1,5-Dipolar Cyclizations

EDWARD C. TAYLOR* and IGNATIUS J. TURCHI*†

Department of Chemistry, Princeton University, Princeton, New Jersey 08540, and Research and Development, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

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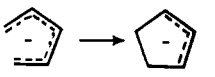
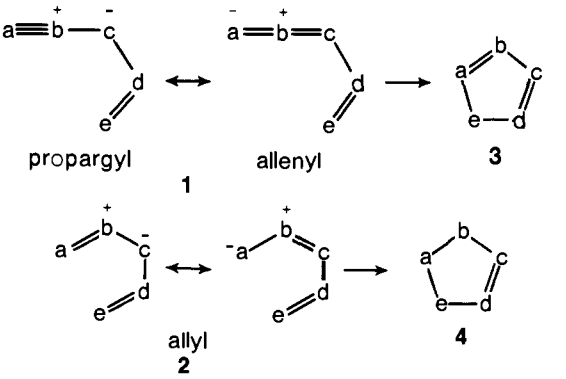
I. Introduction

Heterocyclic chemistry in one form or another comprises a significant fraction of the organic chemical literature. No single development has had a greater impact on this area than the concept of 1,3-dipolar cycloaddition reactions and the related chemistry of 1,3-dipoles. 1,3-Dipolar cycloadditions were reported in the literature as early as the turn of the century, but it was not until ca. 1962 that the pioneering work of Huisgen and his collaborators revealed their enormous scope.[1] Although even today controversy continues over the mechanism of these reactions (concerted[1] vs. diradical[2]), their utility in heterocyclic synthesis cannot be debated. A recent review on intramolecular 1,3-dipolar additions has testified to the potential that this process holds for the preparation of polycyclic heterocycles.[3] Furthermore, over the last decade, advances in the molecular orbital theory of organic chemistry have bestowed on the practicing organic chemist an ability to predict the reactivity of 1,3-dipoles toward various classes of unsaturated systems.[4] With the aid of perturbation MO theory,[5] the regiochemistry of these additions may be predicted with certainty in many cases.[4]

1,3-Dipolar cycloadditions provide but one example (albeit the most important) of a variety of reaction pathways available to 1,3-dipoles. A second process which appears to hold great promise, mainly for the synthesis of five-membered heterocyclic compounds, is the 1,5-electrocyclic ring closure of 1,3-dipoles bound directly to an unsaturated moiety, a process classified by Huisgen as a cycloaddition.[6] Its all carbon analog is the electrocyclic closure of the pentadienyl anion to the cyclopentenyl anion. The present review surveys the literature of 1,5-elec-



trocyclization reactions of 1,3-dipoles of the propargyl–allenyl type **1** and the allyl type **2** up to and including 1978.‡ Table I provides a list of 1,3-dipoles possessing carbon, nitrogen,



† Address inquiries to Research and Development, Smith, Kline, and French Laboratories, Philadelphia, Pa. 19101.

‡ The terms 1,5-electrocyclization and 1,5-dipolar cyclization are used interchangeably throughout the text.

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TABLE I. 1,3-Dipoles Capable of 1,5-Dipolar Cyclizations (R^2 or R^3 = d=e)

Propargyl-Allenyl	
$R^1C{\equiv}\overset{+}{N}\overset{-}{C}R^2R^3 \leftrightarrow R^1\overset{-}{C}{=}\overset{+}{N}{=}CR^2R^3$	nitrile ylides
$R^1C{\equiv}\overset{+}{N}\overset{-}{N}R^2 \leftrightarrow R^1\overset{-}{C}{=}\overset{+}{N}{=}NR^2$	nitrile imines
$N{\equiv}\overset{+}{N}\overset{-}{C}R^1R^2 \leftrightarrow \overset{-}{N}{=}\overset{+}{N}{=}CR^1R^2$	diazomethanes
$N{\equiv}\overset{+}{N}{-}\overset{-}{N}R^2 \leftrightarrow \overset{-}{N}{=}\overset{+}{N}{=}NR^2$	azides
Allyl	
$R^1R^2C{=}\overset{|}{N}{-}CR^3R^4 \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{|}{N}{=}CR\ R$	azomethine ylides
$R^1R^2C{=}\overset{|}{N}{-}NR^3 \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{|}{N}{=}NR^3$	azomethine imines
$R^1R^2C{=}\overset{|}{N}{-}O \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{|}{N}{=}O$	azomethine oxides (nitrones)
$R^1R^2C{=}\overset{|}{N}{-}S \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{|}{N}{=}S$	azomethine sulfides
$R^1N{=}\overset{|}{N}{-}NR^3 \leftrightarrow R^1N{-}\overset{|}{N}{=}NR^3$	azimines
$R^2N{=}\overset{|}{N}{-}O \leftrightarrow R^2N{-}\overset{|}{N}{=}O$	azoxy compounds
$R^2N{=}N{-}S \leftrightarrow R^2\overset{-}{N}{-}\overset{+}{N}{=}S$	azo sulfides
$R^1R^2C{=}\overset{+}{O}{-}CR^3R^4 \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{+}{O}{=}CR^3R^4$	carbonyl ylides
$R^1R^2C{=}\overset{+}{O}{-}NR^3 \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{+}{O}{=}NR^3$	carbonyl imines
$R^1R^2C{=}\overset{+}{O}{-}\overset{-}{O} \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{+}{O}{=}O$	carbonyl oxides
$R^1R^2C{=}\overset{+}{O}{-}\overset{-}{S} \leftrightarrow R^1R^2\overset{-}{C}{-}\overset{+}{O}{=}S$	carbonyl sulfides
$R^1N{=}\overset{+}{O}{-}NR^2 \leftrightarrow R^1\overset{-}{N}{-}\overset{+}{O}{=}NR^2$	nitroso imines
$R^1N{=}\overset{+}{S}{-}NR^2 \leftrightarrow R^1\overset{-}{N}{-}\overset{+}{S}{=}NR^2$	thionitroso imines
$R^2N{=}\overset{+}{O}{-}\overset{-}{O} \leftrightarrow R^2\overset{-}{N}{-}\overset{+}{O}{=}O$	nitroso oxides
$R^2N{=}\overset{+}{S}{-}\overset{-}{O} \leftrightarrow R^2\overset{-}{N}{-}\overset{+}{S}{=}O$	thionitroso oxides
$R^2N{=}\overset{+}{O}{-}\overset{-}{S} \leftrightarrow R^2\overset{-}{N}{-}\overset{+}{O}{=}S$	nitroso sulfides

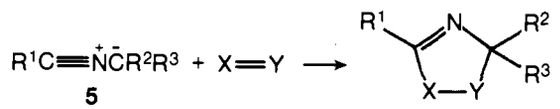
oxygen, and sulfur centers which at least in principle are capable of such a transformation. The unsaturated moieties, d=e, include carbonyl, vinyl, imino, thiocarbonyl, azo, and nitroso groups. 1,7-Dipolar cyclizations are also covered, while 1,5-cyclizations of so-called sextet dipolar species, e.g., vinyl and carbonyl carbenes and nitrenes, fall outside the scope of this review.

In the heading of each subsection, the heterocyclic system which is the immediate product of the 1,5-electrocyclization of the 1,3-dipole described in that subsection is given in parentheses. The actual product observed in each example may or may not be that ring system. Owing to the nature of these transformations and the lability of some of the 1,3-dipoles discussed herein, it was sometimes necessary for the authors of the original papers to speculate on reaction mechanisms. In our discussion of these examples, at least one reasonable mechanism involving a 1,5-dipolar cyclization in at least one of the steps has been proposed, although alternate mechanistic arguments have occasionally been suggested.

II. Propargyl–Allenyl 1,3-Dipoles

A. Nitrile Ylides

Nitrile ylides are highly reactive, nonisolable intermediates possessing the general structure **5**. They combine with a wide variety of multiple bond systems in 1,3-dipolar cycloadditions to provide nitrogen-containing five-membered heterocycles.[7,8]



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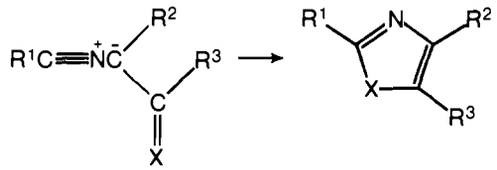
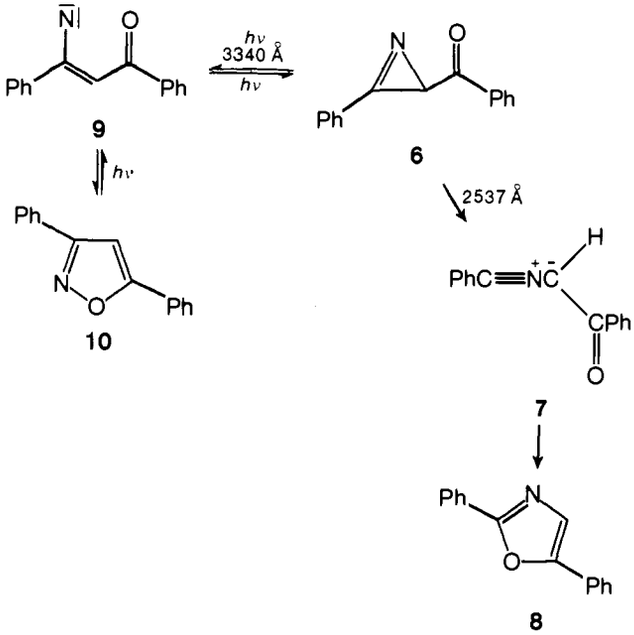
When R^2 or R^3 is some unsaturated moiety, an intramolecular electrocyclic process can in principle occur to afford nitrogen-containing heterocycles.

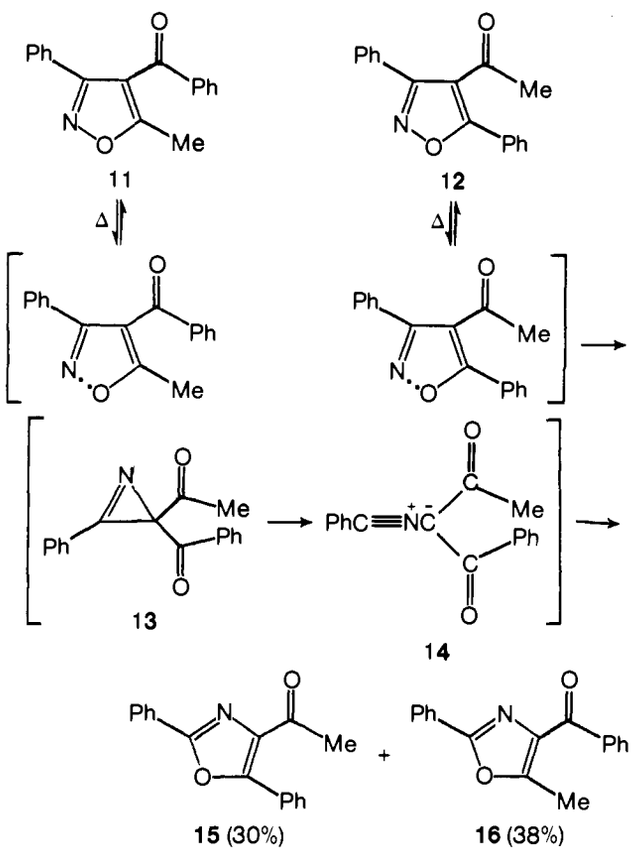


1. Carbonylnitrile Ylides (Oxazoles)

In 1966 Ullman and Singh observed a photochemically induced ring contraction of 3,5-diphenylisoxazole (**10**) to 2-phenyl-3-benzoyl-1-azirine (**6**) which further isomerizes under the reaction conditions to 2,5-diphenyloxazole (**8**).[9-11] The azirine **6** undergoes a photochemical valence isomerism which is remarkably wavelength dependent. When **6** is photolyzed at 3340 Å, the isoxazole **10** is produced while at 2537 Å oxazole **8** arises.

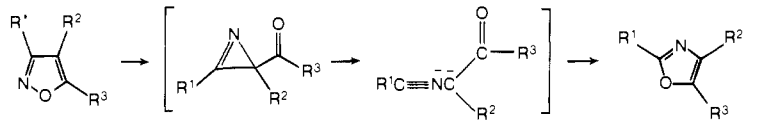


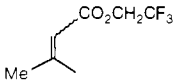
9 **6** **10** **7** **8**



11 **12** **13** **14** **15** (30%) **16** (38%)

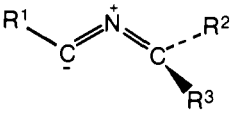
TABLE II



R^1	R^2	R^3	conditions	yield, %	ref
Me	$-(CH_2)_4-$		$h\nu$, EtOH	63	13
CO_2Me	H	H	$h\nu$, Et_2O	5	14
Ph	CONHPh	OEt	$h\nu$, MeCN	(—)	15
Ph	CO_2Et	NH_2	$h\nu$	20	16
Me	COMe	Me	Δ, 230 °C	82	17, 18
Ph	COMe	Me	Δ, 230 °C	100	17, 18
Ph	COPh	Ph	Δ, 240 °C	80	17
Me	COMe	Me	$h\nu$, PhH	96	17, 18
Ph	COMe	Me	$h\nu$, PhH[a]	96	17, 18
Ph	COPh	Me	$h\nu$, PhH[a]	(—)	17
Ph	CO_2Et	Me	$h\nu$, DME	9[b]	18
Ph	$CO_2CH_2CF_3$	Me	$h\nu$, DME	14[b]	18
Ph		Me	$h\nu$, DME	48	18
Ph		Me	$h\nu$, (or Δ)	19[c]	18

[a] Nitrile ylide arises directly from excited isoxazole. [b] Separated from unchanged starting material by thick layer chromatography. [c] Also isolated were unchanged starting material (15%) and azirine (R^1 = Ph, R^2 = MeC=CHCO$_2$CH$_2$CF$_3$, R^3 = Me).

These results were rationalized as follows: selective n → π* excitation of the carbonyl group of **6** causes weakening of the C–N single bond. Cleavage of this bond leads to the vinyl nitrene **9** which collapses to isoxazole **10.** The n → π* excitation of the ketimine chromophore at shorter wavelengths leads to C–C bond cleavage generating the carbonylnitrile ylide **7.** 1,5-Dipolar cyclization of ground-state **7** gives oxazole **8.** This valence isomerization has subsequently aroused the interest of several investigators, and much effort has been expended in outlining the scope and mechanism of this process.[12] Table II lists the oxazoles which have been prepared via 1,5-electrocyclization of carbonylnitrile ylides which were generated from isoxazoles. These reactions generally involve 3-carbonyl substituted 1-azirine intermediates which are not isolated but react further to give the oxazoles. One case where an azirine intermediate is believed not to arise in the isoxazole photorearrangement has been studied by Padwa et al.[17] When 3-phenyl-4-benzoyl-5-methylisoxazole (**11**) or 3,5-diphenyl-4-acetylisoxazole (**12**) was thermolyzed (230 °C), 1-azirine **13** is presumably formed. The latter then opens to the nitrile ylide **14.** Subsequent closure of **14** affords the isomeric oxazoles **15** and **16** in a ratio of 3:4. In sharp contrast, the photolysis of isoxazole **11** affords only oxazole **15.** Here it is postulated that the nitrile ylide **14** is formed directly from excited isoxazole in the conformation **14a.** Ring closure occurs before rotation around the C–N bond yielding only **15.** Recent MINDO/3[19] and ab initio molecular orbital calculations show that the C–N–C angle of nitrile ylides is less than 180° (~168°) in support of the above mechanistic contentions. MINDO/3 calculations suggest that nitrile ylides are best represented by the allenic structure **17.**[19] Thus rotation around the



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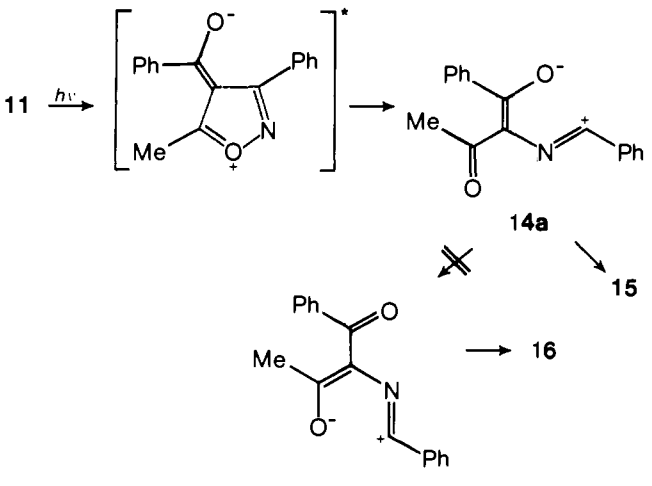
C–N bonds in **14** may be slow relative to ring closure.

