over a tertiary amine and DABCO led to the formation of a dichlorodithiole salt, which in the presence of an oxygen nucleophile (formic acid) gives 5-chlorodithiol-3-one **44** (Scheme 21). The synthesis of 1,2-dithiol-3-ones under unusually mild conditions is exceptional among the known corresponding methods and opened up new wide opportunities for studying this promising chemical class.



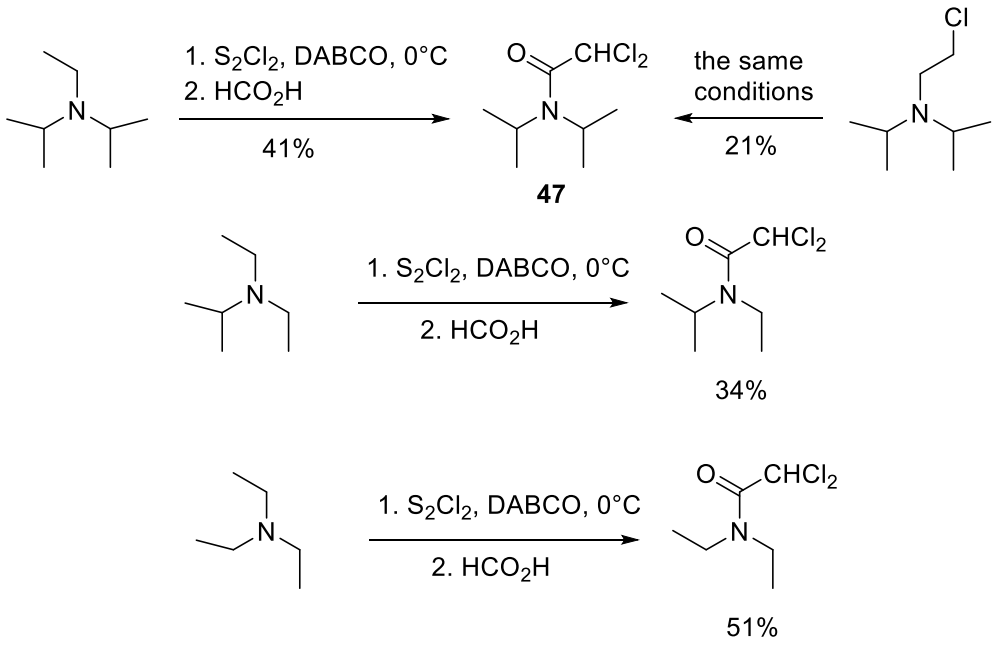
Scheme 21. Synthesis of monocyclic 5-chloro-1,2-dithiol-3-ones **44**.

Professor Rees' research has shown that an isopropyl group attached to a sulfur atom can also undergo similar transformations. Thus, the reaction of diisopropyl sulfide with disulfur dichloride and DABCO led to the formation of 1,2-dithiole-3-thiones **45** and **46**.[38] It was assumed that the formation of the dithiole ring should proceed similarly to the formation of tertiary diisopropylamines. However, in the case of diisopropyl sulfide, only one isopropyl group is activated by the sulfide atom, and then this activation is suppressed during the formation of the dithiolethione ring associated with the sulfur atom (Scheme 22).



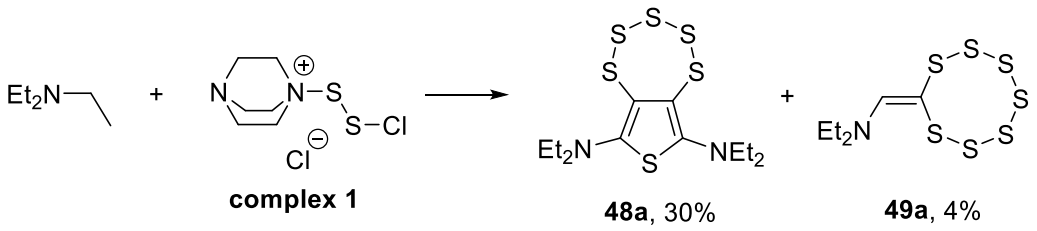
Scheme 22. Reaction of diisopropyl sulfide with disulfur dichloride.

Rees and Rakitin continued their study of the reaction of *N*-ethyldiisopropylamine with disulfur dichloride by increasing the reaction temperature from -15 °C to 0 °C. Unexpectedly, these conditions led to a completely different reaction, in which the isopropyl groups remain unchanged and the ethyl group was converted to the dichloroacetyl group in **47** (Scheme 9).[39] To extend this reaction to other ethyl or substituted ethyl groups, the reaction of a number of tertiary amines with disulfur dichloride and DABCO was investigated at 0 °C. *N*-(2-Chloroethyl)diisopropylamine gave the same dichloroacetyl product **47** as Hünig's base. Similar products were obtained from diethylisopropylamine and triethylamine (Scheme 23).



Scheme 23. Synthesis of dichloroacetyl derivatives.

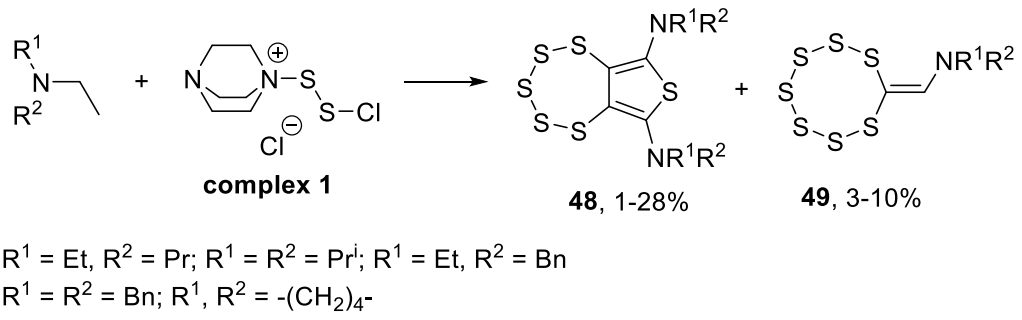
Further investigation of the reaction of triethylamine with a mixture of disulfur dichloride and DABCO gave even more unexpected results. When a 1:1 mixture of disulfur dichloride and DABCO was kept for 1 hour at room temperature (the authors suggest the formation of **complex 1** in this case), the addition of triethylamine leads to the formation of two completely new and unexpected substances - thienopentathiepine **48a** and heptathiocan **49a** (Scheme 24).[40] The first compound is the product of an unprecedented conversion of triethylamine to pentathiepine, in which a thiophene ring is created from two *N*-ethyl groups to form a carbon-carbon bond between the unactivated methyl groups. We found that these two products were not interconverted under the reaction conditions and were presumably formed in simultaneous, competing reactions. The structure of heptathiocan **49a** was confirmed by X-ray diffraction analysis.



