Review Article

Ring-Opening of Five-Membered Heteroaromatic Azides and Nitrenes

Wim Dehaen[a] and Jan Becher[b]

[a] Department of chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Heverlee, Belgium and [b] Department of Chemistry, Odense University, DK-5230, Odense-M, Denmark

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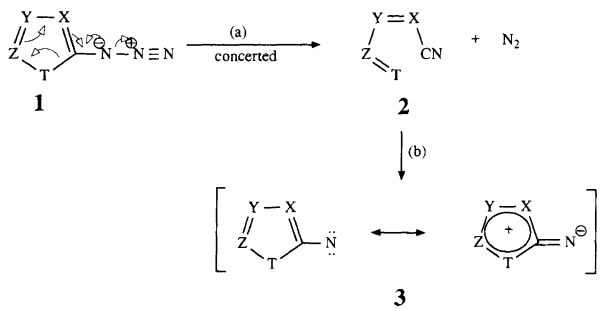
This review article gives an account of the ring-opening of five-membered heteroaromatic azides and nitrenes.

It is concluded that this reaction is quite general, leading to ring cleavage and in many cases subsequent ring-closure reactions. The following heterocyclic systems are discussed in detail: furans and benzofurans, thiophenes and benzothiophenes, pyrroles and fused pyrroles, isoxazoles, oxazoles, isothiazoles and benzoisothiazoles, thiazoles, pyrazoles and indazoles, imidazoles and fused imidazoles, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,3,4-triazoles and 1,2,4-triazoles.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

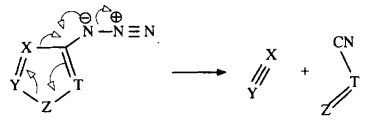
Starting with the pioneering efforts of P. A. S. Smith,[1] the diverse and fascinating chemistry of heteroaromatic azides and nitrenes has been investigated by many researchers. Five-membered heterocycles containing an azide or nitrene function can undergo ring-opening following one of two general schemes (see below). This has not escaped attention, being mentioned before in several reviews concerning azides and nitrenes,[2–4] and in the review by Gilchrist on the ring-opening of five-membered heterocyclic anions.[5] However, no complete account has been given so far of this cleavage reaction. The two general schemes apply to α- or β-substituted heterocycles. Starting from α-substituted azides **1**, two pathways can be considered for the formation of the nitrile **2**: (a) concerted ring-opening or (b) initial formation of a zwitterionic 'stabilized nitrene' **3**, followed by ring-opening to nitrile **2**. This reaction appears to be so general that in most cases ring cleavage competes successfully with other possible processes, such as insertion, dimerization, addition to the solvent, or ring-closure on neighbouring substituents. (Scheme 1).



1 2 3

Scheme 1.

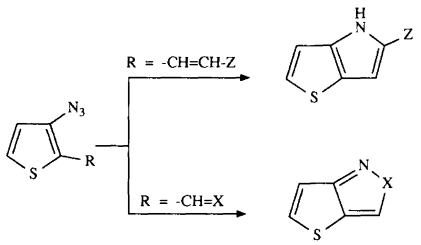
When the azide or nitrene is located in the β-position, as in **4**, a similar scheme can be drawn for ring cleavage with formation of two fragments (Scheme 2). A kinetic



4

Scheme 2.

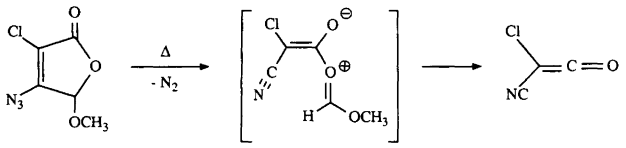
study[6] indicated a concerted mechanism. However, this cleavage is not so general[7] and, for instance, in the thiophene series insertion into a double bond[8] or cyclization with participation of the neighbouring group[9] occurs, leading to fused heterocycles (Scheme 3).



Scheme 3.

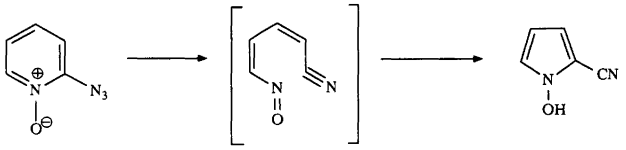
The related 'zwittazido cleavage' reaction (e.g., **5** → **6** → **7**, Scheme 4) which has been reviewed[10] and the work of Abramovitch on ring-contraction of azidopyridine oxides to *N*-hydroxypyrroles[11] (e.g., **8** → **9** → **10**, Scheme 5) and analogues[12] will not be discussed here

as this review concentrates on five-membered heteroaromatic rings. It is quite possible that the mechanisms of these reactions will be different.



5 6 7

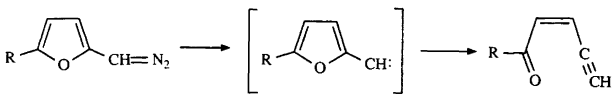
Scheme 4.



8 9 10

Scheme 5.