Table III lists the oxazoles prepared by the 1,5-electrocyclization of carbonylnitrile ylides generated from 3-carbonyl substituted 1-azirines.[7,8] Here the photochemical reactivity of the azirines stands in marked contrast to their thermal reactivity. For example, when 2-phenyl-3-formyl-1-azirine (**18**) is irradiated, C–C bond cleavage results in the formation of nitrile ylide **19** which subsequently cyclizes to 2-phenyloxazole (**20**).[20] Thermolysis of **18,** on the other hand, furnishes 3-phenylisoxazole (**22**) via the vinyl nitrene **21,** the product of C–N single bond rupture. This reactivity difference is reminiscent of the wavelength-dependent photoreactivity mentioned above. A further



14b

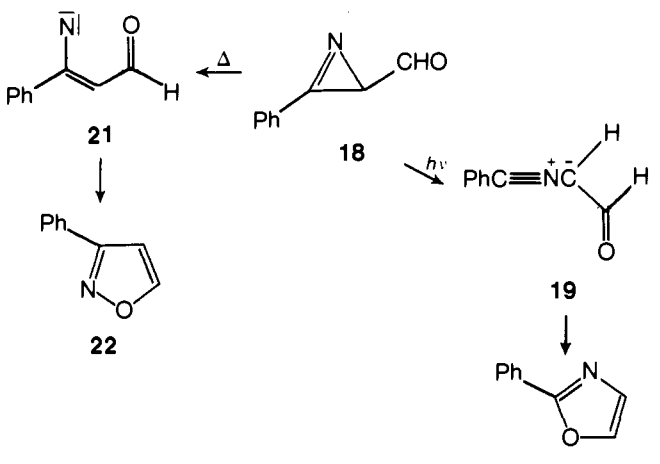


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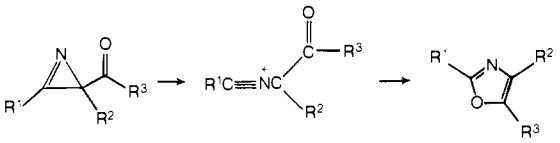
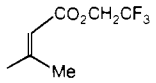
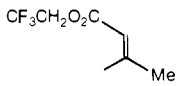
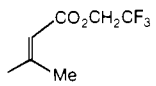
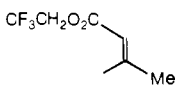
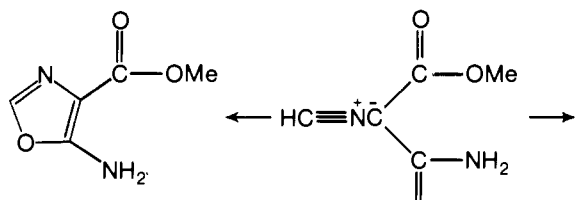
TABLE III



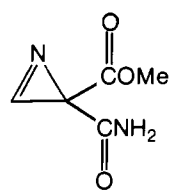
R^1	R^2	R^3	conditions	yield, %	ref
Ph	H	H	$h\nu$	70	20
Ph	H	H	$h\nu$, 2537 Å	(—)	12
Ph	H	H	$h\nu$, 2537 Å	85	9, 12
4-MeOPh	H	Ph	$h\nu$, 2537 Å	85	9, 12
Ph	Ph	Ph	$h\nu$, 2537 Å	(—)	10
Me	H	Ph	$h\nu$, 2537 Å	(—)	12
Ph	H	α-naphthyl	$h\nu$, MeCN	(—)[a]	12
Ph	H	OEt	$h\nu$, 2537 Å	48	21
Ph	H	NH_2	$h\nu$, 2537 Å	5[b]	22
Ph		Me	Δ, 230 °C	76[c]	18
Ph		Me	Δ, 230 °C	49[d]	18
Ph		Me	$h\nu$, DME	89[e]	18
Ph		Me	$h\nu$, DME	96[f]	18

[a] Starting material and 3-phenyl-5-(α-naphthyl)isoxazole were also isolated. The product distribution depends on wavelengths of light and concentration of starting material. [b] The product isolated is *N*-cyanomethylbenzamide which arises from a ring-chain tautomerism of 2-phenyl-5-aminooxazole, the primary photoproduct. [c] The *Z* isomer is isolated in 4% yield. [d] A mixture of *E* and *Z* isomers (43:6) is obtained. [e] A mixture of *E* and *Z* isomers (21:68) is obtained. [f] A mixture of *E* and *Z* isomers (19:77) is obtained.

point should be made here. Whereas allyl type 1,3-dipoles undergo thermal 1,3-electrocyclic ring closures to three-membered heterocycles,[23] this same process for the propargyl–allenyl 1,3-dipoles faces a prohibitive energy barrier. The calculated (MINDO/3) activation energy for the 1,3-cyclization of the dicarbonyl substituted nitrile ylide **23** to the 3,3-dicarbonyl substituted 1-azirine **24** is about 50 kcal/mol,[24] while that of the 1,5-cyclization of **23** to methyl 5-aminooxazole-4-carboxylate (**25**) is 22 kcal/mol.[19] The only reported examples of this 1,3-



25 **23**



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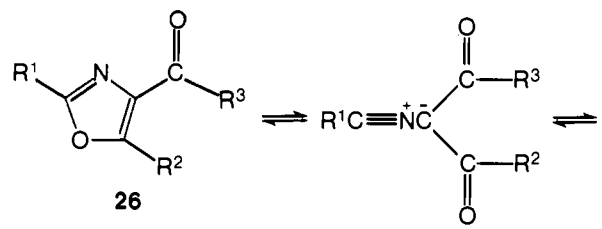
cyclization in the propargyl–allenyl series of 1,3-dipoles involve simple aralkyl nitrile ylides providing the corresponding 1-azirine derivatives in low yield under photochemical conditions in a low-temperature matrix.[25]

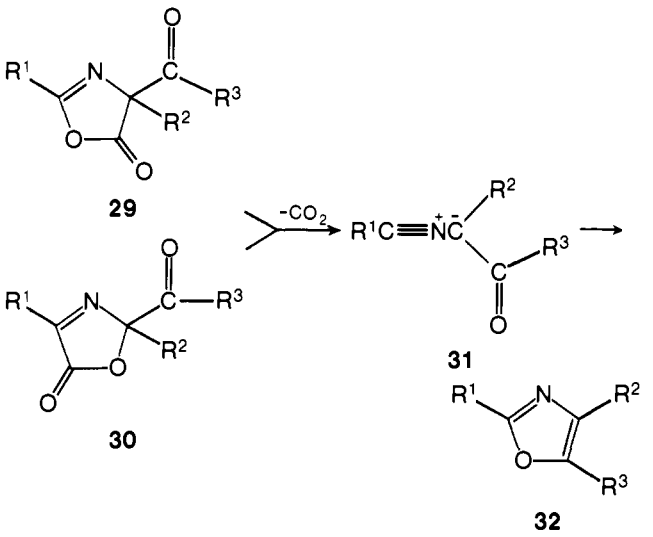
The thermal rearrangement of 4-carbonyl substituted oxazoles **26** to the isomeric 4-carbonyloxazoles **28** was observed by Cornforth nearly 30 years ago.[26] The reaction was postulated to occur via the dicarbonylnitrile ylide **27** which incidentally was the first mention of a nitrile ylide in the literature. Subsequent mechanistic studies by experimental[11,27,28] and theoretical techniques[19] lend support to the proposed mechanism, i.e., electrocyclic ring opening of **26** to generate nitrile ylide **27** fol-



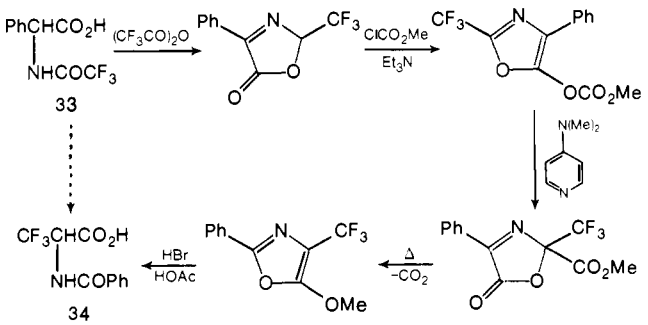
26 **27** **28**

lowed by 1,5-dipolar cyclization of **27** leading to **28**. Whether or not the rearrangement of **26** to **28** occurs depends solely on the free energy difference between **26** and **28** which, in turn, depends on the nature of the substituents R^2 and R^3.[28,29] Table IV gives the 4-carbonyl oxazole derivatives which undergo the Cornforth rearrangement. It will be seen from the table that the isomerization of 5-alkoxyoxazole-4-carboxamides **26** (R^2 = OMe, OEt; R^3 = NRR′) is general, providing alkyl 5-aminooxazole-4-carboxylates **28** (R^2 = OMe, OEt; R^3 = NRR′) in excellent yields.[26-29] 5-Aminooxazoles are precursors of potential therapeutic agents.[30]

Höfle and Steglich have generated carbonylnitrile ylides **31** by a thermally induced 1,3-dipolar cycloreversion reaction of 4-acyl-2-oxazolin-5-ones **29** (200–230 °C) and 2-acyl-3-oxazolin-5-ones **30** (100–130 °C),[31,32] with elimination of carbon dioxide. The resulting ylides experience the usual 1,5-dipolar cyclization to provide the oxazoles **32** in preparatively useful yields. In the case of 2-oxazolin-5-ones **29** (R^1 = alkyl; R^2 = alkyl or Ph; R^3 = Ph, Me, OMe or CO_2Et), oxazoles **32** are produced in yields of 71–95% while for the 3-oxazolin-5-ones (R^1 = alkyl; R^2 = Ph, CF_3; R^3 = Me, Ph, OR, $PhNO_2$-4), the yields of oxazoles



ranged from 8 to 91%. This rearrangement has found utility in effecting the conversion of amino acid **33** to the new amino acid **34** as outlined.[31]



One further transformation where oxazoles may arise via a 1,5-electrocyclic process involving a carbonylnitrile ylide is the reaction of nitrile ylide **37** generated by the base-induced 1,3-elimination of HCl from imidoyl chloride **35**, with benzoyl chloride.[33] Attack of benzoyl chloride on either nitrile ylide **37** with

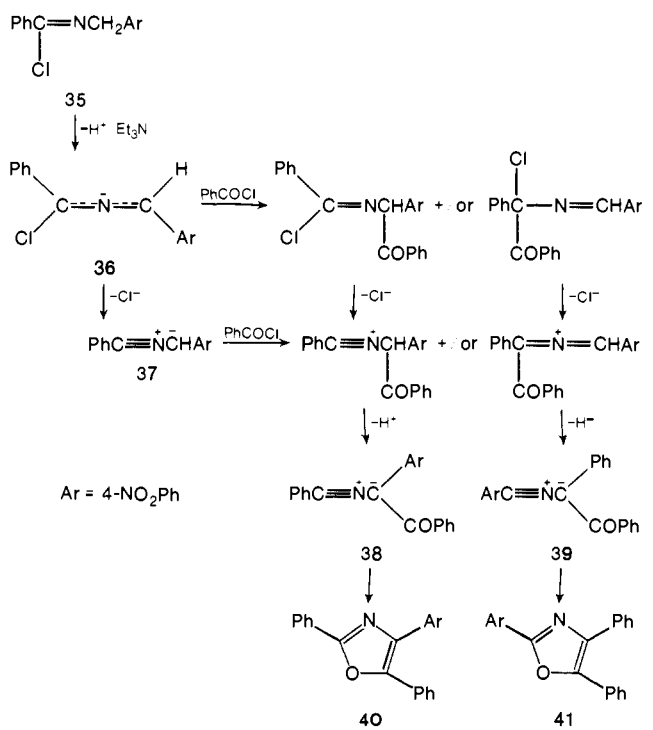
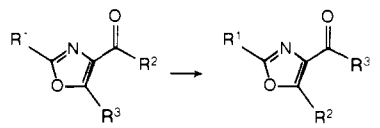


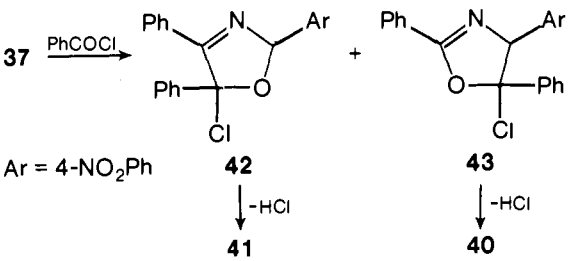
TABLE IV[a]



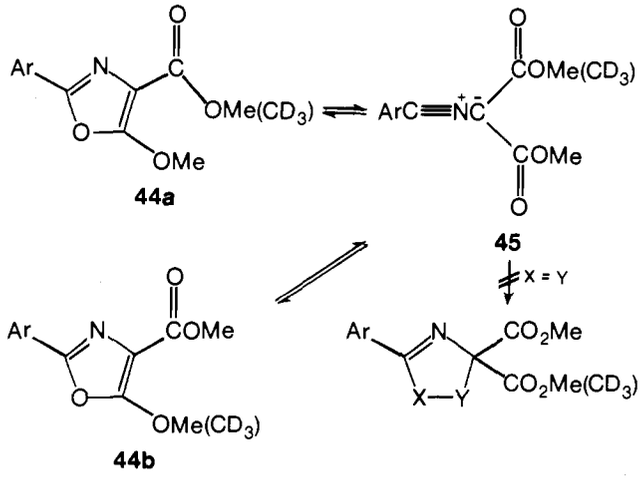
R^1	R^2	R^3	ref
Ph	OH	H	26
n-C_5H_{11}	O^-	H	26
$C_3H_7CH{=}CH$	O^-	H	26
n-C_5H_{11}	OEt	Cl	26
Ph	OEt	Cl	26
$PhCH_2$	OEt	Cl	26
n-C_5H_{11}	Cl	H	26
Ph	Cl	H	26
Ph	OR[b]	NH_2	26-28
$PhCH_2$	OR[b]	NH_2	26
4-XPh[c]	OR[b]	NPhMe	27, 28
Ph	OMe	NHMe	28
Ph	OMe	NMe_2	28
Ph	OMe	NH-*t*-Bu	28
Ph	OMe	NHPhY[d]	28
Ph	OMe	OCD_3[e]	28
Ph	OEt	1-aziridinyl	29
Ph	OEt	1-morpholino	29
Ph	OEt	1-pyrazolyl	29
Ph	OEt	1-(2-methylimidazolyl)	29
Ph	OEt	1-benzimidazolyl	29
Ph	OEt	SPhMe-4	29

[a] Yields of oxazoles are generally ≥90%. [b] R = Me, Et. [c] X = OMe, Me, *t*-Bu, F, H, Br, CF_3. [d] Y = 4-CF_3, 3-CF_3, 3-Cl, H, 4-Me, 4-MeO. [e] Rearranges to a 1:1 equilibrium mixture of **26** and **28**.

subsequent loss of a proton, or on the azaallyl anion **36** followed by elimination of HCl, forms the carbonylnitrile ylides **38** and **39**. Ring closure of **38** and **39** provides the oxazoles **40** and **41**. Alternatively, oxazole formation may be due to 1,3-dipolar addition of the nitrile ylide **37** to the carbonyl group of benzoyl chloride. Elimination of HCl from the initially formed adducts, the chlorooxazolines **42** and **43**, leads to the products **41** and **40**.[33]

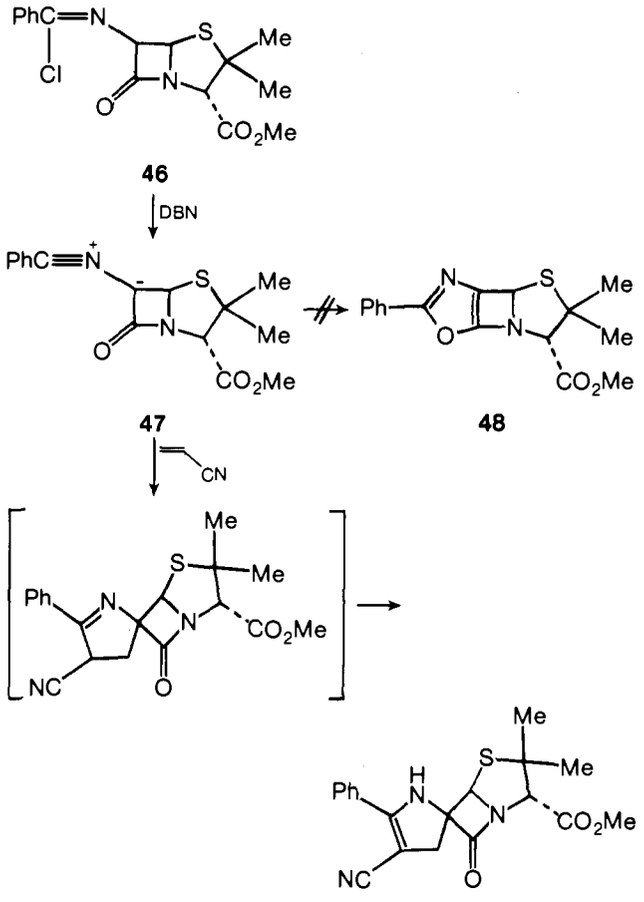


Attempts to trap carbonylnitrile ylides with dipolarophiles to afford 1,3-dipolar cycloadducts have met with failure in all but two exceptional cases. Carbonylnitrile ylides generated by thermolysis of the 4-acylisoxazole system,[17] thermolysis of oxazolin-5-ones,[31] or photolysis of isoxazoles,[13] in the presence of olefins known to give 1,3-dipolar adducts with nitrile ylides, do not give the expected adducts. Instead, oxazole formation is the rule. In the above examples 1,5-cyclization to the oxazoles is irreversible; i.e., the carbonylnitrile ylide is not re-formed under the reaction conditions. In the degenerate thermal Cornforth rearrangement of methyl 2-(4-trifluoromethylphenyl)-5-methoxyoxazole-4-carboxylate (**44**), a small equilibrium concentration of nitrile ylide **45** is always present during the reaction.[28] In order to demonstrate that the rearrangement occurs, a labeling experiment was performed. After 24 h at 95 °C, oxazole **44a** labeled with deuterium at the ester methyl group was converted to a 1:1 equilibrium mixture of **44a** and **44b** labeled at the 5-methoxy group. Even in this system, which should be more conducive to trapping of **45** by added dipolarophiles, no adducts could be obtained.[28] Consequently, 1,5-dipolar cycli-



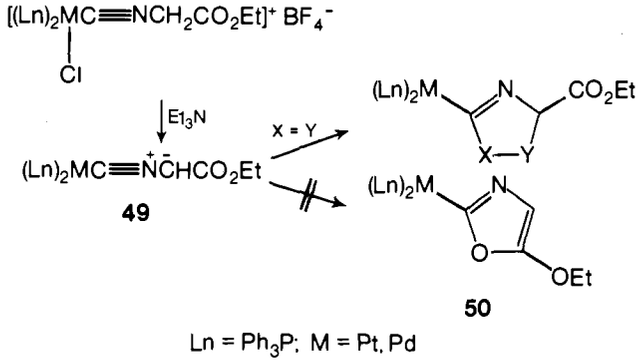
44a 45 44b

zations of carbonylnitrile ylides must be a much more facile process than their addition to external dipolarophiles. It will be seen that the contrary is true for vinylnitrile ylides. As mentioned above, two examples of 1,3-dipolar additions to carbonylnitrile ylides have, however, been observed. When imidoyl chloride **46** is treated with diazabicyclononane (DBN), carbonylnitrile ylide **47** is formed, which can subsequently be intercepted by various dipolarophiles.[34] 1,5-Electrocyclization of **47** to furnish oxazole **48** is not observed, probably as a result of the strain developed in the transition state required for ring closure. Carbonylnitrile



46 47 48

ylides **49** bearing platinum or palladium substituents at the disubstituted carbon have been invoked as intermediates in the synthesis of the metalloheterocycles formed in the 1,3-dipolar cycloaddition of various unsaturated systems to **49**.[35] Dipolarophiles such as olefins, aldehydes, and trifluoromethyl cyanide add to **49** affording pyrrolines, oxazolines, and imidazoles, respectively. None of the oxazole **50** derived from a 1,5-electrocyclization of **49** was isolated. In the last two examples, ex-



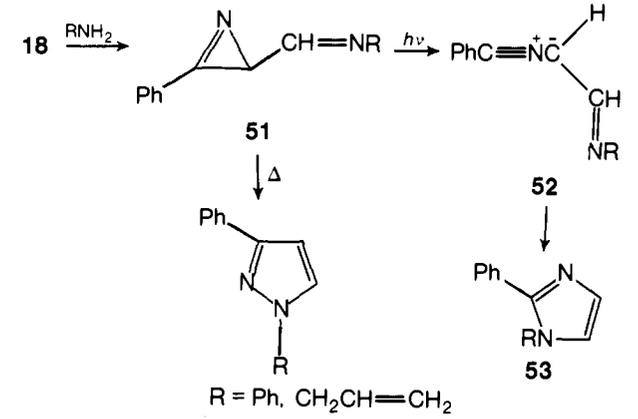
49 50

Ln = Ph_3P; M = Pt, Pd

periments where the reactions were carried out in the absence of dipolarophiles were not reported. Thus it is not known if the ylides **47** and **49** would undergo a 1,5-dipolar cyclization given the opportunity.