Scheme 24. Reaction of triethylamine with **complex 1**.

Because these are ethyl group reactions, Et_3N is the preferred substrate. As expected, similar reactions were observed with other tertiary *N*-ethylamines, but with lower product yields. Diethyl-*n*-propylamine, ethyldiisopropylamine, benzyldiethylamine, dibenzylethylamine, and *N*-ethylpiperidine form thienopentathiepines **48** (1–28%) and the corresponding heptathiocanes **49** (3–10%) (Scheme 25). The structure of bis-piperidinothienopentathiepine was also confirmed by X-ray diffraction analysis. Although the yields of these products are generally low, they are easy to produce in one pot from cheap feedstock. The conversion of Et_3N to pentathiepine and heptathiocan is assumed to be the result of a series of cascade

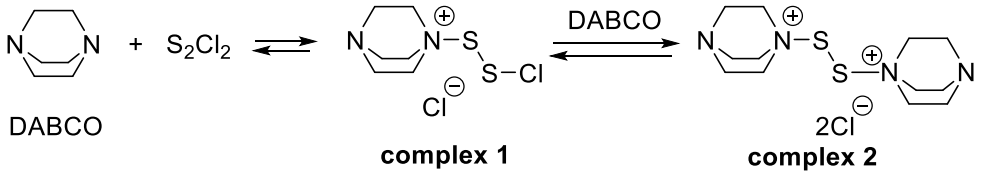
reactions, including the oxidation of one ethyl group and a number of other transformations. The isolated products, thienopentathiepines **48** and heptathiocanes **49**, are likely the most stable members of polysulfur rings containing two and one sp^2 carbon atoms, respectively.



R^1 = Et, R^2 = Pr; R^1 = R^2 = Pr^i; R^1 = Et, R^2 = Bn
R^1 = R^2 = Bn; R^1, R^2 = -$(CH_2)_4$-

Scheme 25. Synthesis of thienopentathiepins **48** and heptathiocanes **49**.

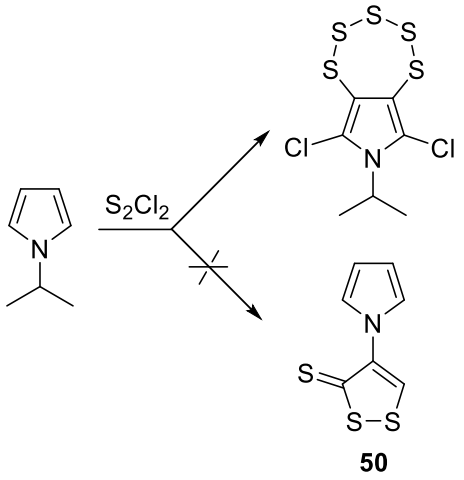
One of the most interesting discoveries was that disulfur dichloride forms reactive complexes with some tertiary amines at low temperature and with 1,4-diazabicyclooctane (DABCO) at room temperature.[41] A mixture of equimolar amounts of S_2Cl_2 and DABCO in chloroform, stored for one hour at room temperature prior to use, gave various reactions with different products from those formed by simultaneous mixing of the heterocycle, S_2Cl_2, and DABCO. Assuming that complexes were formed between S_2Cl_2 and DABCO, their solutions in chloroform were studied by infrared spectroscopy. The S-S absorption band in a 1:1 mixture was shifted from 540 to 580 cm^{-1}, and the S-Cl in S_2Cl_2 absorption bands (υ 436 and 452 cm^{-1}) were present in a 1:1 mixture of S_2Cl_2 and DABCO, but disappeared when a second mole of DABCO was added. Based on these data, it is suggested that a 1:1 mixture predominantly contains **complex 1**, and a 1:2 mixture predominantly contains **complex 2** (Scheme 26).



Scheme 26. Complexes of S_2Cl_2 and DABCO.

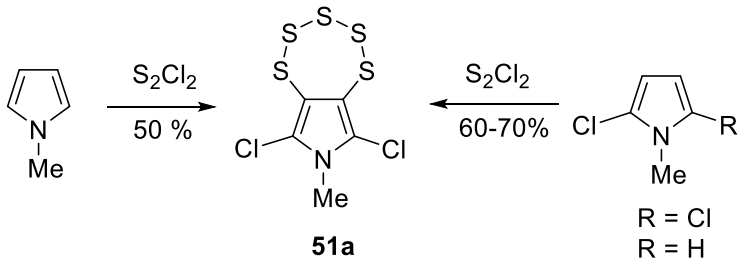
5. Synthesis of Fused 1,2,3,4,5-Pentathiepins

Rees and co-workers discovered an unusual synthesis of pentathiepins fused to another heterocyclic ring.[42] They found that the reaction of simple nucleophilic heterocycles, such as pyrroles and thiophene, as well as their tetrahydro derivatives, with disulfur dichloride and DABCO results in a simple, one-step synthesis of mono- and previously undescribed bis-pentathiepines. This new transformation was discovered unexpectedly while studying the reaction of *N*-isopropylpyrrole with disulfur dicloride in an attempt to obtain *N*-1,2-dithiole-3-thione **50** (Scheme 27). However, it turned out that the pyrrole ring is more reactive than the isopropyl group. The simplicity of this unusual reaction and the availability of the reagents have shown the need for systematic study to find the best conditions for the synthesis of pentathiepines and explore its limits.



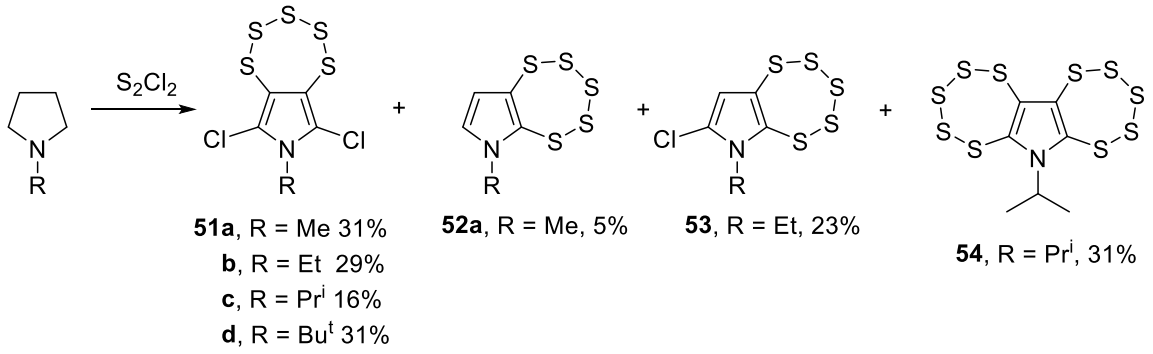
Scheme 27. Discovery of fused 1,2,3,4,5-pentathiepins synthesis.