The isoelectronic α-diazoalkyl or carbene-sunstituted five-membered heterocycles show less consistent behaviour. In the case of furans **11** ring-opening occurs according to Scheme 1 and a conjugated acetylene **12** is formed[13,14] (Scheme 6). Analogous ring-opening reactions take place on thermolysis of oxazoles[15] or (less efficiently) thiophenes.[13] In the triazole series however, the normal carbene adducts are isolated.[16,17] Rearrangement without decomposition has been reported for 5-diazoalkyl-1,2,3-thiadiazoles and 1,2,3-triazoles.[18] Ring fragmentation according to Scheme 2 is known for only a few β-substituted diazoalkyl and carbene heterocycles.[7,19,20]



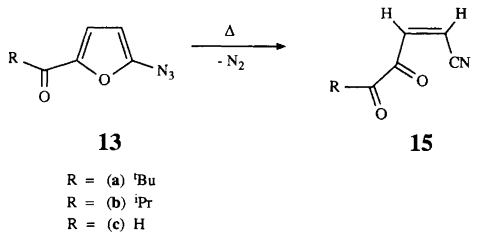
11 12

Scheme 6.

Furans and benzofurans

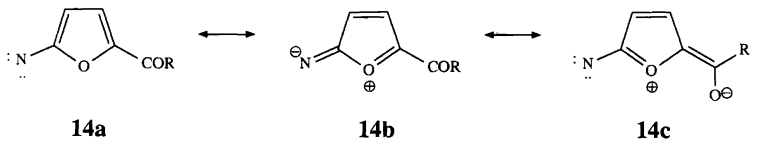
5-Acyl-2-azidofurans **13a–c** decompose at room temperature with loss of nitrogen to give the nitriles **15a–c**. The reaction shows first-order kinetics, and the rate increases as the bulk of R increases[21,22] (Scheme 7). This was explained by assuming **14** as the intermediate. For a bulky carbonyl group (which is no longer 'in-plane') the contribution of resonance form **14b** will increase, whereas that of **14c** will decrease. The resultant stabilization accounts for the increase in the rate of reaction.

2-Azidobenzo[*b*]furan **16** in benzene at 60°C showed first-order decomposition with a half-life of 15 min, forming the tetracyclic azide **18** in 50% yield. Thus, it appears that the intermediate *ortho*-quinoidal enone **17** adds to the furan ring of unchanged **16** to afford **18**[23] (Scheme 8).



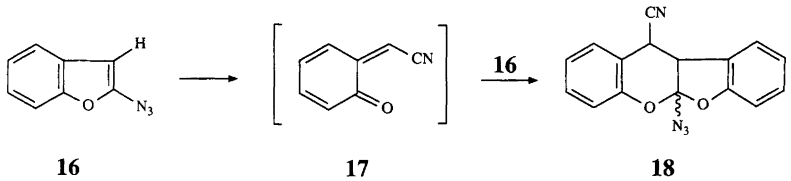
13 15

R = (a) ^{t}Bu
R = (b) ^{i}Pr
R = (c) H



14a 14b 14c

Scheme 7.



16 17 18

Scheme 8.

Thiophenes and benzothiophenes

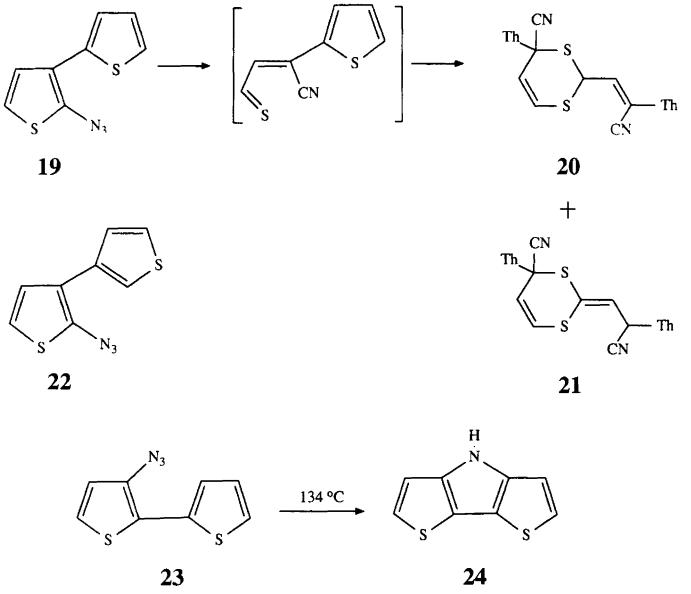
2-Azidothiophene and 2-azidobenzothiophene systems have been reported[24] to be unstable at room temperature, although no decomposition products were isolated. 2-Azido-2',3-bithienyl **19**[25] decomposed to form two 1,3-dithiines **20** and **21**. Probably the azide **19** first ring-opens to form an ene–thione, which then cyclodimerizes to **20** and partly tautomerizes to the product **21**.[26]

Decomposition of the azide **22** under the same conditions gave rise to intractable nitrile-containing materials.

