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Introduction

Heterocyclic chemistry is a vast and important subject. About half the ten million or so compounds recorded in Chemical Abstracts are heterocyclic, as are a high proportion of the most biologically significant natural products and the most widely used synthetic pharmaceutial and agrochemical products. Indeed, so many different heterocyclic ring systems have now been explored that it is no longer easy to find totally new structural types from which to fashion new and useful materials. We have recently discovered a family of such structures however, at the borderline between organic and inorganic chemistry, which are characterised by having an unusually high ratio of heteroatoms (sulfur and nitrogen) to carbon.

Organic heterocyclic rings with a high proportion of heteroatoms are relatively rare; they are usually inaccessible and when they are formed they tend to be unstable. It seemed to us that a possible general approach to more stable heterocyclic structures of this type would be to start with stable inorganic rings, composed wholly of non-carbon atoms, and to introduce carbon atoms into the rings, one at a time. If the model rings were sufficiently stable, the new rings might retain enough of this stability to be useful. In principle, one could apply this idea to any part of the Periodic Table where heterocyclic compounds exist, but we decided to start with the cyclic sulfur nitrides, the cyclothiazenes. We chose these because a number of examples are known, with varying ring sizes (Fig. 1) [1], including delocalised structures where the guiding concept of aromaticity seems to apply quite well, and because sulfur and nitrogen are still two of the three most important heteroatoms in organic chemistry.

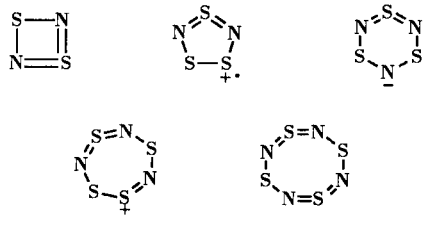


Figure 1

Since each sulfur atom formally contributes two electrons to the delocalised orbitals, as in thiophene, the rings are usually electron rich [2]. Thus the sulfurdiimide group has 4 π electrons distributed over three atoms and the S_3N_2 group has 8 π electrons over five atoms (Fig. 2). The ultimate structure in this sequence is polysulfur-nitride, an anisotropic "metal" which is highly conducting and, at very low temperatures, superconducting [3].

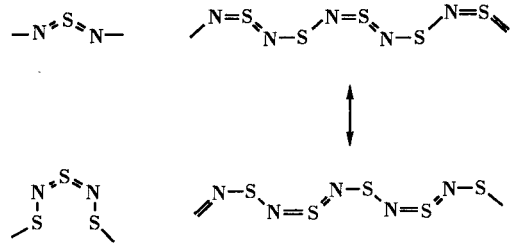


Figure 2

The best known and most widely studied of these binary sulfur-nitrogen compounds is tetrasulfur-tetranitride, S_4N_4, and this provided the starting point for our work, both conceptually and experimentally. It has a completely delocalised structure, but is not planar since it would then be a 12 π antiaromatic system. The four nitrogen atoms are planar, bisecting the tetrahedron of sulfur atoms, with transannular S—S bonding holding the molecule in a highly symmetrical cage structure. It has a rich and varied inorganic chemistry [1], and its structure suggests the possibility of cycloaddition reactions with unsaturated organic substrates. The first indication of something unusual and potentially useful came in the reaction of S_4N_4 with dimethyl acetylenedicarboxylate in boiling toluene (Fig. 3) [4]. The major product was, quite reasonably, the 1,2,5-thiadiazole diester, presumably formed by cycloaddition of the triple bond to a sulfurdiimide unit. There were three minor products: the unexpected 1,2,4-thiadiazole diester, in which the acetylene bond has been completely cleaved, and two novel structures incorporating, respectively, five and six of the original eight heteroatoms of S_4N_4. These surprisingly stable compounds were shown by X-ray crystallography to

have the 7-membered, planar and delocalised structures (1) and (2), the first members of the 10 π aromatic trithiadiazepine and trithiatriazepine ring systems. The aromatic nature of these electron rich rings (10 π over 7 atoms) was also well reflected in their stability, spectroscopy, and chemical reactions.

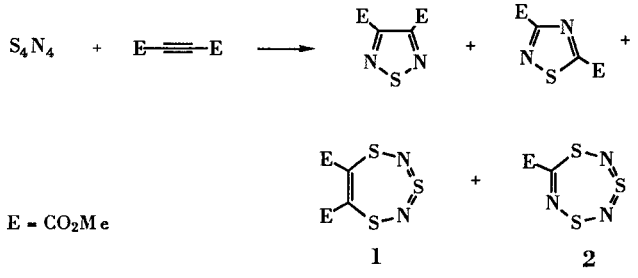


Figure 3

Trithiadiazepines

With the characterisation of the diester (1) as the first trithiadiazepine it was of interest to synthesise the parent ring, to study its chemistry and to see if the ring is still stable in the absence of electron withdrawing groups, and even in the presence of electron releasing groups. The parent compound (3) could not be obtained by hydrolysis and decarboxylation of the diester, but it was synthesised by the chlorination of ethanedithiol to the trichloro stage and condensation of the sulfenyl chloride with bis-(trimethylsilyl) sulfurdiimide. When these reagents in dichloromethane are mixed slowly, in high dilution, cyclisation and spontaneous dehydrochlorination gives the unsubstituted trithiadiazepine (3) in about 30% yield, as colourless, volatile, crystals (Fig. 4) [5]. X-ray diffraction again showed it to be planar with delocalised ring bonds, and its chemistry is in good agreement with 10 π aromaticity [6].

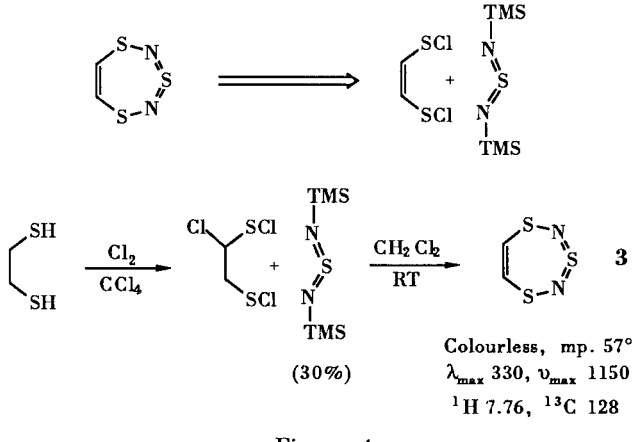


Figure 4

Trithiadiazepine (3) is thermally stable at 180°C and is stable to aqueous acid, organic and Lewis acids, to triethylamine, catalytic hydrogenation, and iodomethane. It is totally resistant to cycloaddition reactions, with 2 π and 4 π electron rich and electron deficient reagents, in striking contrast to S_4N_4 and sulfurdiimides generally. It undergoes standard electrophilic aromatic substitution to give the

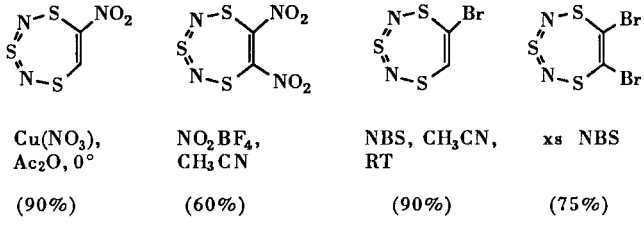


Figure 5

products shown in Fig. 5, including the ready formation of the "*ortho*" dinitro compound, presumably via Wheland intermediates that are well stabilised by delocation of the positive charge onto all the sulfur atoms. It can also be acylated with acid anhydrides in the presence of trifluoromethanesulfonic acid. It readily gives a mono thallium derivative with thallium (III) trifluoroacetate in acetonitrile and the bis(trifluoroacetoxy) thallium intermediate can be converted in high yield into the iodo, cyano, and methoxycarbonyl derivatives by standard procedures. Analogous mercuration, with mercuric acetate, proceeds rapidly to the di-mercurated product in high yield.