Treatment of *N*-methylpyrrole with disulfur dichloride and DABCO yielded dichloropyrrolopentathiepine **51a** in 50% yield.[42] In the formation of **51a** from *N*-methylpyrrole, the pentathiepine ring fused with the pyrrole ring, and both α-positions of pyrrole were chlorinated. Unsurprisingly, 2,5-dichloro- and 2-chloropyrroles gave pyrrolopentathiepine **51a** under similar conditions, and in higher yields (Scheme 28).



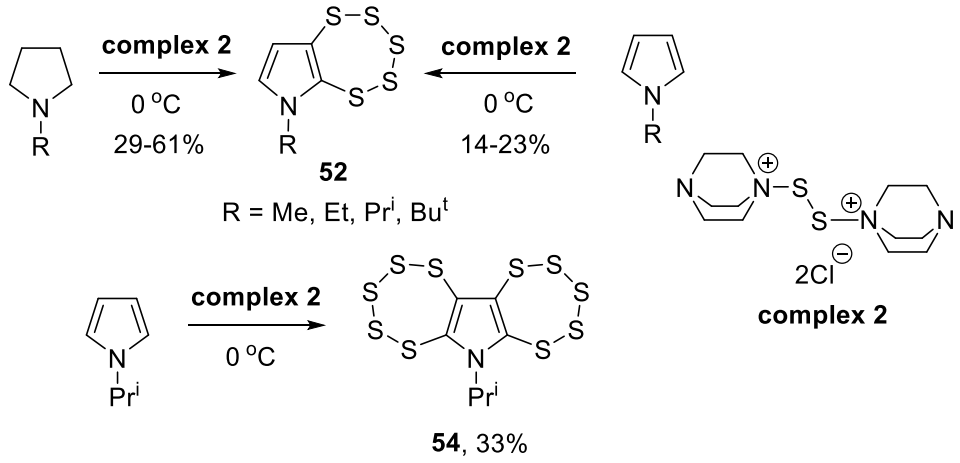
Scheme 28. Synthesis of *N*-methyldichloropyrrolopentathiepin **51a**.

As S_2Cl_2 can also oxidize a pyrrolidine ring to a pyrrole ring, we introduced readily available *N*-alkyl derivatives of pyrrolidine into a similar reaction. *N*-Methyl-, *N*-ethyl, *N*-isopropyl-, and *N*-*tert*-butylpyrrolidines formed the corresponding *N*-alkyldichloropentathiepinopyrroles **51** as the main products in low to moderate yields (16–31%).[43] Additionally, *N*-methylpyrrolidine gave a small amount of non-chlorinated compound **52a** (5%) with a pentathiepine ring conjugated by a 2,3-pyrrole bond, *N*-ethylpyrrolidine gave monochlorinated product **53**, and *N*-isopropylpyrrolidine gave the bispentathiepine **54**, which is the first and only bis-pentathiepine known so far (Scheme 29).



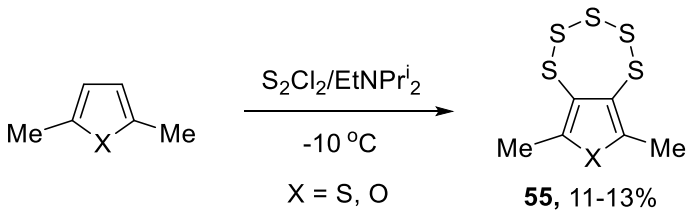
Scheme 29. Reaction of *N*-alkylpyrrolidines with S_2Cl_2.

Disulfur dichloride exhibited both sulfurating (formation of a pentathiepin ring) and a chlorinating (chlorination of the pyrrole ring) properties in these transformations. **Complex 2**, prepared from disulfur dichloride and two equivalents of DABCO, should exhibit predominantly sulfurating, rather than chlorinating, activity. We used it in the reaction with nucleophilic heterocycles. Indeed, the reaction of all *N*-alkylpyrrolidines with **complex 2** selectively gives *N*-alkylpentathiepinopyrroles **52** in moderate yields; chlorinated products were not found in any of these reactions (Scheme 30).[41] The same products were obtained from *N*-alkylpyrroles, but a smaller amount of **complex 2** must be used to carry out the selective process. The yields of pentathiepines **52** were close to those obtained from pyrrolidines. *N*-Isopropylpyrrole selectively gave bis-pentathiepine **54**.



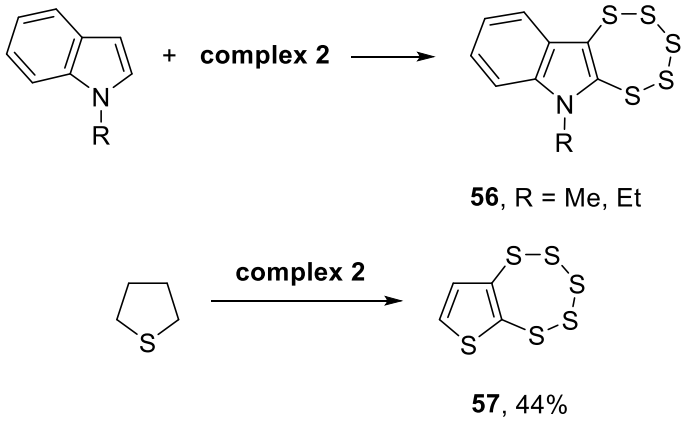
Scheme 30. Selective synthesis of pentathiepinopyrroles **52** and **54**.

Even milder conditions have been used to prepare thienopentathiepin and pentathiepinofuran **55** from the corresponding heterocycles.[44] The reaction of these heterocycles with a mixture of disulfur dichloride and *N*-ethyldiisopropylamine at a low temperature (-10 °C) gives pentathiepines **55**, albeit in low yields (Scheme 31).



Scheme 31. Synthesis of thienopentathiepin and pentathiepinofuran **55**.