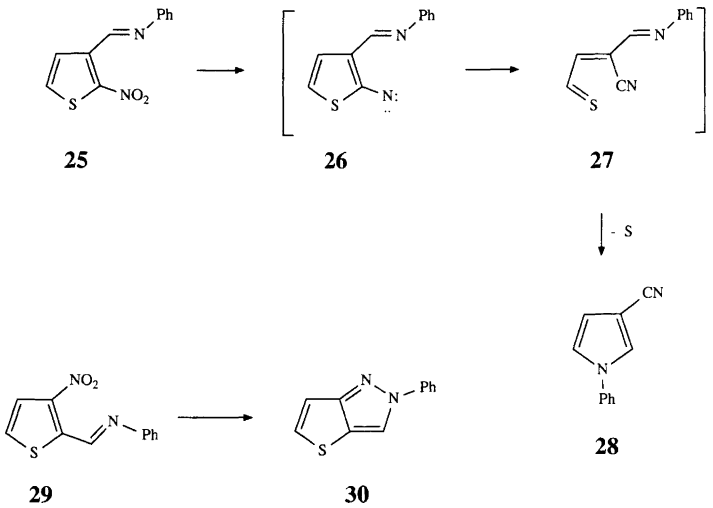
On the other hand, the 3-azidothiophene **23** required a much higher temperature for decomposition and gave the insertion product **24** in high yield (Scheme 9). The formation of insertion or cyclization products from 3-azidothiophenes is well established.[8,9,27,28] One remarkable example of extrusion of acetylene from a 3-azidothiophene through a different mechanism is known.[7]

Treatment of the anil **25** with triethyl phosphite gave 1-phenylpyrrole-3-carbonitrile **28** as the main product. Formation of a nitrene, **26**, probably precedes ring-opening to nitrile **27**, which again ring-closes with loss of sulfur to afford ultimately the pyrrole **28**. The isomeric anil **29** under these conditions gives only the expected thieno[3,2-*c*]pyrazole **30**[29] (Scheme 10).

The thermal fragmentation of the 2-azidobenzothiophene system **31** in the presence of alkenes has been thoroughly studied by Spagnolo and Zanirato.[24,30–32] Decomposition of **31** in benzene at 60°C gave mainly an unresolved mixture of *E*- and *Z*-dibenzo[*bf*]dithiocine-6,12-dicarbonitrile **32**. Again it was suggested that ring-cleavage fragmentation gives an ene–thione intermediate **33**, which

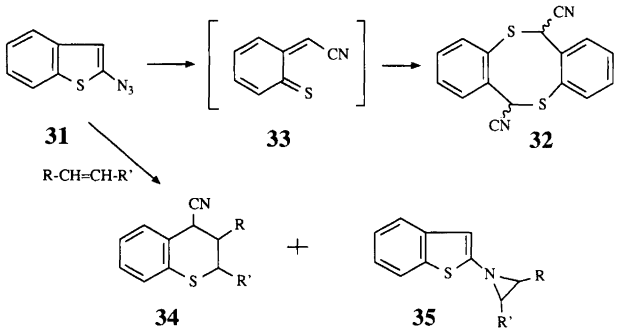


Scheme 9.



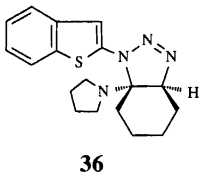
Scheme 10.

cyclodimerizes to the nitriles **32**. An analogous cyclodimerization is known in the literature.[33] In the presence of alkenes the expected thiochromans **34** were found, together with varying amounts of azirine products **35** (Scheme 11). At first it was thought that these azirines **35**

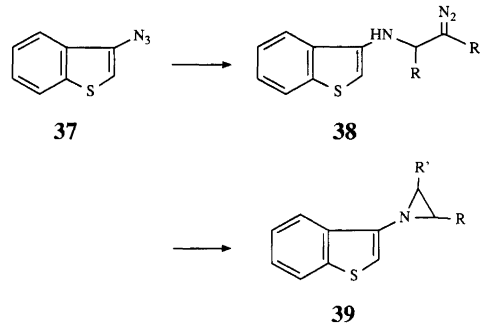


Scheme 11.

resulted from addition of a singlet nitrene onto the olefin.[30] In a recent paper by the same authors[31] the triazoline **36** was isolated, thus excluding a nitrene intermediate in the formation of azirines **35**. From this the authors argued that unimolecular decomposition and ring-opening of azide **31** to **33** probably takes place in a concerted manner. Under the same conditions the 3-azidobenzothiophene **37** afforded only azirines **39**, however at lower temperature diazo compounds **38** were isolated (Scheme 12).

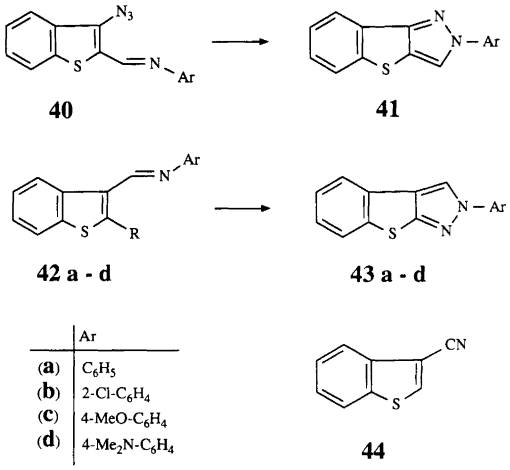


36



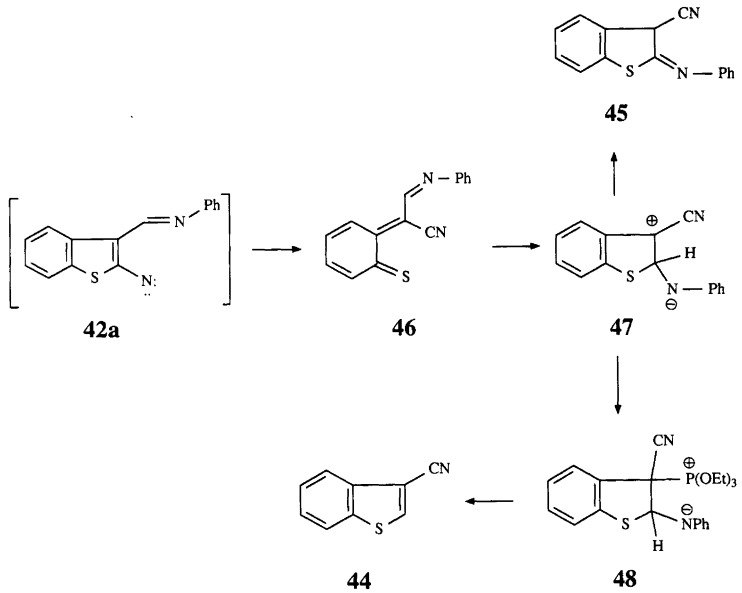
Scheme 12.

