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Azirines as Synthons for Other Heterocycles

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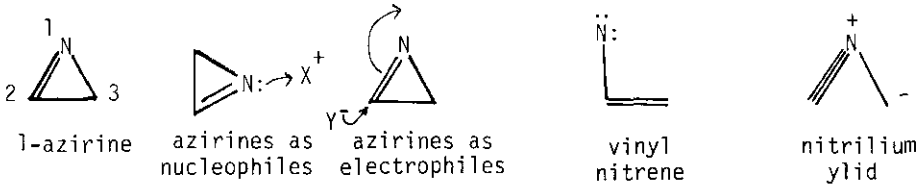
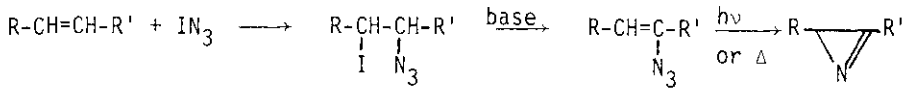
Azirines (azacyclopropenes), the smallest of the nitrogen heterocycles, are a versatile group of reactive small ring molecules. Since the antiaromatic, 4π-electron, 2-azirines are as yet unknown, we shall discuss here solely the readily available 1-azirine ring system. These compounds are not only capable of acting as nucleophiles through N and as electrophiles at the C of the C=N, but they can act as 2π-components or as 4π-components as well. In fact, all three bonds of the 3-membered ring are capable of cleavage during reaction.



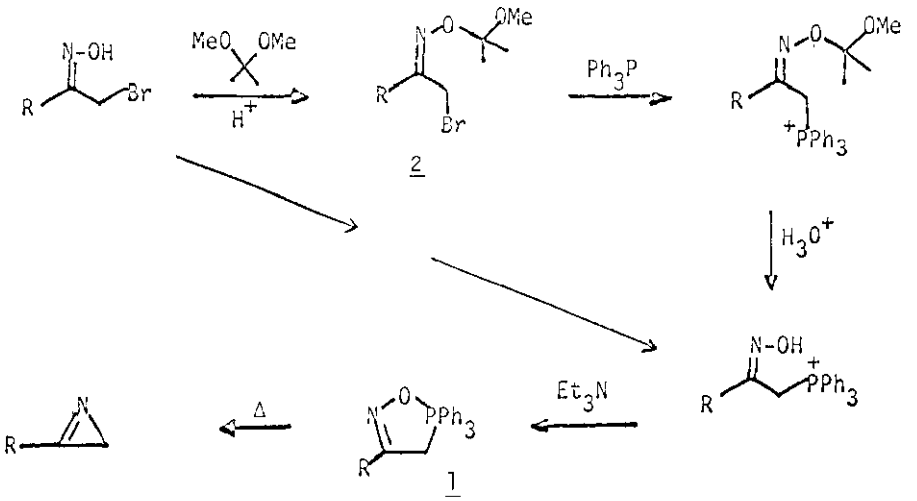
1-azirine | azirines as nucleophiles | azirines as electrophiles | vinyl nitrene | nitrilium ylid

Thus, formal ring cleavage of the C-N bond leads to a vinyl nitrene, whereas C-C bond breaking produces a nitrilium ylid. One can, therefore, readily imagine that reaction of 1-azirines with multiple bonds can lead to a variety of larger ring heterocycles.

Several syntheses of azirines are now available. The most general one starts with an olefin, which is converted in three simple, high yield steps[1] (iodine azide addition, H-I elimination and photolysis or thermolysis) into an azirine as shown

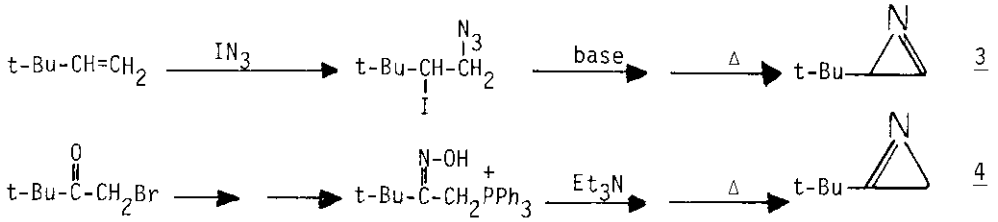


Because the structure of the final product depends on the effect of R' on the highly regioselective IN_3 addition, we have devised an alternate method starting with readily available α-bromoketoximes. The sequence proceeds via α-phosphonium ketoximes which in basic medium are present as the stable isolable oxazaphospholines 1. The latter are known to undergo thermolysis to 1-azirines.

