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Design of sulfur heterocycles with sulfur monochloride: synthetic possibilities and prospects

Lidia S. Konstantinova and Oleg A. Rakitin*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: orakitin@ioc.ac.ru

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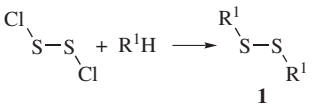
Sulfur monochloride is an important reagent in the synthesis of heterocycles with various numbers of sulfur atoms. The classification is proposed for the selective synthesis of highly interesting sulfur heterocyclic systems from acyclic fragments containing C–H, C=N, C≡N and C–Cl bonds.

Heterocyclic chemistry is an important part of organic chemistry. Cyclic compounds containing sulfur atoms are a high proportion of the biologically significant natural and widely used synthetic pharmaceutical and agrochemical products, and also more recently discovered as compounds with interesting physical properties. Although there are many methods to introduce sulfur atoms into organic molecules, there is a lack of the methods to construct sulfur heterocycles with inclusion of sulfur atoms in the molecule. The preparation of sulfur heterocycles by conventional ways has usually implied many synthetic steps and expensive starting materials. Sulfur monochloride (S_2Cl_2), a commercially available reagent of the sulfur halide series, is considered as one of the best sulfur transfer reagents in heterocyclic synthesis.[1] A few decades ago, a novel strategy for the synthesis of complex sulfur–nitrogen heterocycles from simple (often commercially available and cheap) organic substrates and sulfur monochloride was proposed. This idea is based on the complex reactivity of sulfur monochloride. Usually, this compound is considered as a reactive electrophile,[2] but sulfur monochloride has also chlorinating, oxidative and sulfur-transfer properties. Sulfur monochloride plays an important role with its ability to cyclize organic substances into a heterocyclic ring. Numerous attempts have been undertaken to prepare a sulfurating reagent with carbon, nitrogen, oxygen or sulfur leaving groups to replace the chlorine atom (Scheme 1).[3] However, disulfides **1** do not substitute for sulfur monochloride, and so S_2Cl_2 has ranked among the best sulfur transfer reagents in inorganic and organic chemistry.



1

R^1 = Ar, NR^2_2, OR^2, SR^2

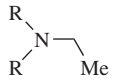
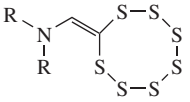
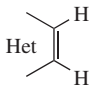
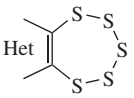
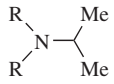
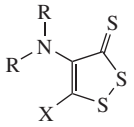
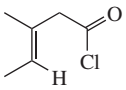
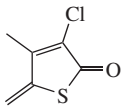
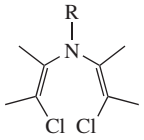
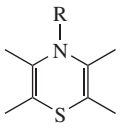
Scheme 1

The main feature of this reagent is the addition of two sulfur atoms between carbon–carbon or carbon–heteroatom bonds to produce heterocycles with two bound sulfur atoms. Yet, often it adds one, three, four, five, six and even more sulfur atoms, sometimes bonded together, sometimes not. These syntheses do not have analogs in the literature; therefore, we cannot initially plan intentional construction of sulfur heterocycles. For a long time, we investigated new reactions; in the course of this study, we found that chemical substances containing activated C–H bonds, nitrile and imino groups are involved in the reaction with S_2Cl_2. Retrosynthetic analysis of these and known transformations showed that the quantity of sulfur atoms in the formed heterocycle and its size depend mainly on the structure of starting substrate and the stability of the final heterocyclic compound. We divided all substrates on the quantity of atoms, which remains in the heterocycle (*A*), and found that the size of the final heterocycle and the quantity of sulfur atoms depend strictly on *A*. This dependence is summarized in Table 1.

Lidia Konstantinova was born in 1949 in the Kemerovo region, Russia. She graduated from the M. V. Lomonosov Moscow Institute of Fine Chemical Technology and then started work at the N. D. Zelinsky Institute of Organic Chemistry where she is a Senior Researcher at the present time. In 1994 she received her Ph.D. degree for synthesis and investigation of properties of new heterocyclic 1,2,5-oxadiazoles. Since 1995 her research interests are in the synthesis of polysulfur-nitrogen heterocyclic systems, including pentathiepins condensed with other sulfur and nitrogen heterocycles.

Oleg Rakitin was born in 1952 in Moscow. He graduated from M. V. Lomonosov Moscow State University in 1974. He was a Junior Researcher, Senior Researcher, and since 1995 Head of the Laboratory at the N.D. Zelinsky Institute of Organic Chemistry. He received his Ph.D. in 1980 and his Doctor of Science in 1992. He has spent a few months in the laboratory of Professor C.W. Rees at Imperial College (London, UK) being awarded a Royal Society Kapitza Fellowship of the Royal Society of Chemistry, three Journals Grant for International Authors and four Royal Society Joint Projects. He has been a Fellow of the Royal Society of Chemistry since 1999. His scientific interests include the synthesis and chemistry of nitrogen and sulfur heterocyclic compounds, particularly polysulfur heterocycles.