Whereas reductive cyclization of 3-nitrobenzothiophene anil **40** (R = NO_2) with triethyl phosphite afforded benzothieno[3,2-*c*]pyrazole **41** in fair yield, the isomeric anils **42a–d** (R = NO_2) gave mixtures of fused pyrazoles **43a–d** and benzothiophene-3-carbonitrile **44**. The amount of cyclization product **43** is higher when the anil carries an electron-donating substituent[34] (Scheme 13).



	Ar
(**a**)	C_6H_5
(**b**)	2-Cl-C_6H_4
(**c**)	4-MeO-C_6H_4
(**d**)	4-Me_2N-C_6H_4

Scheme 13.



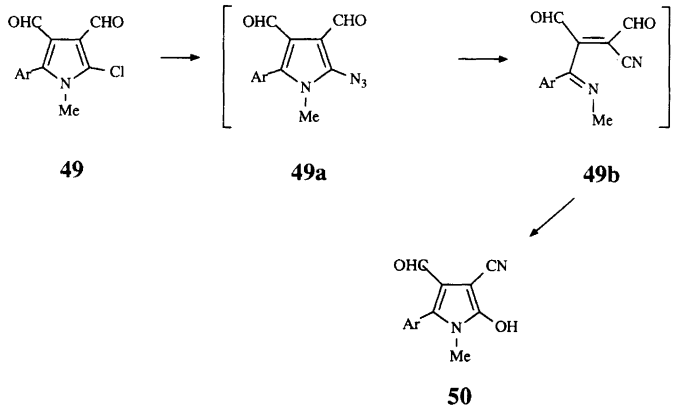
Scheme 14.

The 3-azidobenzothiophene anil **40** cyclized to compound **41** in good yield. Decomposition of 2-azidobenzothiophene **42a** ($R = N_3$) only gave a small amount of the pyrazole **43a** and imine **45** as the main product. The formation of products **44** and **45** may be rationalized in terms of a common intermediate. Ring-opening of the nitrene **42a** (R = N) leads to the ene–thione **46**, which ring-closes to zwitterionic **47**. After a hydrogen shift, the imine **45** is obtained. Alternatively, triethyl phosphite adds to the zwitterion **47**, and **44** is formed after elimination of iminophosphorane from **48** (Scheme 14).

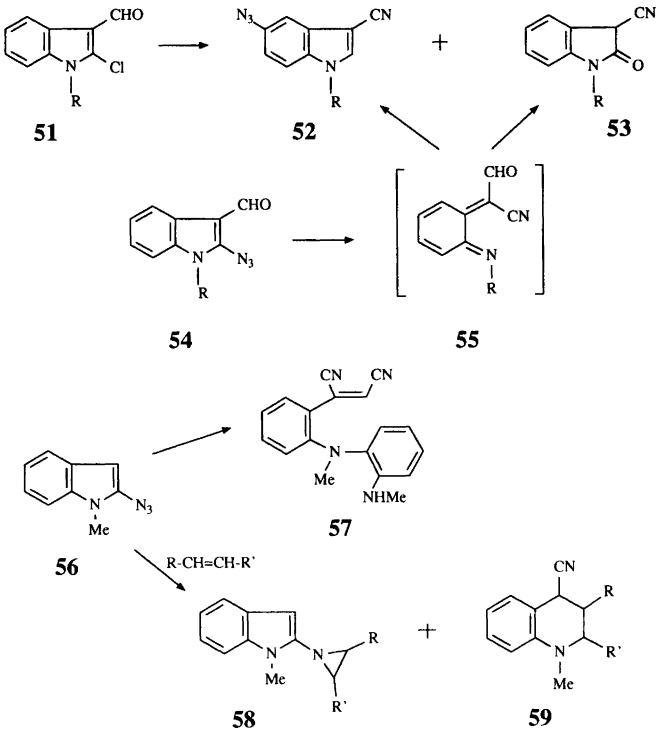
Pyrroles and fused pyrroles

Attempted substitution of 5-chloro-4-formylpyrroles **49** with sodium azide in dimethyl sulfoxide gave good yields of 4-cyano-5-hydroxypyrroles **50**. The expected azidopyrrole **49a** can ring-open to form the unsaturated nitrile **49b**. Cyclization as in Scheme 13 for benzothiophene ultimately gives the hydroxypyrrole **50**[35] (Scheme 15).