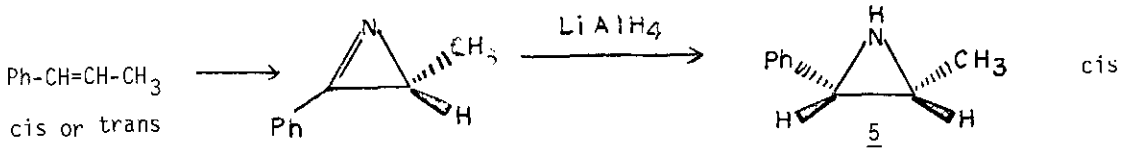


Since phosphine displacement on α-haloketoximes sometimes leads to side reactions, it is advantageous to first protect the oxime function as an acetone ketal 2 prior to displacement. This is followed by mild acid hydrolysis ($HCl-H_2O-MeOH$) and ring closure to 1 with triethylamine. The whole sequence of steps can be carried out in one pot.[2]

That the two methods are complementary is illustrated by the synthesis of 3-t-butyl and 2-t-butyl-1-azirine 3 and 4 respectively:



Addition of nucleophiles to the C=N of azirines proceeds readily and stereospecifically from the least hindered side of the molecule. Even hydride (from $LiAlH_4$) adds stereospecifically to produce cis-aziridines.[3] This permits a stereospecific synthesis of cis-1,2-di-substituted aziridines 5, starting from a stereoisomeric mixture of olefins.



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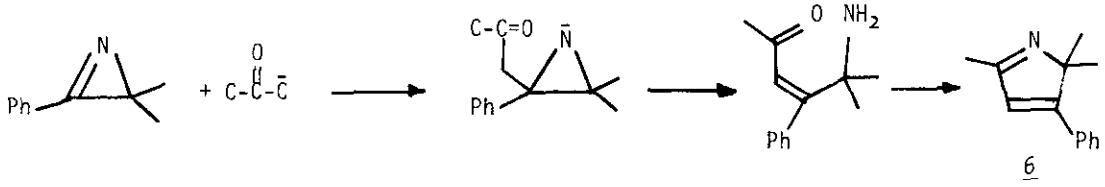
A variety of carbanions have been added to azirines. In the case of ketone enolates, 2H-pyrroles 6 have been isolated by Laurent and coworkers.[4]



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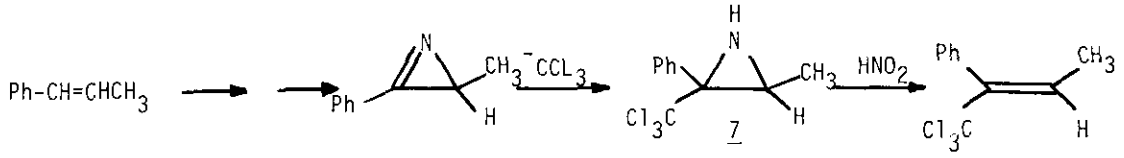
Trichloromethide anion also adds stereospecifically and the adduct 7 can be deaminated with retention of configuration, thus providing a stereospecific synthesis of trisubstituted alkenes from certain 1,2-disubstituted olefins.