Following these standard electrophilic substitutions we were anxious to obtain the aminotrithiadiazepine, as a key compound for further transformations and to assess the effect of an electron releasing group on the π-excessive ring. All our attempts to reduce the mononitro compound to the amine failed, but this problem was eventually overcome in the following simple manner. Inspection of the somewhat elongated shape of the 7-membered ring, with its three large sulfur atoms, suggested that an elimination-addition mechanism via the hetaryne (4) might be possible. The C—C—S internal bond angle

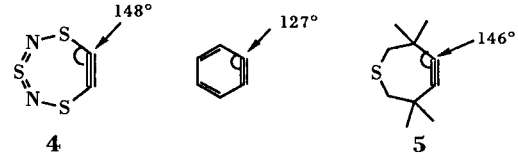
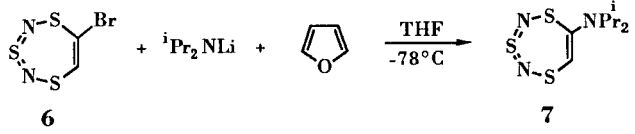


Figure 6

(148°) calculated for (4) is much greater than that

calculated for benzyne (127°) and is close to the measured angle (146°) for the isolable cycloalkyne (5) (Fig. 6). We therefore attempted to generate the hetaryne (4) from the bromo compound (6) with lithium diisopropylamide in the presence of furan (Fig. 7) in the hope of producing the cycloadduct (8) (Fig. 11). The bromo compound reacted slowly but completely, under these mild conditions, but none of the cycloadduct (8) was detected. To our surprise a high yield of the diisopropylamino derivative (7), the first amine of this ring system, was formed as a stable, pale yellow, crystalline solid [7]. This displacement of the bromine under such

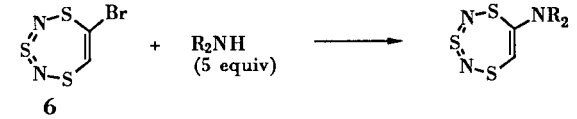


6 7

Figure 7

mild conditions was unexpected since it is not activated to nucleophilic substitution and could even be somewhat deactivated by the electron rich ring. It was also a general reaction, and we soon found that the lithio derivatives were not needed. Simple primary and secondary aliphatic amines, and even ammonia, were reactive enough to give high yields of the corresponding aminotrithiadiazepines in THF at room temperature (Fig. 8). Aniline was not reactive under these conditions, however, and its *N*-lithio derivative was required to produce the anilinotrithiadiazepine.

The primary and particularly the secondary amines are somewhat sensitive to oxidation and heat, but they are all crystalline and have been fully characterised. As to the question of the interaction between the exocyclic nitrogen lone pair of electrons and the ring orbitals, the X-ray diffraction results for the amino, dimethylamino, and morpholino derivatives are clear. In all three the amino group is still pyramidal and twisted completely out of the plane of the ring so that the lone pair orbital is in the plane of the ring, orthogonal to the aromatic orbitals (Fig. 9). The bond lengths and angles in the heterocyclic rings are very close to those of the parent compound, and clearly the amino groups are not conjugated with the ring and are only exerting their electron-withdrawing inductive effects.



6

R_2NH :	$^{i}Pr_2NH$	NH_3	Me_2NH	$PhCH_2NH_2$		PhNHLi
% Yield :	70	86	76	78	84	70

Figure 8

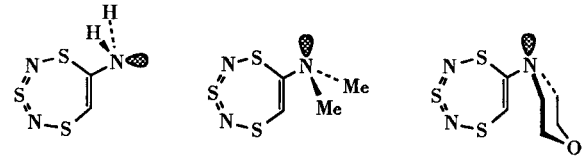
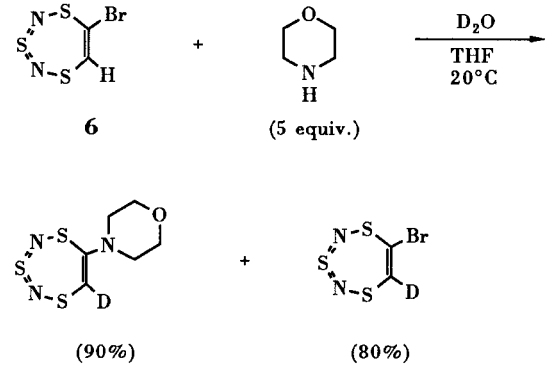


Figure 9

No cycloadduct (8) was detected in any of these reactions run in the presence of furan, and an elimination - addition seemed unlikely in the absence of a strong base. However, 6,7-*di* bromotrithiadiazepine was totally inert towards these amines and so the elimination of HBr from the bromo compound (6) had to be considered. Therefore deuterium exchange was investigated, in the reaction of the bromo compound with morpholine, and found to be fast and extensive in both the product and in the recovered starting bromide (Fig. 10). Thus the bromocarbanion appears to be formed rapidly, followed by loss of Br^- to give the hetaryne (4) to which the amines and amide ions would add. The absence of the furan - aryne cycloadduct could result from this nucleophilic addition being faster than furan cycloaddition, in interception of the aryne [7].



6 (5 equiv.)

(90%) (80%)

Figure 10

Cycloaddition to the aryne should then be facilitated by replacing the above amines with a non-nucleophilic base such as Hünig's base, $EtNPr_2^{i}$. When the bromo compound (6) was treated with this base in THF and furan, the cycloadduct (8) was indeed formed. However the reaction was slow, requiring a few days for completion, but we found that methanol had a strong catalytic effect and with Hünig's base in methanol the reactions were complete in 5-10 minutes. Other dienes also intercepted the aryne under these conditions and the yields of crystalline cycloadducts are shown in Fig 11.

With cyclopentadiene the aryne trapping was nearly quantitative; in the absence of Hünig's base there was no reaction [7].

Participation of the hetaryne (4) now seemed much more reasonable and we found that it could also be intercepted by a range of oxygen and sulfur nucleophiles to give new derivatives of the trithiadiazepine ring. Since the aryne mechanism provided the only route for nucleophilic substitution in this ring, and since formation of the initial carbanion proceeds under such mild conditions, we sought further evidence for this elimination-addition mechanism. We generated the aryne (4) and allowed it to compete for the highly reactive diene diphenylisobenzofuran and a series of amines of decreasing nucleophilicity (morpholine, diisopropylamine, and 2,2,6,6-tetramethylpiperidine), and the results clearly showed the involvement of a reactive intermediate that was intercepted in both Diels-Alder and nucleophilic addition reactions. We also studied competition between furan and 2,5-dimethylfuran for the aryne generated from three different precursors, the chloro, bromo, and iodotrithiadiazepines. The ratio of the two cycloadducts formed in each case was identical, and so the same species is presumably undergoing the Diels-Alder reaction each time, and hetaryne (4) seems to be the only reasonable candidate.

