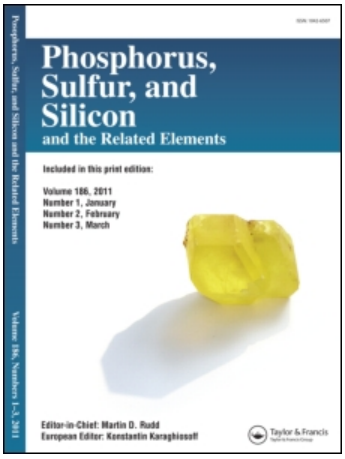

Phosphorus, Sulfur, and Silicon and the Related Elements

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Trithiadiazepyne

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TRITHIADIAZEPYNE

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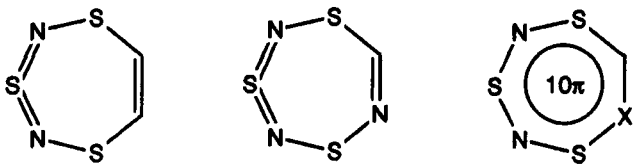
Abstract Amino derivatives of the trithiadiazepine ring system are described for the first time. They are available by nucleophilic aromatic substitution under remarkably mild conditions, though only via the hetaryne intermediate. Firm evidence is presented for the involvement of this relatively stable aryne, and some new rearrangements accompanying or following its interception by dienes and dipoles are described.

INTRODUCTION

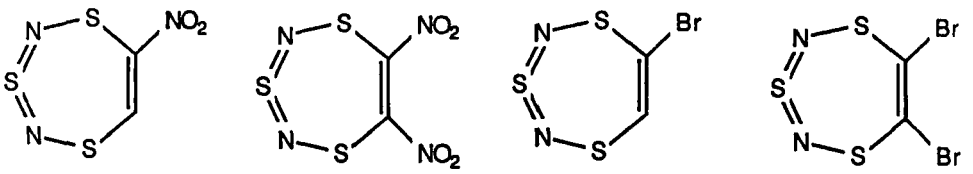
We have recently discovered a new family of heterocylic compounds, on the border of organic and inorganic chemistry, which are characterised by an unusually high proportion of nitrogen and sulphur heteroatoms.[1] These compounds were initially derived, both conceptually and experimentally, from tetrasulphur tetranitride and related inorganic compounds with rings composed wholly of alternating sulphur and nitrogen atoms. Organic heterocyclic rings with a high proportion of heteroatoms are relatively rare; they are usually inaccessible, and when they are known they tend to be unstable. It occurred to us that a possible general approach to more stable compounds of this type would be to start with stable rings composed entirely of "heteroatoms" and to introduce one or two carbon atoms into them. In this way we have uncovered the organic heterocyclothiazenes as stable, planar, delocalised, aromatic systems. The trithiadiazepines (1) and trithiatriazepines (2) (Fig. 1) are typical; they are electron rich with 10 π electrons delocalised over the seven ring atoms. They are formed by the cycloaddition of alkynes to S_4N_4, and the parent trithiadiazepine (1) has been



1 2

FIGURE1

synthesised independently.[2] The delocalised structures proposed are based on spectroscopy and X-ray structure determination; for the trithiadiazepines this is supported by their chemical properties.[3] Thus trithiadiazepine (1) readily undergoes electrophilic substitution to give the mono- and di- nitro and bromo derivatives under the conditions shown (Fig. 2).



$Cu(NO_3)$, Ac_2O, 0° (90%) | NO_2BF_4, CH_3CN (60%) | NBS, CH_3CN, RT (90%) | xs NBS (75%)

FIGURE 2

This electrophilic substitution provides access to trithiadiazepines bearing electron withdrawing groups. We also wished to obtain derivatives with electron releasing groups, notably NH_2 and OH, because of their key role in functional group transformations, and their interest as strongly electron releasing groups on the π-excessive ring.

NUCLEOPHILIC SUBSTITUTION

Such derivatives are, of course, the common products of nucleophilic aromatic substitution and this process was therefore important to us. It became particularly so when we failed, after many attempts, to reduce the readily available nitro derivative to the primary amine (Fig. 3).[3] Unfortunately, standard

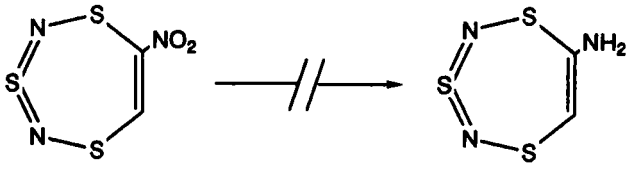
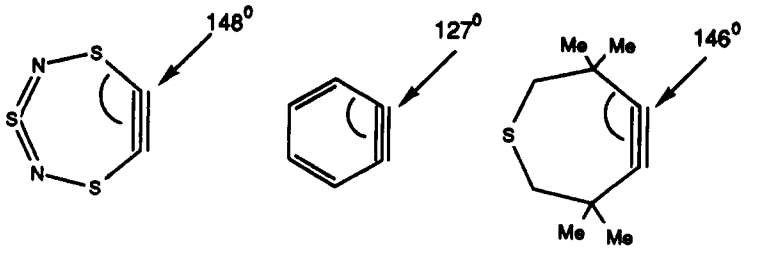


FIGURE 3

nucleophilic displacement of halogen from the mono bromo derivative appeared unpromising since the trithiadiazepine ring is rather unstable towards alkaline conditions. However, inspection of the seven membered ring with its three large sulphur atoms suggested that an elimination-addition mechanism, via the hetaryne (3), might be possible.[1] This thought was encouraged by the slightly elongated shape of the trithiadiazepine ring, as shown by X-ray diffraction, and the C-C-S internal bond angle (148°) calculated for the aryne (3)[4] which is much greater than the analogous angle calculated for benzyne (127°), and is close to the measured angle (146°) for the isolable cycloalkyne (4)[5] (Fig. 4). Furthermore there is only one possible aryne here with a formal carbon-carbon triple bond, and this is highly symmetrical (3).

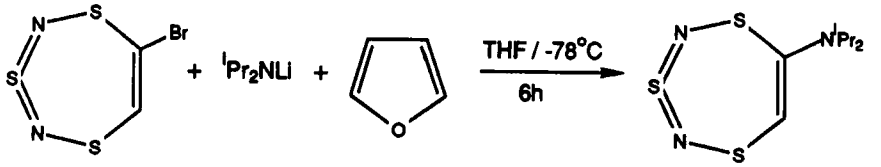
AMINOTRITHIADIAZEPINES

We therefore attempted to generate the aryne (3) from the bromo compound (5) with lithium diisopropylamide (LDA) in the presence of furan (Fig. 5). The bromo compound reacted slowly but completely, under these very mild conditions, but none of the



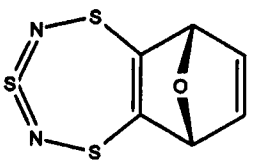
3 4

FIGURE 4



5 6 (80%)

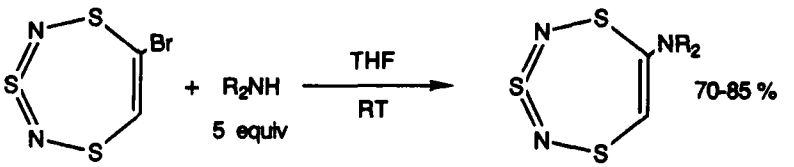
FIGURE 5



7 (0%)

furan-aryne cycloadduct (7) was detected. To our surprise, a high yield of the diisopropylamino derivative (6), the first amine of this ring system, was formed as a stable, pale yellow, low melting crystalline solid. This unexpectedly mild reaction proved to be general, and indeed we soon found that the lithio derivatives were not required; simple primary and secondary aliphatic amines, and even ammonia, were reactive enough to give high yields (Fig. 6) of the corresponding amino trithiadiazepines in THF at room temperature. Aniline did not react under these

conditions, however, and its N-lithio derivative was required for the formation of anilinotrithiadiazepine in good yield. Whilst the primary and, particularly, the secondary amines are somewhat



5

FIGURE 6

sensitive, they are all crystalline compounds which have been fully characterised. 6-Aminotrithiadiazepine is a fawn solid, m.p. 56-57°C.