2. *Iminonitrile Ylides (Imidazoles)*

The condensation of amines with 2-phenyl-3-formyl-1-azirine (**18**) yields the imines **51** which upon irradiation suffer C–C bond cleavage.[20,36] 1,5-Dipolar cyclization of the resulting iminonitrile ylides **52** provides imidazoles **53** in good yields. The photochemical and thermal reactivity of the imines **51** parallels completely that of the 3-carbonyl-1-azirines (vide supra).

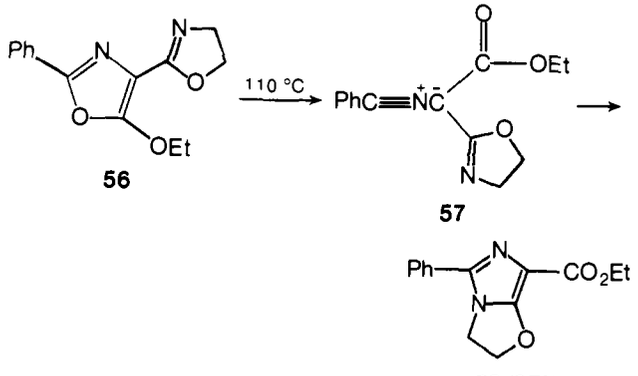


51 52 53

R = Ph, $CH_2CH{=}CH_2$

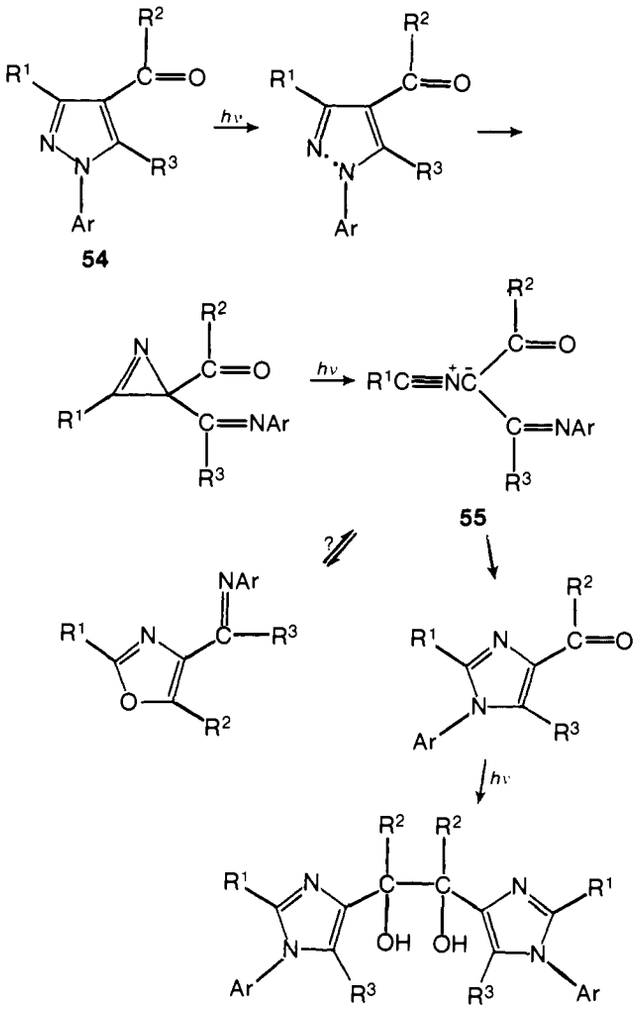
Photolysis of the pyrazole-4-carboxaldehydes **54** affords imidazoles presumably via the pathway outlined in Scheme I.[37] The sequence of steps postulated here is not certain; however, the transposition of ring nitrogens in the pyrazole affording the imidazole is analogous to the isoxazole–oxazole photoisomerization discussed above. It is thus likely that a 1,5-electrocyclic ring closure of iminonitrile imine **55** is responsible for imidazole formation.

5-Phenyl-7-carboethoxyimidazo[4,1-*b*]-2,3-dihydrooxazole (**58**) has been prepared in 97% yield by the Cornforth rearrangement of 2-(2-phenyl-5-ethoxyoxazolyl)-2-oxazoline (**56**) via the intermediate iminonitrile ylide **57**.[29]



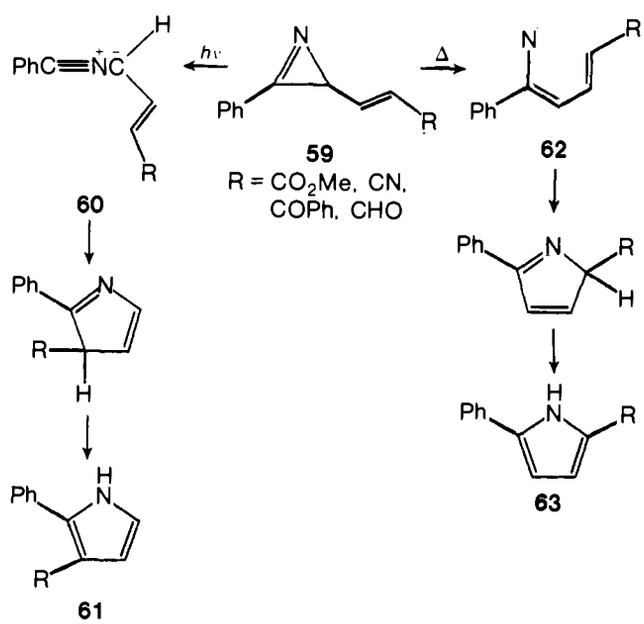
56 57 58 (97%)

SCHEME I

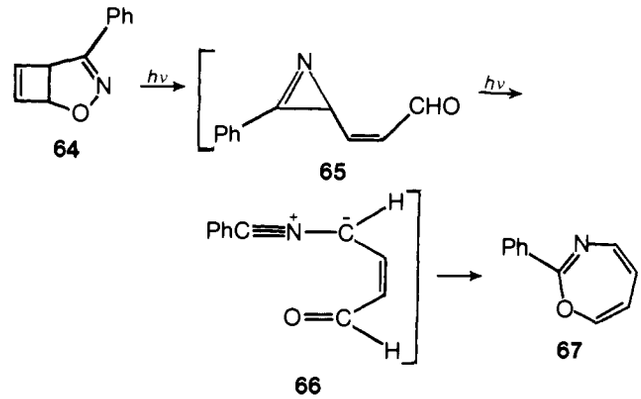


3. Vinylnitrile Ylides (Pyrroles)

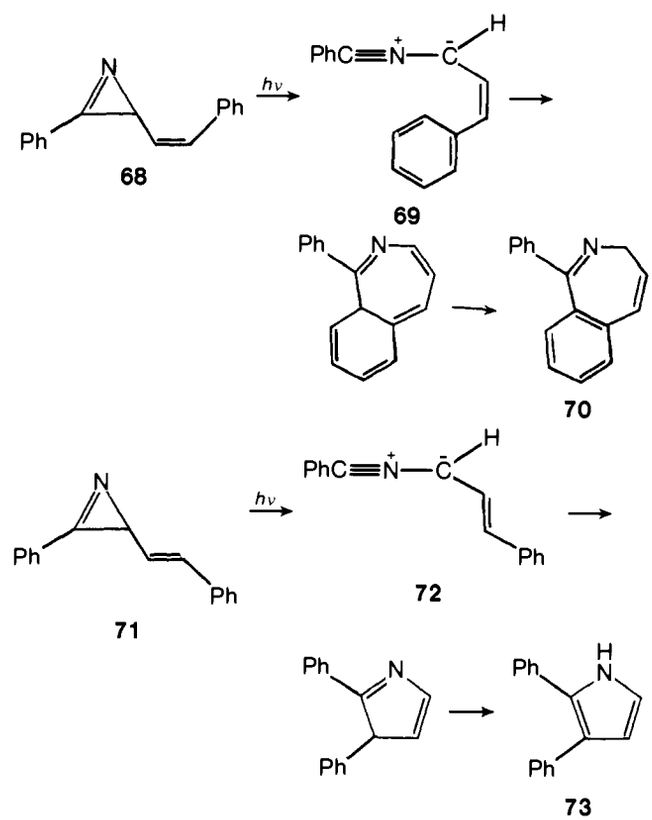
The synthesis of a number of pyrrole derivatives **61** has been effected by the photoinduced conversion of 3-vinyl-1-azirines **59** to vinylnitrile ylides **60** followed by 1,5-electrocyclization of **60**.[20] Thermolysis of **59** affords the isomeric pyrroles **63** presumably via vinyl nitrenes **62**. In the above examples only the *E* isomers of azirine **59** could be prepared. It is noteworthy that the photochemical conversion of the bicyclic isoxazoline **64** is



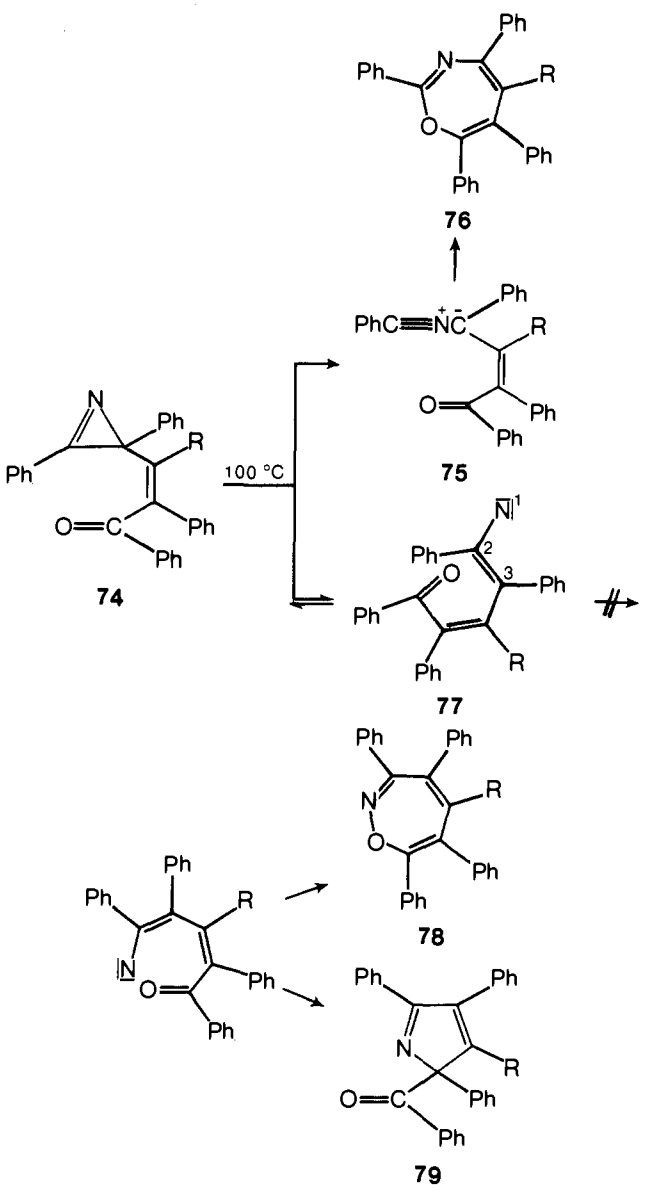
believed to involve the intermediacy of the *Z* isomer of **59, 65** (R = CHO).[38,39] This species could not be isolated but goes on to give nitrile ylide **66**. *1,7-Electrocyclization* leads to the oxa-



zepin **67** in 80% yield. Because of steric constraints it is clearly impossible for the (*E*)-vinylnitrile ylide **60** (R = CHO) to undergo a 1,7-cyclization. Analogous results are secured in the photochemical ring opening of the (*Z*)- and (*E*)-3-styryl-1-azirines **68** and **71**. (*Z*)-Styrylnitrile ylide **69** formed in the irradiation of **68** affords benzazepin **70** in 80% yield by a 1,7-electrocyclization followed by a 1,5-sigmatropic shift. A trace of 2,3-diphenylpyrrole **73** was also found.[20] The isomeric (*E*)-styrylnitrile ylide derived from the photolysis of **71** gives only pyrrole **73** (85%) via a 1,5-dipolar cyclization of **72**.[20]

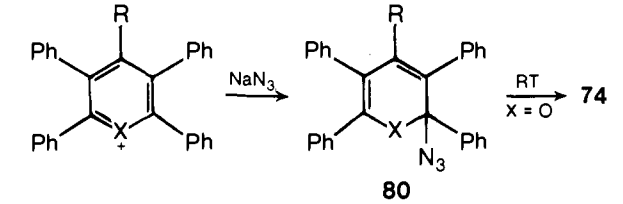


The tetraphenyloxazepins **76** (R = H, Ph) have been isolated in 90% yield from the *thermolysis* of (*Z*)-vinyl-1-azirines **74**.[40] As was mentioned above, the products formed upon thermolysis of 1-azirines usually derive from vinyl nitrenes. In this instance, C–N single bond rupture of azirine **74** may occur reversibly, but owing to restricted rotation around the C_2–C_3 bond of the initially formed vinyl nitrene **77** the conformation required for ring closure to **78** or **79** is inaccessible. The irreversible step is the formation of vinylnitrile ylide **75** which closes in a 1,7-fashion. A reversible 1-azirine to vinyl nitrene interconversion followed by irreversible opening of the azirine ring to a nitrile ylide was postulated in order



to rationalize the formation of the products isolated in the flash vacuum pyrolysis of aralkyl-1-azirines.[41]

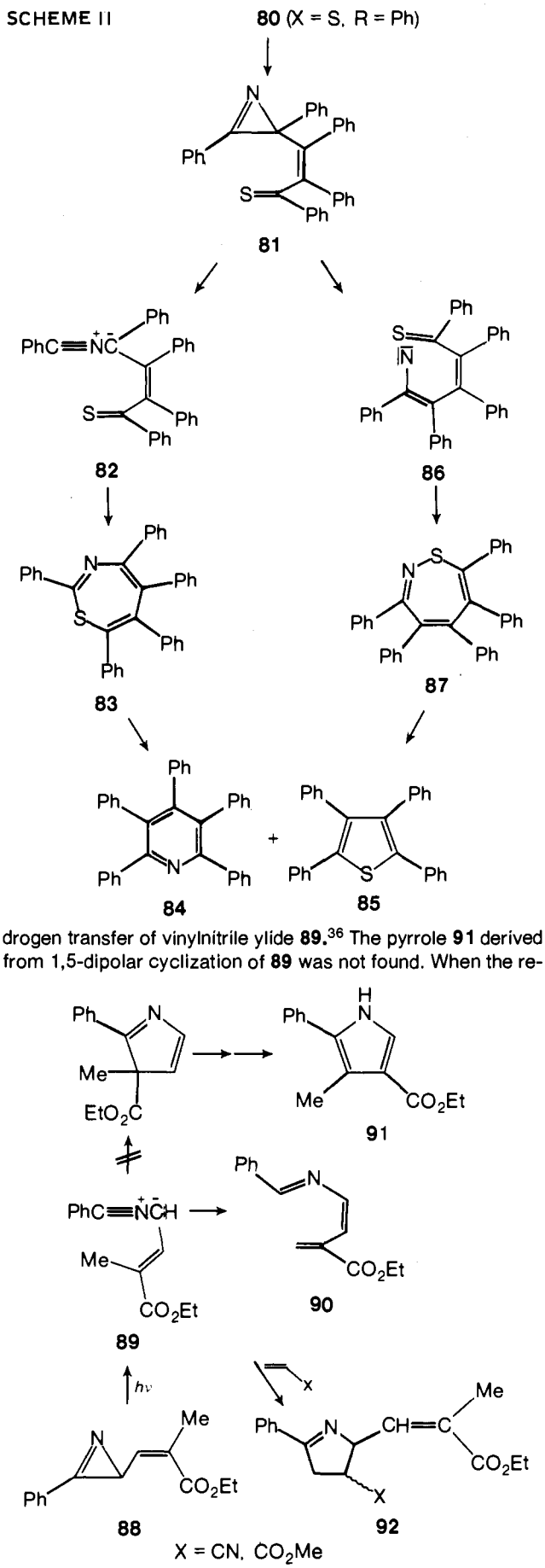
The azirine **74** may be prepared from 5-azidopyran derivatives **80** (X = O) when the latter are allowed to stand at room temperature. On the other hand, the thiapyrans **80** (X = S, R = Ph)

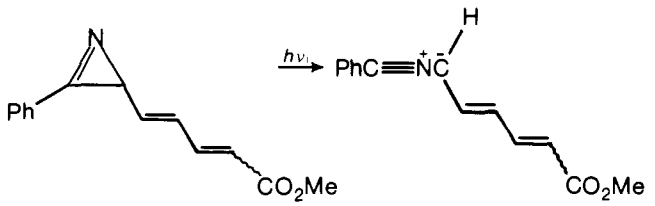


require elevated temperatures in order to effect their decomposition. The products of this transformation are pentaphenylpyridine (**84**, 37%) and tetraphenylthiophene (**85**, 12%).[40] Two pathways may be envisaged for this reaction. The first involves formation of azirine **81** which is unstable under the reaction conditions. Azirine **81** suffers C–C bond cleavage affording vinylnitrile ylide **82** which undergoes 1,7-electrocyclization to 2,4,5,6,7-pentaphenyl-1,3-thiazepin (**83**) from which either sulfur or benzonitrile is extruded. Alternatively, **81** may produce the vinyl nitrene **86** which cyclizes to 3,4,5,6,7-pentaphenyl-1,2-thiazepin (**87**). Elimination of sulfur or benzonitrile from **87** leads to **84** or **85** (Scheme II).