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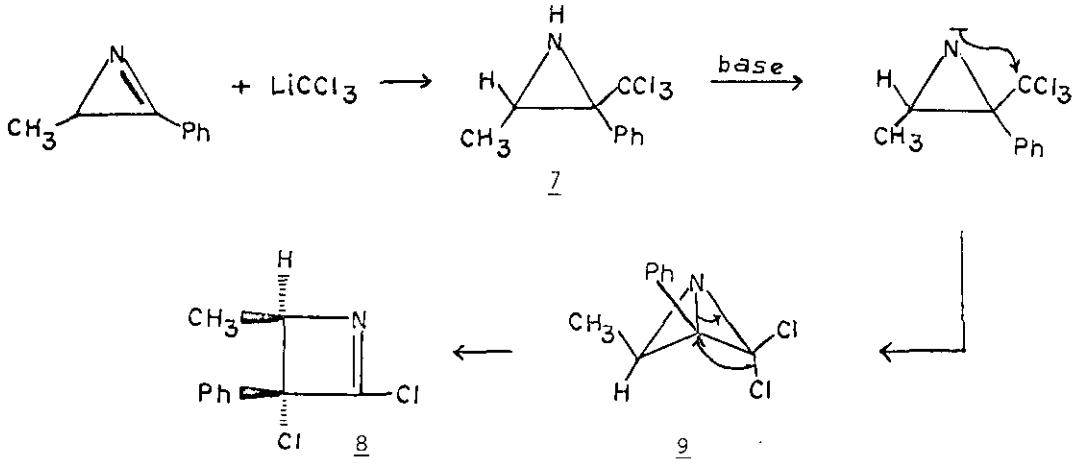
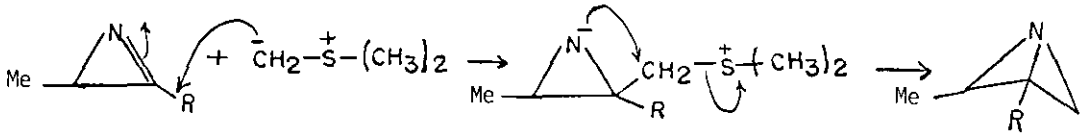
Attempted ring-closure of 7 to an azabicyclobutane lead to isolation of the 4-membered ring azetine 8. The unique stereochemistry of 8 suggests that the bicycle 9 may be an intermediate and is rearranged by an intramolecular

chloride shift.[5]



7 8 9

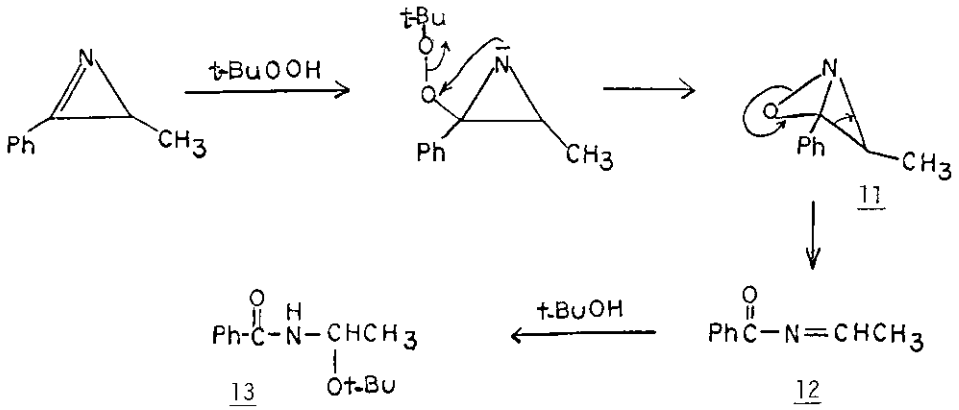
A bonafide non-chlorinated azabicyclobutane 10 can be obtained by dimethylsulfonium ylid addition to an azirine.[6]



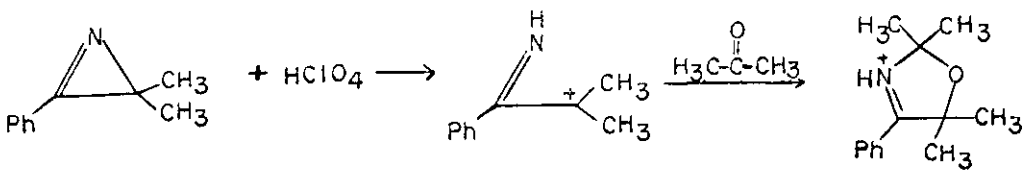
10

The spectral properties, especially ^{13}C data, of the bicycle 10 differ drastically from those of the 4-membered ring 8.