TRITHIADIAZEPYNE

No furan-aryne cycloadduct was detected in any of these reactions and an elimination-addition mechanism seemed somewhat unlikely in the absence of a strong base. Indeed the reaction conditions, e.g. dry ammonia gas in THF at room temperature, were extremely mild for the displacement of bromine from an electron rich aromatic, by whatever mechanism! However, 6,7-dibromotrithiadiazepine was totally inert towards these amines, and thus the possibility of elimination of hydrogen bromide from bromo compound (5) had to be considered. Therefore deuterium exchange was investigated, in the reactions with morpholine (Fig. 7). This exchange was rapid (much faster than conversion of the

bromide to the amine in the absence of D_2O) and extensive, not only in the product but also in recovered starting bromide. This suggests that the bromocarbanion is formed rapidly; by analogy

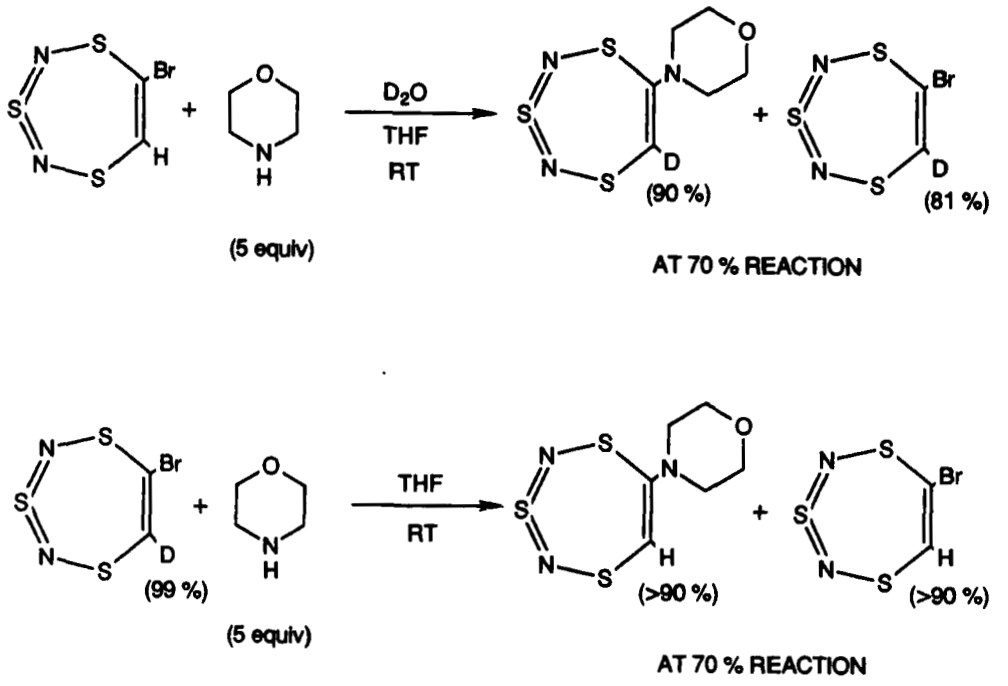


FIGURE7

with benzyne generation, this could be followed by loss of Br^- to give the hetaryne to which the amines (and amide ions) would add nucleophilically (Fig. 8). The absence of furan-aryne cycloadducts in the earlier reactions is then explained by the greater reactivity of the amines (and amides) over furan in intercepting the aryne.

Cycloaddition to the aryne should then be facilitated by replacement of the above amines with non-nucleophilic bases, and for this we chose Hünig's base, $EtNPr^i_2$. When the bromo compound (5) was treated with this base in THF and furan the cycloadduct

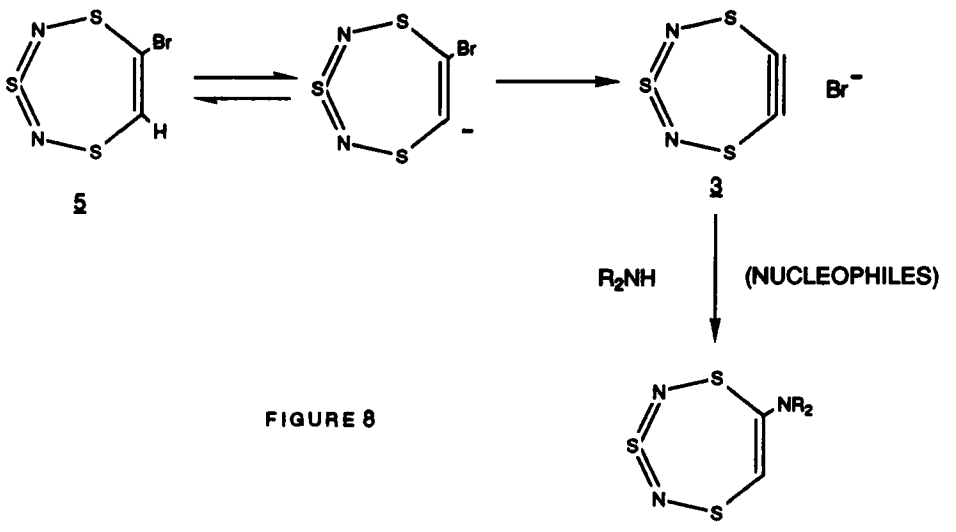
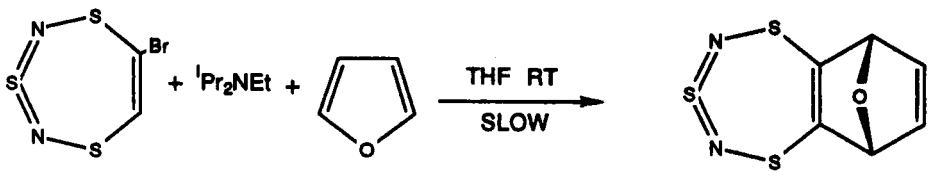


FIGURE 8

(7) was indeed formed. However the reaction was slow, requiring several days for completion. We noticed previously that the D_2O exchange reactions were much faster, and D_2O and H_2O were found to have a marked catalytic effect on the aryne-adduct forming reaction. However a high proportion of water in the solvent caused decomposition of the bromo compound (5); fortunately methanol had the same strong catalytic effect without causing decomposition. In dry methanol the reactions were over in 5-10 minutes, and Hünig's base in methanol became our standard for aryne generation. Other dienes also intercepted the aryne under these conditions, and the yields of crystalline cycloadducts isolated are shown in Fig. 9; these yields increase steadily with the diene reactivity, as expected; with cyclopentadiene the aryne trapping is very nearly quantitative. In the absence of Hünig's base there is no reaction.

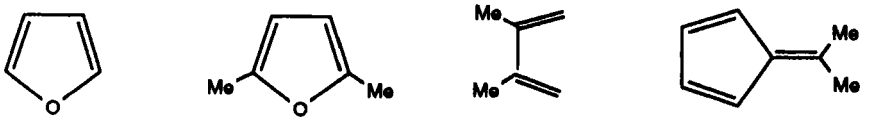
The aryne mechanism now seems much more reasonable; it was also supported by formation of the anilino derivative (Fig. 10) from the bromo compound and aniline in the presence (but not in the absence) of Hünig's base. The hetaryne (3) could also be



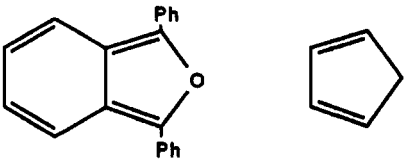
5 7

H_2O OR MeOH ACCELERATES THE REACTION

REACTION VERY FAST IN MeOH

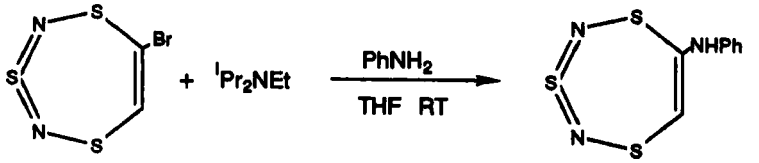


54 % 58 % 66 % 70 %



83 % 95 %

FIGURE 9



64 %

FIGURE 10

intercepted by oxygen and sulphur nucleophiles.[6] Alkoxides rapidly gave ethers under very mild conditions (Fig. 11) though