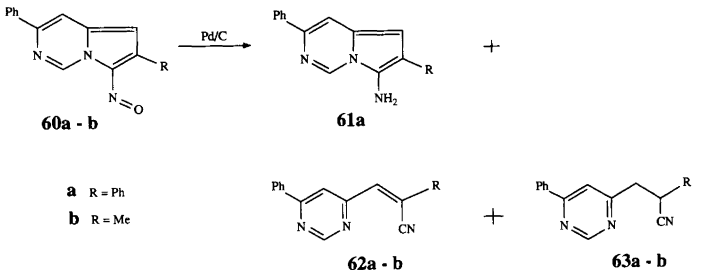
Reaction of 2-chloro-3-formylindole **51** with sodium azide in dimethyl sulfoxide at 100°C gave 5-azido-3-cyanoindole **52**.[35,36] Cyanoindolones **53** were obtained as by-products. The initially formed azide **54** is assumed to form the *o*-quinoid imine **55**. This unstable compound could cyclize as above to give the nitrile **53** or add a second molecule of azide before cyclizing to azidoindole **52**. Substitution of chlorides **51** could also be effected at room temperature, and almost quantitative yields of azides **54** were obtained. 2-Azido-1-methylindole **56** decomposed in the same way as the benzothiophenes to form the cyclodimerization product **57** or aziridines **58**



Scheme 15.



Scheme 16.



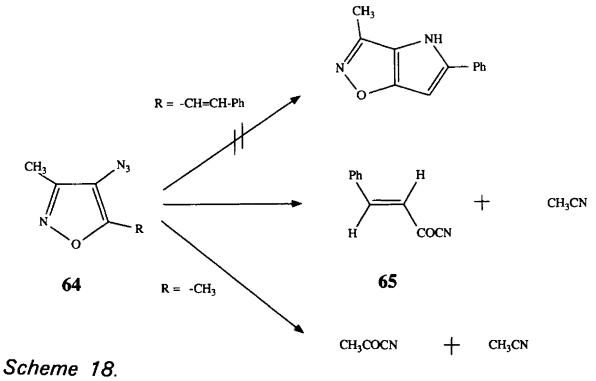
Scheme 17.

and tetrahydroquinolines **59** in the presence of alkenes[23] (Scheme 16).

The preparation of 7-amino-3,6-diphenylpyrrolo-[1,2-*c*]pyrimidine **61a** was attempted via the reduction of the corresponding nitroso compound **60a**. This yielded a mixture of three compounds, one of them the expected amine **61a**, and the other two the acrylonitrile **62a** and propiononitrile **63a**. Catalytic reduction of 6-methyl-7-nitroso-3-phenylpyrrolo[1,2-*c*]pyrimidine **60b** yielded a mixture of 2-methyl-3-(6-phenylpyrimidin-4-yl)acrylonitrile **62b** and the corresponding propionitrile **63b**. The acrylonitriles **62** were also obtained under non-reducing conditions from amines **61** with palladium–carbon in ethanol or oxidation with lead tetraacetate[37] (Scheme 17).

Isoxazoles

Two examples of ring fragmentation of 4-azidoisoxazoles **64** have been reported.[6,38] Ring-scission of **64** (R = 2-phenylethenyl) to form the unsaturated acylnitrile **65** takes preference over ring-closure. A kinetic study of the decomposition of **64** (R = Me) indicated a concerted mechanism since the reaction rate was solvent-independent[6] (Scheme 18).

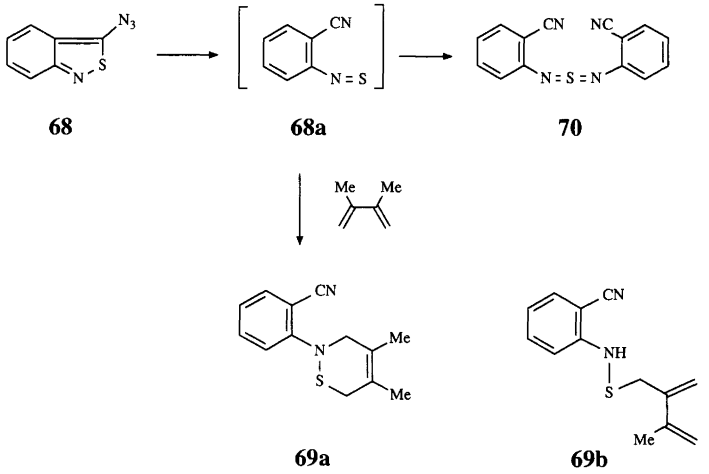


Scheme 18.

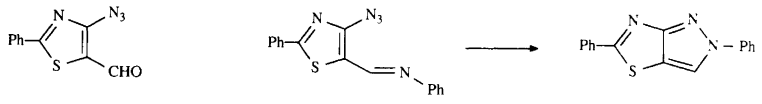
Oxazoles

5-Azido-4-trifluoromethyloxazoles **66** are very labile and decompose within 1–2 h at room temperature to form the reactive 1-oxa-3-azabutadienes **67** (*E*/*Z* mixtures), a new class of hetero-1,3-diene, in high yields[39] (Scheme 18a).

Scheme 18a.



Scheme 19.



71 72 73

Scheme 20.

Isothiazoles and benzoisothiazoles

Although no examples are known in the isothiazole series, 3-azidobenz[*c*]isothiazole **68** has been reported to form the unstable thionitrosobenzonitrile **68a** on heating.[40,41] This compound (**68a**) has been trapped with dienes to form adducts **69a** or ene products **69b**. In the absence of trapping agents a sulfur diimide **70**, is formed (Scheme 19) [see also Ref. 41(b)].