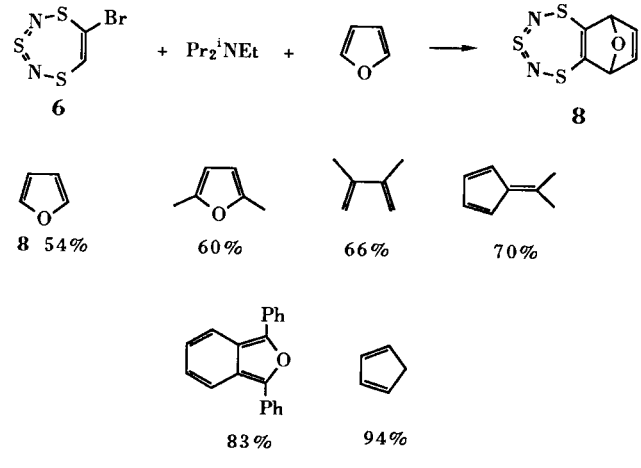


Figure 11

These results lead most reasonably to the overall reaction scheme shown (Fig 12); the most puzzling feature of this scheme is the rapid formation of the carbanion under such mild conditions. It must presumably be highly stabilised, and this may result from delocalisation of the negative charge onto the heteroatoms, with carbene-like canonical forms making a contribution to the structure (Fig. 13). This is analogous to, but presumably greater than, the well known stabilisation of anions of 5-membered heterocyclic rings such as thiazoles [8]. The negative charge may also be stabilised by the

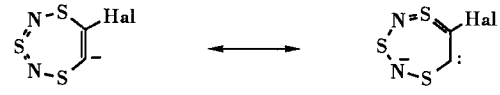


Figure 13

adjacent (α) sulfur atom, and by the β sulfur where there is an antiperiplanar relationship between the sp^2 carbanion orbital and the antibonding σ* C—S orbital [7].

1,2,3-Dithiazoles

One interesting cycloaddition reaction of the aryne (4) was with diaryldiazomethanes; this general reaction gave high yields of the crystalline cycloadducts, such as (9) (Fig. 14) [9]. Since these products are cyclic azo compounds it might be possible to extrude molecular nitrogen from them to produce new fused trithiadiazepines. On very brief heating at about 200°C the solid adducts decomposed rapidly, with vigorous gas evolution, to form deep red products. These were found by X-ray diffraction to be the first examples of the tricyclic ring system (e.g. 10) (Fig. 14). On the basis of spectroscopy and elemental analysis we had initially

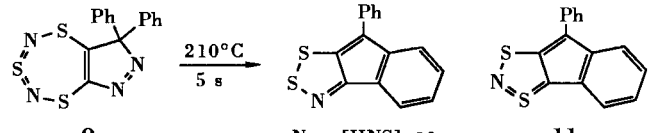


Figure 14

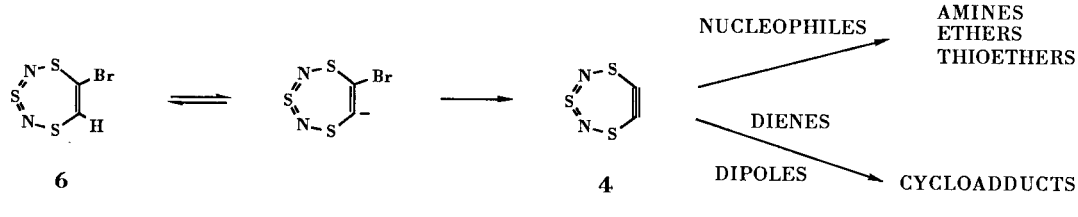


Figure 12

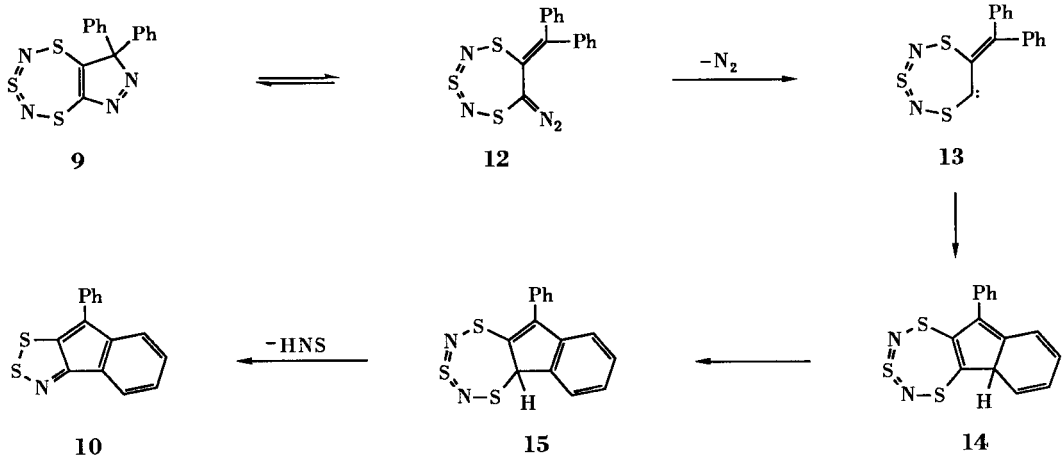


Figure 15

deduced the isomeric structure (11) for this product, where the alternation of the S and N atoms in the starting material was preserved. In this extensive and unexpected rearrangement the normally stable trithiadiazepine ring has not survived the extrusion of nitrogen from the 5-membered ring and the resulting molecular rearrangement; the elements of HNS have also been lost [9].

A possible mechanism for the rearrangement is shown in Fig 15. The cyclic azo compound could undergo reversible electrocyclic ring opening to the diazo compound (12) which would be stabilised by extensive delocalisation. The diazo compound could then lose nitrogen to form a carbene (13), also stabilised by delocalisation, which would cyclise onto one of the phenyl rings. The intermediate (14) has a stable trithiadiazepine ring which could be disrupted by a 1,5-hydrogen shift to give a more stable benzene ring and a more reactive array of heteroatoms in (15). Exactly how these heteroatoms rearrange and extrude HNS is much more speculative, though a possible mechanism is shown in Fig. 16. Good evidence for the key intermediate (15) was obtained by studying the thermolysis of the cycloadduct (9) in solution. In boiling xylene (25 min.) the red product (10) was again obtained, together with two other products, an orange oil and a yellow solid. The orange oil was found to be an intermediate on the way to the red product (10) and also to dimerise to the yellow solid. The orange compound was assigned structure (16) on the basis of its spectral and analytical properties, and the yellow dimeric compound was found by X-ray crystallography to have structure (17). The structure of (17) provides strong support for the structure of its monomer (16), particularly with respect to the sequence of the heteroatoms. The dimer (17)