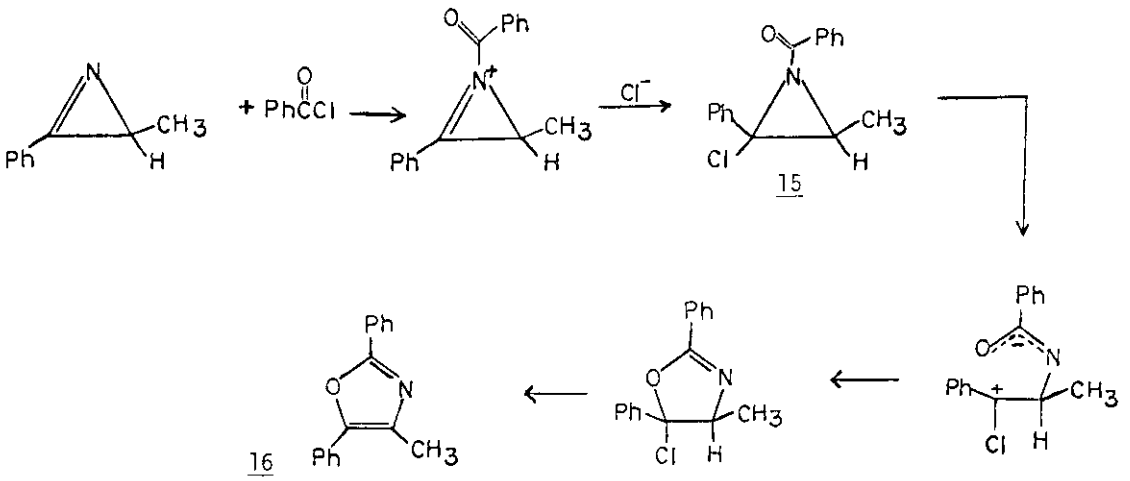
Attempts to epoxidize azirines have failed so far to produce oxazabicyclobutanes 11. When t-butylhydroperoxide is employed, the acylimine 12 or its alcohol addition product 13 can be isolated. It is possible, though not necessary, that 11 is an intermediate in the reaction.[7]



The basicity of the nitrogen in 1-azirines is much weaker than that in corresponding open chain imines. For instance, most azirines are insoluble in 5% HCl but dissolve in conc. HCl. Similarly, no reaction occurs with methyl iodide or benzyl chloride and ^{13}C-H coupling in azirines suggest a high degree of s-character for the exocyclic bonds and thus for the unshared electron pair on nitrogen. Yet, reaction occurs with a variety of acidic reagents, presumably via azirinium ion species. Thus, anhydrous perchloric acid in acetone leads via ring opening to oxazoline 14.[8] Better nucleophiles (even Cl^-) are able to

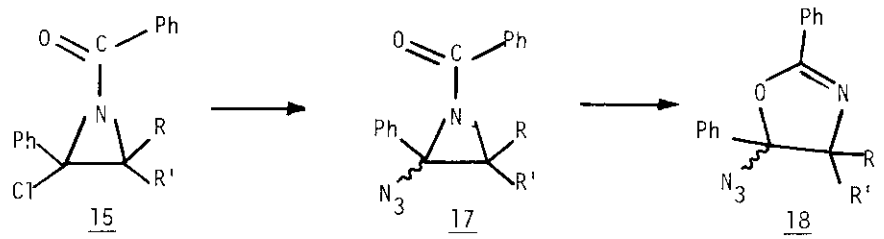


add to the primarily formed azirinium ion, so that adducts such as 15 can be isolated from reaction of acid chlorides with azirines.[9] In polar solvents 15 ring opens by solvolysis thus leading to cleavage of the original C=N with

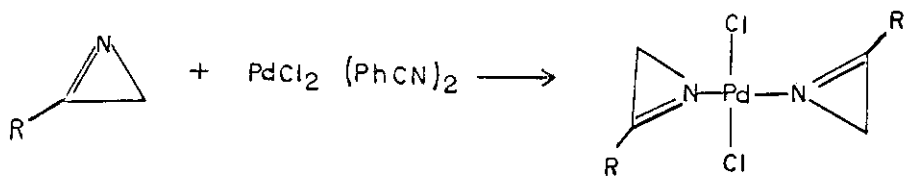


formation of oxazole 16. Note that the regiochemistry of 15 and 16 are opposite because a different reaction pathway is followed.