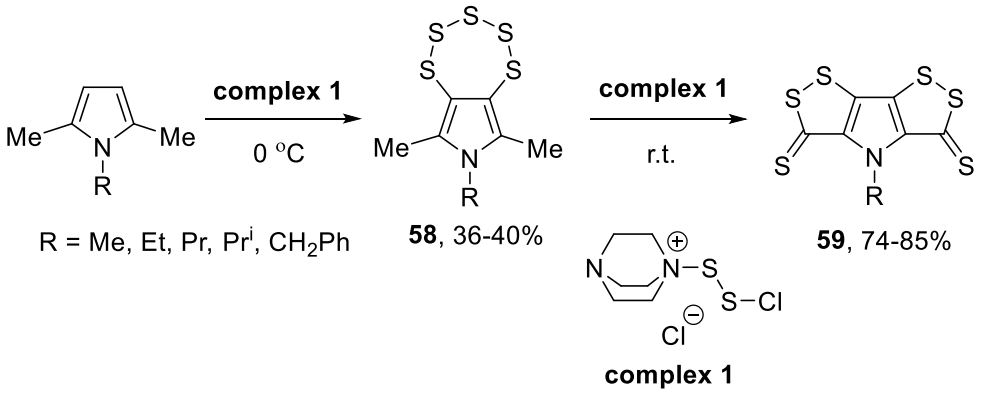
We extended these reactions to other heterocycles, with moderate success. *N*-Alkylindoles reacted like pyrroles to give pentathiepines **56** in moderate yields, and tetrahydrothiophene gave the corresponding pentathiepine **57** in good yield (Scheme 32). Unfortunately, more aromatic heterocycles such as thiophene, benzothiophene, and furan did not react with **complex 2**.



Scheme 32. Reaction of *N*-alkylindoles and tetrahydrothiophene with complex **2**.

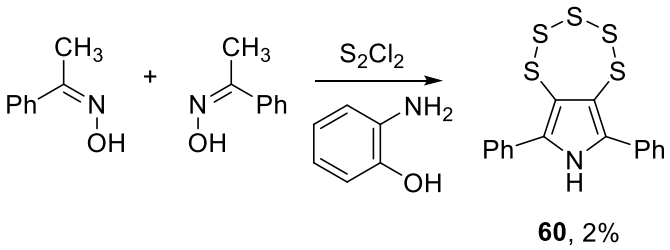
Little is known about the nature of all these reactions, although possible general reaction routes have been proposed, including dehydrogenation of tetrahydroaromatic compounds, chlorination and sulfuration of aromatic compounds and their conversion to -SSCl derivatives, and the formation of a pentathiepin ring.

If the pyrrole α-positions are substituted, the pentathiepin ring is added at the 3,4-pyrrole bond to form pentathiepinopyrroles **58** in moderate yield.[45] A study of the synthesis of pentathiepinopyrroles from 2,5-dimethylpyrroles showed that the best yields of pentathiepines **58** were obtained using **complex 1** as a reagent at a low temperature (0 °C). At room temperature, pentathiepins **58** gave bis(dithiolo)pyrroles **59** in high yields with **complex 1** (Scheme 33).[45] Although pentathiepin rings and methyl groups usually do not react with mixtures of S_2Cl_2 and DABCO at room temperature,[46] pyrroles **58** containing both of these fragments reacted in an extensive cascade sequence. Presumably, the electron-releasing pyrrole nitrogen activated **58** by attacking either the pentathiepin ring or the methyl group with an electrophilic reagent. A plausible mechanism for this transformation has been proposed.



Scheme 33. An unusual route from 2,5-dimethylpyrroles to bis(dithiolo)pyrroles **59**.

Pyrrolopentathiepin **60** was isolated as a minor side product in a very curious and completely unexpected reaction between acetophenone oxime and disulfur dichloride in the presence of pyridine and *o*-aminophenol (Scheme 34).[17]



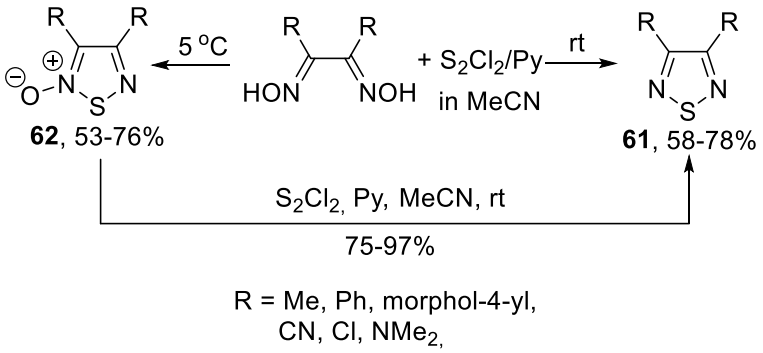
Scheme 34. Synthesis of pyrrolopentathiepin **60**.

6. Development of the Chemistry of Disulfur Dichloride After the Death of Professor C. W. Rees

After the death of Professor Rees, his ideas were successfully developed by his coworker Professor O. Rakitin.

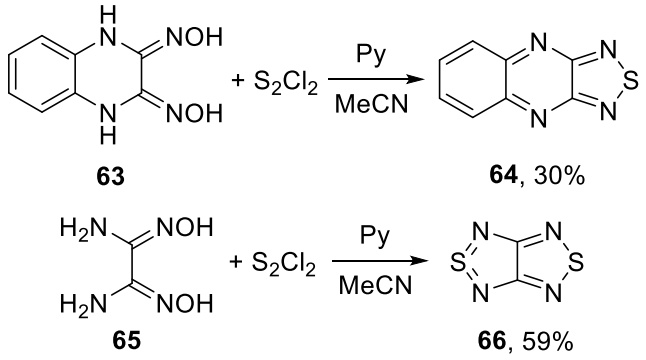
6.1. Synthesis of 1,2,5-thiadiazoles

Rakitin et al. showed that the reaction of *vic*-glyoximes with S_2Cl_2 and pyridine in acetonitrile at room temperature gives selectively monocyclic 1,2,5-thiadiazoles **61** in moderate yields. Treatment of the same reagents at low temperature (5 °C) leads to the formation of rare 1,2,5-thiadiazole-2-oxides **62** (Scheme 35).[47] Not surprisingly, 1,2,5-thiadiazole *N*-oxides **62** were converted in high yields to thiadiazoles **61** by treatment with S_2Cl_2 and pyridine in acetonitrile at room temperature. Monosubstituted glyoximes gave 4-substituted 3-chloro-1,2,5-thiadiazoles under the same conditions.[48]



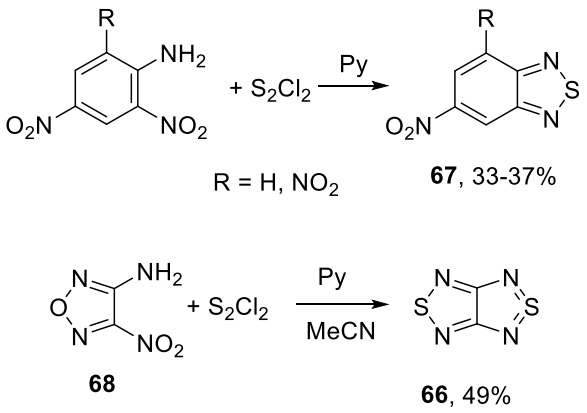
Scheme 35. Synthesis of 1,2,5-thiadiazoles from *vic*-glyoximes.