Irradiation of the 3-vinyl-1-azirine **88** gives, among other products, the azatriene **90** which arises via intramolecular hydrogen transfer of vinylnitrile ylide **89**.[36] The pyrrole **91** derived from 1,5-dipolar cyclization of **89** was not found. When the reaction is run in the presence of acrylonitrile or methyl acrylate, the 1,3-dipolar cycloadducts **92** (X = CN, CO_2Me) are obtained in high yield, thus arguing for the intermediacy of the nitrile ylide

SCHEME II

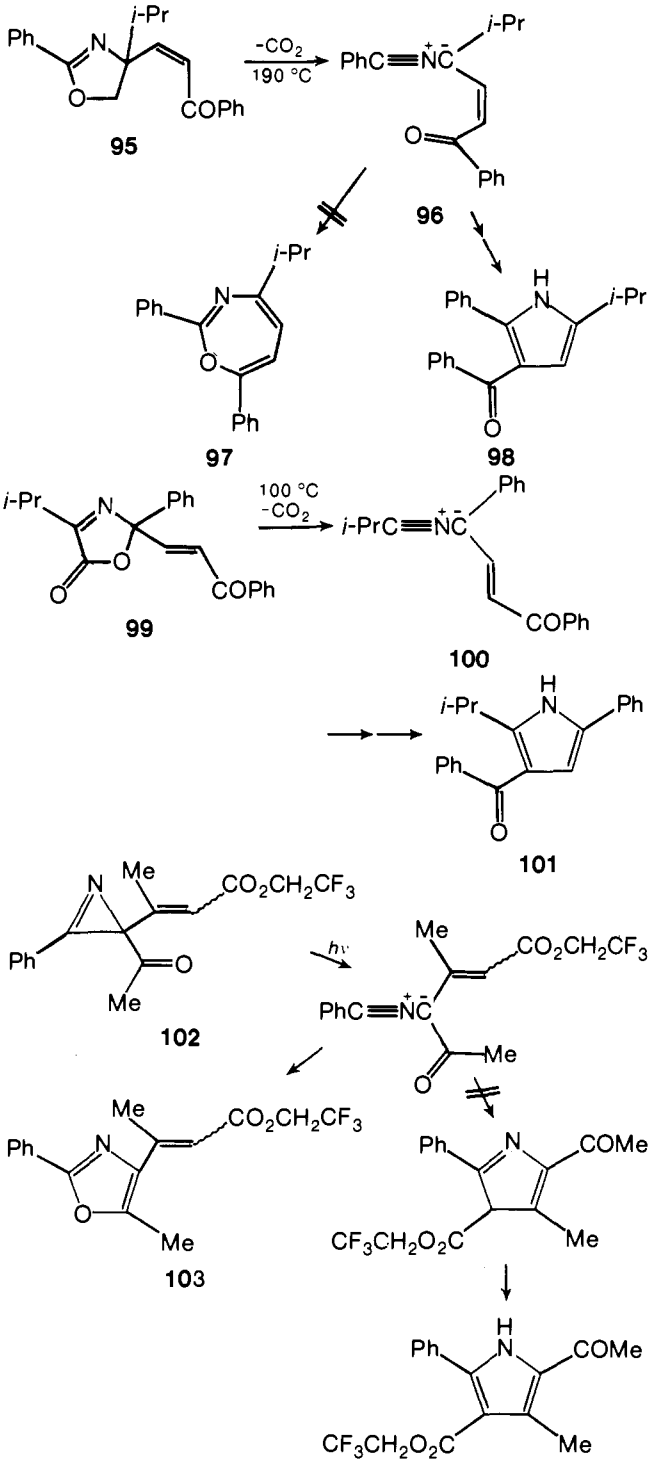




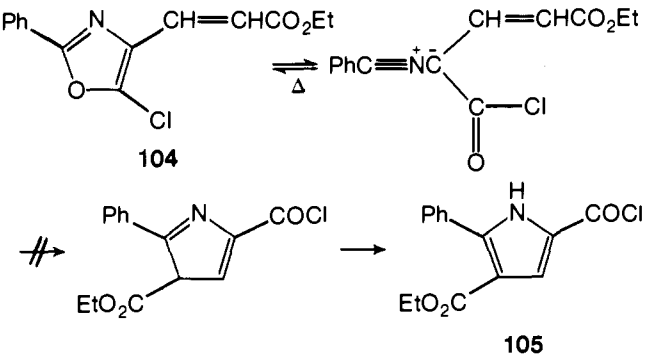
93 94

89.[36] Attempts to effect a dipolar cyclization of the butadienylnitrile ylide **94** generated by photolysis of 1-azirine **93** failed; only a complex mixture of products was obtained.[36]

The vinylnitrile ylides **96** and **100** generated from 2-oxazolin-5-one **95** and 3-oxazolin-5-one **99**, respectively, cyclize only to the pyrrole derivatives **98** and **101.**[42] Although a 1,7-dipolar cyclization of **96** is possible, the 1,3-oxazepin **97** was not detected.

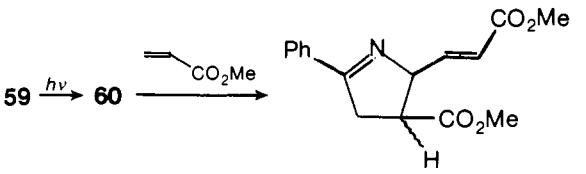


When nitrile ylides bear both a vinyl and a carbonyl substituent at the trisubstituted carbon atom, two cyclization modes are possible, i.e., to carbon or to oxygen. Such nitrile ylides have in fact been generated, and only 1,5-cyclization to oxygen ensues yielding oxazoles rather than pyrroles. For example, irradiation of azirine **102** provides only the oxazole **103.**[18] Similarly, thermolysis of oxazole **104** fails to furnish pyrrole **105;** only unchanged starting material was recovered.[29]



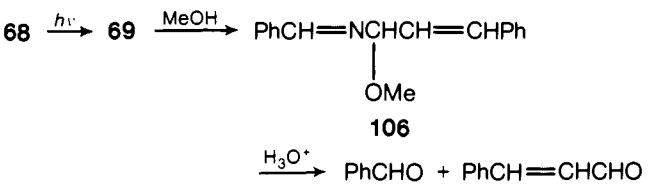
104 105

In general, carbonylnitrile ylides do not give 1,3-dipolar cycloadducts with dipolarophiles due to the facility with which they undergo electrocyclic processes. Vinylnitrile ylides can indeed be intercepted with a variety of dipolarophiles, to the total exclusion of 1,5-electrocyclizations. When 1-azirines **59** are irradiated in the presence of methyl acrylate, no 1,5-dipolar cyclization occurs; rather, the nitrile ylide is instead diverted to the 1,3-dipolar cycloaddition pathway.[20]



cis and trans

Nitrile ylides are known to give products of 1,3-addition of alcohols.[7,8] The styrylnitrile ylide **69,** which yields benzazepin **70** when generated in benzene solution, furnishes the adduct **106** when generated from azirine **68** in methanol.[20]



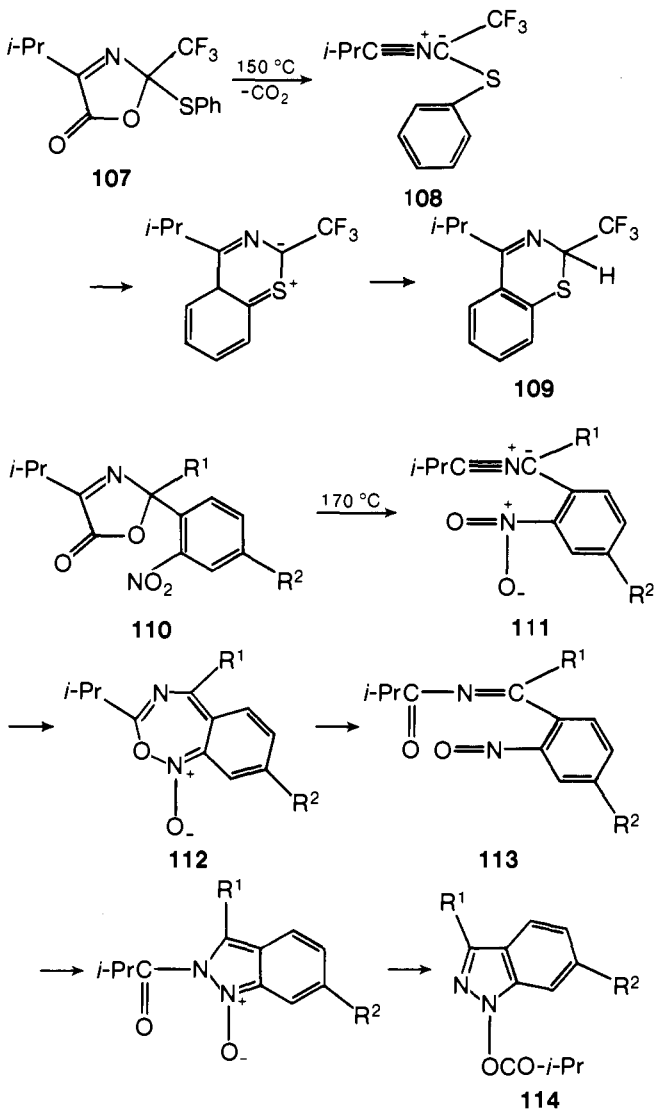
106

From the reactions discussed in this section, a general pattern of reactivity appears to emerge. 1,5-Electrocyclizations of carbonylnitrile ylides are the most facile processes followed by 1,3-dipolar additions, 1,5-hydrogen transfers, 1,5- and 1,7-cyclizations of vinylnitrile ylides, in that order.

4. *Miscellaneous*

The conversion of the 2-thiophenyl-3-oxazolin-5-one **107** to the 2*H*-1,3-benzothiazine **109** requires a 1,6-cyclization of thionitrile ylide **108.**[43]

Thermal elimination of carbon dioxide from 2-(2-nitrophenyl)-3-oxazolin-5-one **110** leads to the formation of the nitrile ylide **111.**[44] 1,7-Cyclization of **111,** followed by ring opening of the resulting intermediate **112** and ring closure of the 2-nitrosobenzaldehyde imine **113** thus formed, offers a rationale to explain the production of the observed product, the 1-acyloxyindazole **114.**

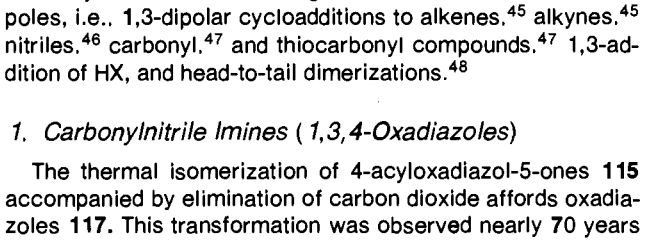


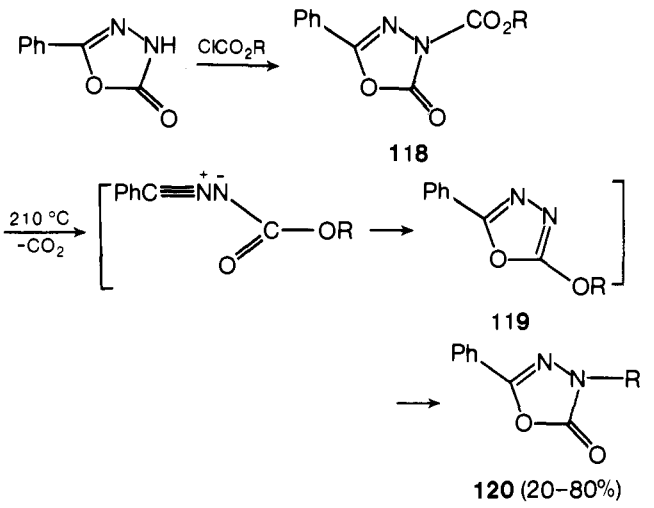
B. Nitrile Imines

Nitrile imines are most commonly generated by the thermally induced elimination of small stable molecules such as carbon dioxide, nitrogen, or sulfur dioxide from five-membered nitrogen-containing heterocycles. Alternatively, 1,3-elimination of HX from hydrazidoyl halides leads to nitrile imines. Simple aryl or aralkyl nitrile imines undergo the usual reactions of 1,3-dipoles, i.e., 1,3-dipolar cycloadditions to alkenes,[45] alkynes,[45] nitriles,[46] carbonyl,[47] and thiocarbonyl compounds.[47] 1,3-addition of HX, and head-to-tail dimerizations.[48]

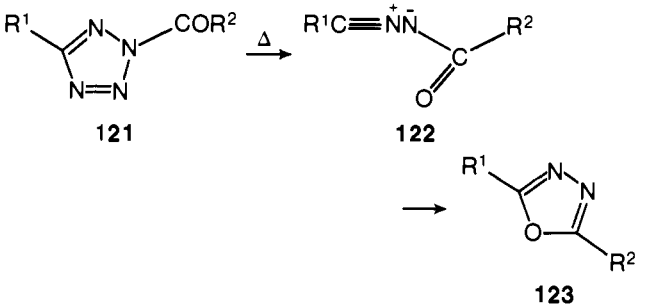
1. Carbonylnitrile Imines (1,3,4-Oxadiazoles)

The thermal isomerization of 4-acyloxadiazol-5-ones **115** accompanied by elimination of carbon dioxide affords oxadiazoles **117.** This transformation was observed nearly 70 years ago.[49] The reaction most likely proceeds via carbonylnitrile imine **116** although the nature of this dipolar species was not perceived at that time. Much later Golfier et al. prepared 4-alkoxycarbonyl-1,3,4-oxadiazol-5-ones **118** and found that upon heating at 210 °C these compounds suffer 1,3-dipolar cycloreversion of CO_2 to provide 4-alkyl-1,3,4-oxadiazol-5-ones **120.**[50] The latter are derived from the 5-alkoxy-1,3,4-oxadiazoles **119** which rearrange under the reaction conditions.



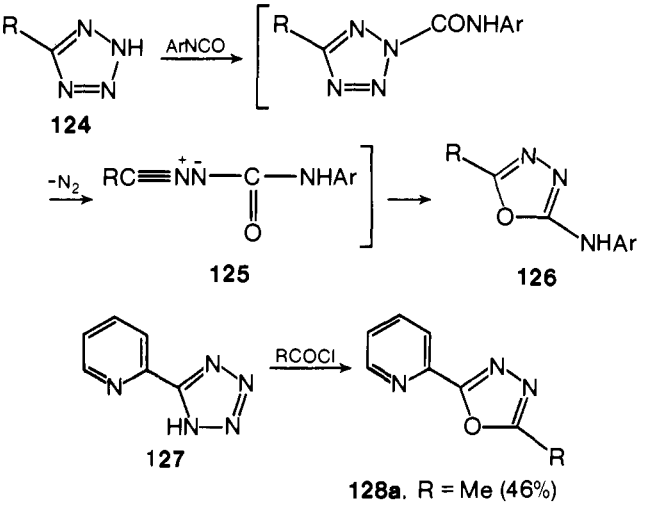


Huisgen and co-workers observed that the thermal elimination of nitrogen from *N*-aroyl- or *N*-acyltetrazoles **121** affords 1,3,4-oxadiazoles **123** in excellent yields.[51,52] This reaction,



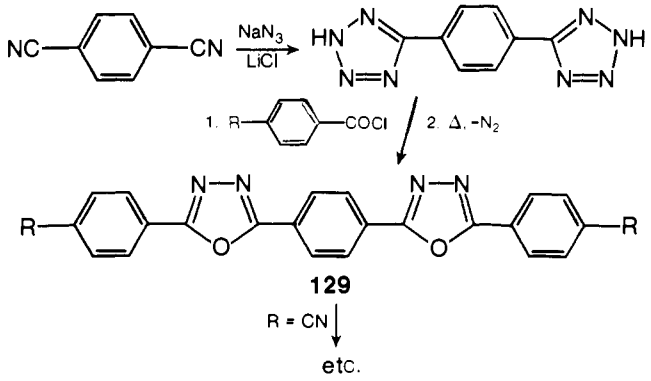
R^1 = alkyl; aryl; R^2 = alkyl, aryl, CO_2R

which involves a 1,5-electrocyclization of carbonylnitrile imines **122,** was shown to be of broad scope in the preparation of alkyl-, aryl-, or aralkyl-1,3,4-oxadiazoles.[51] The starting acyl- or aroyltetrazoles are simply prepared by the reaction of an N-unsubstituted tetrazole, e.g., **124,** with an acid chloride. When **124** is allowed to react with aryl isocyanates at 140–150 °C, the 5-arylamino-1,3,4-oxadiazoles **126** are isolated in good yields.[52]



128a, R = Me (46%)
b, R = NMe_2 (36%)

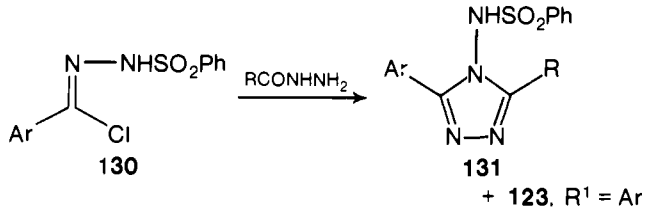
SCHEME III



The mechanism is analogous to those described above and requires a 1,5-electrocyclization of nitrile imines **125.** In like manner 5-(2-pyridyl)tetrazole **127** furnishes 1,3,4-oxadiazoles **128**a and **128b** when heated with acetyl chloride and *N,N*-dimethylcarbamoyl chloride, respectively.[53]

The synthesis of oxadiazole-containing polyaryls, e.g., **129,** was realized utilizing the same principles (Scheme III).[54,55] The UV spectral properties of these polyaryls were observed and compared to the corresponding polyphenyls.