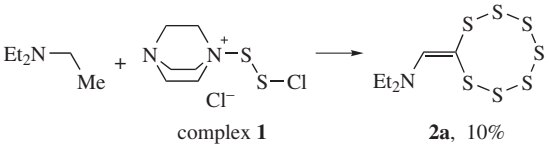
Table 1 Dependence of the size of the heterocycle and the quantity of sulfur atoms in it on *A*.

Quantity of atoms in starting substrate which remains in the heterocycle (*A*)	Examples of starting substrates	Quantity of sulfur atoms inserted into the heterocycle	Examples of heterocycles formed
1		7	
2		5	
3		2	
4		1	
5		1	

Let us consider every type of reactions in detail.

A = 1. *Synthesis of 1,2,3,4,5,6,7-heptathiocanes*

As a rule, usually, more than one carbon atom in a substrate is included in the transformation. The only known example is the reaction of tertiary *N*-ethylamines with complex **1** produced from S_2Cl_2 and DABCO.[4] If triethylamine treated with this complex, heptathiocane **2a** was isolated in 10% yield (Scheme 2).[5] The structure of **2a** was confirmed by X-ray analysis (Figure 1). The heptathiocane ring has the expected crown conformation close to the conformation of the most stable elemental sulfur.



complex **1** **2a**, 10%

Scheme 2

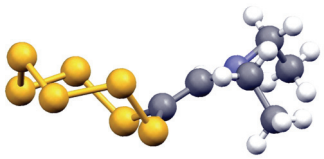
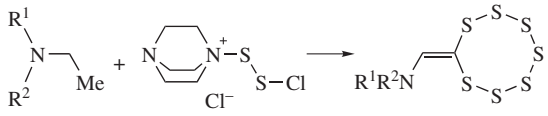


Figure 1 X-ray structure of 8-(*N*,*N*-diethylaminomethylene)-1,2,3,4,5,6,7-heptathiocane **2a**.

Given that these are reactions of the ethyl group, Et_3N should be a favoured substrate; the same reactions were observed with other tertiary *N*-ethylamines but in lower yields. Diethyl *n*-propylamine, ethyldiisopropylamine, benzyldiethylamine, dibenzylethylamine, and *N*-ethylpiperidine all gave corresponding heptathiocanes **2b–f** (3–10%) (Scheme 3). Whilst the yields of hepthiocanes **2** were mostly low, they are readily prepared in one pot from cheap starting materials.[5]



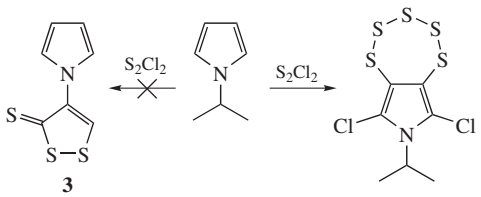
complex **1** **2b–f**, 3–10%

b R^1 = Et, R^2 = Pr
c $R^1 = R^2 = Pr^i$
d R^1 = Et, R^2 = Bn
e $R^1 = R^2$ = Bn
f $R^1 + R^2 = (CH_2)_4$

Scheme 3

A = 2. *Synthesis of 1,2,3,4,5-pentathiepins*

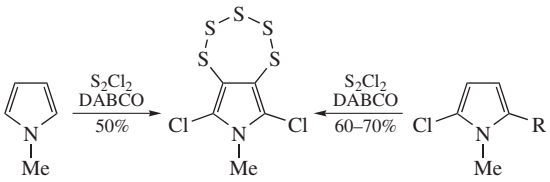
If in the reaction with S_2Cl_2 two neighbouring carbon atoms are involved, fused 1,2,3,4,5-pentathiepins are formed.[6] We have found that the treatment of simple nucleophilic heterocycles like pyrroles and thiophene, and their tetrahydro derivatives with sulfur monochloride and DABCO provides a simple one-pot synthesis of mono and bis(pentathiepins). Actually, this new transformation was discovered accidentally when we investigated the reaction of *N*-isopropylpyrrole with sulfur monochloride trying to obtain *N*-1,2-dithiole-3-thione **3**. We found that a pyrrole ring is more reactive than the isopropyl group (Scheme 4). This unusual reaction could thus provide an attractive route to fused pentathiepins, and we studied this reaction systematically to find the best reaction conditions and to explore its scope.