The formation of 15 appears to be reversible because it reacts fast with azide ions to produce a stereoisomeric mixture of azidoaziridine 17. The latter readily rearranges in polar medium to azidooxazoline 18.[10]



1-Azirines also form very stable square planar complexes 19 with Pd or Pt salts. The slightly shortened Pd-N bond (x-rays) suggests metal backbonding from Pd to N.[11]



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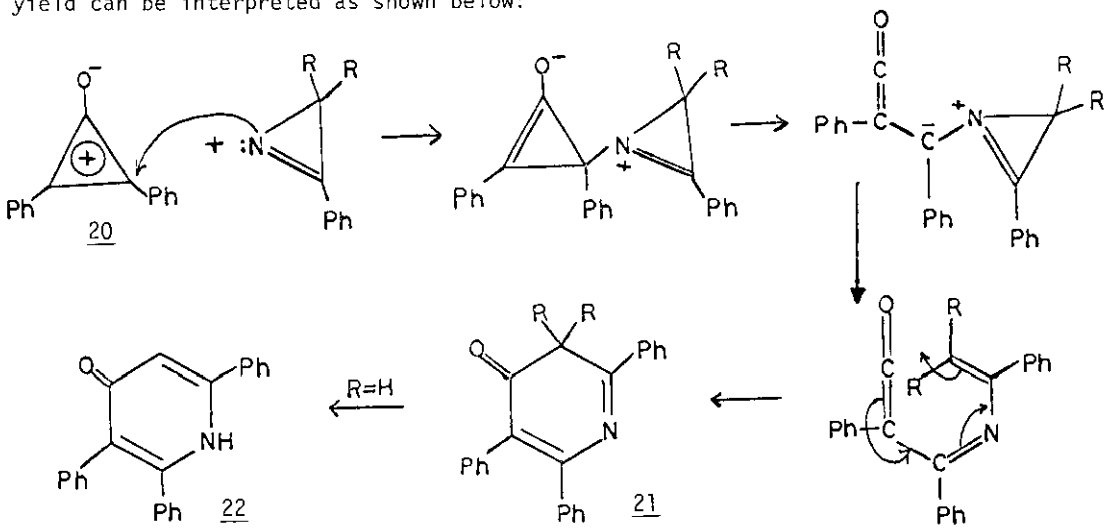
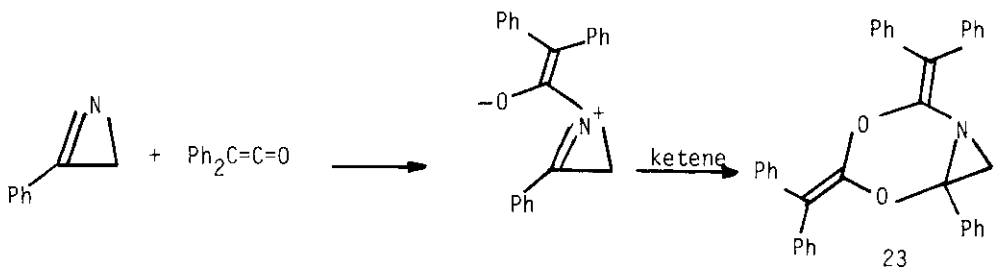
Apparently azirines are sufficiently nucleophilic to react with diphenylcyclopropenone (see dipolar structure 20). The formation of 4-pyridones 22 in good yield can be interpreted as shown below:[12]

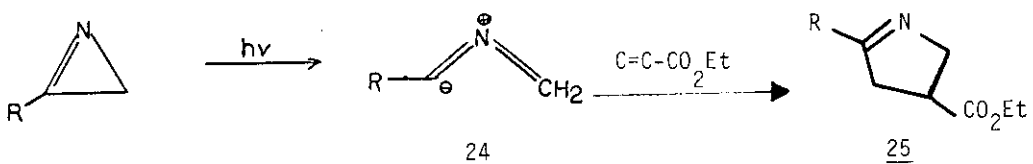


When R:CH_3 the product isolated is the geminally substituted pyridone 21.