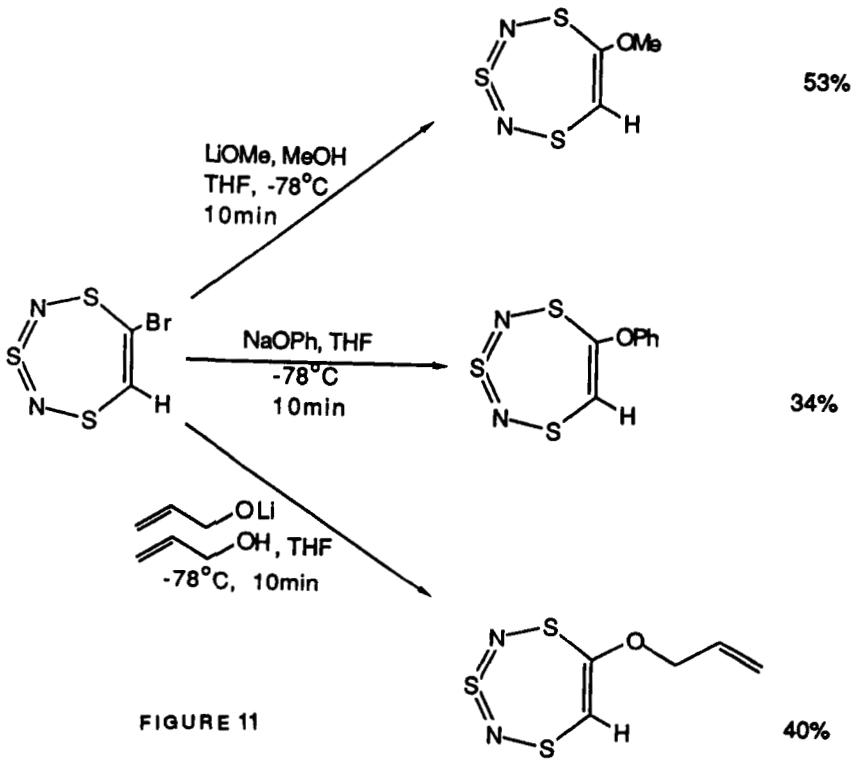


FIGURE 11

the yields are lower, probably reflecting the greater sensitivity of the trithiadiazepine ring towards alkoxides. In the presence of furan the aryne cycloadduct (7) is again formed, though in very low yield; furan presumably competes rather poorly with alkoxide ion for the aryne (Fig. 12). Reaction of the bromo compound (5) with analogous sulphur anions is distinctly more complex and lower yielding (Fig. 13); presumably these more strongly thiophilic species destroy the heterocyclic ring even faster.

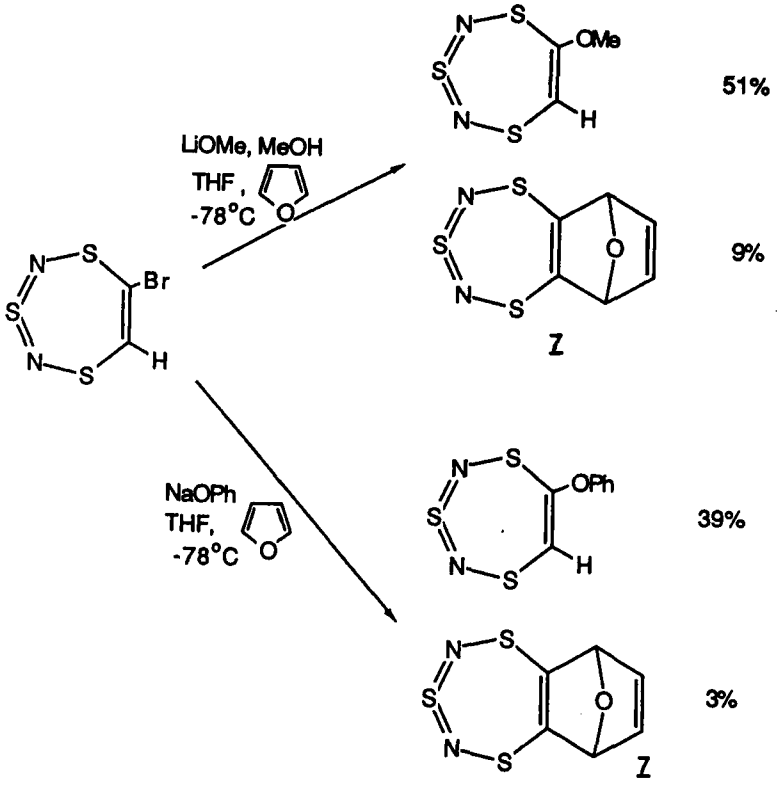


FIGURE 12

THE ARYNE MECHANISM

In contrast with nucleophilic aromatic substitution generally, where elimination-addition mechanisms via aryne intermediates are of relatively minor importance, the aryne pathway proposed here, if correct, provides the only route for nucleophilic substitution in our trithiadiazepines. We therefore considered it important to establish the mechanism more firmly, and to explain why the reaction proceeds under such mild conditions. We have therefore investigated its response to structural changes in the aryne precursor and the diene, and have performed various competition

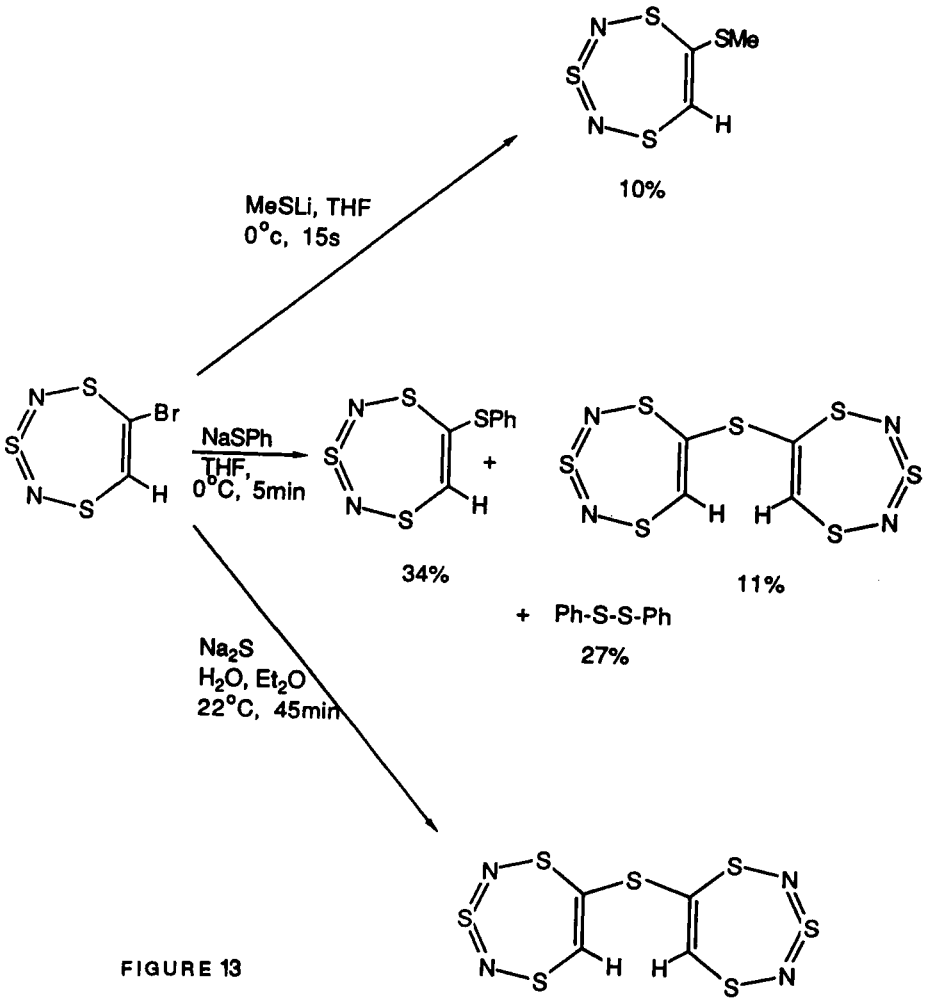


FIGURE 13

experiments. Whilst the high symmetry of the hetaryne (3) presumably increases its stability, the absence of ring substituents precludes one of the easier ways of establishing the presence of an (unsymmetrical) aryne.

We first studied the competition between a highly reactive, high-yielding diene, diphenylisobenzofuran, and three amines of widely differing nucleophilicity, with the results shown in Fig. 14.