3

Scheme 4

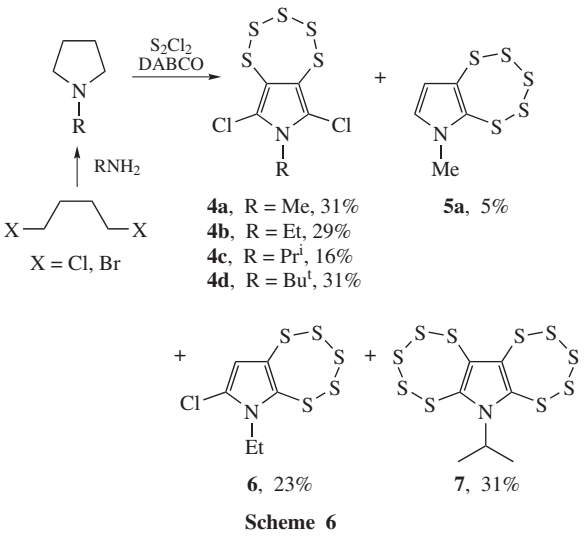
The reaction of *N*-methylpyrrole with sulfur monochloride and DABCO gave dichloropyrrolopentathiepin **4a** under best conditions in 50% yield. In the formation of **4a** from *N*-methylpyrrole, a pentathiepin ring has been fused to the pyrrole ring and both pyrrole α-positions were chlorinated. It is not surprising that 2,5-dichloro- and 2-chloropyrroles gave in the same way pyrrolopentathiepin **4a** even in higher yields (Scheme 5).[7]



4a R = H, Cl

Scheme 5

Since S_2Cl_2 could also, in principle, oxidize pyrrolidine to pyrrole, we studied the same reaction of *N*-alkyl derivatives of pyrrolidine, which are readily available from the reaction of dichloro- or dibromobutanes and corresponding amines. *N*-Methyl-, *N*-ethyl, *N*-isopropyl- and *N*-*tert*-butylpyrrolidines all gave the corresponding *N*-alkyl dichloropentathiepinopyrrole **4** as the main product in low to moderate yield (16–31%). Additionally, *N*-methylpyrrolidine afforded a small amount (5%) of unchlorinated compound **5a** with the pentathiepin ring fused across the 2,3-pyrrole bond, *N*-ethylpyrrolidine – monochlorinated product **6**, and isopyrrolidine – bis(pentathiepin) **7**, which is the first bis(pentathiepin) reported (Scheme 6).[7]



Scheme 6

The structure of **4a** was confirmed by X-ray analysis (Figure 2). Pentathiepin ring is characterized by the expected chair-type conformation. The geometrical parameters are close to those in the previously investigated pentathiepins.

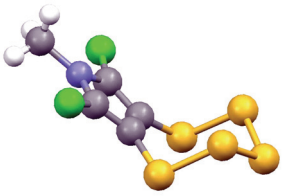
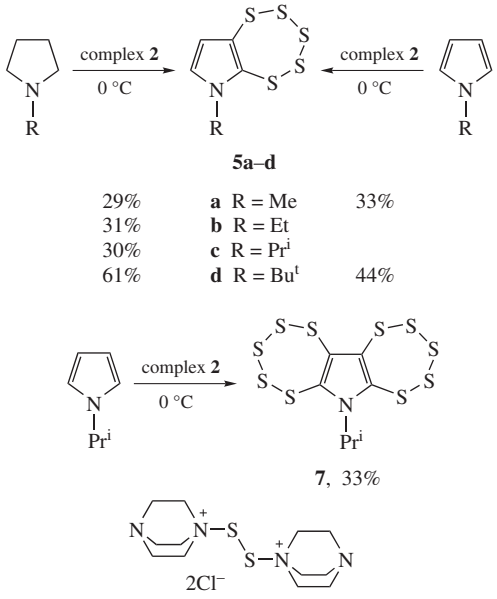


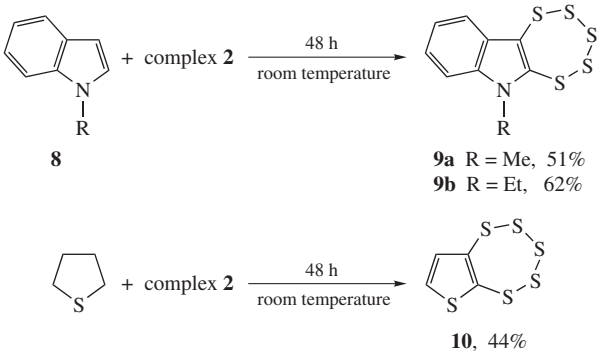
Figure 2 X-ray structure of 6,8-dichloro-7-methyl-7*H*-[1,2,3,4,5]pentathiepino[6,7-*c*]pyrrole **4a**.

Sulfur monochloride acted simultaneously as a sulfurating (formation of pentathiepin ring) and chlorinating (chlorination of pyrrole ring) agent. Obviously, complex **2** prepared from sulfur monochloride and two equivalents of DABCO should exhibit mainly sulfurating rather than chlorinating ability, and we used it in the reaction with nucleophilic heterocycles. Indeed, the reaction of all tested *N*-alkylpyrrolidines with complex **2** gave selectively *N*-alkylpentathiepinopyrroles **5** in moderate yields; no chlorinated products were detected in these reactions. The same products were obtained from *N*-alkylpyrroles, but in that case it is necessary to use a lower amount of complex **2** to get selective process and the yields of pentathiepins were comparable with those obtained from pyrrolidines. *N*-Isopropylpyrrole gave selectively bis(pentathiepin) **7** (Scheme 7).[4]



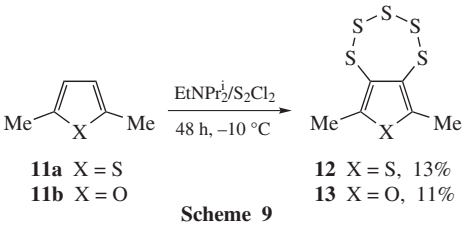
Scheme 7

We tried to spread these reactions to other heterocycles. *N*-Alkylindoles **8** reacted, as pyrroles, to give pentathiepins **9** in moderate yields.[4] Tetrahydrothiophene also afforded corresponding pentathiepin **10** in a good yield (Scheme 8).[4] Unfortunately, more aromatic heterocycles such as thiophene, benzothiophene and furan did not react with complex **2**.