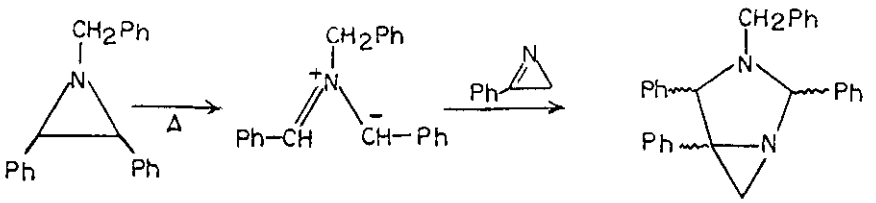
Ketenes are also attacked by azirines but in this case 2:1 adducts 23 are formed.[13]



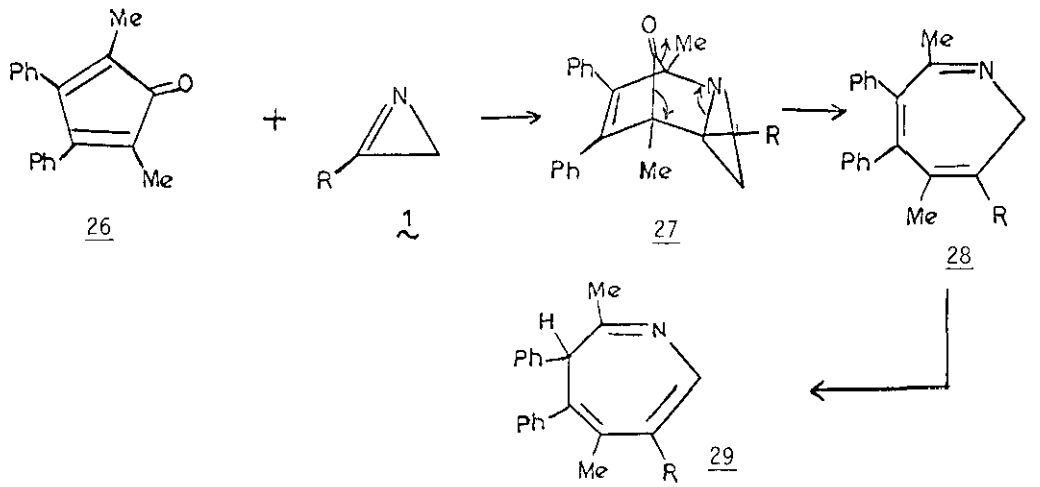
Photolysis of 1-azirines produces nitrilium ylid intermediates 24 which can be trapped by various dipolarophiles to form five-membered ring heterocycles (e.g., 25).[14]



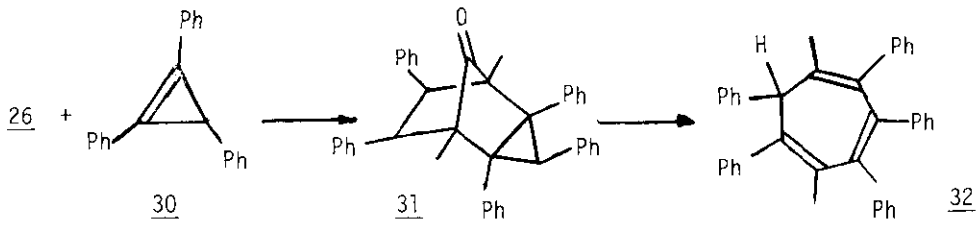
The C=N of azirines is capable of serving as the 2π-component in 2 + 4 cycloadditions. Reaction with 1,3-dipoles occurs readily as shown in the example below:[15]



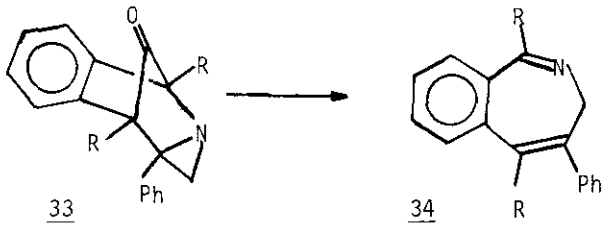
With cyclopentadienones 26 a clean thermal reaction takes place leading to 3H-azepines 29 with expulsion of CO. The structure of 29,[16] based largely on nmr and mass spectra, indicates cleavage of the C=N in the azirine and suggests a Diels-Alder addition to the cyclopentadienones 26. Although the logical intermediates 27 could not be isolated, reaction of 26 with 30, the carbocyclic