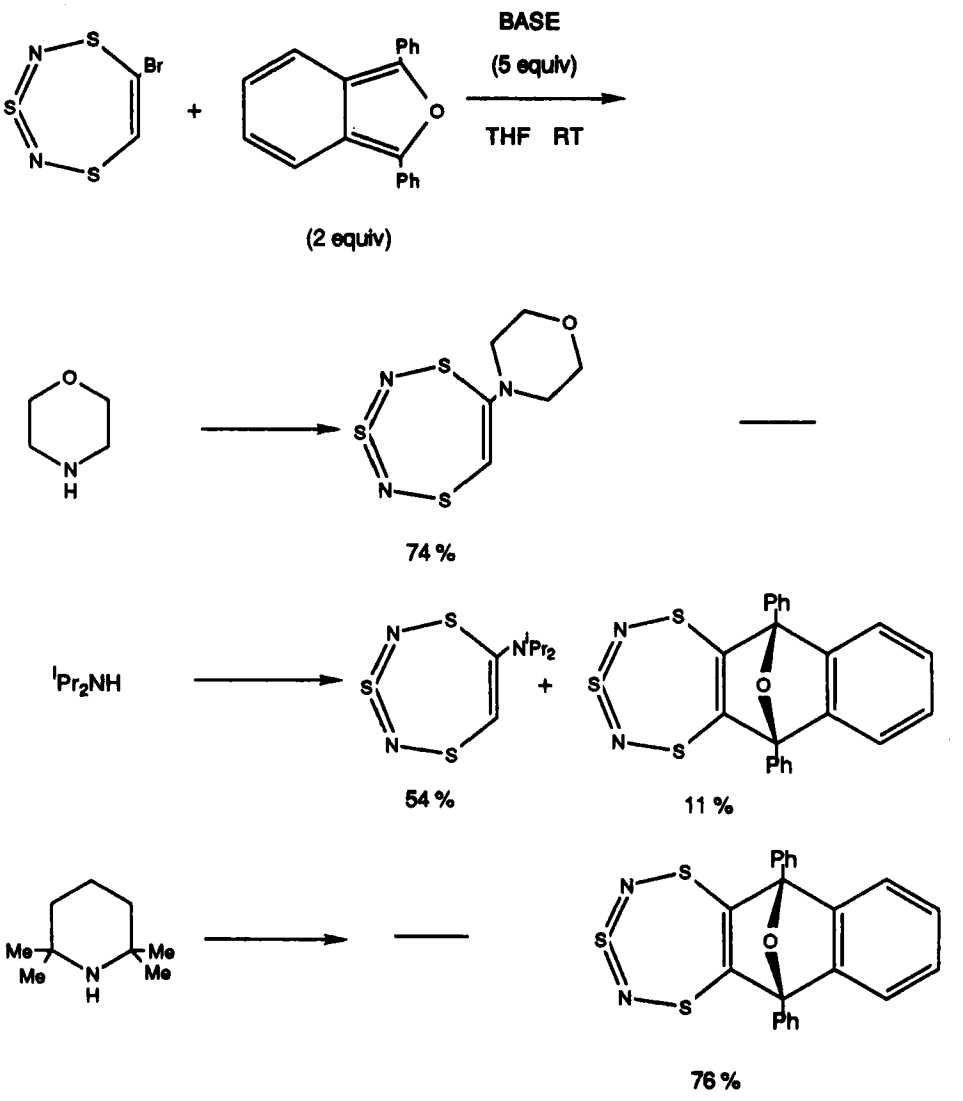


FIGURE 14

The strong nucleophile morpholine gave almost exclusively the morpholino derivative, the weak nucleophile diisopropylamine gave

the diisopropylamino derivative together with some isobenzofuran cycloadduct, and the non-nucleophilic tetramethylpiperidine gave almost exclusively the cycloadduct. With the much less reactive diene furan, diisopropylamine gave only the amine product, and tetramethylpiperidine gave much less cycloadduct (15%). Control experiments established that the cycloadduct was not destroyed by the amines used. These results thus require the involvement of a reactive intermediate that can be intercepted by both Diels-Alder and nucleophilic addition reactions.

We next studied the competition between furan and dimethylfuran for the aryne generated from three precursors, the chloro, bromo, and iodo-trithiadiazepines (Fig. 15). The molar ratios of the two furans were adjusted to give approximately equal amounts of the two cycloadducts as shown. The ratio of the

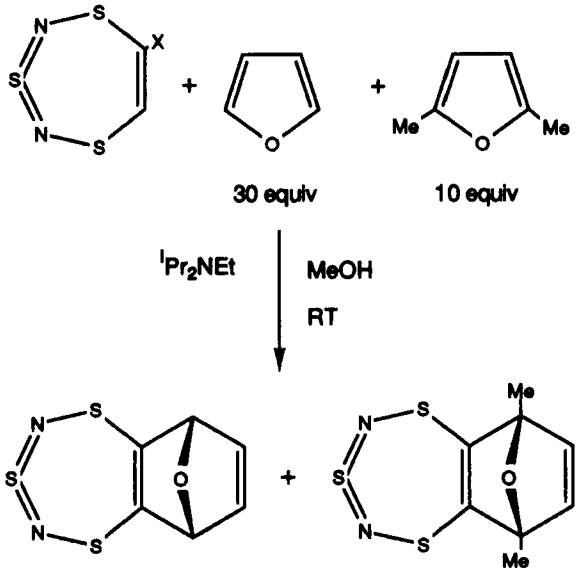


FIGURE 15

aryne adducts from each precursor was carefully determined by ^{1}H nmr on the total reaction product. The three ratios were found to be identical within experimental error; they are actually closer than the analogous figures for benzyne cycloadditions.[7] Thus the same species is presumably undergoing the Diels-Alder reactions in each case, and the hetaryne (3) seems to be the only reasonable candidate.

On the basis of an aryne mechanism the rate of cycloadduct formation should be independent of the nature of the diene. With this in mind we estimated, qualitatively, the rate of consumption of the bromo compound in the absence and presence of dienes, under standard conditions (Fig. 16). The solvent mixture of methanol (45%) and THF (55%) was selected to give convenient reaction rates, and the times shown are for disappearance of the starting bromide (5); (5) could be clearly monitored by thin layer chromatography. This time did depend upon the presence and structure of the diene; it fell from 9 to 2 hours in the presence of the diphenylisobenzofuran (1 equiv.) and to 3.5 hours with the less reactive dimethylfuran. To explain this we assume that formation of the aryne and bromide from the trithiadiazepine carbanion is reversible (as in the analogous formation of benzyne), and bromide ion is competing with diene for the aryne. This was further supported by the much slower consumption, from 9 to 55 hours, of bromide (5) in the presence of an excess of Hünig base hydrobromide (10 equiv.). Added bromide ion would increase the rate of reversal of aryne to bromocarbanion, but this effect is swamped by the highly reactive isobenzofuran (Fig. 16).

If the aryne does react with bromide ion it should react similarly with iodide; this was demonstrated by ready conversion of bromo compound (5) into the corresponding iodo compound with tetrabutylammonium iodide (Fig. 17). (The iodo compound is also formed when (5) is treated with Hünig's base in the presence of