Scheme 8

Thienopentathiepin **12** and pentathiepinofuran **13** were synthesized by the reactions of 2,5-dimethylthiophene **11a** and 2,5-dimethylfuran **11b** with S_2Cl_2 and *N*-ethyldiisopropylamine in chloroform at low temperature, although in low yields (Scheme 9).[8]

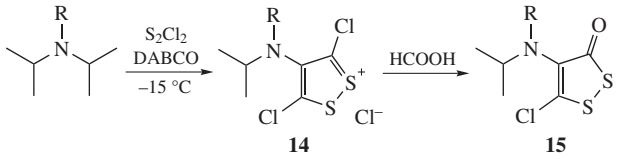


Scheme 9

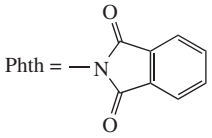
A = 3. *Synthesis of 1,2-dithioles and 1,2,3-dithiazoles*

If two carbon atoms, or a carbon and nitrogen separated by one carbon are present in the substrate, two sulfur atoms are inserted into the structure of the molecule. This is the most frequently observed reaction type because in this case it is not necessary to cut one sulfur atom from sulfur monochloride or add sulfur atoms to five or seven ones as shown above. We have found that the *N*-isopropyl group in tertiary amines can be transformed into a 1,2-dithiole ring. The main condition for the successful synthesis of monodithioles is a low temperature (–15 °C). In agreement with the proposed mechanism, the combination of an excess of sulfur monochloride over tertiary amine and the presence of DABCO is expected to yield dichlorodithiolium salt **14**, which in the absence of a strong base gives 5-chlorodithiol-3-one **15** (Scheme 10).[9] Our synthesis of 1,2-dithiol-3-ones under unusually mild conditions is exclusive among known relevant methods and provides new wide possibilities for the study of this promising chemical class.

However, at room temperature, further reactions involving the second isopropyl group can proceed. Previously, we discovered that *N*-ethyldiisopropylamine, initially used as an 'inert' base, reacted with sulfur monochloride and DABCO by a single step reaction to give an unexpected and novel multisulfur-nitrogen system, tricyclic bis(dithiolo)thiazine dithione **16** (Scheme 11).[10] In this one-pot conversion of *N*-ethyldiisopropylamine, a new heterocyclic system was obtained by mixing two simple commercially available compounds in high yield under mild condi-



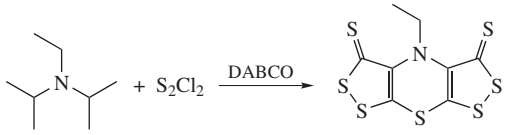
14 **15**



a R = CH_2CH_2Phth, 67%
b R = CH_2CH_2Cl, 45%
c R = $CH_2CH_2N_3$, 45%
d R = $CH_2CH_2CO_2Et$, 55%
e R = CH_2CH_2SPh, 72%
f R = CH_2CH_2CN, 47%
g R = $CH_2CH_2SO_2Ph$, 64%
h R = CH_2CH_2OCHO, 45%
i R = CH_2Ph, 48%

Scheme 10

tions; besides 14 isopropyl C-H bonds were replaced by 10 C–S and two C–C double bonds, while the ethyl group remained intact.



16, 40%

Scheme 11

We called compound **16** 'Scorpionine' and it adopts 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 (Figure 3).

This was a remarkable reaction; it turned out that by addition of various substances to these two compounds, *N*-ethyldiisopropylamine and sulfur monochloride, 16 compounds can be obtained (Scheme 12). Some of these one-pot conversions proceed selectively and in high yields.[11–15]