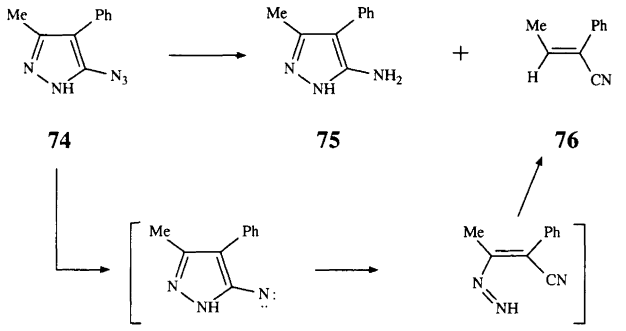
Thiazoles

4-Azido-5-formylthiazole **71** and 5-azido-4-trifluoromethylthiazole **66** (X = S) are reported to be stable heterocyclic azides and no data are known so far on their thermal behaviour.[39,42]

Thermolysis of the anil **72** gives quantitatively the pyrazolothiazole **73**[43] (Scheme 20) [see also Ref. 42(b)].

Pyrazoles and indazoles

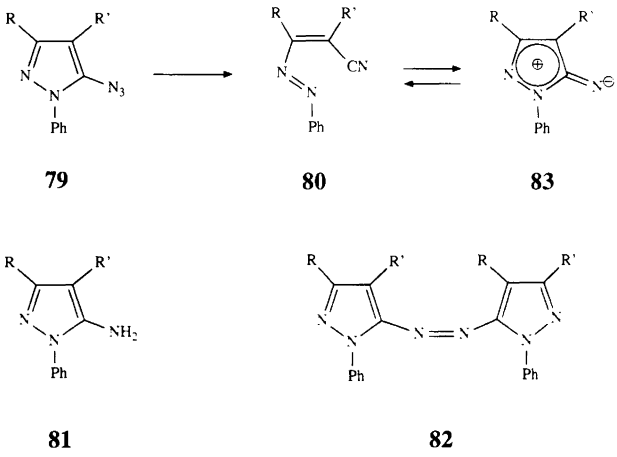
The slow thermal decomposition of the 5-azidopyrazole **74** leads to the formation of the amine **75**, along with 2-phenylcrotononitrile **76**.[44] The formation of the azo intermediate **78** was inferred from the appearance of **76**. Here hydrogen abstraction of the nitrene **77** seems to compete successfully with ring opening, to form the amine **75**. The diazene **78** probably acts as the hydrogen donor, and polymerisation of the resulting radical thus accounts for the formation of large amounts of tarry material formed (Scheme 21).



74 75 76

Scheme 21.

The 1-phenyl-substituted analogues **79** undergo a much faster decomposition and a quantitative conversion into the azo compound **80** was observed.[45] Oxidation of the amine **81** under various conditions yielded **80** contaminated with the nitrene dimer **82**. The authors observed that thermolysis of **80** gave **82**, and postulated that **80** must be in fast equilibrium with a stabilized nitrene **83** (Scheme 22).



79 80 83

81 82

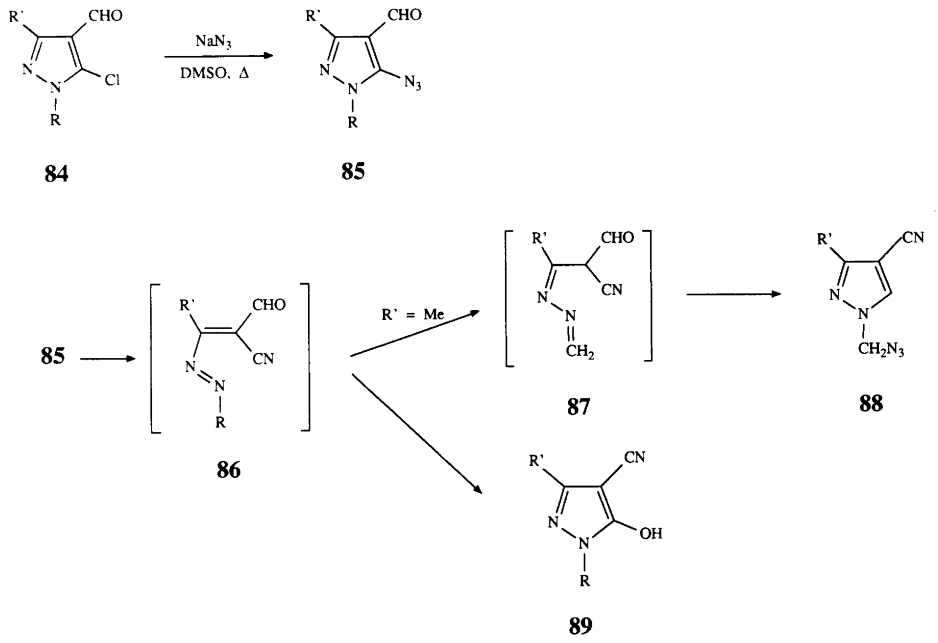
Scheme 22.