Interesting and somewhat unexpected results were obtained in the reaction of diaminoglyoximes with disulfur dichloride. Treatment of 1,4-dihydroquinoxaline-2,3-dionedioxime **63** with S_2Cl_2 in the presence of pyridine in acetonitrile led to the formation of [1,2,5]thiadiazolo[3,4-*b*]quinoxaline **64** in moderate yield (Scheme 36).[47] In this case, two processes occurred simultaneously: the formation of a thiadiazole ring from the dioxime fragment and the dehydration of dihydropiperazine into an aromatic pyrazine ring, presumably under the action of disulfur dichloride. The reaction of readily available diaminoglyoxime **65** with S_2Cl_2 in the presence of pyridine in acetonitrile led to [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **66** in moderate yield (Scheme 36).



Scheme 36. Synthesis of [1,2,5]thiadiazolo[3,4-*b*]quinoxaline **64** and [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **66**.

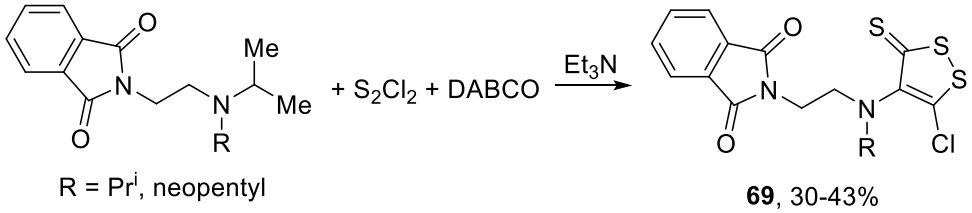
A new and original approach to fused 1,2,5-thiadiazoles was described (Scheme 21).[49] Treatment of *ortho*-nitroanilines with S_2Cl_2 in the presence of pyridine selectively gave 2,1,3-benzothiadiazoles **67** in moderate yields (Scheme 37). The reaction of 4-amino-3-nitro-1,2,5-oxadiazole **68** with the same mixture led to the formation of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **66**. However, *ortho*-nitroaniline and other *ortho*-aminonitroheterocycles upon treatment with S_2Cl_2 gave products of sulfurization or substitution of nitro and amino groups by chlorine atom, which means that the reaction is very sensitive to the structure of the starting material.[50]



Scheme 37. Synthesis of fused 1,2,5-thiadiazoles from *vicinal* nitroamines.

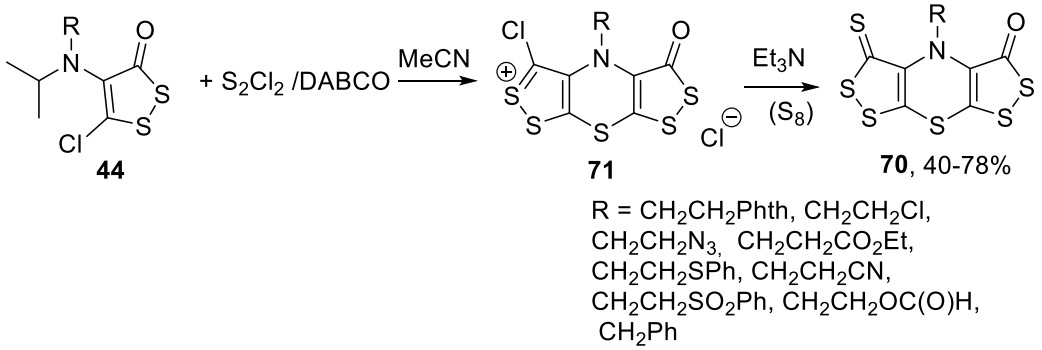
6.2. Synthesis of 1,2-dithioles

5-Chloro-1,2-dithiole-3-thiones **69** were synthesized by treating *N*-(2-phthalimidoethyl)-*N*-alkylisopropylamines with a mixture of disulfur dichloride and DABCO followed by reaction with triethylamine.[51] The stability of thiones **69** was attributed to the dipole-dipole interaction between the electron-rich 1,2-dithiole-3-thione ring and the electron-poor phthalimide groups (Scheme 38).



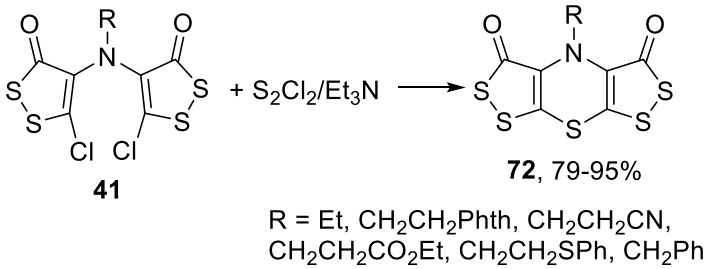
Scheme 38. Synthesis of *N*-(2-phthalimidoethyl)-*N*-alkylisopropylamines **69**.

Rakitin and collaborators decided to use readily available 5-chloro-1,2-dithioles **44** in reactions with disulfur dichloride. Treatment of these compounds with S_2Cl_2 and DABCO in acetonitrile, a solvent rarely used in S_2Cl_2 reactions, led to the formation of ketothione bisdithiolothiazines **70** after treatment with triethylamine as the base.[52] Bisdithioloketothiones **70** were obtained selectively with moderate to high yields (Scheme 39). To the best of our knowledge, this is the first time that a chlorine substituent in salt **71** has been replaced by sulfur under the electrophilic action of disulfur dichloride and a base.



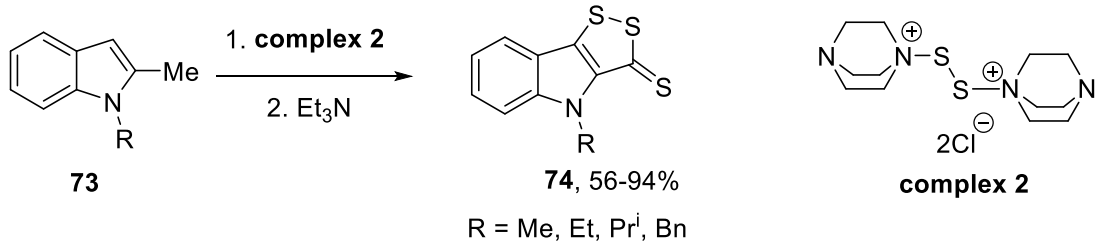
Scheme 39. Synthesis of bisdithiolothiazine ketothiones **14**.

To expand the sulfurizing ability of S_2Cl_2 in reactions with 5-chloro-1,2-dithioles, the reaction of *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines **41** with disulfur dichloride and base was studied . Treatment with S_2Cl_2 and triethylamine gave bis-dithiolothiazines **72** in high yields. The novelty of these transformations is the replacement of chlorines by sulfur in the reaction with electrophilic disulfur dichloride and its mixtures with tertiary amines.