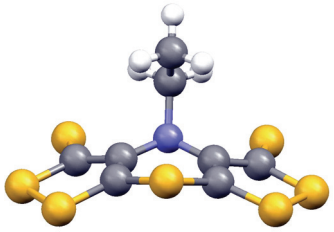
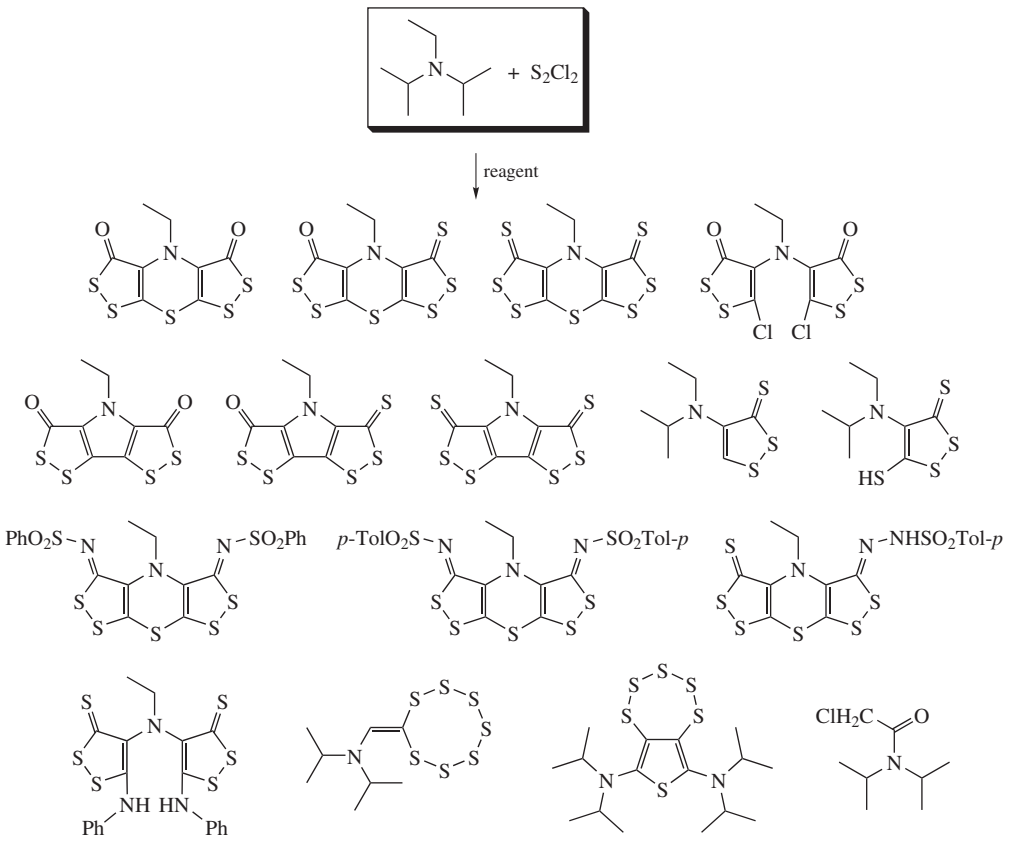


Figure 3 X-ray structure of 4-methyl-3*H*,4*H*,5*H*-bis[1,2]dithiolo[3,4-*b*:4′,3′-*e*]-[1,4]thiazine-3,5-dithione **16**.

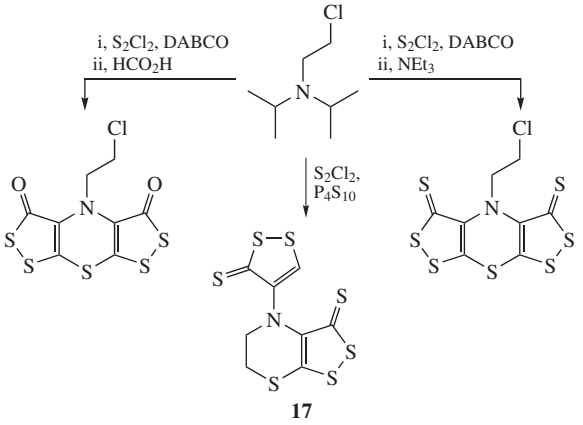
N-(2-Chloroethyl)diisopropylamine constitutes a very special case. Its reaction with sulfur monochloride in the presence of formic acid or triethylamine gives tricyclic bis[1,2]dithiolo[1,4]-thiazine derivatives (Scheme 13). The course of the reaction is completely changed by the addition of phosphorus pentasulfide at the last stage of the reaction. In this case, the chlorine atom is replaced by sulfur both in the lateral chain and in the intermediate salt, thus giving a new [1,2]dithiolo[1,4]thiazine ring system.[16] This new compound **17** has shown a notable antitumor activity against breast cancer cells at a low concentration (10^{-4} mol dm^{-3}).

Nitrogen heterocycles containing methyl group and C–H group in *ortho* positions are structurally similar to the *N*-isopropyl group. Treatment of N-substituted 2-methyl-1*H*-indoles **18** with S_2Cl_2 and DABCO in chloroform gave corresponding [1,2]dithiolo-[4,3-*b*]indole-3(4*H*)-thiones **19** by the addition of triethylamine in high yield (Scheme 14).[17] The best yields were achieved when complex **2**, which is a more selective sulfurating agent, was used in this reaction.