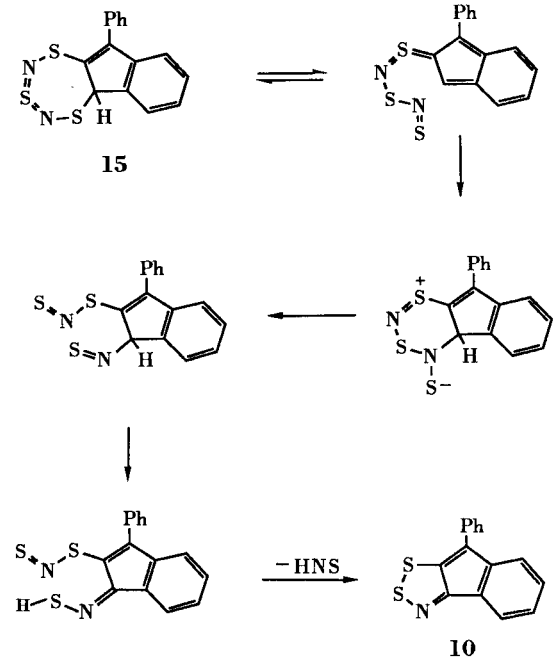
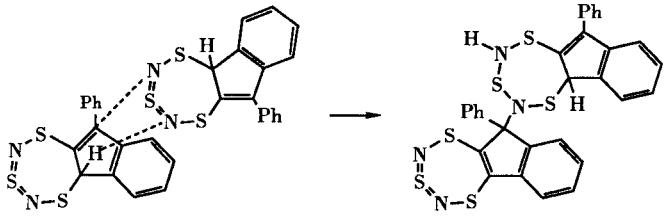


Figure 16

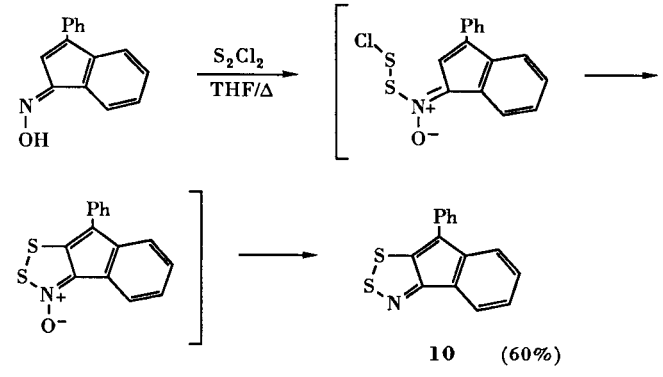
could be formed directly, as shown, by an 8-electron ene-type reaction, though this is formally disallowed as a suprafacial process. A strong driving force for the reaction could be provided by the aromatisation of one of the trithiadiazepine rings and the reduction of S^{IV} to S^{II} in the other. The dimer could also be formed in a more conventional 6-electron ene reaction with the hydrogen atom initially transferred to sulfur, followed by its 1,2-migration to nitrogen [9].

An independent synthesis of the dithiazole (10) was achieved as shown in Fig 18.



16 17

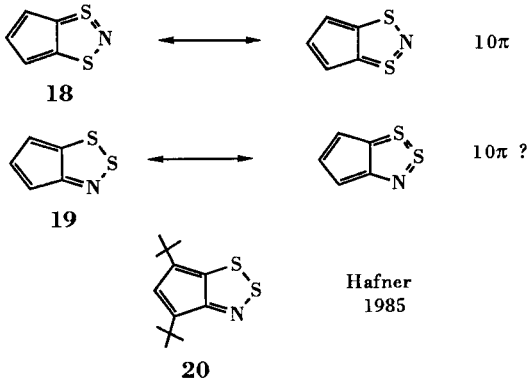
Figure 17



10 (60%)

Figure 18

The chance discovery of the indenodithiazoles (e.g. **10**) described above led us to consider the simpler bicyclic system (**19**). The high thermal stability and deep red colour of the former suggested that they could be delocalised structures and hence the latter might be a 10 π aromatic system in spite of its formal S—S single bond. Presumably the isomeric and symmetrical 1,3,2-dithiazole system (**18**) would be even more delocalised and could well be a stable electron rich aromatic system, derivatives of which are as yet unknown. The di-t-butyl compound (**20**) has been reported by Hafner and coworkers as a stable violet oil [10]. We are investigating such 1,2,3- and 1,3,2-dithiazoles and will now describe the chemistry of one readily available intermediate (**21**) which we have found to be a useful starting point for some new heterocyclic synthesis.

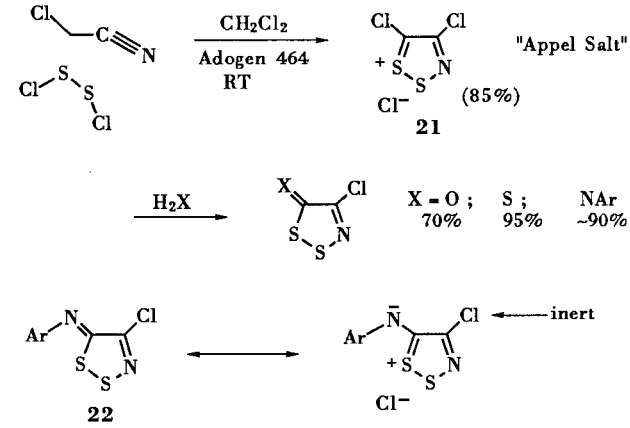


18 19 20

Figure 19

4,5-Dichloro-1,2,3-dithiazolium Chloride (21)

The ready preparation of this salt from chloroacetonitrile and disulfur dichloride and some of its chemistry was described by Appel and coworkers in 1985 (Fig. 20) [11]. The presence of the phase transfer catalyst improves the quality, but not the yield (85%), of the salt which is a pale greenish yellow solid, insoluble in organic solvents. It is completely stable in a dry inert atmosphere but reacts slowly with water to form 4-chloro-1,2,3-dithiazol-5-one and with hydrogen sulfide to form the 5-thione as deep maroon crystals, solutions of which are yellow. It reacts readily with anilines



22

Figure 20

in the presence of pyridine to give very stable *N*-arylimines (**22**) as yellow to pale orange solids. The second chlorine is inert to nucleophilic displacement, presumably because of the 6 π aromatic character of the heterocyclic ring. Appel also described the reaction of phenol with the dithiazolium salt (**21**) to form the *p*-hydroxyphenyl derivative in high yield [11]. We have isolated a small amount of the *ortho* isomer as well; with aqueous acetone both give the zwitterionic compounds shown as deep purple metallic crystals (Fig. 21). The *ortho* compound is much less polar than the *para* because of the neutralising interaction between the adjacent oxygen and sulfur atoms. Appel prepared an "*ortho* " compound from *p*-cresol and showed that the O ····· S distance (2.16 Å) was much less than the sum of the van der Waals radii (3.25 Å). We observed very similar reactions with 1- and 2-naphthol, but a new and more extensive process with anthrone (Fig 22). This reacted with the salt (**21**) in dichloromethane at room temperature to give a pale yellow product which was clearly of a different type. Analysis and spectroscopy showed it

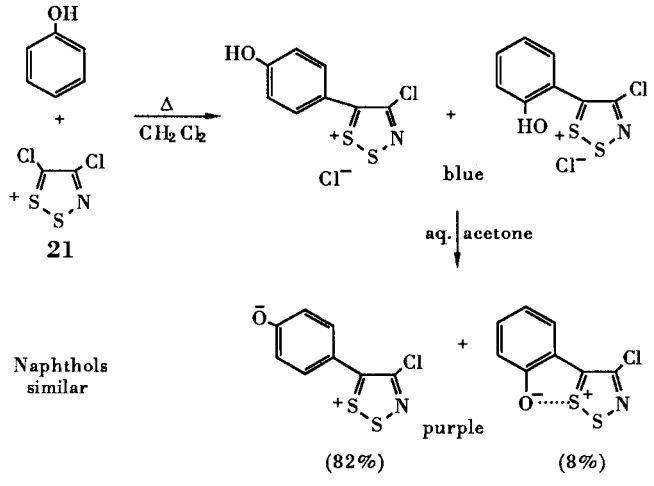


Figure 21

to be the anthracenothiophene (**23**). We propose that the first reaction is formation of a dithiazole by substitution of the phenolic tautomer of anthrone in the *para* position, as with phenol; then this product undergoes the electrocyclic reaction shown to give a pentacyclic intermediate which finally suffers electrocyclic fragmentation to give the cyanothiophene (**23**), hydrogen chloride, and sulfur. The overall process is the fusion of an S—C—CN unit onto the anthrone in one, very mild, reaction and we shall see further examples of this shortly. Somewhat surprisingly thiophenol did not react with the dithiazolium salt (**21**), and nor did anisole [12].