Azidopyrazole aldehydes **85**, prepared via substitution of chlorides **84** with sodium azide in dimethyl sulfoxide, decomposed similarly to azo compounds **86**. These were not isolated but reacted further under the reaction conditions. When R = methyl **86** undergoes a 1,5-hydrogen shift to form the methylene azine **87**. After addition of a second equivalent of azide anion, and ring-closure, the 1-azidomethylpyrazole **88** was formed. When R = phenyl no such hydrogen shift is possible and ring-closure now takes place at the formyl group, to form a hydroxy nitrile **89**. In fact, varying amounts of **89** (R = methyl) were isolated as a by-product from the thermolysis of **86** (R = methyl). Substitution of the chloride **84** at lower temperatures cleanly gives the azide **85**, which gave **89** on thermolysis in toluene, proving the intermediacy of **85**.[35,46] (Scheme 23).

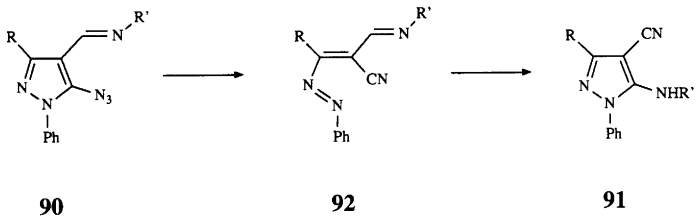
In the same way, 4-(substituted)iminomethyl-5-azido-1-phenylpyrazoles **90** are converted in high yields into the 5-anilinopyrazoles **91**. In one case (R = NHCOOEt), the azo intermediate **92** was isolated[47] (Scheme 24).

4-Azidopyrazoles **93** thermolyse to form two nitriles **96** and **97**, in some cases along with the dimeric azo compound **98**. Thus, dimerization of nitrene **94** may compete successfully with ring fragmentation. Deoxygenation of 4-nitrosopyrazoles **95** gives low yields of the nitriles **96** and **97**[44] (Scheme 25).

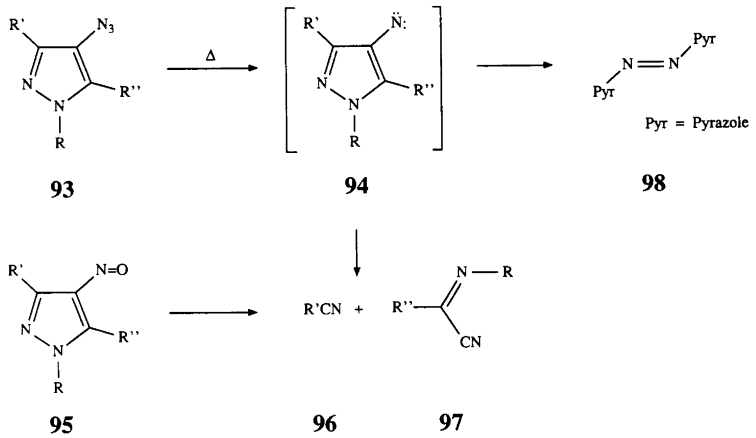
3-Azido-2-phenylindazole **99** (R = N_3) was converted quantitatively into 2-cyanoazobenzene **100** on being



Scheme 23.



Scheme 24.



Scheme 25.

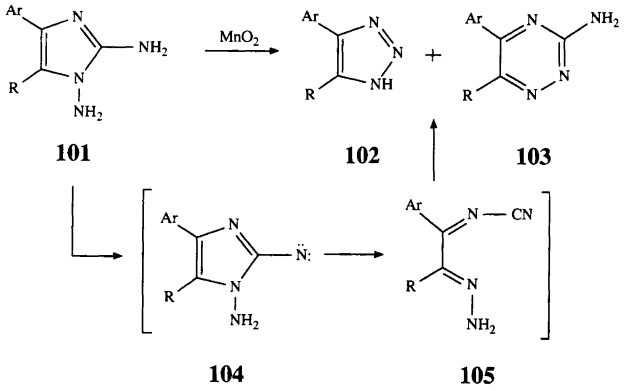
heated in tetrachloromethane for 5 min. Oxidation of 3-aminoindazole **99** (R = NH_2) with lead tetraacetate at room temperature also gave **100** in quantitative yield[40] (Scheme 26).

99 **100**

Scheme 26.

Imidazoles and fused imidazoles

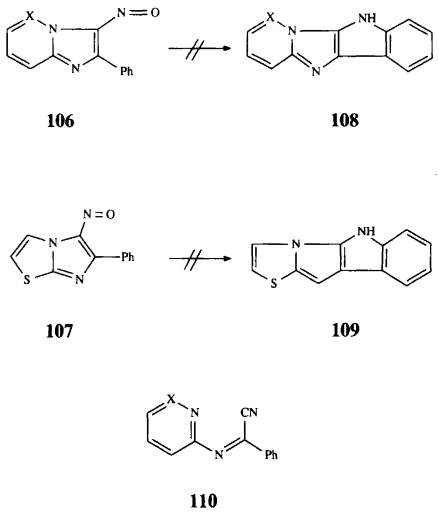
Manganese dioxide oxidation of aryl-1,2-diaminoimidazoles **101** gives 1,2,3-triazoles **102** and 1,2,4-triazines **103** as the main products. The formation of these two products was rationalized in terms of formation of the *C*-nitrene **104** which undergoes ring-opening to the α-hydrazonocyanoimine **105**, and subsequently to compounds **102** and **103**. 1,2-Diaminobenzimidazole under the same conditions gave no benzotriazole, only benzotriazine and 1-aminobenzimidazole were formed[48,49] (Scheme 27).



101 **102** **103** **104** **105**

Scheme 27.