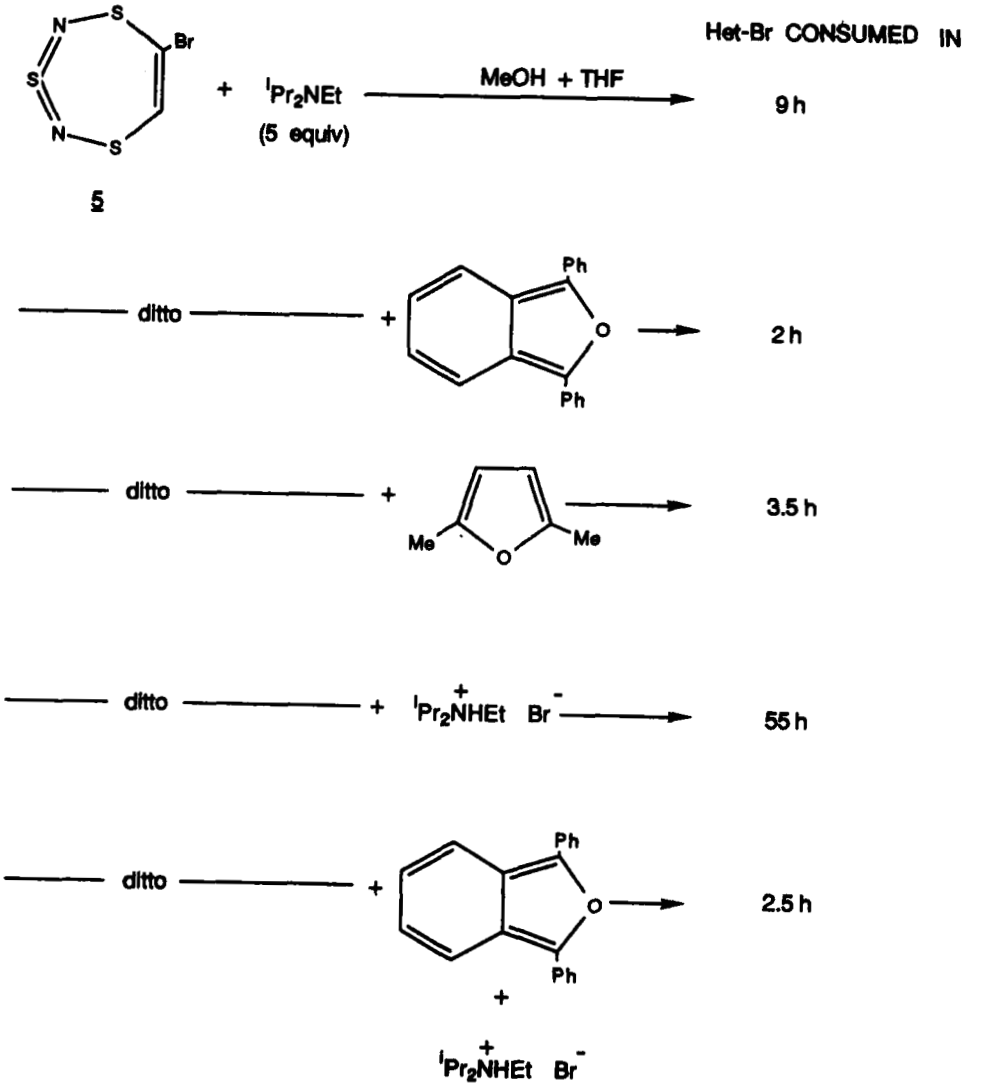


FIGURE 16

the quaternary iodide, but the reaction is less clean and the yield is lower since Hünig's base also reacts with the iodotrithiadiazepine). We see, in Fig. 17, that iodide ion not only reacts with the aryne but is nucleophilic enough to generate it via the carbanion! So also is bromide ion since tetrabutylammonium

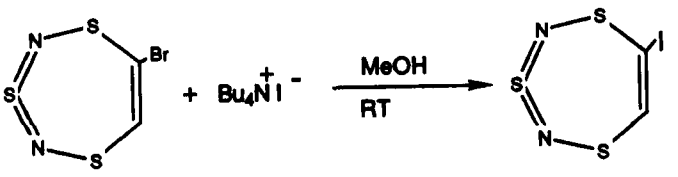


FIGURE 17

bromide accelerates the rate of hydrogen-deuterium exchange (described earlier).

All of these results lead most reasonably to the overall reaction scheme shown (Fig. 18), where the aryne (3) is formed reversibly via the carbanion and then reacts irreversibly with dienes and most nucleophiles. The initiating base, B, can be an amine, amide ion, alkoxide or phenoxide and their sulphur analogues, bromide or iodide. If there is no diene or nucleophile present to intercept the aryne the reaction is messy; the dimer and trimer of the aryne are not formed in detectable amounts. With these interesting compounds in mind we hope to synthesise trithiadiazepines analogous to those benzyne precursors, such as 1-aminobenzotriazole or benzenediazonium carboxylate, which are known to yield the dimer and trimer of benzyne.

Perhaps the most puzzling feature of the scheme in Fig. 18 is the very ready formation of the carbanion and its presumed stability. Its negative charge can be considerably delocalised into the polyheteroatom ring if carbene-like canonical forms are considered (Fig. 19); this is analogous to the well known stabilisation of anions on five-membered heterocyclic rings such as thiazoles (Fig. 19).[8] Stabilisation of the negative charge can also be envisaged by the adjacent (α) sulphur atom, and by the non-adjacent (β) sulphur where there is an antiperiplanar relationship between the sp^2 carbanion orbital and the antibonding σ^* C-S orbital. Furthermore we have seen that water and,

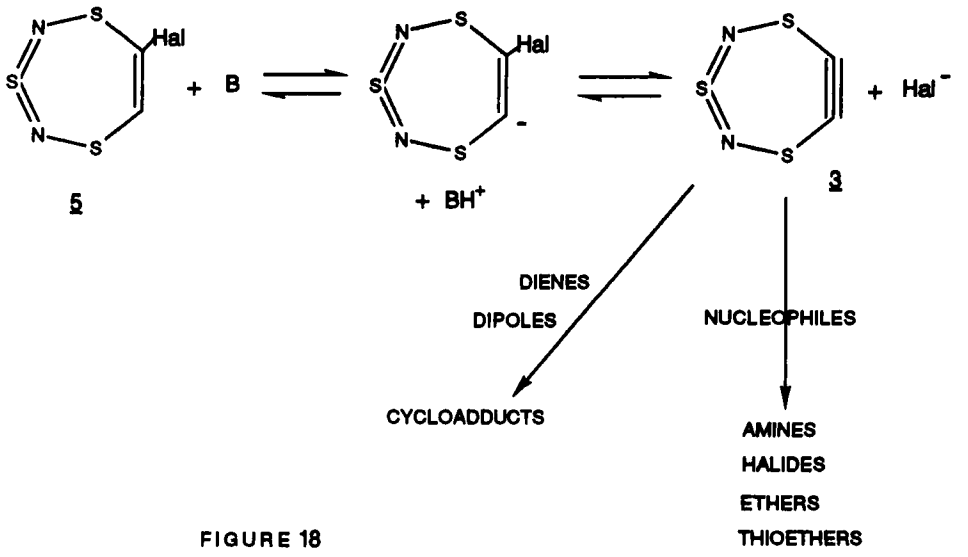


FIGURE 18

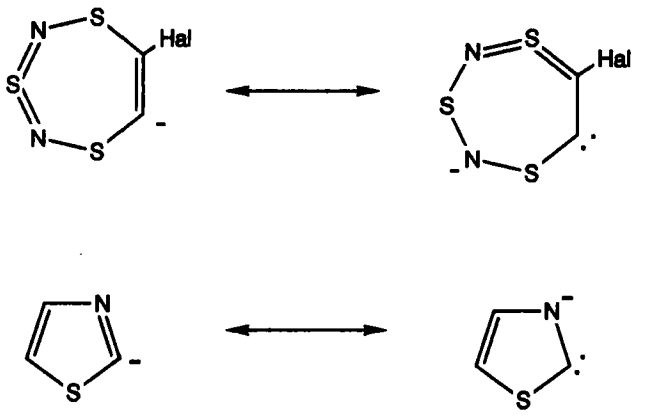


FIGURE 19

especially, methanol increase the rate of aryne formation dramatically and this could result, in part, from H-bonding stabilisation of the carbanion, though H-bonding solvation of the departing bromide and of the ring heteroatoms (activating proton

loss) are other possibilities.

We have already mentioned that the measured shape of the trithiadiazepine ring and the calculated shape of its didehydro derivative are compatible with a relatively stable hetaryne, and we now hope that with more appropriate precursors we shall be able to measure the spectra of the aryne and, just possibly, isolate it.