Appel had shown that cyanoacetate esters condensed with (**21**) to give dithiazol-5-ylidenes (Fig. 23) [11]. This, together with our anthrone reaction, suggested that other enolisable carbonyl compounds could react analogously to phenol and this was so, though yields of the yellow to orange 5-ylidenes were often low. Diethyl malonate reacted very slowly and malononitrile not at all. Nor was there any reaction with diphenylmethane, but the anticipated product (**24**) was readily prepared by treating 4-chloro-1,2,3-dithiazol-5-thione with diphenyldiazomethane. The reaction was very rapid in benzene or dichloromethane at room temperature; a gas was evolved, sulfur precipitated, and the desired compound (**24**) was formed in high yield as an orange oil. This was not very stable and it decomposed cleanly on standing overnight to give 2-cyano-3-phenylbenzothiophene in high yield. This transformation is analogous to that observed with anthrone (Fig. 22) and presumably proceeds by the same mechanism; again the S—C—CN unit has been introduced from the dithiazolium reagent (**21**) [12].

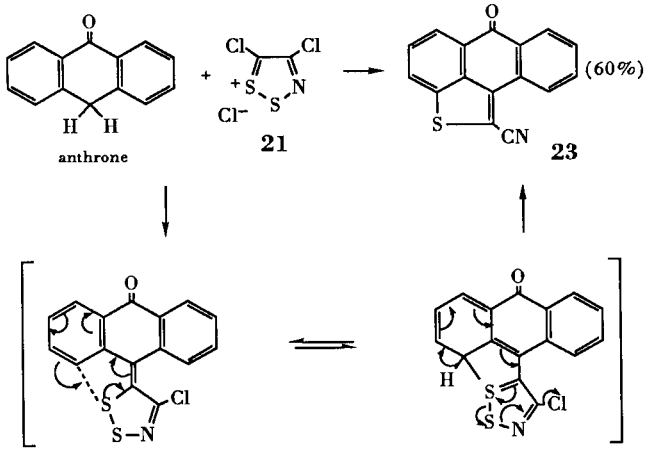


Figure 22

The preparation of (**24**), based on the Barton two-fold extrusion reaction, is notable for requiring neither heat, nor a trivalent phosphorus reagent to remove the sulfur. Ethyl diazoacetate and diethyl diazomalonate reacted similarly with the thione, but the former was less reactive than diphenyldiazomethane and required boiling in benzene; the latter was less reactive still (Fig. 24). Both gave a

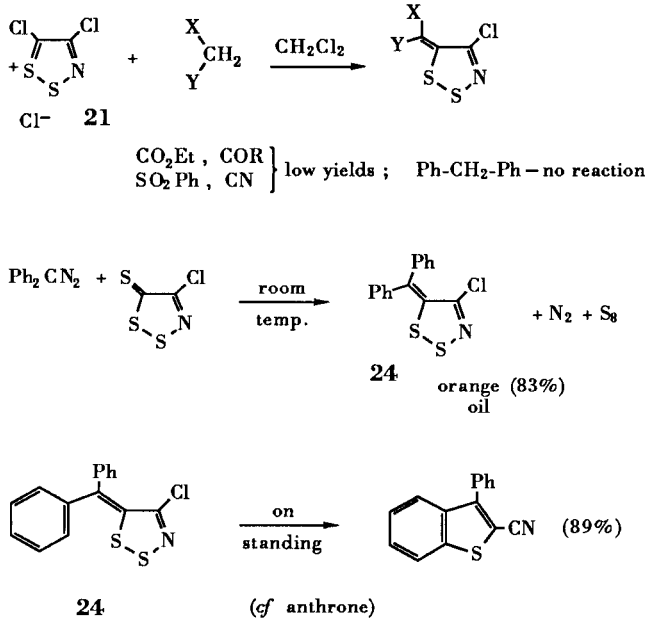


Figure 23

single geometric isomer only, presumably that shown, because of the attractive O ···· S interaction, which was also reflected in the carbonyl infrared absorptions.

Since the *N*-arylimino dithiazoles (**22**) are so read-

ily available we have explored some of their chemistry, particularly with regard to their use in heterocyclic synthesis [12]. Firstly their thermolysis: we have already seen how the diphenylmethylene derivative (**24**) spontaneously cyclises with elimination of sulfur and hydrogen chloride to give 2-cyano- 3-phenylbenzofuran in high yield. The analogous anilino compound (**25**) is much more stable, as expected (Fig. 20), but on vigorous heating it underwent the same reaction process to give

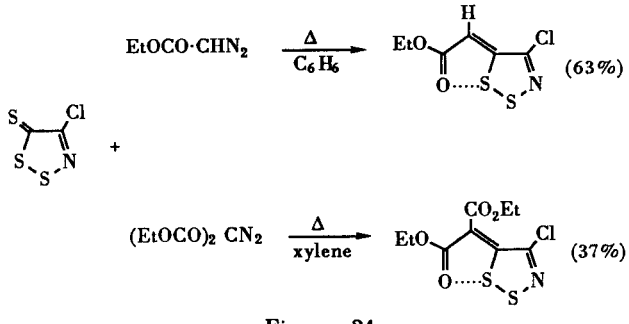


Figure 24

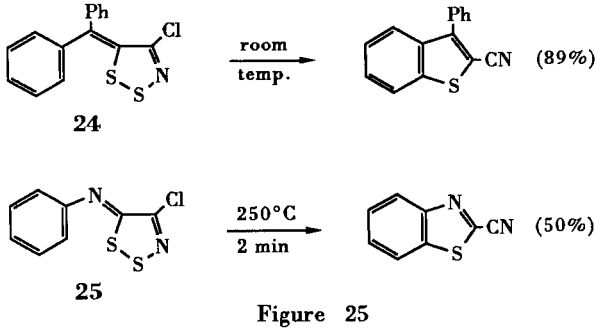


Figure 25

sulfur, hydrogen chloride, and 2-cyanobenzothiazole (Fig. 25). This new method for converting aniline into 2-cyanobenzothiazole in two simple steps would probably be useful for the synthesis of more highly substituted derivatives. We looked briefly at the effect of electron withdrawing and releasing groups in the phenyl ring (Fig. 26). A *m*-methoxy group, which releases electrons to the site of cyclisation, enhances the rate to give both possible products in high combined yield (85%). On the other hand *m* - and *p*-nitro groups reduced the yield of the analogous products dramatically, the major product in both cases being the cyano-imidoyl chloride (Fig. 26). The *p*-nitro compound was hydrolysed to the cyanoformamide with moist ethanol, and was also synthesised independently. A possible mechanism for these thermolytic reactions is shown in Fig. 27. The benzothiazoles are presumably formed by the electrocyclisation and fragmentation sequence seen already. The imidoyl chloride formation involves the loss of both sulfur atoms, and this could possibly occur by their direct loss as S_2 to form the nitrilium salt shown, which would collapse to the observed product.