Imidazoindole derivatives **108** (X = CH) and **109** were reported to be formed via reduction of the nitroso compounds **106** and **107**.[50] Later on this was refuted and the structure of the reduction product of **106** (X = CH, N) was shown to be the *N*-substituted benzimidoyl cyanide **110**.[51,52] Although the reduction of **107** has not been reinvestigated, it is to be expected that a similar ring-opening will occur (Scheme 28).



106 **108** **107** **109** **110**

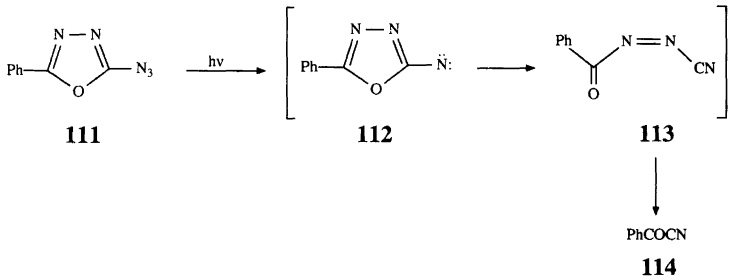
Scheme 28.

1,3,4-Oxadiazoles

Irradiation of 5-azido-1,3,4-oxadiazole **111** gave benzoyl cyanide **114** as the sole non-volatile product. The transient nitrene **112** rearranges to the azo intermediate **113**. This expels a second molecule of nitrogen to form the acyl cyanide **114**.[53] This reaction sequence has been used in a novel approach towards the synthesis of peptides (Scheme 29).

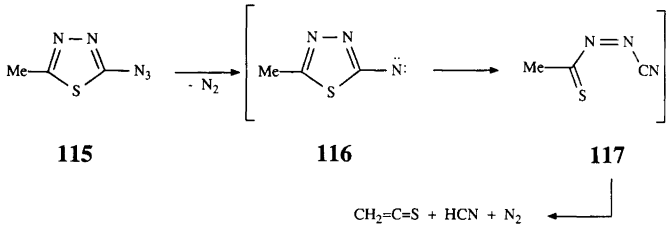
1,3,4-Thiadiazoles

The flash thermolysis of 2-azido-5-methyl-1,3,4-thiadiazole **115** at low pressure has been studied by ultraviolet photoelectron spectroscopy. The products detected ($H_2C=C=S$, HCN and N_2) suggest that the initially formed nitrene **116** undergoes a ring-opening to form the linear thione **117**, which then generates thioketene, HCN and a second molecule of nitrogen. This has been theoretically analysed by the MNDO method [54] (Scheme 30).



111 **112** **113** **114**

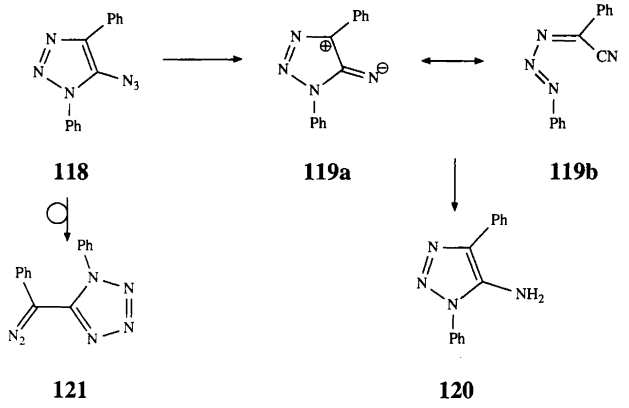
Scheme 29.



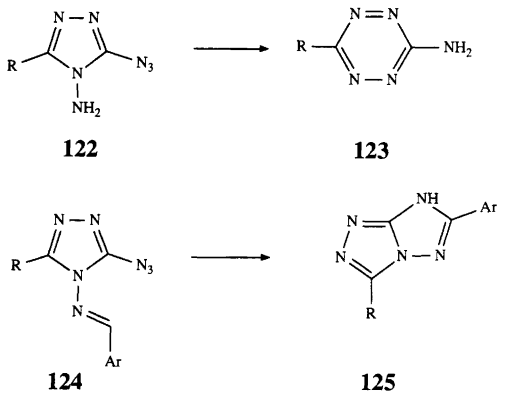
Scheme 30.

1,2,3-Triazoles

The earliest example of ring-opening of heterocyclic azoles was studied by Smith and coworkers.[1] 5-Azido-1,4-diphenyltriazole **118** (R = Ph) decomposed in refluxing benzene to form a nitrene **119a**, which was believed to be in equilibrium with cyanotriazene **119b**. Evidence of this was found in the reduction of **119**, which leads to amine **120**. A crystallographic study later revealed the structure of the decomposition product to be **119b**.[55] Recent work[56] by the same group showed that the chemical behaviour of compound **119** does not necessarily imply the presence of **119a**. For triazoles **118** that have an electron-withdrawing group in the 4-position [e.g., COOMe, CHO, $PO(OEt)_2$, $PhSO_2$] rearrangement can occur before the azide decomposes, to form a diazo substituted tetrazole **121**[57,58] (Scheme 31).



Scheme 31.



Scheme 32.

1,2,4-Triazoles

Heating 4-amino-3-azido-1,2,4-triazole **122** in chlorobenzene at 110°C gave smoothly the tetrazine **123**.[59] The formation of **123** is analogous to the formation of triazines **105** in the case of imidazoles. On the other hand, the imine derivatives **124** gave cleanly the insertion products **125** without fragmentation[60] (Scheme 32).

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