REACTIONS AND REARRANGEMENTS WITH CYCLOPENTADIENONES

In keeping with a relatively stable hetaryne structure, we found that dienes whose Diels-Alder reactivity is diminished for steric or electronic reasons do not intercept the aryne. Even tetracyclone (8), which is normally an excellent aryne trap, did not react with trithiadiazepyne in methanol. In THF, with tetramethylpiperidine as base, it gave the unexpected dithiin (9) in low yield (Fig. 20) together with the product (10) of reaction of the aryne with the very hindered amine used. The dithiin structure is interesting since the aryne appears to have been incorporated twice! A possible pathway for its formation is shown in Fig. 21. Normal aryne cycloaddition would give the bridged intermediate (11) from which carbon monoxide is expected to be readily extruded. Tetraphenylbenzo trithiadiazepine (12) would then have to be unstable at room temperature, unlike benzotrithiadiazepine itself, possibly because of steric compression between the buttressed phenyl rings and the "peri" related sulphur atoms. If this were sufficient to cause the heterocyclic ring to lose N_2S in some way, the resulting ortho dithioquinone (13) (or its dithiete valence isomer) could be finally intercepted by the aryne to give the dithiin (9). It was decided to explore this reaction further, firstly with phencyclone (14) (Fig. 22) in which the steric compression between the aryl substituents would probably be less than in tetracyclone. Boiling acetonitrile was found to be a good medium for the

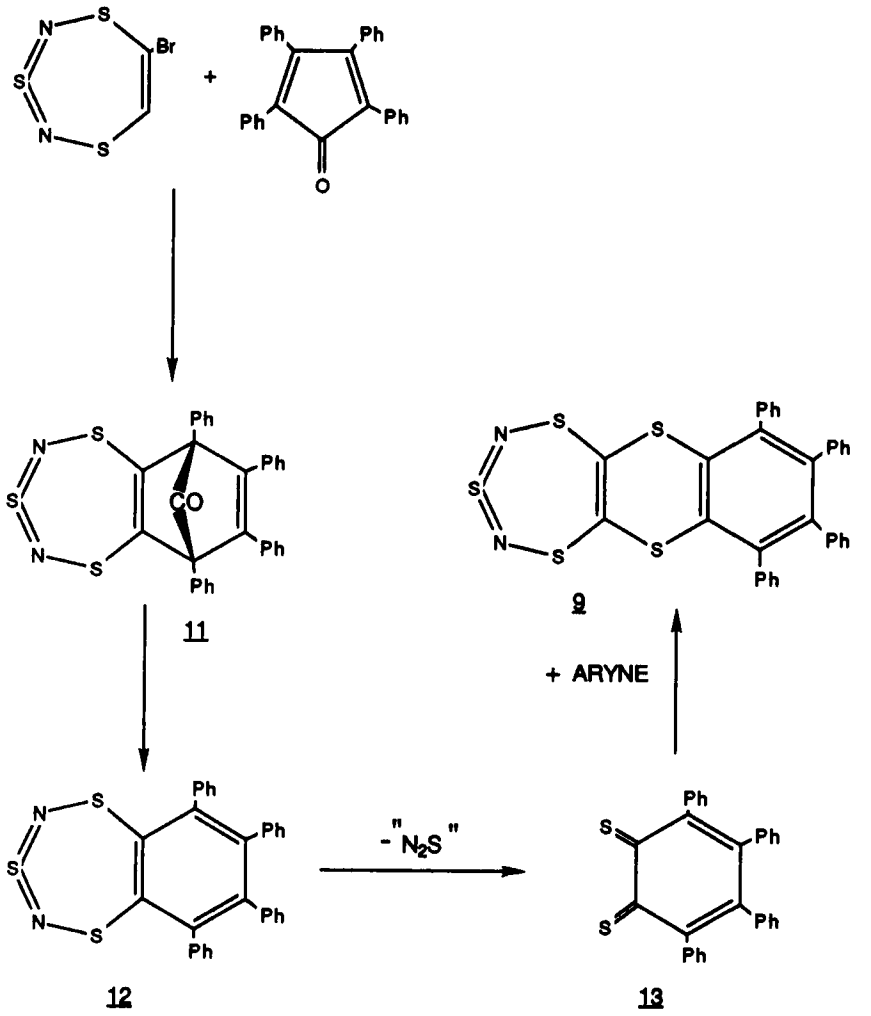


FIGURE 21

thermolysis of (18) carbon monoxide was extruded quantitatively to give the benzotrithiadiazepine (19), which on stronger heating lost N_2 to give benzotrithiole (20) (Fig. 23). It thus seemed possible that the dithiin (9) isolated in the tetracyclone reaction (Fig. 20) was derived from a trithiole, with loss of sulphur, rather than from the o-dithiaquinone (13) (Fig. 21).

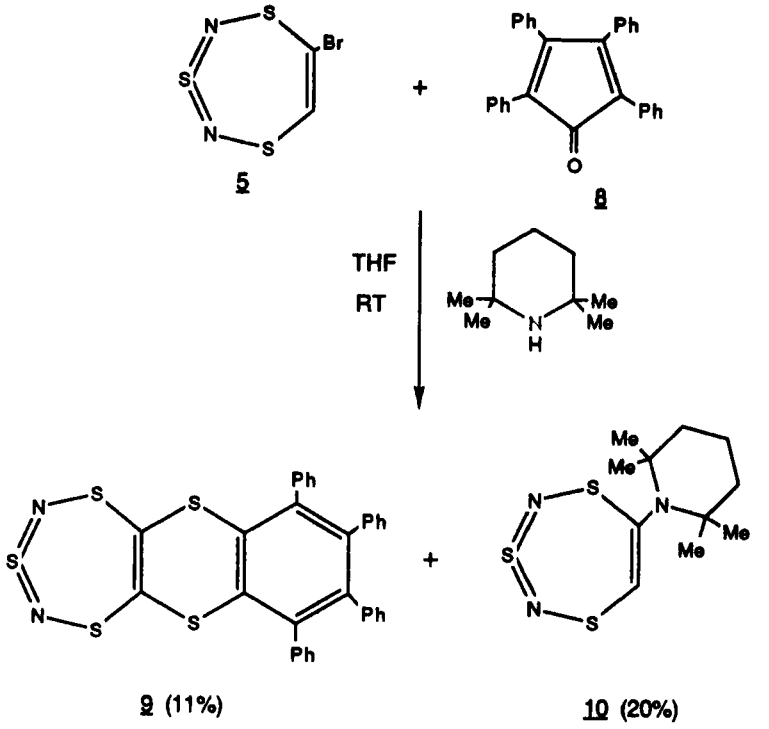
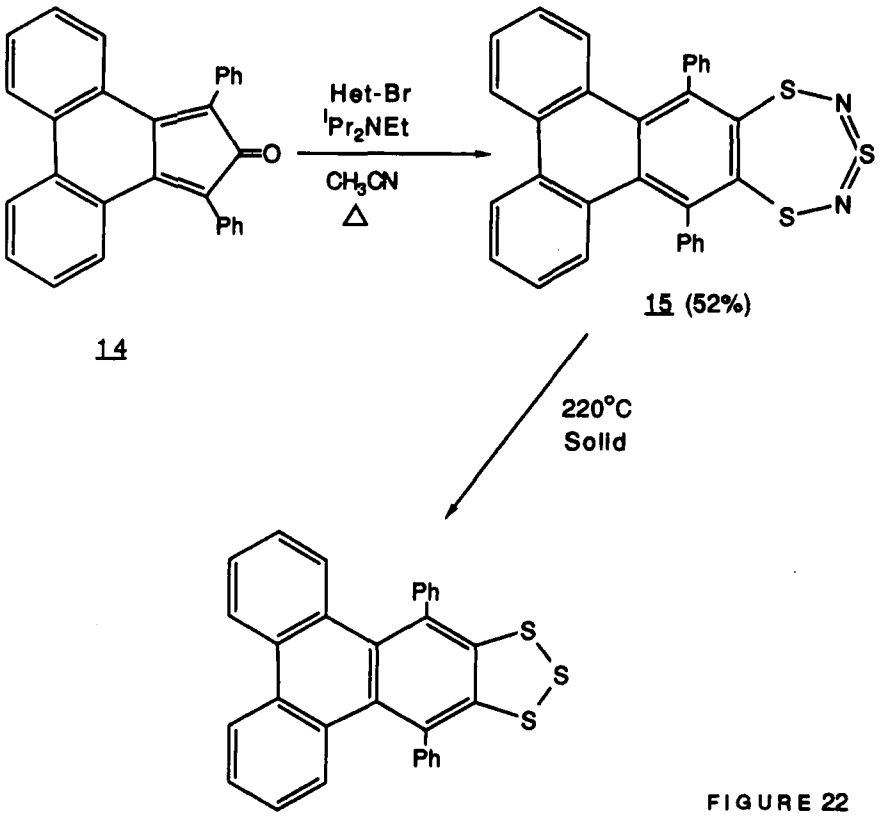


FIGURE 20

formation and trapping of the aryne with this diene; the reaction was rapid (15 min) and a reasonable yield of the analogous benzotrithiadiazepine (15) was now isolated, thus supporting the first two steps of the proposed mechanism (Fig. 21). On strong heating this product decomposed with loss of nitrogen to give the trithiole (16) (Fig. 22), with all of the sulphur atoms retained.