An interesting variation of the tetrazole–oxadiazole interconversion has been observed in the reaction of hydrazidoyl chloride **130** with acid hydrazides.[56] The products of this reaction are 1,3,4-triazoles **131** along with 1,3,4-oxadiazoles **123.** The

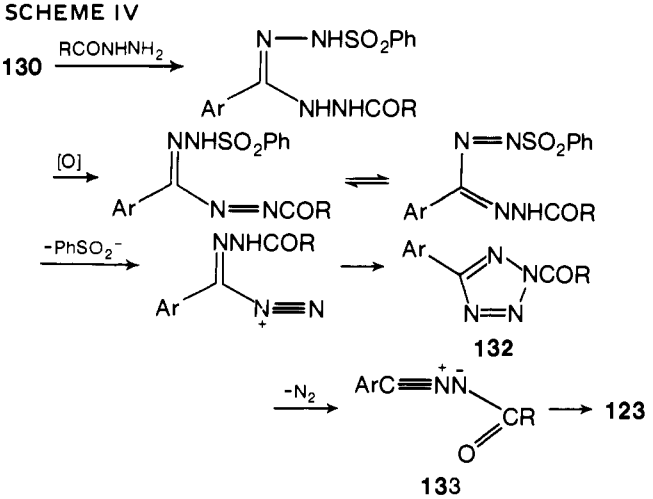


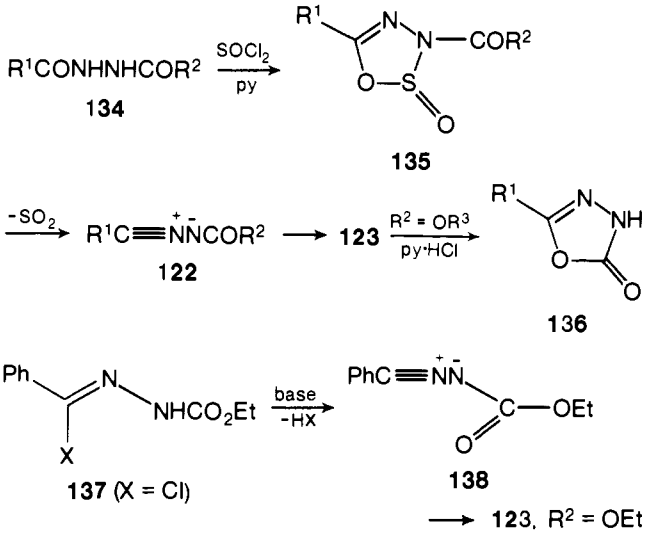
mechanism of the formation of **123** may involve *N*-acyltetrazole **132** (Scheme IV) which goes on to give nitrile imine **133** and ultimately **123.** Other mechanisms not requiring the intermediacy of **132** and **133** may be envisaged, however.

Treatment of the 1,2-diacylhydrazines **134** with thionyl chloride/pyridine affords 1,2,3,4-oxathiadiazole 2-oxides **135** (45–66%).[57] Thermal elimination of SO_2 from **135** gives 1,3,4-oxadiazoles **123** in good yields, again via carbonylnitrile imine **122.** When $R^2 = OR^3$, the 1,3,4-oxadiazol-5-ones **136** are obtained upon reaction of **123** ($R^2 = OR^3$) with pyridine hydrochloride.

The base-induced 1,3-elimination of HX from hydrazidoyl halides **137** gives 5-alkoxy-1,3,4-oxadiazoles **123** (R^2 = OEt)

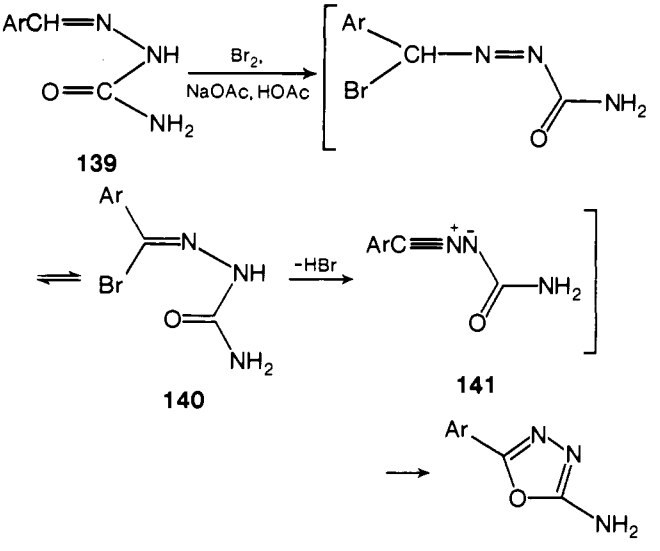
SCHEME IV



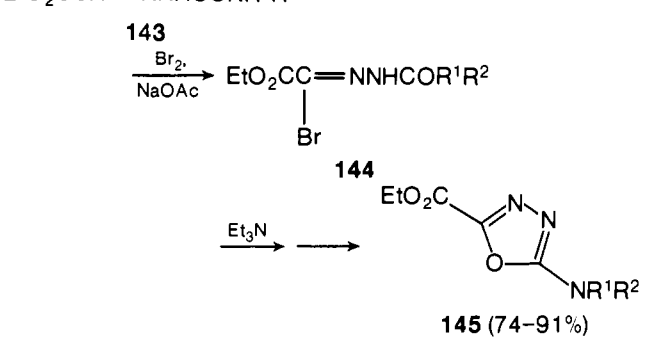


through carbonylnitrile imine **138.**[58]

When the aldehyde semicarbazones **139** are treated with bromine in acetic acid containing anhydrous sodium acetate, 5-amino-1,3,4-oxadiazoles **142** are formed presumably via nitrile imines **141** which arise when the hydrazidoyl bromides **140** are dehydrobrominated.[59,60]

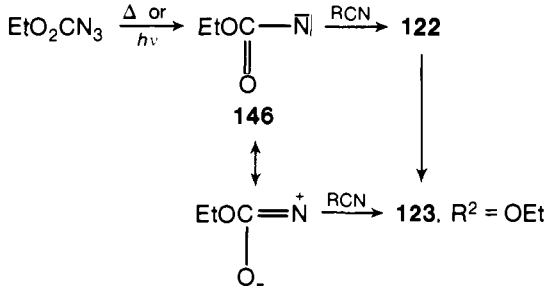


Hydrazidoyl bromides **144** can be isolated when semicarbazones **143** are allowed to react with bromine/NaOAc. Ethyl 5-amino-1,3,4-oxadiazole-2-carboxylates **145** are produced in good yield by dehydrobromination of **144.**[60]



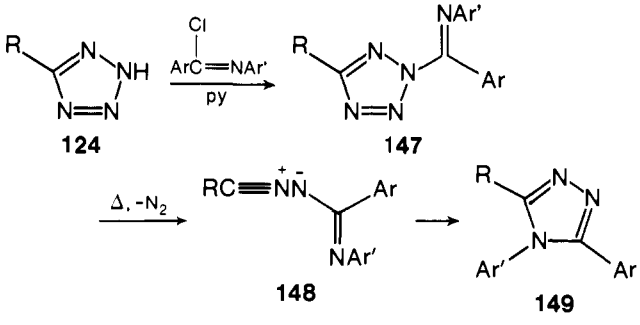
Ethoxycarbonyl nitrene (**146**), generated by thermolysis or photolysis of ethyl azidoformate, adds to nitriles to provide 5-ethoxy-1,2,4-oxadiazoles **123** (R^2 = OEt).[61,62] Two plausible mechanisms have been proposed to rationalize this transfor-

mation. The first involves addition of nitrene **146** to the nitrile nitrogen atom affording nitrile imine **122** (R^2 = OEt) which subsequently undergoes 1,5-electrocyclization. The second mechanistic proposal invokes a 1,3-dipolar addition of **146** to the carbon–nitrogen triple bond.[61] A third, less likely mechanism not involving ethoxycarbonyl nitrene (**146**) requires 1,3-dipolar cycloaddition of ethyl azidoformate to the nitrile to give tetrazole **121** (R^2 = OEt) which loses nitrogen leading to **122** and ultimately to **123.** The latter pathway can be excluded, however, since azides add only to highly electron-deficient nitriles such as perfluoroalkyl nitriles. The experimental evidence, although equivocal, supports the direct 1,3-dipolar addition route to the oxadiazole.[62]



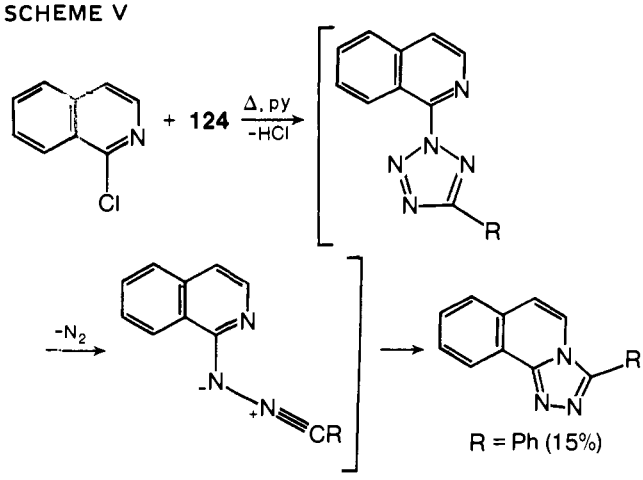
2. *Iminonitrile Imines (1,3,4-Triazoles)*

The methods described above for the generation of carbonylnitrile imines are analogous to those utilized in forming iminonitrile imines. 5-Alkyl- or 5-aryltetrazoles **124** react with diarylimidoyl chlorides in pyridine to afford 1,3,4-triazoles **149** in high yields.[63] The reaction proceeds via the intermediate tetrazoles **147,** which lose nitrogen to give iminonitrile imines **148.**

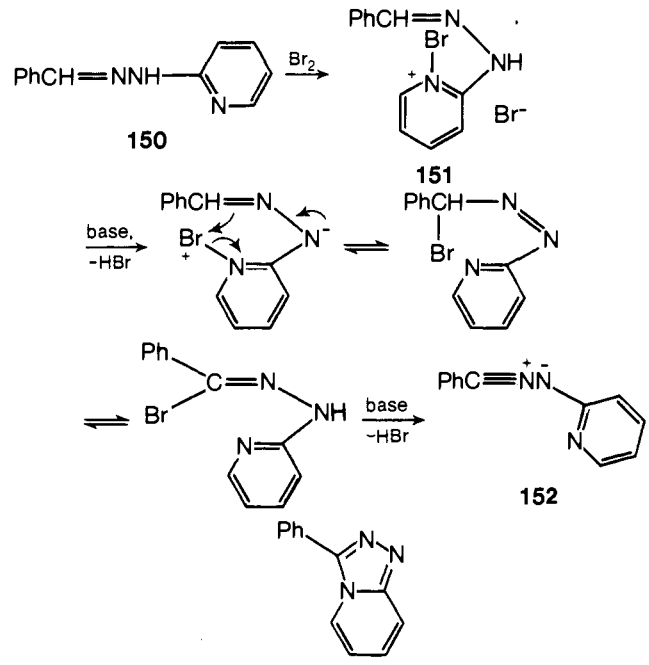


1,5-Electrocyclization of **148** gives the observed products **149.** Tetrazoles **124** when heated in pyridine in the presence of 2-chloropyridines,[52] 4-chloroquinazolines,[52] cyanuric chloride,[52] or 1-chloroisoquinolines,[64,65] yield the corresponding fused triazole derivatives directly without isolation of the intermediate tetrazoles (Scheme V, shown for the 1-chloroisoquinoline case).

SCHEME V

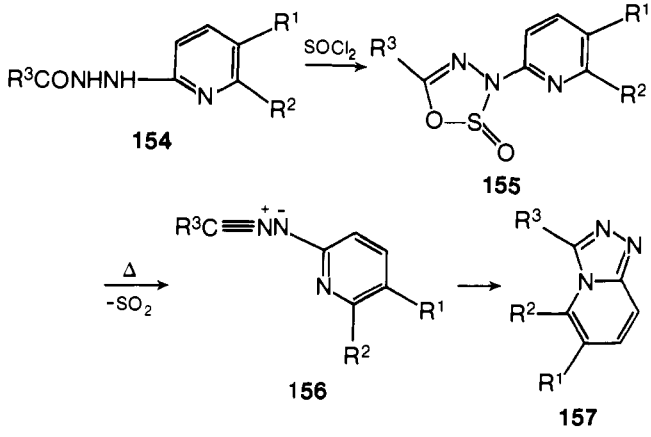


SCHEME VI



Bromination of benzylidene 2-pyridylhydrazone (**150**) produces a 1:1 adduct possessing the structure **151.** In the presence of base, **151** suffers elimination of two molecules of HBr to furnish 3-phenyl-*s*-triazole[4,3-*a*]pyridine (**153**).[66] A reasonable intermediate in this conversion is the iminonitrile imine **152** (Scheme VI).

The action of thionyl chloride on 2-hydrazidopyridines **154** causes their conversion to 3-(2-pyridyl)-1,2,3,4-oxathiadiazole 2-oxides **155.**[64] Thermolysis of these sulfur-containing heterocycles gives triazolopyridines **157** in high yields via 1,5-cyclization of nitrile imines **156.**



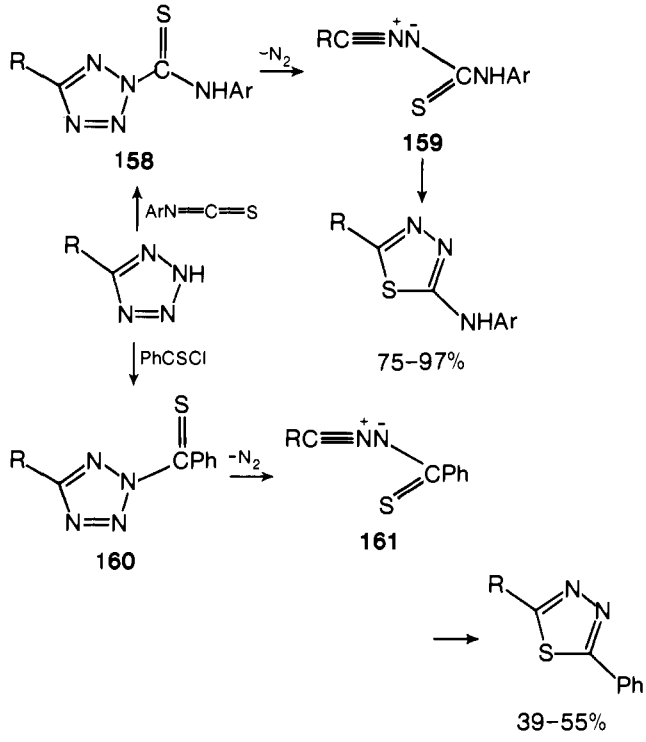
3. *Thiocarbonylnitrile Imines (1,3,4-Thiadiazoles)*

1,3,4-Thiadiazoles have been prepared by 1,5-electrocyclization of thiocarbonylnitrile imines **159** and **161** generated from the corresponding 2-thiocarbonyl substituted tetrazoles **158** and **160,** respectively (Scheme VII).[52]

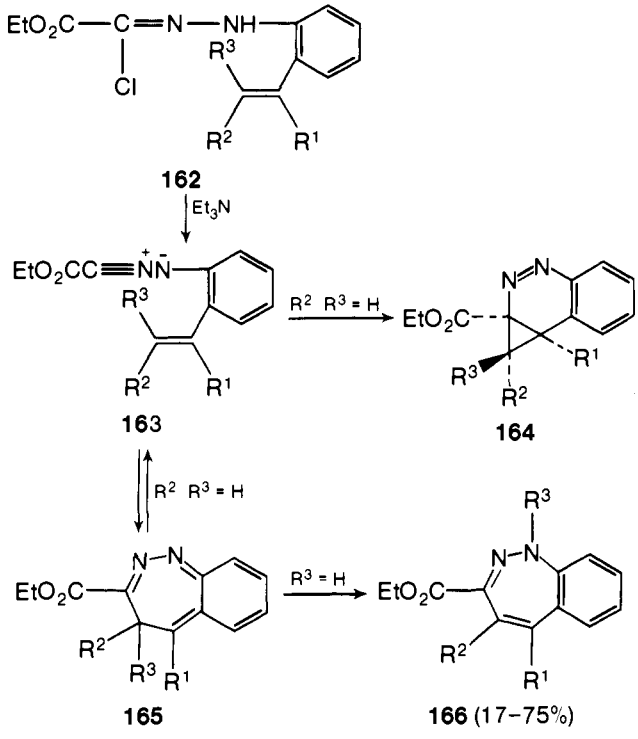
4. *1,7-Electrocyclizations and Miscellaneous*

A 1,7-electrocyclization of nitrile imines **163** with a subsequent prototropic shift of the initially formed products **165** appears to be responsible for the formation of 1*H*-1,2-benzodiazepins **166** when the hydrazidoyl chlorides **162** (R^3 = H) are treated with triethylamine (Scheme VIII).[67] Interestingly, when no possibility for a prototropic rearrangement of **165** exists, i.e.,