Scheme 40. Reaction of bis(dithiolyl)amines **41** with S_2Cl_2.

Professor Rees showed that *N*-isopropyl groups with S_2Cl_2 can be converted into *N*-(1,2-dithiole-3-thiones) (see Section 4). Nitrogen heterocycles containing methyl and CH groups in the ortho positions, such as 2-methylindoles, which are readily and commercially available, are structurally similar to the isopropyl group and can be considered as potential intermediates in the synthesis of dithioloindolothiones. The reaction of 1,2-dimethylindole **73a** with a five-fold excess of **complex 1** in chloroform for 48 h at room temperature, after treatment with Et_3N, formed dithiolothione **74a** in moderate yield (34%).[53] It is not surprising that **complex 2**, which is more selective sulfurating agent, reacts more simply with **73a** (R = Me) to form thione **74a** (R = Me) in high yield (94%) under the same conditions (Scheme 41). Subsequently, this reaction was extended to other *N*-substituted 2-methylindoles **73**. Fused dithioloindoles **74** were obtained in moderate and high yields from *N*-alkyl- and *N*-benzyl-2-methylindoles **73**.

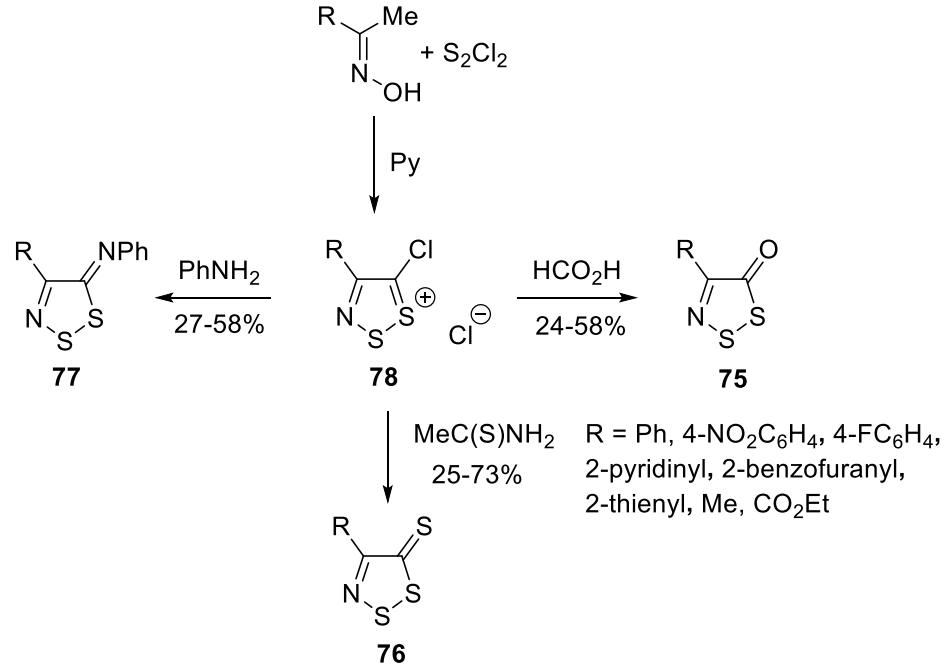


Scheme 41. Synthesis of *N*-substituted [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thiones **74**.

6.3. Synthesis of 1,2,3-dithiazoles

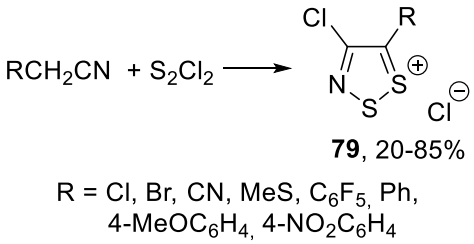
Thiéry and Rakitin developed earlier ideas put forward by Professor Rees on the preparation of 1,2,3-dithiazoles from substituted ethanone oximes.[16,17] They found that 5-one- **75**, 5-thione- **76** and 5-phenylimino-1,2,3-dithiazoles **77** can be selectively prepared by reacting various ethanone oximes with disulfur dichloride in the presence of pyridine as the base in acetonitrile, followed by treatment with the appropriate nucleophiles (formic acid, thioacetamide, and aniline) in high to moderate yields (Scheme 42).[54] The key intermediates in the formation of 1,2,3-dithiazoles were 1,2,3-dithiazolium chlorides **78**, which were unstable and converted into keto-, thio-, and arylimino derivatives upon reaction with the corresponding nucleophiles

in situ. The yield of dithiazoles **75**–**77** depends on the reaction conditions, including the reaction time and temperature, the nature of the solvent, and the base used.



Scheme 42. Synthesis of 1,2,3-dithiazoles from ethanone oximes.

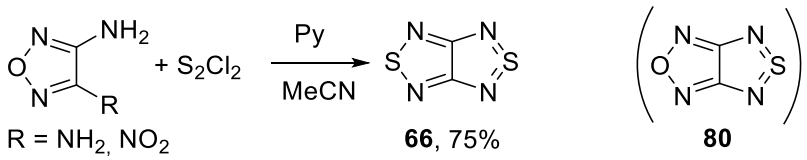
Recently, a series of 5-substituted-4-chloro-1,2,3-dithiazolium chlorides **79** were prepared by Koutentis in the reaction of monosubstituted acetonitriles with disulfur dichloride (Scheme 43).[55,56] The chloride salts were transformed into the corresponding perchlorates sufficiently stable to be characterized if the 5-substitutent was not a readily leaving group.



Scheme 43. Synthesis of monocyclic 1,2,3-dithiazoles from substituted acetonitriles.

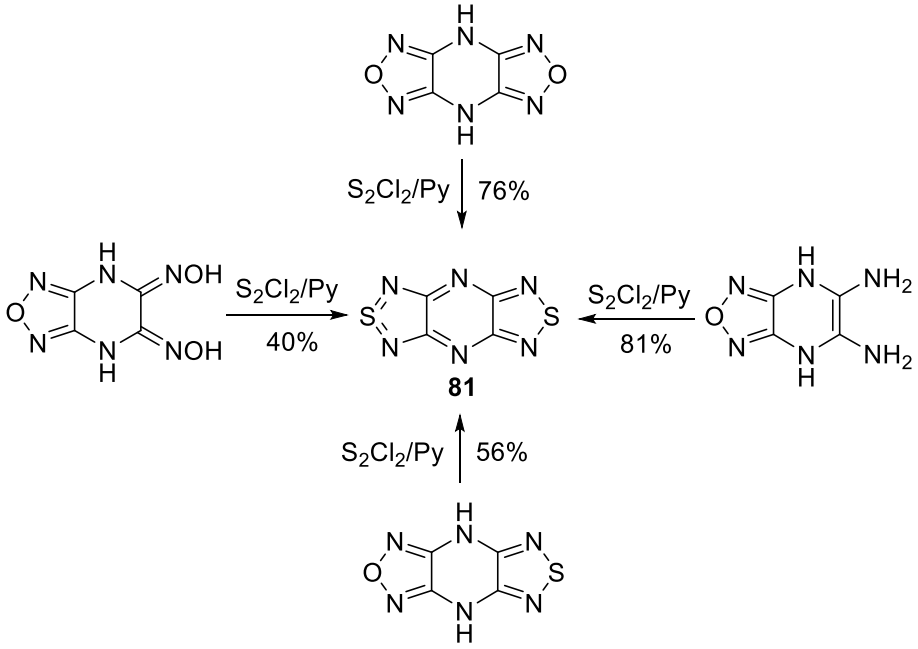
6.4. Chalcogen exchange in 1,2,5-oxa- and 1,2,5-selenadiazoles