We then turned to dimethyldiphenylcyclopentadienone (17) as a more reactive aryne trap in the hope that we might be able to isolate an earlier intermediate in the reaction sequence, and in this we were successful since we could now isolate the initial cycloadduct (18) in reasonable yield (Fig. 23). Such norbornadien-7-ones are normally very elusive species.[9] On mild



14

15 (52%)

16 (47%)

FIGURE 22

In the hope of throwing light on this problem we turned to methyltriphenylcyclopentadienone (21), of reactivity intermediate between the tetraphenyl and dimethyldiphenyl analogues. This aryne trap did indeed give both a dithiin (22) and a trithiole (23), though in low yields (Fig. 24). However, this meant that we could explore the proposed conversion : trithiole + aryne ⟶ dithiin under the aryne-generating conditions, and we found no sign of this transformation (Fig. 24). Furthermore, when the aryne reaction with methyltriphenylcyclopentadienone (21) was run in the presence of S_8, dithiin (22) was no longer observed,

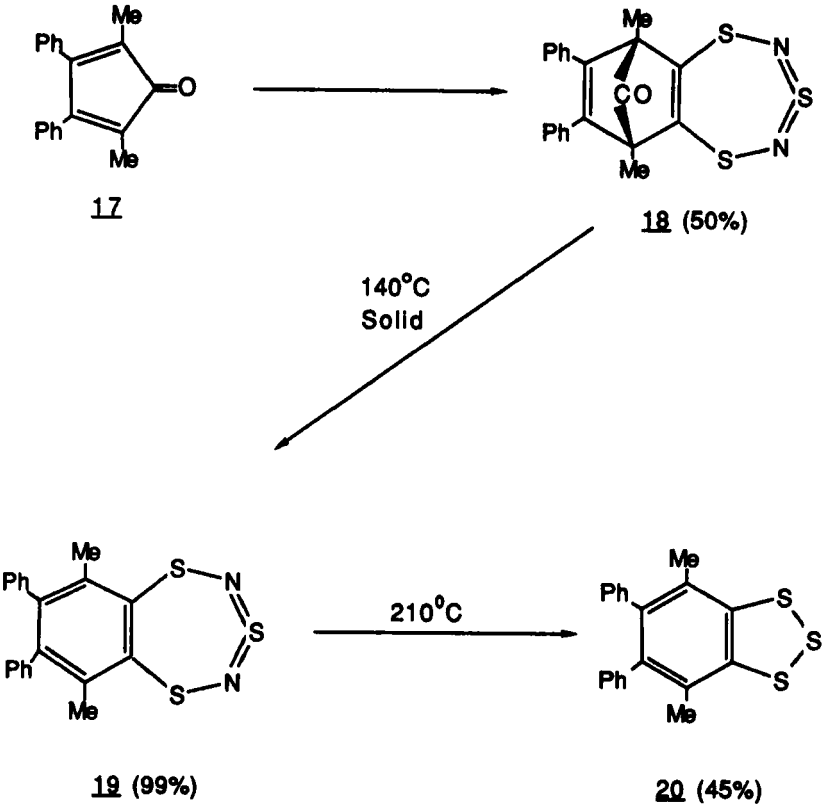


FIGURE 23

but more trithiole (23) (35%). On the basis of the evidence so for available the simplest overall scheme would appear to be as shown in Fig. 25 (the cyclopentadienone substituents are omitted for clarity). When the methyltriphenylcyclopentadienone reaction was run in the resence of dimethyl acetylene dicarboxylate (E-≡-E) the new dithiin (24) was formed to the exclusion of the dithiin and trithiole products shown in Fig. 24. It is not known how N_2S is lost, but possible mechanisms are shown in Fig. 26. Ring contraction of the 7-membered heterocyclic ring by N-N bond formation could be encouraged by the steric compression invoked earlier. This could be followed by rearrangement to an

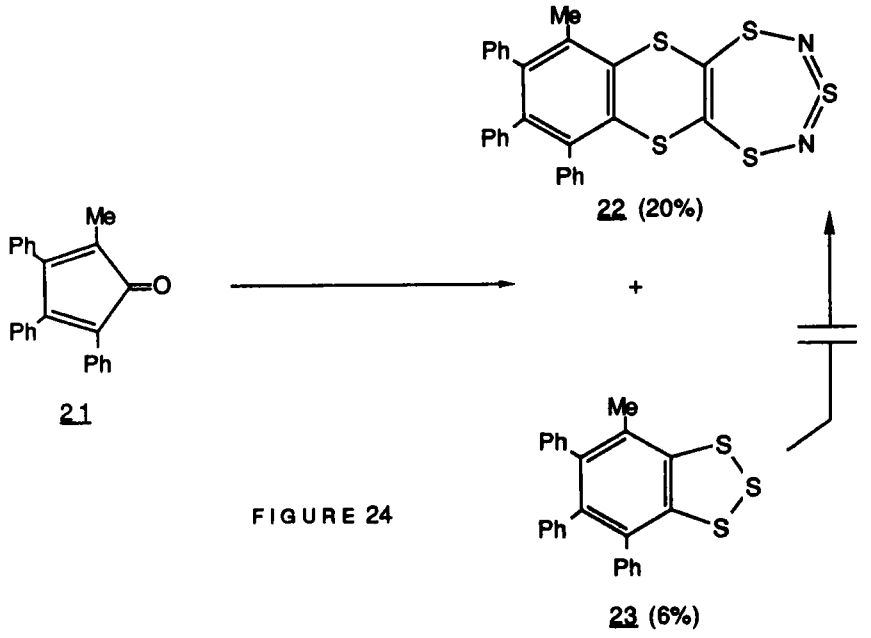


FIGURE 24

unstable N-sulphide (25) which could lose S and N_2 to give the proposed dithiaquinone or could rearrange to an isomeric trithiadiazepine (26) which would readily lose N_2 as shown. The reactive S_3 species so produced could then collapse to a trithiole or undergo cycloaddition with the aryne or dimethyl acetylenedicarboxylate with loss of the third sulphur atom occurring at the end of the sequence.

REACTIONS AND REARRANGEMENTS WITH DIAZOALKANES

We have seen that dienes of low Diels-Alder reactivity do not intercept the aryne; the same applies to 1,3-dipoles. Thus the aryne did not react with azides and nitrones, though it formed high yields of the expected cycloadducts (e.g. 27) with diaryl diazomethanes (Fig. 27). The fused bicyclic products are stable crystalline solids which have been fully characterised. Since they are cyclic azo compounds they could, on pyrolysis, lose nitrogen to yield other fused trithiadiazepine derivatives. On