SCHEME VII

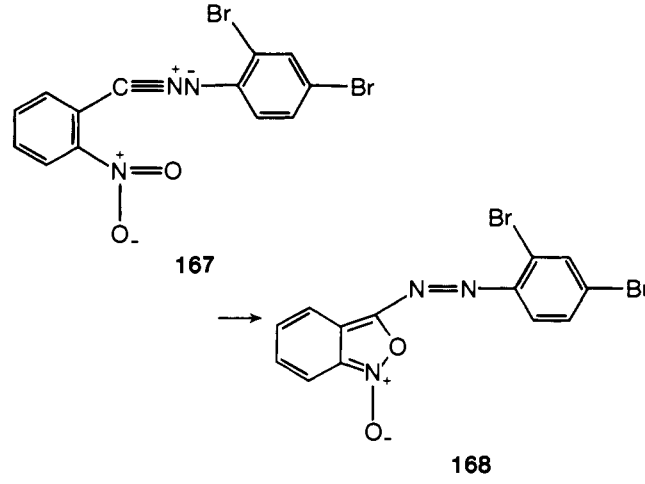


SCHEME VIII



R^2 and $R^3 \neq H$, the products isolated are 1a,7b-dihydro-1*H*-cyclopropa[*c*]cinnolines **164** in 65–80% yields (Scheme VIII).[67] One possible rationale for the formation of **164** is that the initial 1,5-cyclization is reversible in cases where tautomerization to **166** is impossible. Intramolecular 1,1-cycloaddition of **163** would, in fact, give the cyclopropanes.[67] Such intramolecular 1,1-cycloadditions have been observed in the nitrile ylide series.[68]

Lippmann and co-workers have recently reported the results of a study concerning the competition of various modes of intramolecular cyclization reactions of nitrile imines in those cases where two such modes exist.[69] Nitrile imines possessing a C-(2-nitrophenyl) substituent, as in **167**, undergo an intramolecular



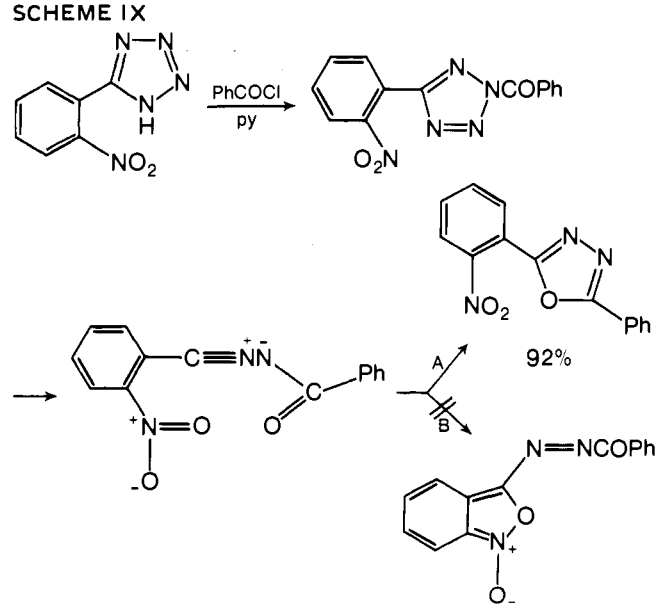
cyclization affording anthranil 1-oxide **168**.[59]

In the Lippmann investigation,[69] two such C-(2-nitrophenyl)-nitrile imines were generated. Each had an alternate cyclization pathway open to it, i.e., 1,5-dipolar cyclization (path A) and intramolecular attack by the 2-nitro group (path B). In both examples the 1,5-electrocyclization (path A) occurred to the complete exclusion of anthranil 1-oxide formation (path B). These processes are outlined in Schemes IX and X.

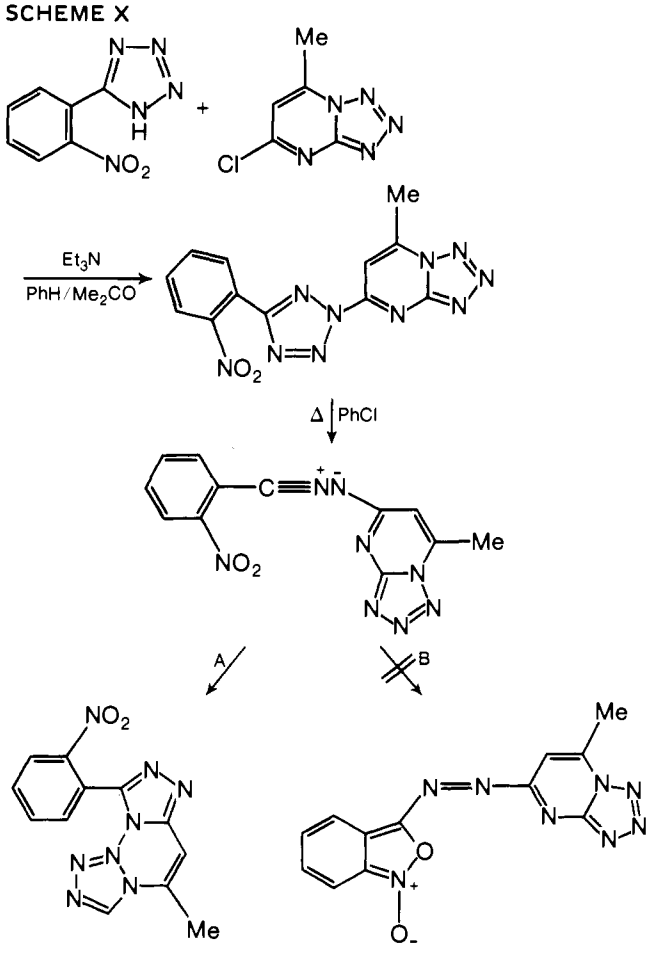
A second experiment was performed in order to test the facility of the 1,5-dipolar cyclization (path A) vs. 1,7-dipolar cyclization (path C) of a nitrile imine bearing an *N*-(2-nitropyrimidinyl) group, i.e., **169**.[69] Here 1,5-cyclization of iminonitrile imine **169** yields triazolopyrimidine **170** while 1,7-ring closure would lead ultimately to the 1-aroyloxypyrimidotriazole **172** after rearrangement of the initially formed cyclization product **171**. In the event, 1,5-cyclization is by far the more facile process (Scheme XI). Finally, in an attempt to determine the facility of pathway B vs. C, 1-(2,4-dinitrophenyl)-5-(2-nitrophenyl)tetrazole (**173**) was prepared and thermolyzed. Unfortunately, an inseparable mixture of products was obtained, none of which could be identified.[69]

The sulfonylnitrile imine **174** has been generated in the reaction of 5-phenyltetrazole with *p*-toluenesulfonyl chloride in warm pyridine.[52] The final product obtained was 1,4-di(4-toluenesulfonyl)-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine (**175**) which arises via a head-to-tail dimerization of **174**. 1,5-Dipolar cyclization to the 1,2,3,4-oxathiadiazole **176** does not occur.

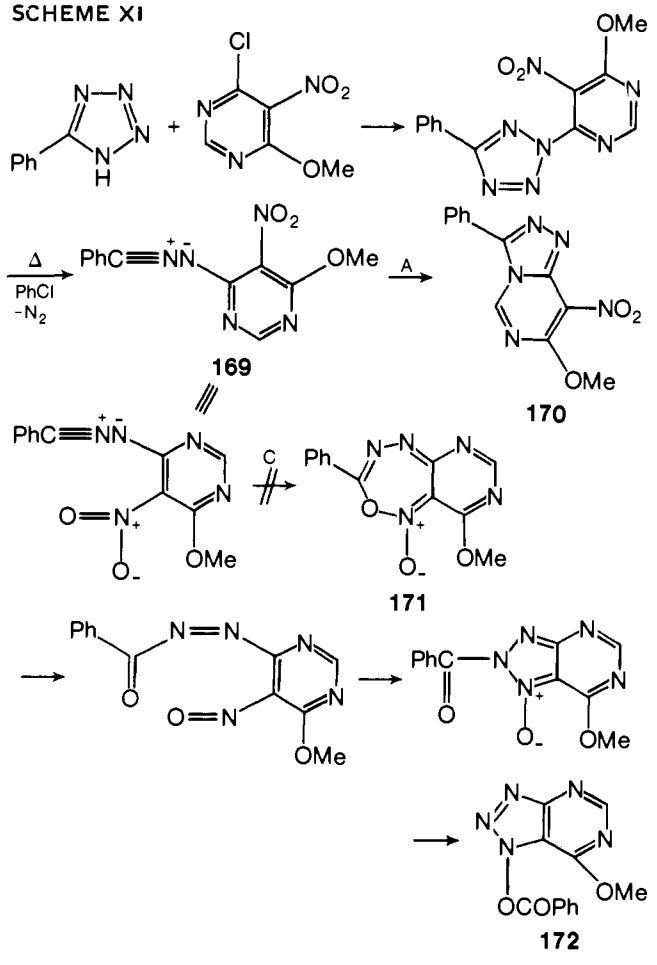
SCHEME IX

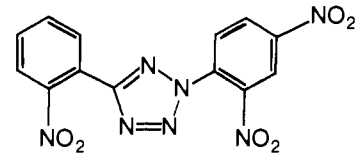


SCHEME X

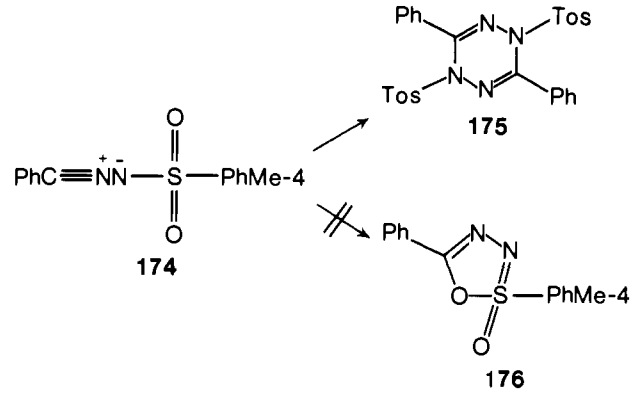


SCHEME XI





173

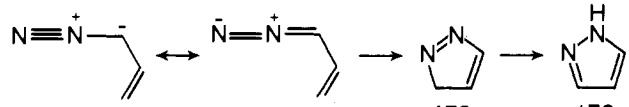


174 175 176

C. Diazomethanes

1. *Vinyldiazomethanes (5H-Pyrazoles)*

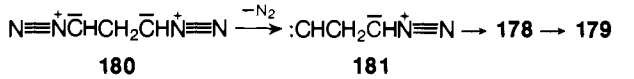
Although the first report of the preparation of vinyldiazomethane (**177**) appeared some 70 years ago,[70] it took an additional 25 years for the appearance of a report on its cyclization to pyrazole (**179**).[71,72] Table V gives examples of 1,5-dipolar



177 178 179

cyclization reactions of various vinyldiazomethane derivatives. Additional examples are discussed in the text.

Studies conducted by Ledwith and Parry on the photochemical rate enhancement of the vinyldiazomethane–pyrazole interconversion suggest that the primary photochemical process involves pyrazolenine (**178**) rather than **177**.[79] Brewbaker and Hart found that substituents have little effect on the rate of cyclization of vinyldiazomethanes as would be expected of an electrocyclic process.[73] The activation energy for the cyclization **177** → **178** (→**179**) is 22.6 kcal/mol while the activation entropy is −3.6 eu at 34 °C in ether.[80] The formation of pyrazole (**179**) was also observed in the thermal decomposition of 1,3-bisdiazopropane (**180**).[81] A mechanism involving elimination of 1 mol of nitrogen to give the carbene **181** followed by C–H insertion to give vinyldiazomethane (**177**) and 1,5-dipolar cyclization of **177** to afford pyrazole (**179**) was discounted. Vinyldiazomethane (**177**) produces pyrazole (**179**) at a lower rate than does 1,3-bisdiazopropane (**180**) under identical reaction conditions, and no build-up of the former could be detected in decomposing solutions of **180**. Two other mechanistic pathways were discussed; the authors favored direct cyclization of the carbene **181** to pyrazolenine (**178**) which tautomerizes to **179**.



180 181

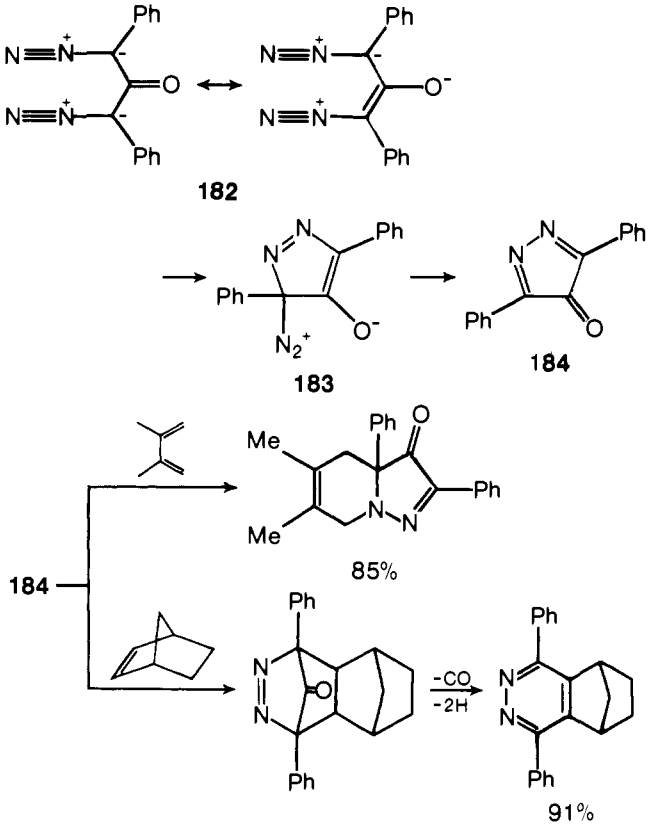
1,3-Bisdiazo-1,3-diphenyl-2-propanone (**182**) (prepared by the diazo group transfer reaction of *p*-toluenesulfonyl azide with 1,3-diphenylpropanone in the presence of base) affords upon heating 2,5-diphenyl-3,4-diazacyclopentadienone (**184**) presumably via 1,5-electrocyclization of **182** and elimination of nitrogen from **183**.[82] The unstable diazacyclopentadienone **184** can be trapped in Diels–Alder reactions either as a dienophile

TABLE V. Vinyldiazomethanes → Pyrazoles

vinyldiazomethane	pyrazole (yield, %)	ref
1. *trans*-1-diazo-2-butene[a]	3(5)-methylpyrazole (100)	73
2. 3-diazo-2-methylpropene[a]	4-methylpyrazole (100)	73
3. 3-diazopropene[a]	pyrazole (100)	73
4. *trans*-3-diazo-1-(*m*-nitrophenyl)propene[a]	3(5)-(*m*-nitrophenyl)pyrazole (89)	73
5. *trans*-3-diazo-1-(*p*-chlorophenyl)propene[a]	3(5)-(*p*-chlorophenyl)pyrazole (87)	73
6. *trans*-3-diazo-1-phenylpropene[a]	3(5)-phenylpyrazole (86)	73
7. *trans*-3-diazo-1-(*p*-tolyl)propene[a]	3(5)-(*p*-tolyl)pyrazole (—)	73
8. 3-diazo-1-butene[a]	3(5)-methylpyrazole (—)	73
9. (*E*)-1-diazo-2-methyl-2-butene[b]	3,4-dimethylpyrazole (60)	74
10. (*E*)-4-diazo-3-methyl-2-pentene[b]	3,4,5-trimethylpyrazole (21)	74
11. (*E*)-1-diazo-1,3-diphenyl-2-butene[b]	3,4-diphenyl-5-methylpyrazole (100)	75
12. *trans*-1-diazo-2-butene[b]	3(5)-methylpyrazole (75)	76
13. (*E*)-1-phenyl-3-diazopropene[b]	3(5)-phenylpyrazole (83)	76
14. (*E*)-1-phenyl-3-diazo-1-butene[b]	3-methyl-5-phenylpyrazole (100)	76
15. 1-formyl-3-diazopropene[c]	3-formylpyrazole[d]	77
16. 1-formyl-3-phenyl-3-diazopropene[c]	3-formyl-5-phenylpyrazole[d]	77
17. (*E*)-2-oxo-5-diazo-3-hexene[c]	3-acetyl-5-methylpyrazole[d]	77
18. (*E*)-1-phenyl-1-diazo-4-oxo-2-pentene[c]	3-acetyl-5-phenylpyrazole[d]	77
19. 2-diazo-1-benzylidenecyclohexane[b]	3-phenylcyclohexa[*d*]pyrazole (77)	78
20. 2-diazo-1-benzylidenecyclopentane[b]	3-phenylcyclopenta[*d*]pyrazole (71)	78
21. 2-diazo-1-ethylidenecyclopentane[b]	3-methylcyclopenta[*d*]pyrazole (82)	78

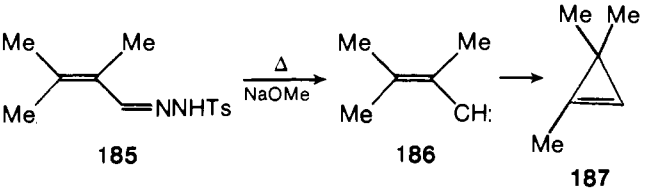
[a] Prepared by base-induced decomposition of the corresponding *N*-vinyl-*N*-nitrosourethane. [b] Generated by base-induced decomposition of the tosylhydrazones of α,β-unsaturated aldehydes and ketones. [c] Prepared by the reaction of 1-methoxypyridazinium salts with aqueous KOH (see text). [d] Yields range from 60 to 80%.