An important example of five-membered heterocycles obtained from three atom moiety ($A = 3$) is the synthesis of 1,2,3-dithiazoles from substituted ethanone oximes.[18] Various 4-substituted 1,2,3-dithiazolium chlorides have been prepared from the reaction of ethanone oximes with sulfur monochloride and pyridine in acetonitrile. These salts are unstable, and they were converted

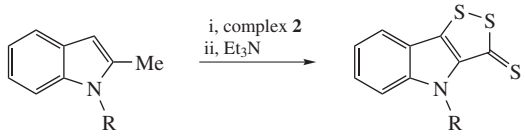


Scheme 12



17

Scheme 13

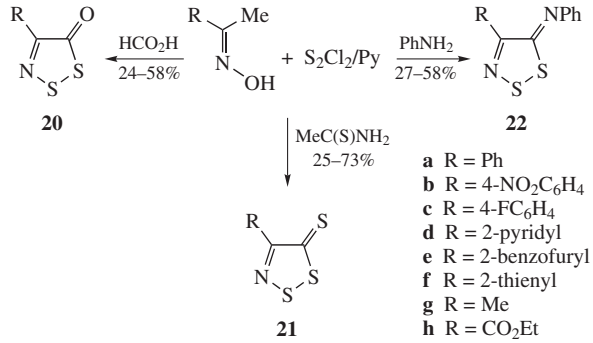


18

19a R = Me, 94%
19b R = Et, 56%
19c R = Pr^i, 66%
19d R = Bn, 70%

Scheme 14

in situ into stable 1,2,3-dithiazole derivatives **20**–**22** by treatment with corresponding nucleophiles (formic acid, thioacetamide and aniline, respectively) in high to moderate yields (Scheme 15).



20 **22**

21

a R = Ph
b R = 4-$NO_2C_6H_4$
c R = 4-FC_6H_4
d R = 2-pyridyl
e R = 2-benzofuryl
f R = 2-thienyl
g R = Me
h R = CO_2Et

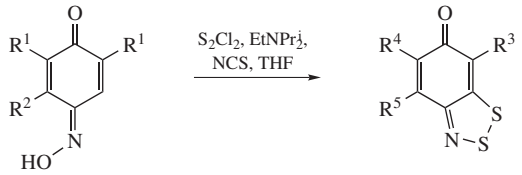
Scheme 15

Fused 1,2,3-dithiazoles can be easily obtained in the reaction of cyclic oximes and sulfur monochloride.[1] For example, 6*H*-1,2,3-benzodithiazol-6-ones **23** were prepared from *p*-benzoquinone-4-oximes, S_2Cl_2, *N*-ethyldiisopropylamine and NCS (Scheme 16).[19] Ring chlorination occurred and 2,6-substituents were retained in the products except for the *tert*-butyl group, which was replaced by chlorine. 1,4-Naphthoquinone 4-oxime and 1,2-naphthoquinone 2-oxime similarly gave dithiazole derivatives **24** and **25**.

In all the cases when *A* = 3, planar sulfur heterocycles (1,2-dithioles or 1,2,3-dithiazoles) were formed; they are more stable than other heterocycles with three or more sulfur atoms in the ring.

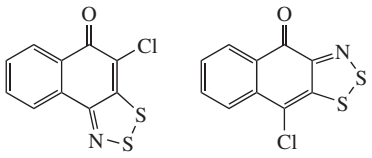
A = 4. *Synthesis of fused thiophenones*

There is an example of such transformations. Treatment of inden-3-ylacetic acid with S_2Cl_2, *N*-ethyldiisopropylamine and NCS afforded, along with other products, 3,8-dichloro-2*H*-indeno[2,1-*b*]thiophen-2-one **26** with extensively delocalized structure, which has been confirmed by X-ray crystallography (Figure 4).[20] The formation of fused thiophenone **26** is unprecedented in S_2Cl_2 reactions. Since S_2Cl_2 has been shown to



23

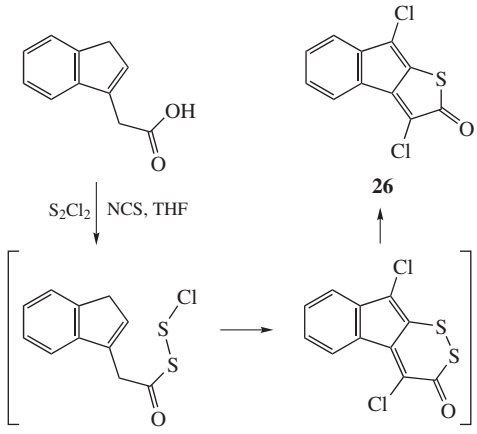
R^1 = H, Me, Pr^i, Bu^t, Cl
R^2 = H, Me
R^3 = Me, Pr^i, Bu^t, Cl, $ClCH_2$
R^4 = Me, Pr^i, Cl
R^5 = H, Me, Cl



24 **25**

Scheme 16

convert carboxylic acids into acid chlorides,[20] it is possible that some intermediate in this transformation (such as **27**) could be diverted by cyclization ultimately to form thiophene **26** by extrusion of sulfur from intermediate **28** (Scheme 17). The driving force of the last stage is the formation of planar and stable thiophenone ring.