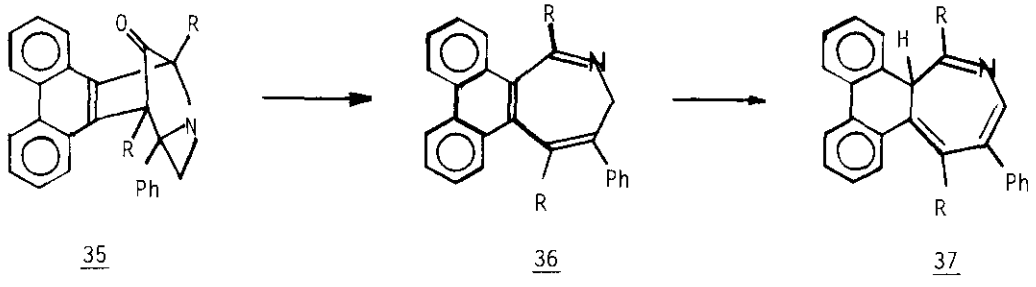


analogue of azirines lead to quantitative formation of tricyclic ketone 31. Heating of the latter produced 32, the carbocyclic analogue of 29.

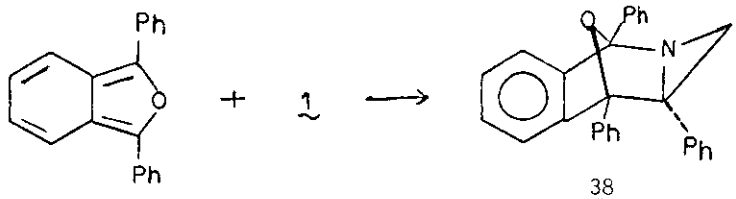


The two most likely pathways from 27 to 29 involve thermal loss of CO either (a) with concomitant involvement of the double bond or (b) with opening of the three-membered ring. In systems such as 33 and 35 where double bond migration is unfavorable because of the presence of the aromatic rings, pathway (b) is followed and 2H-azepines 34 and 36 (normally such are unstable azepine isomers) are isolated. Of the latter, 2H-azepine 36 rearranges by a thermally allowed 1,5-H shift to the 3H-azepine 37. This indicates that pathway (b), namely 27 → 28 → 29 is involved in these transformations.[16]





An endo attack by the azirine is suggested, leading to endo 33 which undergoes an allowed concerted disrotatory ring opening with loss of CO. Evidence for such a process is provided by the isolation of a thermally stable exo adduct in the carbocyclic series related to 33. Apparently an exo adduct 38 is also isolated from the isobenzofuran analog.[17]



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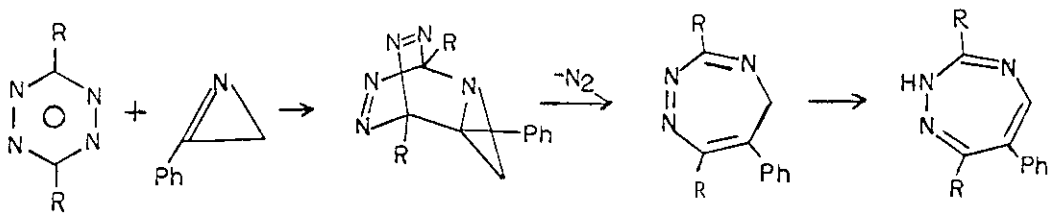
A Diels-Alder reaction followed by loss of N_2, instead of CO, is also involved in the formation for triazepines 42 from reaction of tetrazines 39 with azirines. 40 and 41 are logical intermediates. Further thermolysis of 42 leads



39 40 41 42

to a variety of other heterocycles, including pyrimidines, triazoles, pyrazoles.[18] The possible pathways of these reactions will be discussed.

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References

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