We have also studied the reaction of the dithiazolium salt (**21**) with anilines bearing nucleophilic *ortho* groups, looking particularly for the displacement of the second chlorine in (**21**) [12]. *o*-Aminophenol condenses with (**21**) in high yield and when the product (**26**) is converted into the phenoxide ion this cyclises readily to give the desired dithiazolobenzoxazine (**27**) as a yellow crystalline solid, which is thermally very stable. The intermolecular equivalent of this cyclisation could not be achieved with sodium phenoxide and 4-chloro-5-phenylimino-1,2,3-dithiazole (**25**) under more vigorous conditions. Thermolysis of the neutral *o*-hydroxyphenylimine involved the loss of sulfur as well as hydrogen chloride to give 2-cyanobenzoxaxole in high yield, as shown (Fig. 28), thus providing a new and simple two-step route for this cyclisation

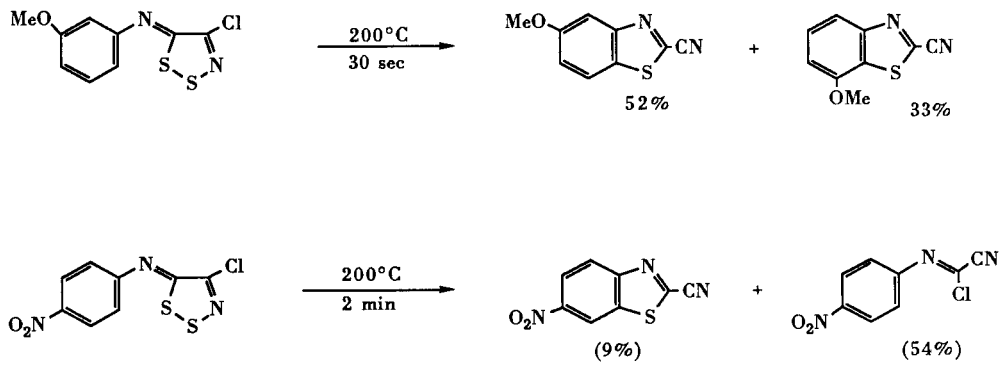


Figure 26

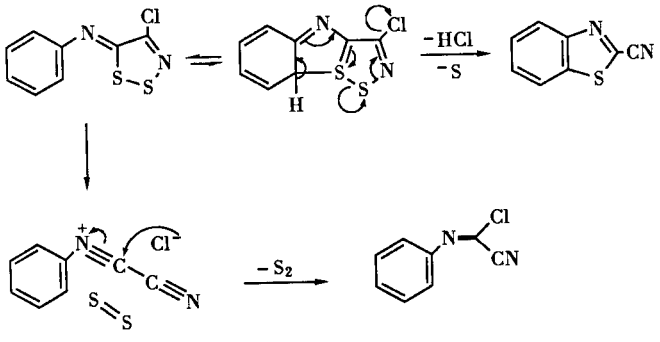


Figure 27

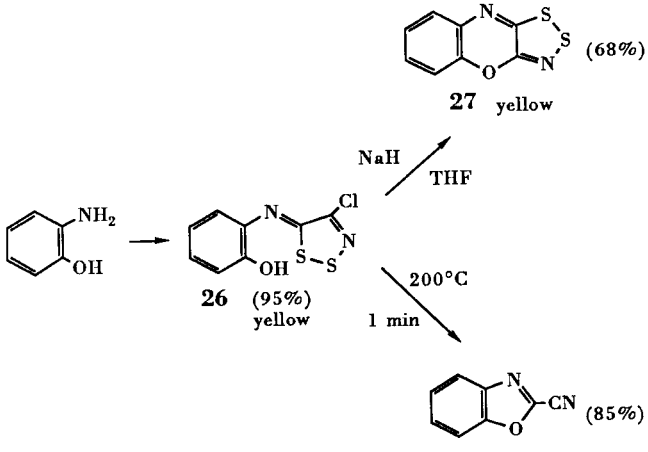


Figure 28

of *o*-aminophenols. Possible mechanisms for this transformation are shown in Fig. 29. Again S_2 could be lost to form the nitrilium salt which would

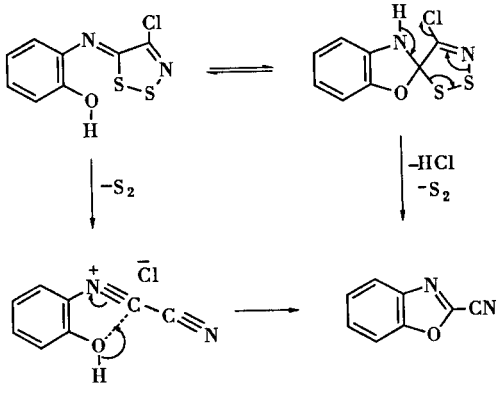


Figure 29

collapse to the benzoxazole, but cyclisation to the spiro compound with subsequent loss of HCl and S_2 is perhaps more likely. The dithiazolobenzoxazine (**27**) is not an intermediate in this thermolysis since it is unchanged at 200°C.

Thus we have seen that the dithiazolium salt (**21**) is a useful reagent for the preparation of 2-cyanothiophenes, benzothiazoles, and benzoxazoles, and cyanoimidoyl chlorides. Finally we will describe the application of another readily available reagent, trithiazyl trichloride, in heterocyclic synthesis.

Trithiazyl Trichloride

Trithiazyl trichloride (**28**) [1] is a stable, but moisture sensitive, yellow crystalline solid. It is prepared by heating ammonium chloride and disulfur dichloride, followed by chlorination. Its six-membered ring is a flattened chair with all the chlorines axial on the same side of the ring, thus leaving the other side well exposed for substitution and addition reactions. The ring bonds are delocalised, all being of the same length. On heating in solution above about 60°C it is in equilibrium with the monomer, NSCl, which appears to be green. The dissociation is favoured by certain impurities [13], and may be subject to catalysis. Various canonical forms, including a nitrene structure, can be written for the reactive monomer. The inorganic chemistry of (**28**) has been extensively studied, but its reactions with organic substrates are relatively rare [1]. These include reactions with nitriles, amidines, amines, alkenes and perhaloalkenes; these reactions are usually rather complex, yields are often low, and their generality has not been

Trithiazyl Trichloride, $(NSCl)_3$

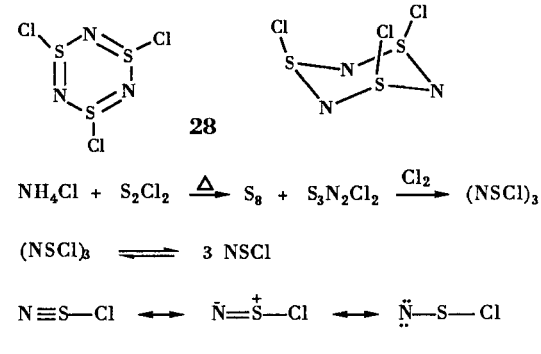


Figure 30

established. We decided to explore the scope of the reagent (**28**) as a source of the S—N unit in organic cycloaddition reactions [14].

Our first target was the 1,2,4-thiadiazole ring; there are various ways of constructing this important ring system, but none are based on the C—N—C + N—S disconnection shown. We therefore treated the simple imine (**29**) with (**28**) in boiling chloroform containing pyridine and obtained a modest yield of 3,5-diphenyl-1,2,4-thiadiazole

(30), together with four very minor products. Formation of the 1,3,5-triazine and S_4N_4 was not surprising but 7-phenyltrithiatriazepine and 3,7-diphenyldithiatetrazocine were totally unexpected, and the mode of their formation is puzzling.