26

27 **28**

Scheme 17

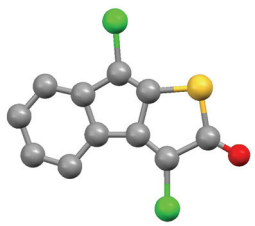
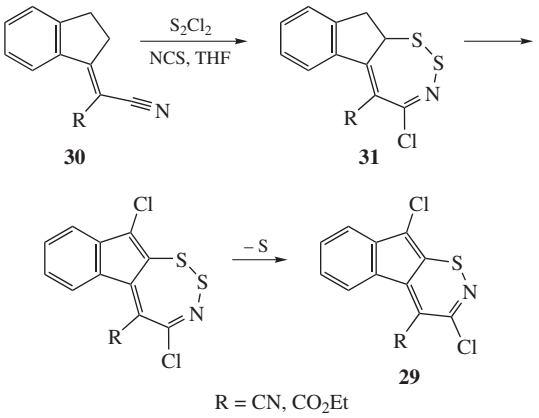


Figure 4 X-ray structure of 3,8-dichloro-2*H*-indeno[2,1-*b*]thiophen-2-one **26**.

A = 5. *Synthesis of 1,2- and 1,4-thiazines*

We have discovered few reactions, which can be referred to this type. The first one is the formation of 3,9-dichloroindeno-[1,2-*e*][1,2]thiazines **29** from 1-substituted 1-(cyanomethylene)-indanes **30** by treatment of the latter with S_2Cl_2, *N*-ethyldiisopropylamine and NCS in THF at 0 °C for three days.[20] A reasonable pathway for this conversion is given in Scheme 18. Addition of S_2Cl_2 to a nitrile group[21] followed by cyclization onto an activated allylic position would give dithiazepine **31**; standard chlorination–dehydrochlorination followed by sulfur extrusion (*cf.* ref. [22]) would then give planar and formally aromatic products **29** (Figure 5).



Scheme 18

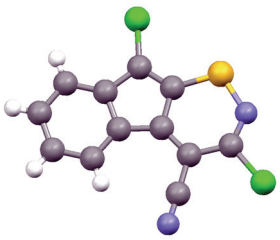
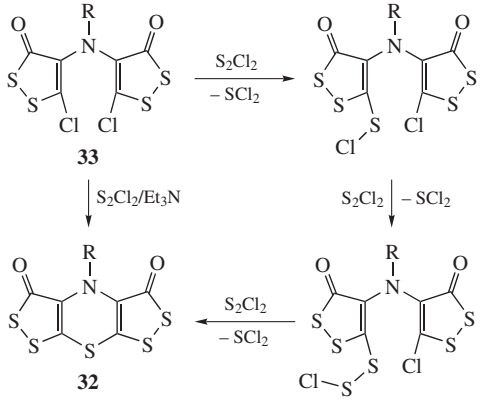


Figure 5 X-ray structure of 3,9-dichloroindeno[1,2-*e*][1,2]thiazine-4-carbonitrile **29**.

Another example for $A = 5$ is the formation of bis(dithiolo)thiazines **32** from bis(dithiolyl)amines **33**.[23] Investigation of the reaction of *N*,*N*-bis(5-chloro-3-oxo[1,2]dithiol-4-yl)amines **33** with sulfur monochloride and a base showed that DABCO was inert in this reaction, which was not surprising because bicyclic compounds **33** were obtained in the presence of DABCO.[12,23] Treatment of **33** with S_2Cl_2 and triethylamine in chloroform for three days at room temperature followed by heating under reflux for 3 h gave bis(dithiolo)thiazines **32** in high yields (Scheme 19).



a R = Et, 93%
b R = CH_2CH_2Phth, 95%
c R = CH_2CH_2CN, 80%
d R = $CH_2CH_2CO_2Et$, 82%
e R = CH_2Ph, 79%
f R = CH_2CH_2SPh, 87%