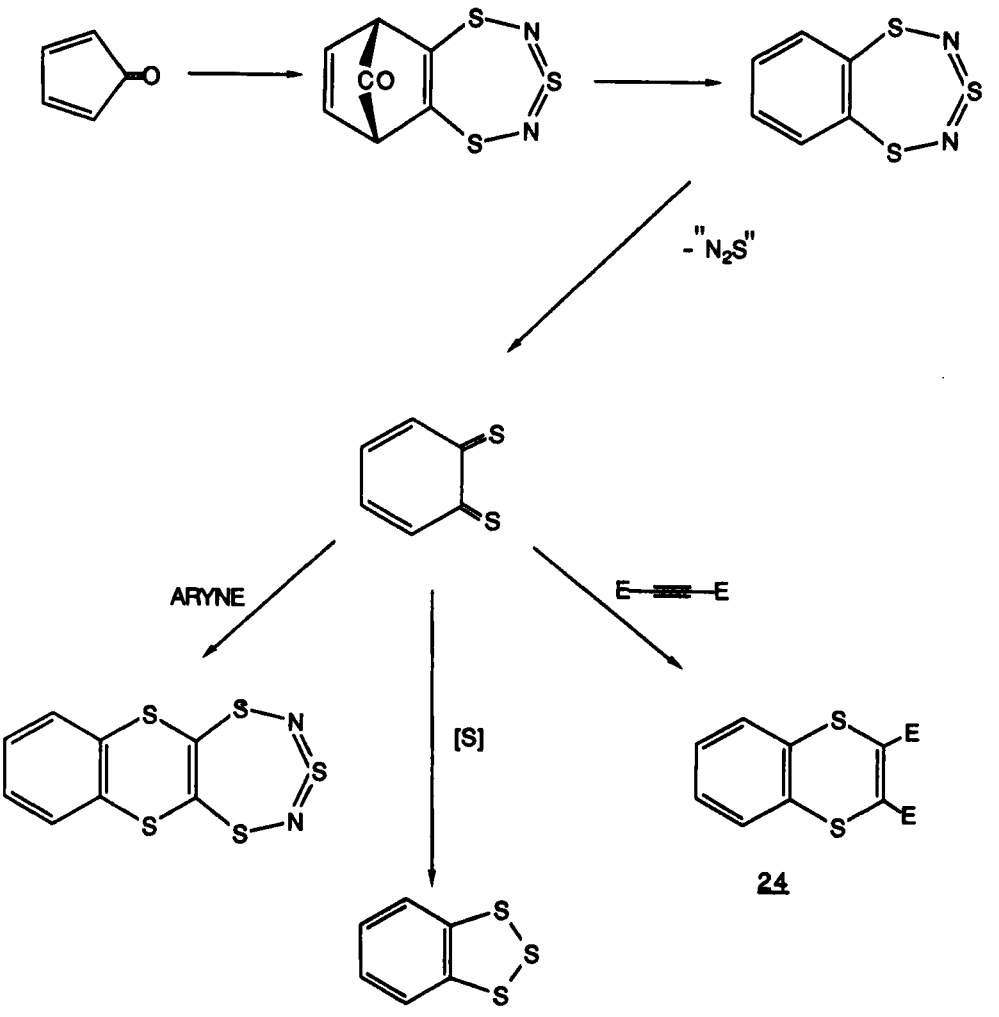


FIGURE 25

very brief heating of the crystalline solids at about 200°C, rapid decomposition occurred, with vigorous gas evolution, to form deeply coloured products which were found, by X-ray crystallography,[10] to be the first examples of a 5-5 ring fused

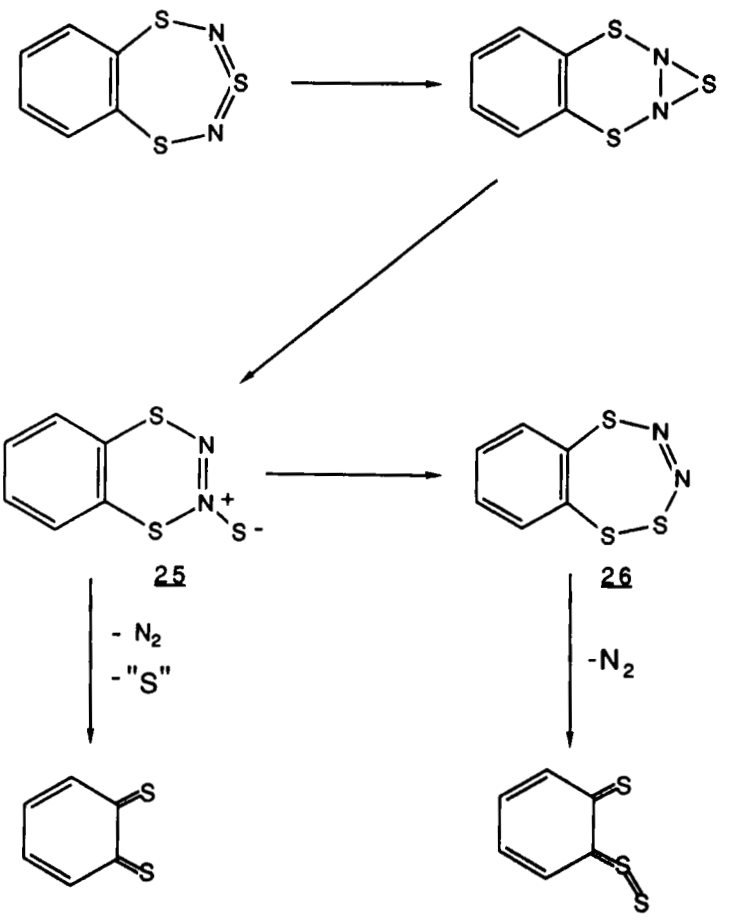
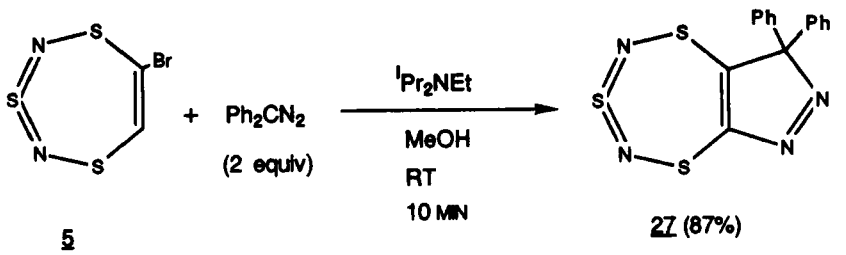


FIGURE 26

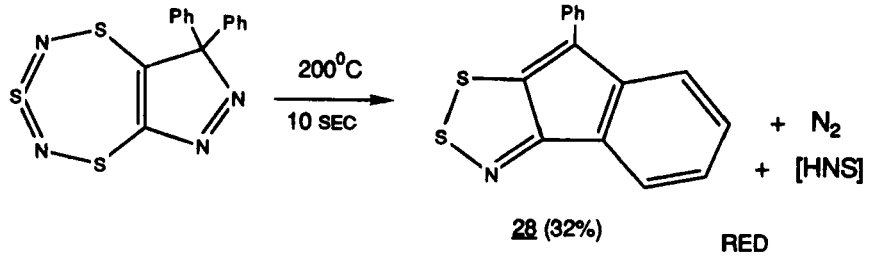
system (e.g. 28); the diphenyl compound is typical (Fig. 28). On the basis of spectroscopy and elemental analysis we had deduced the isomeric structure (29) for this product, where the alternation of S and N atoms is preserved; it remains to be seen whether (29) is an intermediate on the way to (28).

In this deep-seated and unexpected rearrangement, the trithiadiazepine ring (normally so stable thermally) has not



5 27 (87%)

FIGURE 27



28 (32%) RED

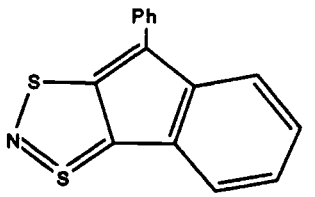
NOT  29

FIGURE 28

survived the extrusion of nitrogen from the 5-membered ring and the resulting molecular rearrangement; the elements of HNS have also been extruded. Whilst the fine details of this ring contraction and rearrangement are not yet known, a reasonable overall process is shown in Fig. 29.

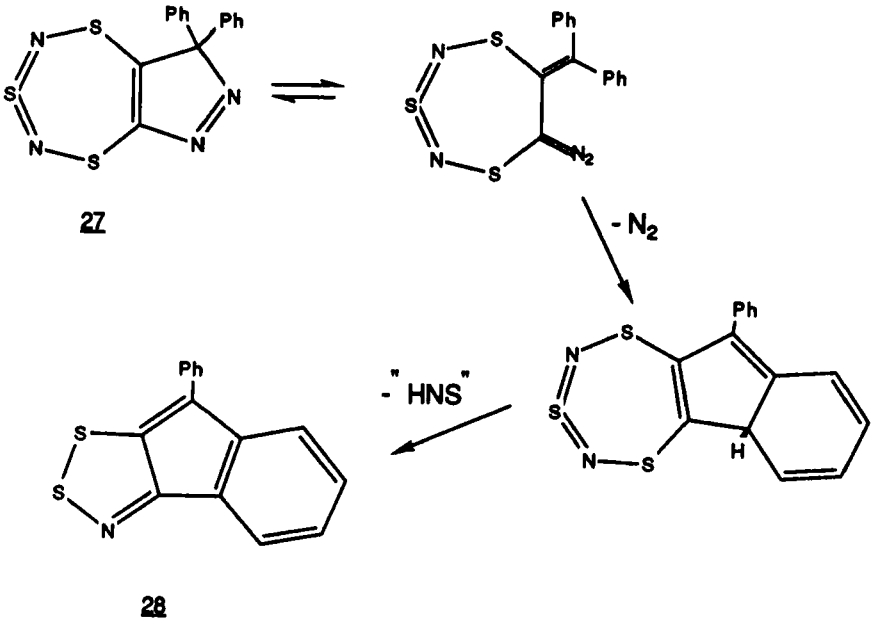


FIGURE 29

We are investigating the scope and mechanism of this unusual rearrangement, together with the chemistry and independent synthesis of its products.

We are also exploring the structural and synthetic chemistry of the trithiadiazepinylamines described here. These are now readily available by the hetaryne pathway which we believe to be firmly established.

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