This reaction, like many other reactions of disulfur dichloride, was discovered by accident. A study of the reaction of 3,4-diamino-1,2,5-oxadiazole with disulfur dichloride and pyridine in acetonitrile showed that, as a result of the reaction, [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **66** was formed in high yield (Scheme 44) instead of [1,2,5]oxadiazolo[3,4-*c*][1,2,5]thiadiazole **80**.[57] The most interesting feature of this transformation is the replacement of the oxygen atom in 1,2,5-oxadiazole ring with a sulfur atom in reaction with disulfur dichloride. Later it was shown that another oxadiazole derivative, 4-amino-3-nitro-1,2,5-oxadiazole **68**, can also undergo a similar transformation with S_2Cl_2.[49]



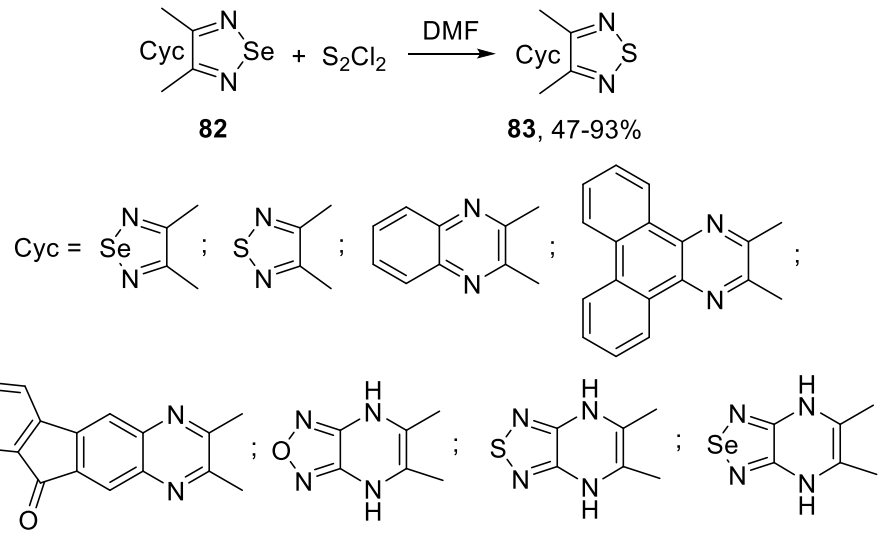
Scheme 44. Synthesis of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **66** from 3,4-diamino- **79** and 3-nitro-4-amino-1,2,5-oxadiazoles **68**.

Similar processes were found for the reactions of piperazinooxadiazoles: in all cases, tricyclic bis([1,2,5]thiadiazolo)[3,4-*b*;3',4'-*e*]pyrazine **81** was isolated in moderate to high yields (Scheme 45).[47,58] Surprisingly, other unfused 1,2,5-oxadiazoles, 2,1,3-benzooxadiazoles, and 5,6-disubstituted [1,2,5]oxadiazolo[3,4-*b*]pyrazines in these conditions did not react with S_2Cl_2. An analysis of these results led the authors to the conclusion that the successful conversion of 1,2,5-oxadiazoles to 1,2,5-thiadiazoles requires the presence of one or two NH_2 or NH groups attached directly to the oxadiazole ring in the molecule.



Scheme 45. Synthesis of bis([1,2,5]thiadiazolo)[3,4-*b*;3',4'-*e*]pyrazine **81**.

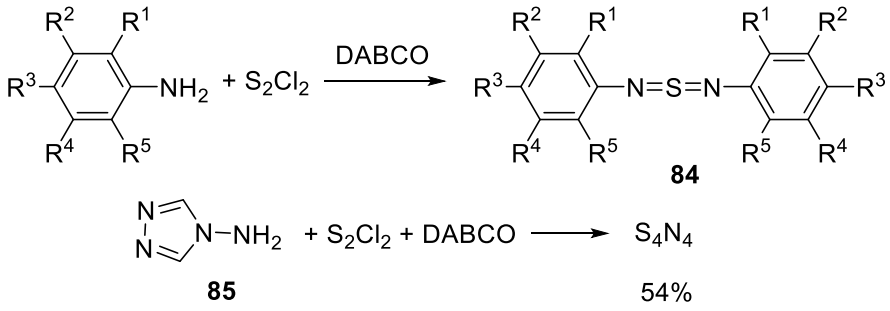
The reaction of replacing a chalcogen atom with a sulfur atom under the action of disulfur dichloride turned out to be applicable for 1,2,5-selenadiazoles as well. The reaction of 1,2,5-selenadiazoles **82** fused with electron-withdrawing heterocycles such as 1,2,5-thiadiazole, 1,2,5-selenadiazole, quinoxaline, etc., with S_2Cl_2 in DMF led to the corresponding mono- and bis(1,2,5-thiadiazoles) **83** in moderate to good yields (Scheme 46).[58] Using an excess of disulfur dichloride for heterocycles containing two selenadiazole rings, both selenium atoms were replaced by sulfur atoms to form bis(1,2,5-thiadiazoles). 2,1,3-Benzoselenadiazole and 3,4-diphenyl-1,2,5-selenadiazole do not react with disulfur dichloride in organic solvents even under extreme conditions (boiling in acetonitrile or heating in DMF at 100 °C for 10 h) and were isolated from reaction mixtures in almost quantitative yields. Apparently, the key condition for the successful replacement of a selenium atom in a heterocycle with a sulfur atom is the presence of a strong electron-withdrawing heterocycle attached to selenadiazole.



Scheme 46. Synthesis of mono- and bis(1,2,5-thiadiazoles) **83** from the corresponding 1,2,5-selenadiazoles **82**.