We then established good conditions for thiadiazole formation: treatment of the imine with two equivalents of trimer (28) in boiling chloroform containing 6 equivalents of pyridine for about 10 hours. The "mixed" imines shown also reacted well, but isomeric pairs gave the same mixture of (readily separated) products (Fig. 33). The more electron withdrawing group favoured position-3 of the thiadiazole ring, and electron releasing groups

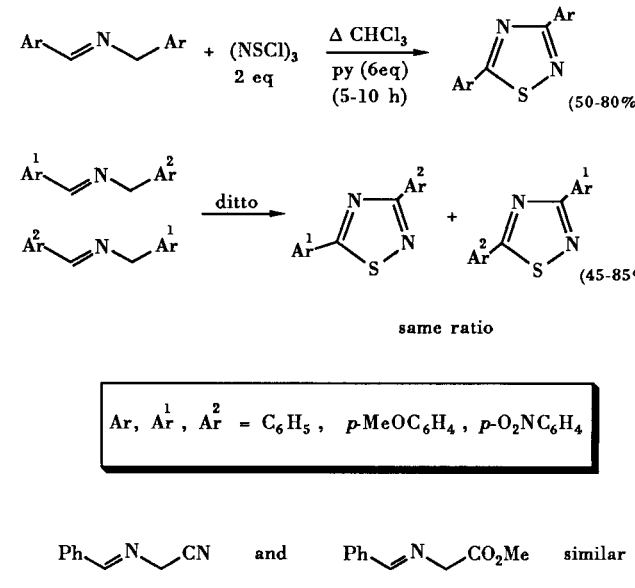


Figure 33

lowered the overall yields. The functionalised imines shown (Fig. 33) also reacted similarly. The mechanism of these reactions is not yet known, and it must be complex to explain formation of all the minor products, but for the major reaction the monomer could be involved as shown in Fig. 34. The intermediate dihydro compound could be readily aromatised by the excess of trimer (28), possibly via chlorination.

Although the scope and mechanism of this reaction need further clarification, it does provide a new and simple route to 1,2,4-thiadiazoles [14].

With the possible involvement of the monomer, NSCl, we wondered if this could be intercepted in a Diels-Alder reaction, for example with 2,5-diphenylfuran. The trimer (28), in boiling tetrachloromethane, reacted cleanly with this furan to give one major product, a dehydrochlorinated 1:1-adduct, in good yield. The product contained a carbonyl group, probably a benzoyl group, suggesting that

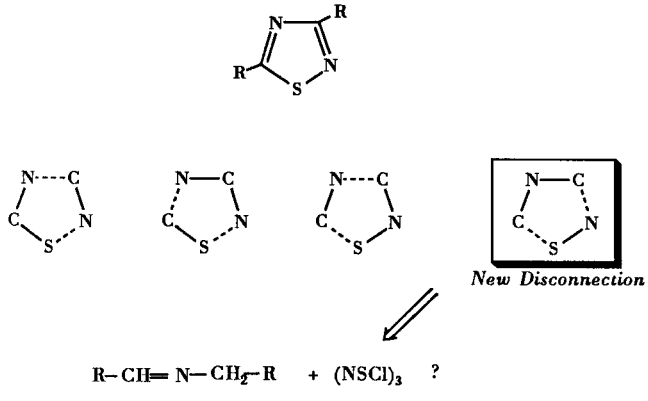


Figure 31

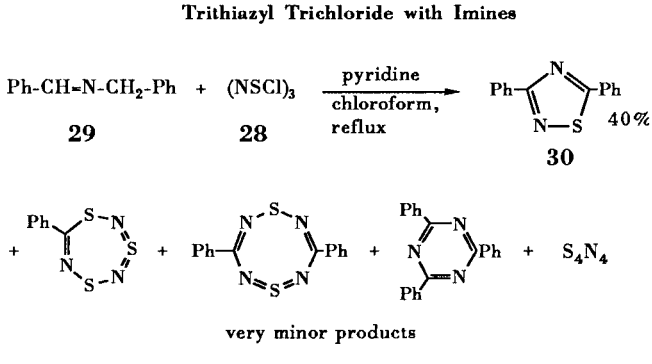


Figure 32

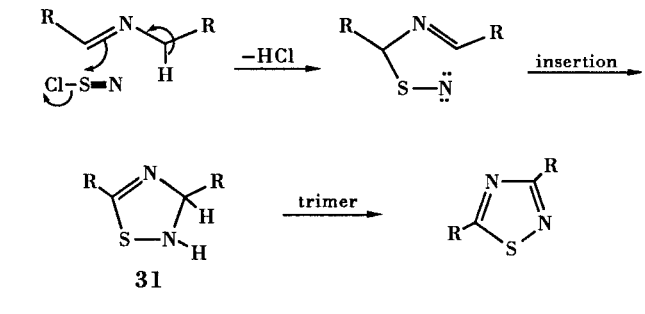


Figure 34

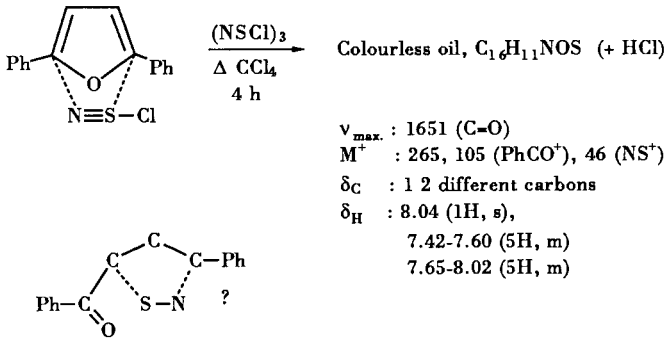


Figure 35

the furan ring had undergone cleavage of an O—C bond and that an S—N unit had become incorporated, possibly as shown (Fig. 35). Indeed the product proved to be 5-benzoyl-3-phenylisothiazole, in agreement with all the spectroscopic data. The same reaction process was observed with 2,3,5-triphenylfuran. No isomers of the products

Trithiazyl Trichloride with Furans

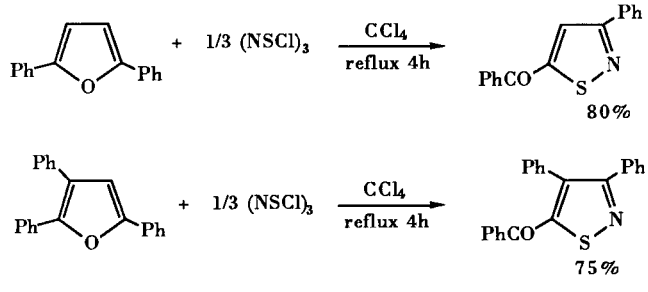


Figure 36

were observed and so incorporation of the S—N unit is regiospecific. The yields were high, and these are based upon conversion of three molecules of furan by one of trithiazyl trichloride. This transformation is a new reaction of furans and a new route to isothiazoles. There are rather few good syntheses of the isothiazole ring (Fig. 37) and this simple reaction could provide a very useful additional route, and we are now exploring its scope and mechanism [14]. For example, 2,5-diphenyloxazole gave the analogous thiadiazole, though in low yield, together with 3-phenyl-1,2,5-thiadiazole (Fig. 38), indicating a possible mechanistic complexity (see below). A first attempt at reacting the trimer (28) with 2,5-diphenylthiophene has given the same product as 2,5-diphenylfuran; probably the thiophene is reacting in the same way as the furan but the thioketone so produced is oxidised to the ketone by more trimer (Fig. 38).