SCHEME XII

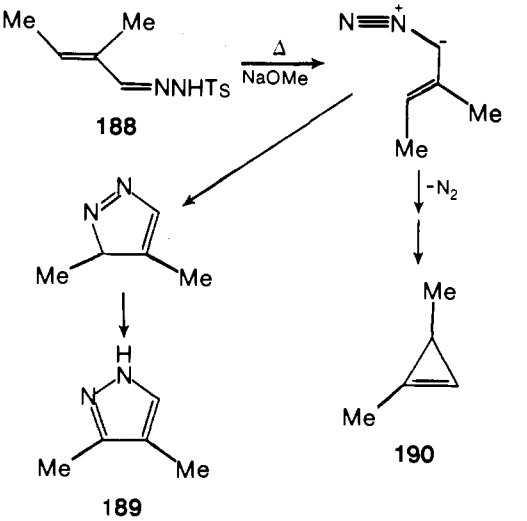


with 2,3-dimethylbutadiene or as a diene with norbornene (Scheme XII).[82]

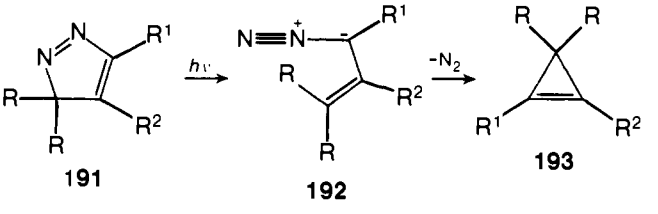
In the examples described above vinyldiazomethanes are prepared and isolated by treatment of the corresponding *N*-nitrosourethanes with base. Toluenesulfonyl hydrazones of α,β-unsaturated aldehydes and ketones give vinyldiazomethanes upon thermolysis in the presence of base. At these elevated temperatures vinyldiazomethanes are labile and with few exceptions escape isolation. The nature of the products obtained is highly dependent upon the structure of the tosylhydrazones. Methyl substitution on the β-carbon retards 1,5-dipolar cyclization; nitrogen elimination and subsequent cyclopropene formation become the main mode of decomposition. For example, **185** when heated with sodium methoxide affords 1,3,3-trimethylcyclopropene (**187**) in 72% yield via vinylcarbene **186**.[74]



In contrast, tiglaldehyde tosylhydrazone (**188**) provides 1,3-dimethylcyclopropene (**190**) in only 4% yield; the major product is 3,4-dimethylpyrazole (**189**, 60%). Pyrazolenines **191** are stable under the conditions of the tosylhydrazone decomposition and thus are not intermediates in cyclopropene formation. Ir-

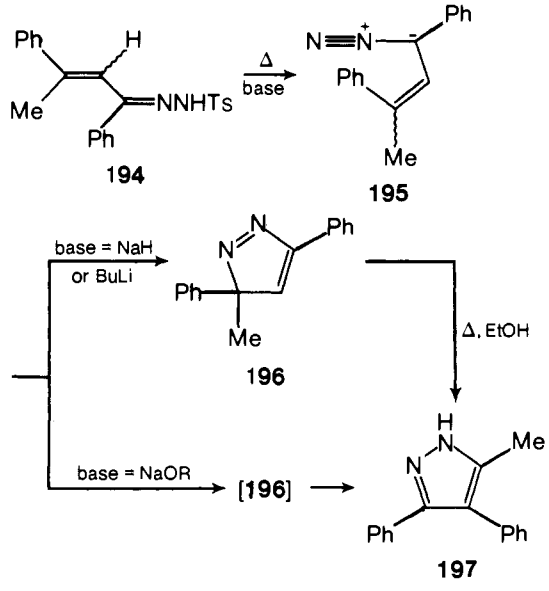


radiation of **191** (R ≠ H), however, gives cyclopropene **193** presumably via electrocyclic ring opening to the vinyldiazo-



methane **192.** Loss of nitrogen and cyclization of the resulting carbene gives **193.**[83]

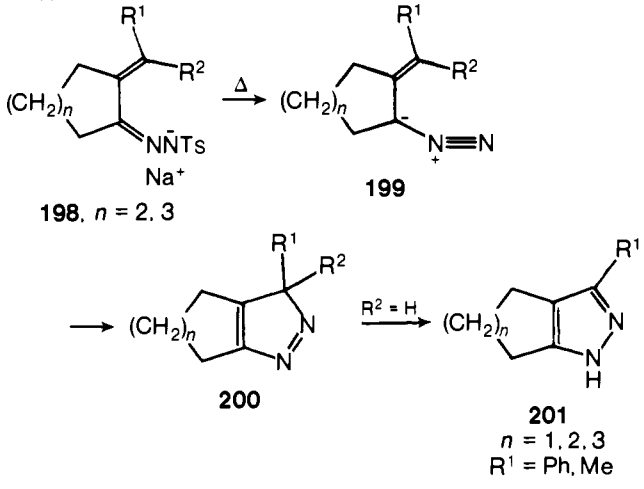
Pyrolysis of dypnone tosylhydrazone (**194**) in hexane in the presence of sodium hydride or *n*-butyllithium furnishes the product expected from a 1,5-dipolar cyclization of vinyldiazomethane **195,** 3,5-diphenyl-5-methylpyrazolenine (**196**).[75] When



the reaction is carried out utilizing alkoxide as base in a protic solvent (ethylene glycol), the product obtained is that resulting from a phenyl migration in intermediate **196,** i.e., 3,4-diphenyl-5-methylpyrazole (**197**). Refluxing **196** in ethanol provides **197.**

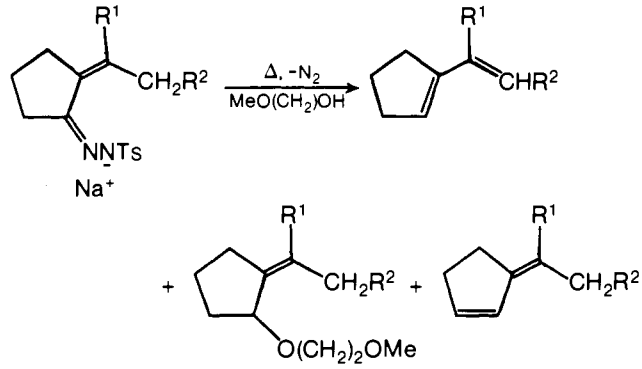
The sodium salts of methylenecyclohexanone and -cycloheptanone tosylhydrazones **198** (n = 2, 3) when heated (80–120 °C) afford pyrazolenines **200** (R^1, R^2 = Me, Ph) or pyrazoles **201** (R^2 = H) via vinyldiazomethanes **199** as outlined in Scheme XIII.[78] For **198** (n = 1, R^1 = H), pyrazoles **201** (n = 1) can also

SCHEME XIII

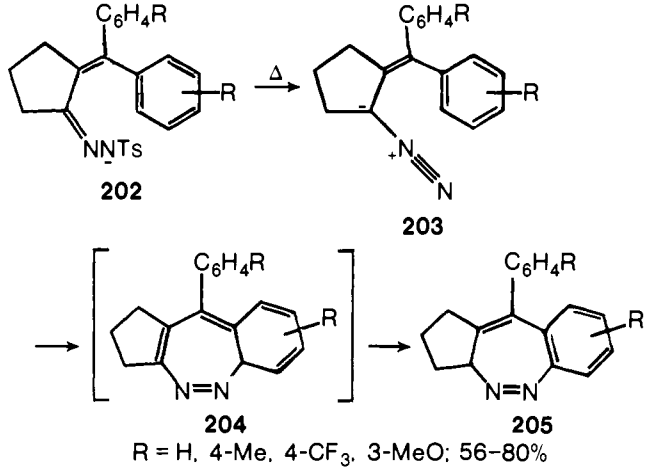


be isolated. However, in the thermolysis of **198** (n = 1; R^1, R^2 = $-(CH_2)_4-$ or Me) in ethylene glycol methyl ether, pyrazolenines **200** (n = 1; R^1, R^2 = $-(CH_2)_4-$ or Me) were not detected and only the products arising from nitrogen elimination could be obtained (Scheme XIV).[78] The difference in reactivity between the cyclohexyl substrates was attributed to the sensitivity of the 1,5-electrocyclization of **199** to steric factors, i.e., the greater distance between the termini of the π system in **199** (n = **1**) and the blocking effect of the alkyl groups in the more rigid five-membered ring system. These factors tend to reduce the rate of electrocyclization relative to nitrogen elimination in the cyclopentyl series.

SCHEME XIV

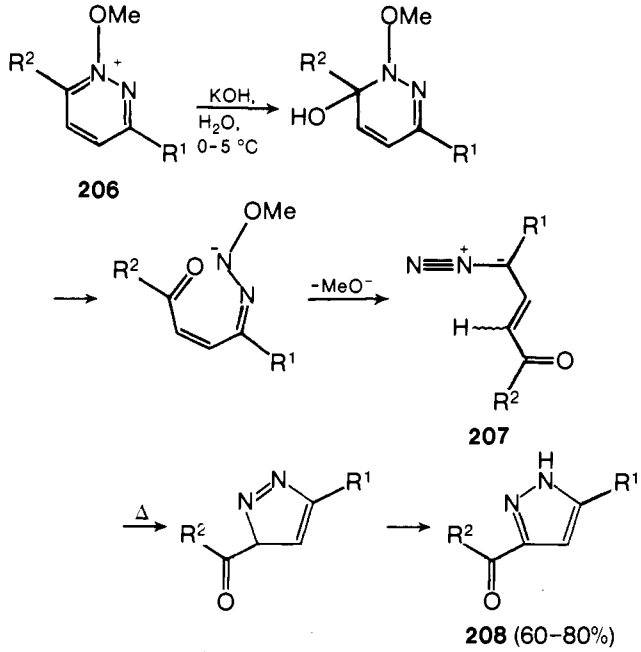


An example of a 1,7-dipolar cyclization of diazoalkenes **203** occurs in the pyrolytic decomposition of tosylhydrazones **202** to produce ultimately benzodiazepins **205** via **204.**[78]



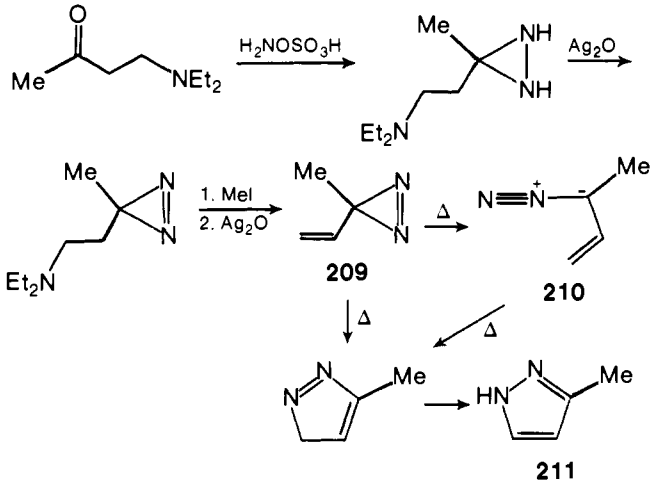
R = H, 4-Me, 4-CF_3, 3-MeO; 56–80%

Vinyldiazomethanes **207** have been synthesized by the reaction of 1-methoxypyridazinium salts **206** with KOH. These 1,3-dipolar species are converted to 3-acylpyrazoles **208** in good yields when heated.[77]



The synthesis of 3-methyl-3-vinyldiazirine (**209**), which is isomeric with 3-diazo-1-butene (**210**), has been accomplished as outlined in Scheme XV.[84] Upon standing for several days in ethanol or heating to 200 °C, **209** provides 3(5)-methylpyrazole (**211**) in 90% yield. The question of whether the diazo compound

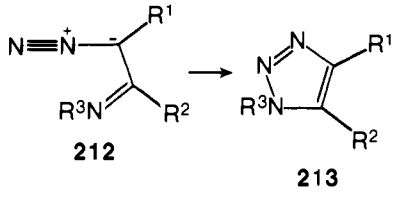
SCHEME XV



210 intervenes in this process or whether the reaction can best be described as a concerted rearrangement not requiring the intermediacy of **210** is unresolved.

2. *Iminodiazomethanes (1,2,3-Triazoles)*

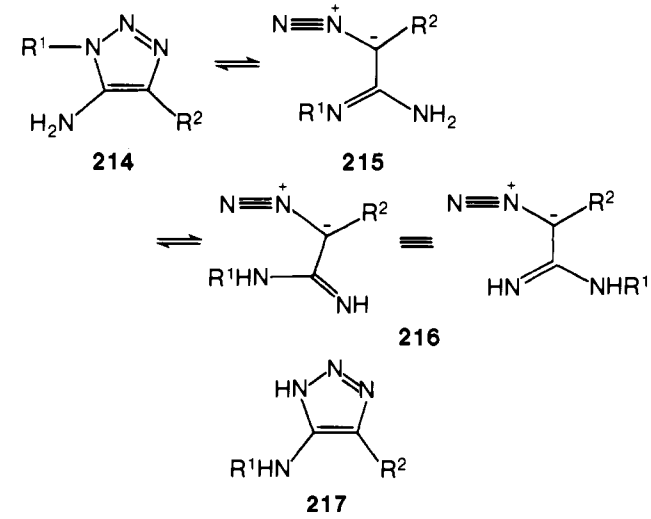
Iminodiazomethanes **212** are not as a rule isolable substances but once generated undergo spontaneous 1,5-electrocyclization to afford 1,2,3-triazole derivatives **213.** Since Regitz has dis-



cussed various aspects of the chemistry of iminodiazomethanes including their 1,5-dipolar cyclizations in his review of the transfer of diazo groups,[85] our concern in this section is to consider work not included in his review.

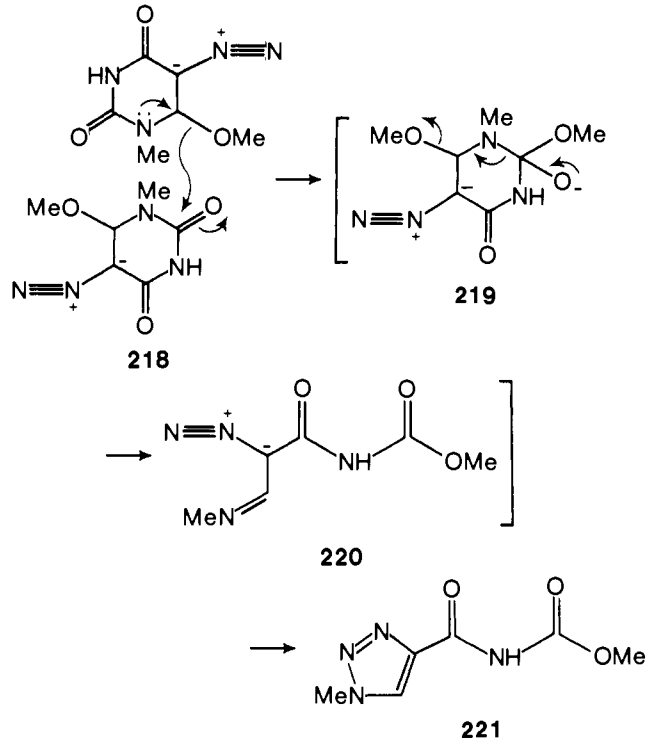
Studies of the mechanism of the thermal rearrangement of 5-amino-1,2,3-triazoles **214** (Scheme XVI) support the intermediacy of iminodiazomethanes **215** which arise from the electrocylic ring opening of **214.**[86,87] A prototropic shift in **215** gives new iminodiazomethanes **216** which cyclize to the isomeric 5-amino-1,2,3-triazoles **217.**

SCHEME XVI

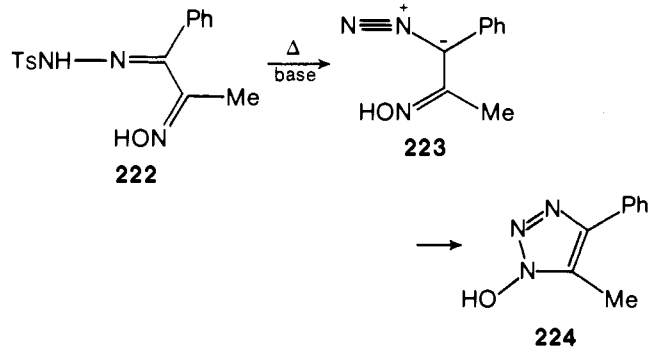


At 150 °C the 5-diazouracil derivative **218** is converted to the 1,2,3-triazole **221** presumably through iminodiazomethane **220.**[88] Isotopic labeling experiments lend support to the proposed mechanism as given in Scheme XVII.

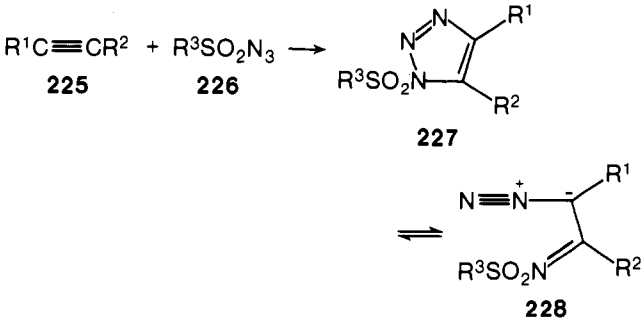
SCHEME XVII



1-Hydroxy-4-phenyl-5-methyl-1,2,3-triazole (**224**) is formed in 85% yield via iminodiazomethane **223** when tosylhydrazone **222** is heated in the presence of base.[76]



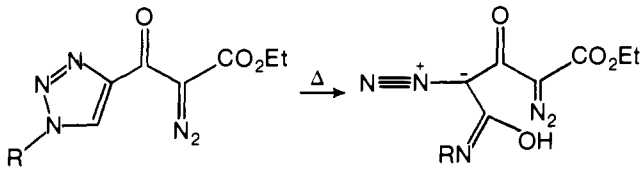
The products obtained from the reaction of sulfonyl azides **226** with ynamines **225** (R^1 = H, Me; R^2 = NRR')[89,90] or alkoxyacetylenes **225** (R^1 = H, R^2 = OR) are either triazoles **227** or the corresponding isomeric iminodiazomethanes **228.** In the majority of cases, however, the products are iminodiazomethanes **228** which arise by an electrocyclic ring opening of the initially



R^1 = H, Me; R^2 = NRR', OR

formed triazole **227.** In solution a tautomeric equilibrium between **227** and **228** occurs.