6.5. Synthesis of sulfur diimides

Direct and efficient synthesis of symmetrical sulfur diimides from commercial anilines and disulfur dichloride was developed by Rakitin et al. It was shown that treatment of anilines with a mixture of S_2Cl_2 and DABCO in chloroform followed by reflux led to the formation of symmetrical sulfur diimides **84** in high yields (Scheme 47).[59] 4*H*-1,2,4-Triazol-4-amine **85** unexpectedly gave tetrasulfur tetranitride under these conditions in moderate yield.



Scheme 47. Synthesis of diarylsulfur diimides **84** from anilines.

7. Conclusions

The reactions described show that the methodology developed by Professor Rees represents a rapid and convenient route to sulfur-containing heterocyclic systems, which in many cases are difficult or impossible to obtain using traditional methods. As a result, these unique heterocycles have a number of features in contrast to carbon-containing compounds, and have promising properties in both the pharmaceuticals and agrochemical fields,[13,60,61] as well as compounds with interesting physical properties in optoelectronics,[62-64] magnetism, and electrical conductivity.[65,66] All the described reactions show that disulfur dichloride is an important reagent for the synthesis of heterocycles with different numbers of sulfur atoms, or even without sulfur atoms. An important feature of this reagent is that it can add to a molecule not only two sulfur atoms,

as one might expect, but also one, three, four, five and even more atoms, and the structure of the final compound often depends on its stability. The wide range of new polysulfur-nitrogen heterocycles, their interesting characteristics, and rapid synthesis methods from readily available materials make this strategy very promising. Professor Rees's role in the development of disulfur dichloride chemistry cannot be overestimated.

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Thierry Besson was born in Dieppe (Fr) (1964) and is currently Professor of Medicinal Chemistry in the Pharmacy Department at the University of Rouen Normandie, France. He obtained his doctorate (1989-1992) at the University of Orléans under the supervision of Professor Gérald Guillaumet. He first met C.W. Rees at the BOSS congress in 1992 and joined Imperial College London in January 1993 for nine months, until he was appointed Assistant-Professor in a newly opened university on the French Atlantic coast (La Rochelle). This post-doctoral experience was the starting point of a fruitful collaboration that led to the co-authorship of 19 papers, most of them including the contribution of Dr Valérie Thiéry, who joined Besson's group after her post-doc with CWR. His research work focuses on the use of Appel's salt (4,5-dichloro- 1,2,3-dithiazolium chloride) for the microwave-assisted synthesis of various S,N-containing compounds, with a particular focus on bioactive thiazole-fused heterocyclic systems inspired by marine and terrestrial alkaloids.

Lidia Konstantinova graduated at M. V. Lomonosov Moscow Institute of Fine Chemical Technology in 1972. She received her PhD in 1994 and her Doctor of Science Degree in 2009 in the N.D. Zelinsky Institute of Organic Chemistry, where she is working since 2009 as a Main Researcher. She collaborated with Professor C.W. Rees from 1997 up to his death in 2006 at Imperial College (London, UK). She has published with Professor C.W. Rees 18 scientific papers and reviews. Her scientific interests include the synthesis of polysulfur-nitrogen heterocyclic systems.

Panayiotis A. Koutentis was born in Bristol (1969) in the United Kingdom and is Professor in Organic Chemistry at the University of Cyprus, Nicosia. He obtained his bachelor (1992) and doctorate (1997) degrees at Imperial College London working under the supervision of Professor Charles W. Rees. This was followed by a short stay with Professor Roger Alder, University of Bristol (1997), postdoctoral work with Professor Fred Wudl (1997-8), University of California, Los Angeles (UCLA), and with Professor Robert Haddon (1999) at the University of Kentucky, Lexington. His research activities focus on the synthesis and reactivity of novel and unusual S,N-heterocyclic compounds and the design and synthesis of organic magnets based on radical and diradical polyazaheterocyclic systems.

Oleg Rakitin was born in 1952, in Moscow. Graduated at M. V. Lomonosov Moscow State University in 1974. He received his PhD in 1980 and his Doctor of Science Degree in 1992 in the N.D. Zelinsky Institute of Organic Chemistry, where he is working since 1995 as a Head of the laboratory. He collaborated with Professor C.W. Rees from 1992 up to his death in 2006 at Imperial College (London, UK) being awarded a Royal Society Kapitza Fellowship a Royal Society of Chemistry, three Journals Grant for International Authors and four Royal Society Joint Projects. He has published with Professor C.W. Rees 38 scientific papers, reviews and patents. His scientific interests include the synthesis and chemistry of nitrogen and sulfur heterocyclic compounds.

Sivaprasad Sivadasan was born in India (1967) and emmigrated to London, UK at the age of 10. He graduated in chemistry (BSc.) from North London university in 1989 and worked at GlaxoSmithKline, (1989-1990). He left GSK to do is PhD at Imperial College London and obtained his doctorate (1990-1993) under the supervision of Professor Charles W. Rees. After his graduation he worked at Merck Generics (1994-1998) as a development chemist. In 1998 he moved to Sweden to work for AstraZeneca (AZ) as Senior Scientist. He left AZ in 2013 as Global Stability Manager. Since then, he has obtained a teachers degree from Stockholm university (2016-2018), Siva is a high school teacher, teaching chemistry and mathematics, currently working in a juvenile detention center.

Valérie Thiéry was born in 1968, in Orléans (France). She received her master and PhD degree in organic chemistry (University of Orléans, France) under the supervision of Professor Guillaumet. After a post-doctoral fellow position in the group of Pr. Charles W. Rees at Imperial College of London in 1995-1996, she joined La Rochelle University as assistant professor in 1996 and since 2007 she is Full Professor of organic chemistry (La Rochelle University, LIENSs laboratory, France). Her current research interests include: medicinal chemistry applied to kinase inhibitors, heteroatomic chemistry (N,S), microwave assisted methodologies and eco-extraction processes, and valorization of marine or terrestrial alkaloids in cancerology.

Tomás Torroba was born in Valladolid, Spain, 1956, PhD from the University of Valladolid, 1982, under the supervision of Prof. Angel Alberola, current position as Professor of Organic Chemistry, Department of Chemistry, University of Burgos since 1998. Assistant in the Department of Organic Chemistry of the Faculty of Science, University of Valladolid, 1978-1982, Lecturer in the Department of Organic Chemistry, Faculty of Veterinary Medicine, University of Extremadura, 1983-1998, Dean of the Faculty of Science, University of Burgos, 2000-2004. Main research topics: Sulfur-Nitrogen Heterocyclic Compounds, under the supervision of Professor Charles W. Rees, 21 articles from 1993 to 2001, Multicomponent Reactions with Dr. S. Marcaccini, Univ. Florence, Italy, 38 articles from 1987 to 2013, nowadays working in Chemical Sensors and Supramolecular Chemistry, a total of 140 articles throughout his academic career (WoS), h-index: 32.