Conversion of the furan into the isothiazole can be formally represented as cycloaddition of NSCl across the furan 2 and 4 positions, with accompanying ring opening, as shown (Fig. 39). Alternatively the same overall transformation could be achieved by electrophilic attack on the furan by NSCl (= $NS^+ Cl^-$), through S at the β-position or through N at the α-position, as shown (Fig. 39). The opposite modes of cycloaddition or substitution lead to the regioisomer which is not observed. But perhaps a more realistic mechanism is that shown in

Synthetic Methods for Isothiazoles

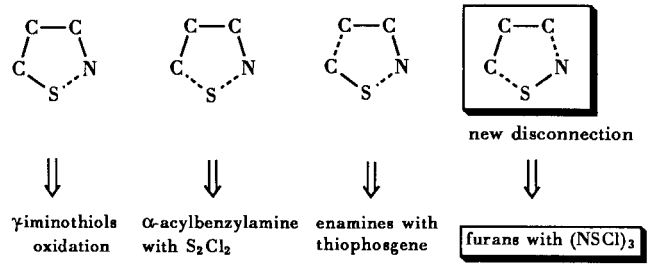


Figure 37

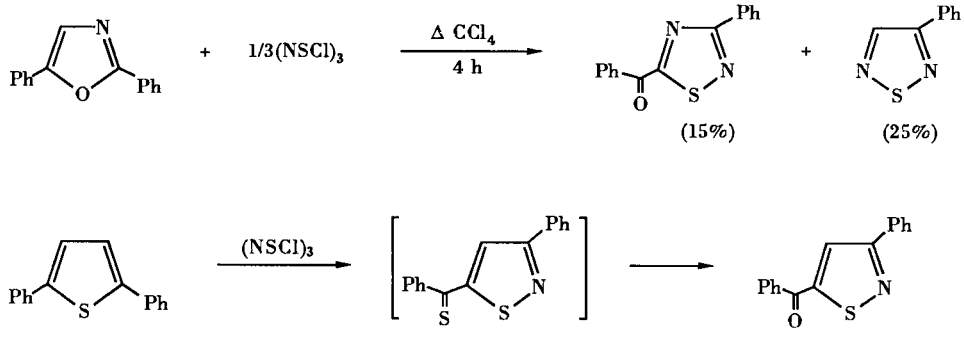


Figure 38

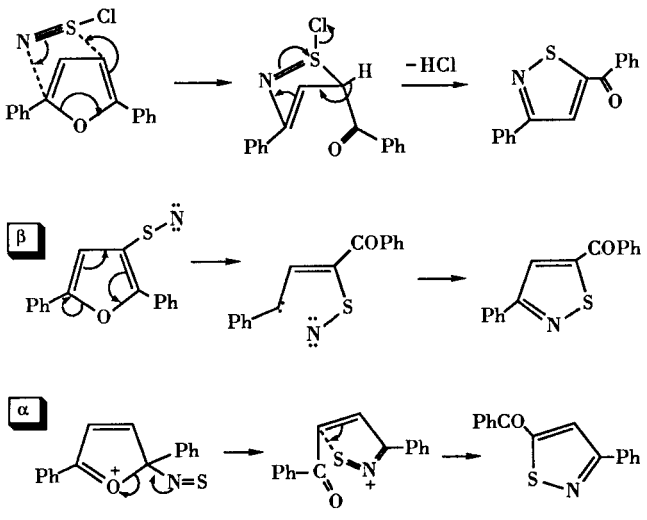


Figure 39

Fig. 40. This is initiated by the originally envisaged Diels-Alder process, followed by rearrangement of the strained cycloadduct (**32**) and aromatisation. The observed regiochemistry is also explicable on this mechanism, since the product formed is determined by which C—O bond is broken in the cycloadduct rearrangement. If this bond cleavage can be considered as having some heterolytic character, the ionic species (**33**) and (**34**) shown represent the two extreme possibilities. These species would be expected to differ substantially in stability because of the inherent polarisation of the $S^+—N^-$ bond, and the isomer actually formed is that corresponding to the more stable species (**33**).

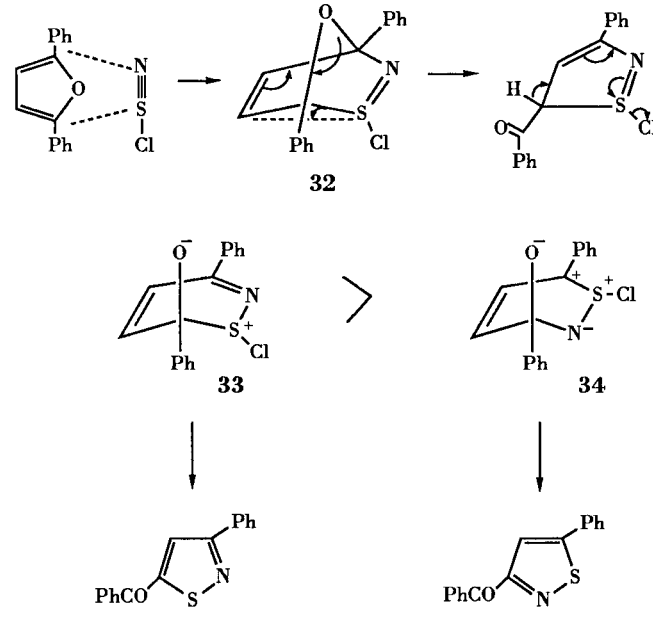


Figure 40

Furthermore, if we write the same mechanism for the diphenyloxazole reaction (Fig. 41), two bicyclic intermediates (**35**) and (**36**) are now possible; if these open in the same sense as above (i.e. cleavage of the C—O bond more remote from the sulfur atom) this leads directly (Fig. 41) to the observed products (Fig. 38). Further work is underway to define the reaction mechanism more closely and to explore the scope of these novel reactions as widely as possible.

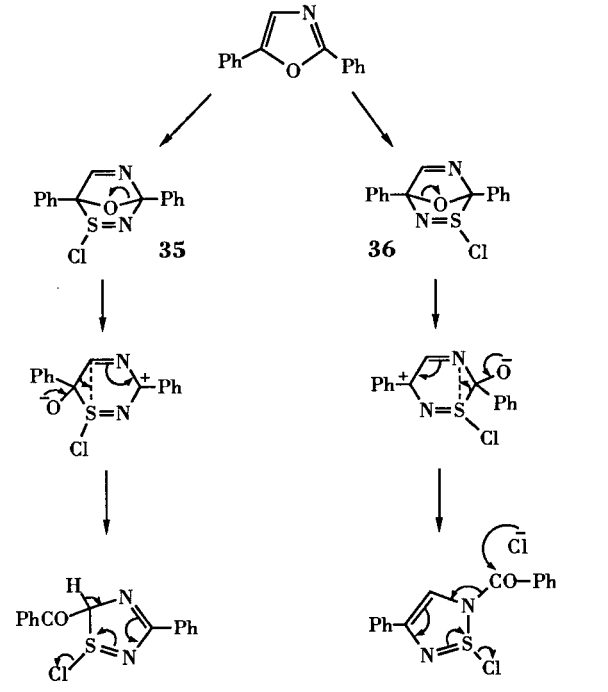


Figure 41

Acknowledgements

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