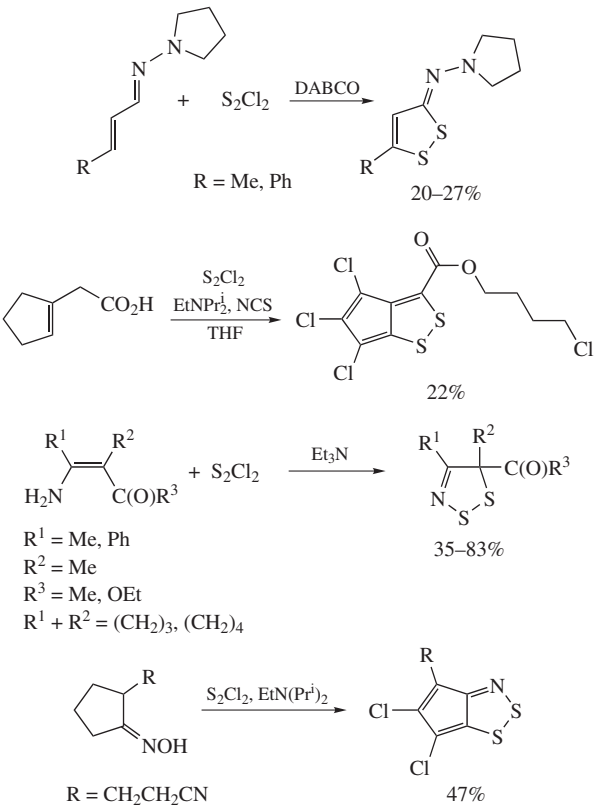
Scheme 19

The novelty of this transformation is in replacing chlorine atoms by sulfur in the reaction with electrophilic sulfur monochloride and its mixtures with tertiary amines. The key steps may be explained by the addition of sulfur monochloride to the C–Cl bond with further extrusion of SCl_2 from intermediates (Scheme 19), as stated for polysulfur chain extension in the formation of pentathiepins.[7] The described experimental procedures may serve as an efficient basis for new syntheses of sulfur compounds from readily available chloro derivatives.

Thus, we have proposed a new classification for the synthesis of sulfur-containing heterocycles from organic substrates and sulfur monochloride. The structure of the compounds obtained and the quantity of sulfur atoms included in the heterocyclic ring is directly depended on the quantity of atoms in the substrate, which remained in the same cycle. If there are two or more reactive groups in the starting molecule, several transformations can proceed simultaneously or one after another. The typical example is the synthesis of tricyclic bis(dithiolo)thiazine **16** from *N*-ethyldiisopropylamine (Scheme 11): three heterocycles – two 1,2-dithioles ($A = 3$) and 1,4-thiazine ($A = 5$) were formed from isopropyl and diethylamino fragments, respectively.[11]

Depending on the reaction conditions, different groups may be involved in the reaction with sulfur monochloride. For example, the same *N*-ethyldiisopropylamine in the reaction with S_2Cl_2 and DABCO at room temperature gave bis(dithiolo)thiazine **16** (Scheme 11), whereas at 0 °C with complex **1** – heptathiocane **2c** (Scheme 3). It is important that the reaction may be directed to the desired way and these products can be obtained selectively.

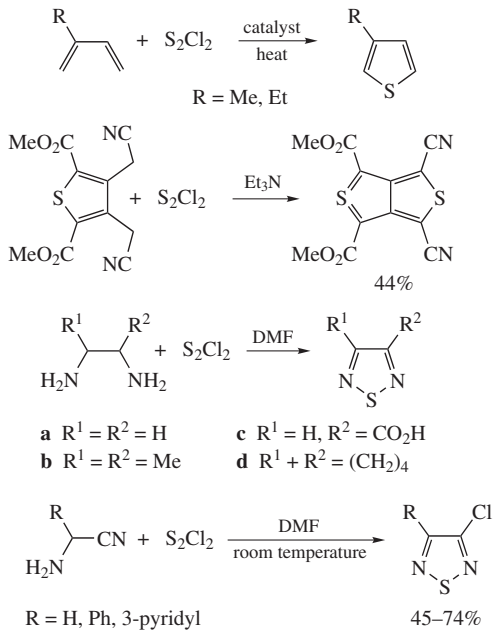
Having all the literature data of the use of sulfur monochloride in the synthesis of heterocyclic compounds collected and reviewed,[1] we could check how known reactions of S_2Cl_2 are in accordance with our classification. In fact, practically all syntheses of sulfur heterocycles from S_2Cl_2 may be included in one or another type shown in Table 1. For example, many syntheses of 1,2-dithioles and 1,2,3-dithiazoles from substrates with three atoms included in a heterocycle ($A = 3$) are known;[24–27] some of them are shown in Scheme 20.



Scheme 20

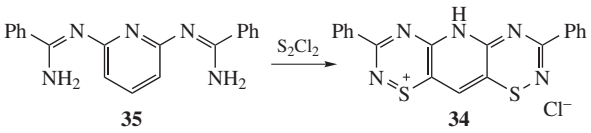
Thiophenes and 1,2,5-thiadiazoles are often prepared from acyclic C–C–C–C and N–C–C–N groupings ($A = 4$), respectively (Scheme 21).[28–31]

Finally, reactions with five atom groupings ($A = 5$) may be completed by the synthesis of bis(thiadiazinyl)pyridinium salt **34** from bifunctional amidine **35** and sulfur monochloride

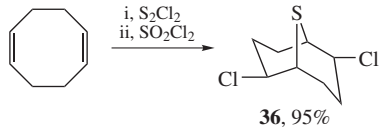


Scheme 21

(Scheme 22)[32] and the synthesis of 2,6-dichloro-9-thiabicyclo-[3.3.1]nonane **36** containing a six-membered tetrahydrothiopyran ring from 1,5-cyclooctadiene and sulfur monochloride (Scheme 23).[33]



Scheme 22



Scheme 23

In conclusion, the reactions discovered show that sulfur monochloride is an important reagent in the synthesis of heterocycles with various numbers of sulfur atoms. The classification proposed allows one to plan the selective preparation of highly interesting sulfur heterocyclic systems from acyclic fragments containing C–H, C=N, C≡N and C–Cl bonds and to develop rapid synthetic methods from easily available materials.

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