Electrocyclic ring opening of 1,2,3-triazole **229** affords the bisdiazo carbonyl compound **230.**[91]



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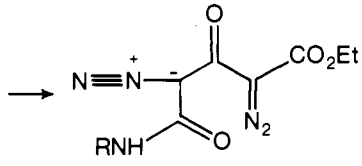
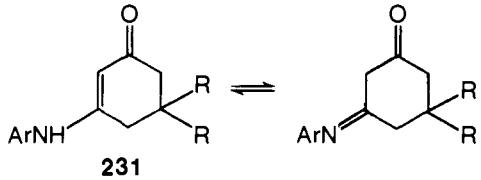
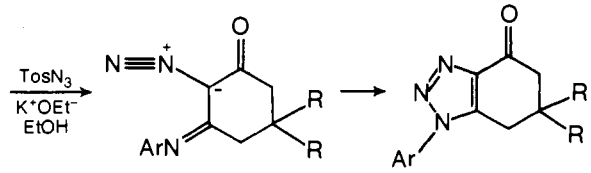


230

A diazo group transfer to 1-anilino-3-oxocyclohexenes **231** is effected by treatment of **231** with tosyl azide and potassium ethoxide in ethanol. While the intermediate iminodiazomethane **232** can be detected (IR) in the crude product, recrystallization leads to 1,2,3-triazoles **233** exclusively.[92a]

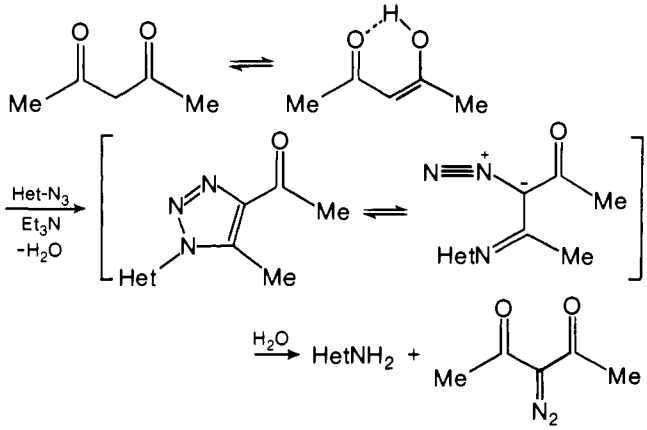


231



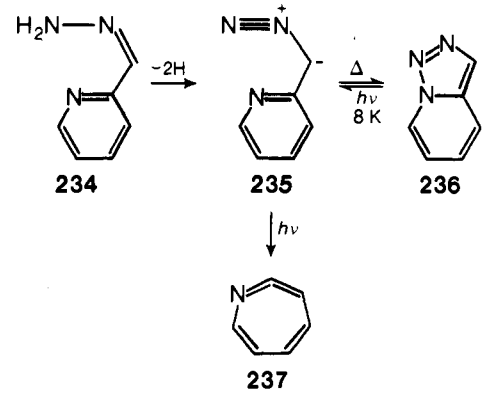
232 **233** (62–91%)

Heterocyclic azides have been reduced to the corresponding amines in good yield by the method outlined below.[92b]



Dehydrogenation of pyridine-2-carboxaldehyde hydrazone (**234**) affords 1,2,3-triazolo[3,4-*a*]pyridine (**236**) through the intermediate α-pyridyldiazomethane (**235**).[85] Intermediate **235** is not insolable under the reaction conditions. Irradiation of **236** in an argon matrix at 8 K causes an electrocyclic ring opening to give **235** for which IR spectral data were reported.[93] Further irradiation of **235** facilitates nitrogen elimination and furnishes the novel heterocycle, 1-aza-1,2,4,6-cycloheptatetraene (**237**) isolated in the matrix.

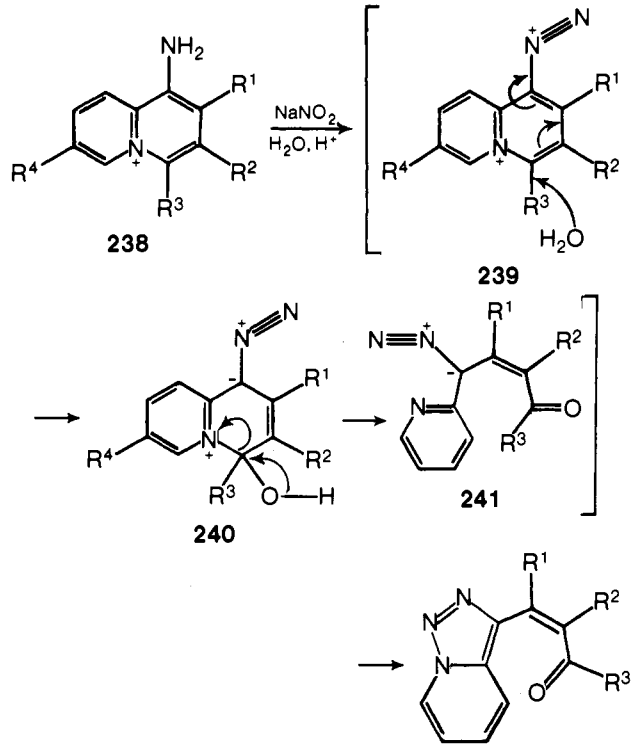
Attempted diazotization of 4-aminoquinolizinium salts **238** does not give the expected results but instead leads to the formation of *v*-triazolo[1,5-*a*]pyridines **242.**[94] The mechanism postulated for this interesting transformation involves nucleophilic attack of water at the 1 position of the intermediate diazonium salt **239.** Ring opening of **240** gives iminodiazomethane **241,** which undergoes electrocyclization to the observed product **242** (Scheme XVIII).



234 **235** **236**

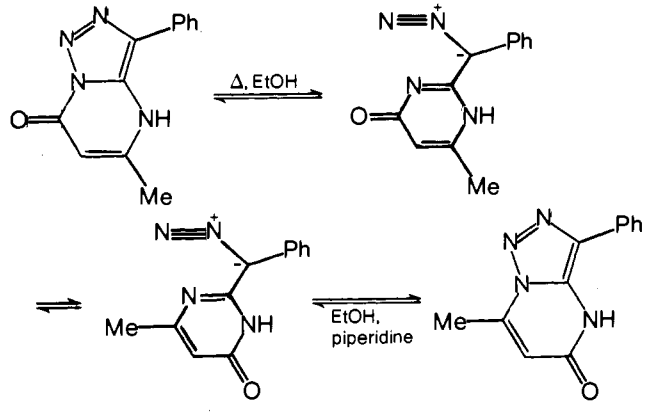
237

SCHEME XVIII

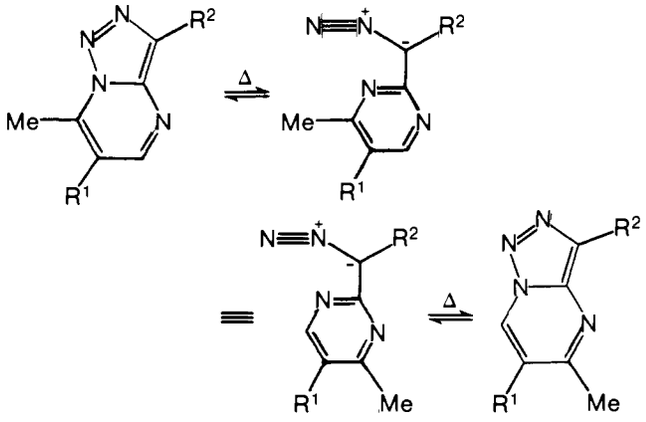


Tennant and co-workers[95-100] and others[101] have shown considerable interest in the thermal[99-101] and acid-catalyzed[95-98] interconversions of 1,2,3-triazolopyrimidine

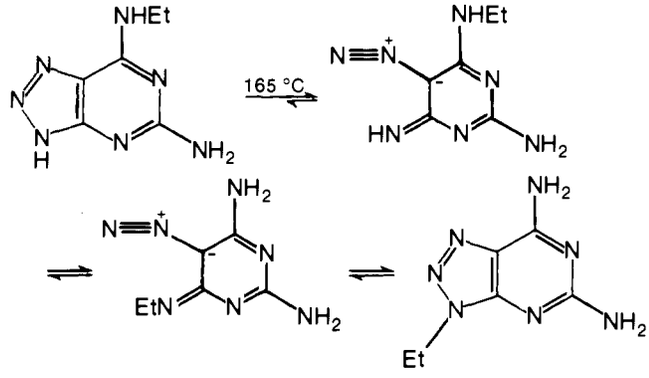
SCHEME XIX[99]



SCHEME XX[100]



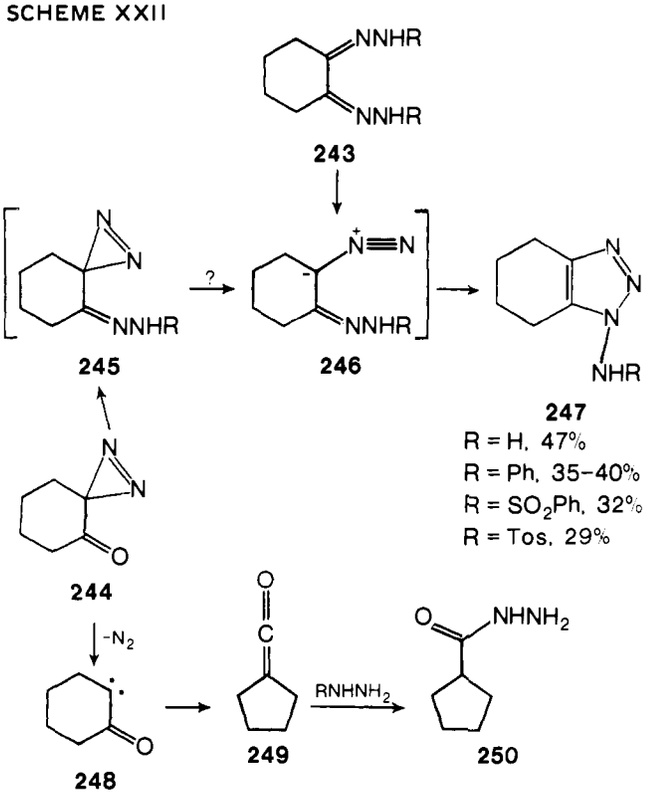
SCHEME XXI[101]

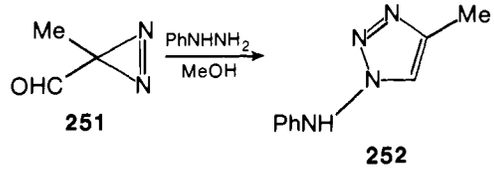


isomers. These transformations probably proceed via iminodiazomethanes, at least in the thermal cases. Some examples are outlined in Schemes XIX–XXI.

While α-carbonyldiazirines are stable, isolable substances, attempts to prepare α-hydrazinodiazirines from the corresponding ketones result only in ring expansion to 1-amino-1,2,3-triazoles.[102,103] For example, when α-ketodiazirine **244** is allowed to react with hydrazine, phenylhydrazine, benzenesulfonyl hydrazine, or tosylhydrazine, 1-amino-1,2,3-triazoles **247** are formed.[102] 1-Amino-1,2,3-triazole **247** (R = SO_2Ph) was prepared independently from the bishydrazone **243** (Scheme XXII).[102] Beside triazoles **247**, cyclopentanecarboxylic acid hydrazides **250** were isolated from these reactions generally as minor products. The ring-contracted products probably arise via Wolff rearrangement of ketocarbene **248** to ketene **249** (Scheme XXII). 3-Methyl-3-formyldiazirine (**251**) and phenylhydrazine react in a similar manner to afford 1-anilino-4-methyl-1,2,3-triazole (**252**) in 27% yield.[103] Again it is not certain whether the 1-aminotriazoles derive directly from the diazirines or if iminodiazomethanes are involved in this ring expansion.

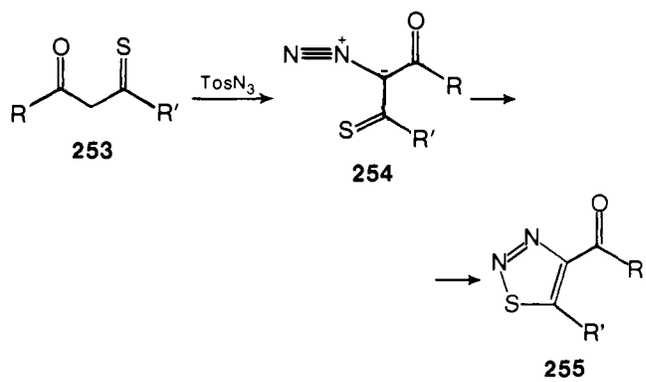
SCHEME XXII





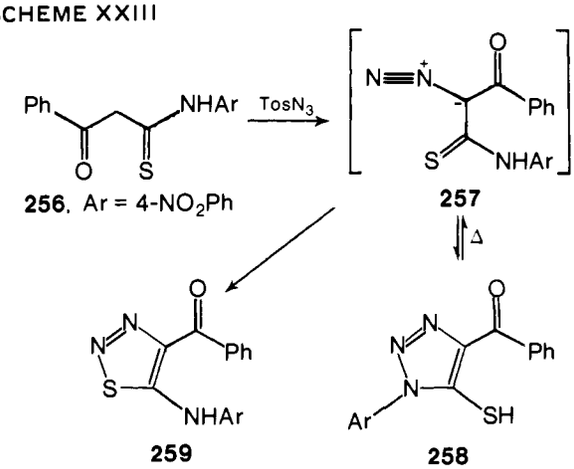
3. *Thiocarbonyldiazomethanes (1,2,3-Thiadiazoles)*

4-Acyl-1,2,3-thiadiazoles **255** have been prepared in good yields by the reaction of 2-oxothiones **253** with tosyl azide.[85,104] The intermediate thiocarbonyldiazomethanes **254** have not been isolated but undergo spontaneous 1,5-electrocyclization yielding **255.**

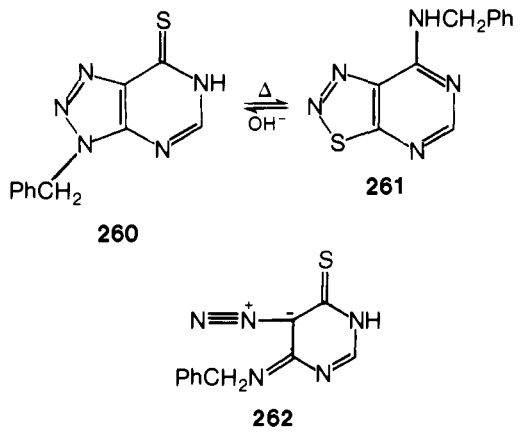


N-(4-Nitrophenyl)benzoylthioacetamide (**256**) and tosyl azide in ethanol combine to provide two isomeric heterocycles, 4-benzoyl-5-(4-nitroanilino)-1,2,3-thiadiazole (**259**, 55%) and 1-(4-nitrophenyl)-4-benzoyl-5-mercapto-1,2,3-triazole (**258**, 21%).[85] When heated 5-mercaptotriazole **258** isomerizes to 1,2,3-thiadiazole **259** presumably through thiocarbonyldiazomethane **257** (Scheme XXIII).

SCHEME XXIII

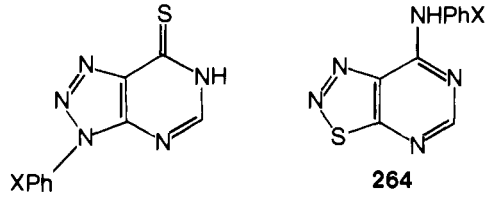


Heating 1,2,3-triazolopyrimidine **260** in ethanol leads to the formation of the 1,2,3-thiadiazolopyrimidine **261** presumably via thiocarbonyldiazomethane **262.**[105] The fused thiadiazole **261**



260 261 262

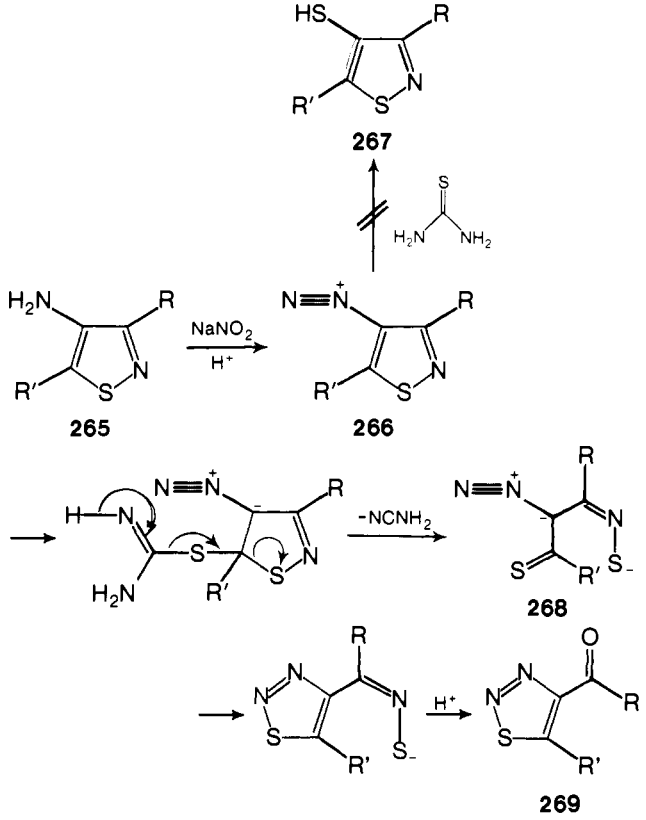
is reconverted to **260** when heated in refluxing aqueous NaOH. An equilibrium between the related systems **263** and **264** is established when either substance is heated in refluxing alcohols.[106] Under these conditions the thiadiazole **264** is the more stable isomer and the amount present at equilibrium increases at the expense of **263** with increasing temperature and electron-withdrawing power of the group X. Interestingly, in Me_2SO the equilibrium constant indicates almost equal amounts of **263** and **264.** This change in the equilibrium constant was rationalized in terms of hydrogen bonding between solutes and solvents.



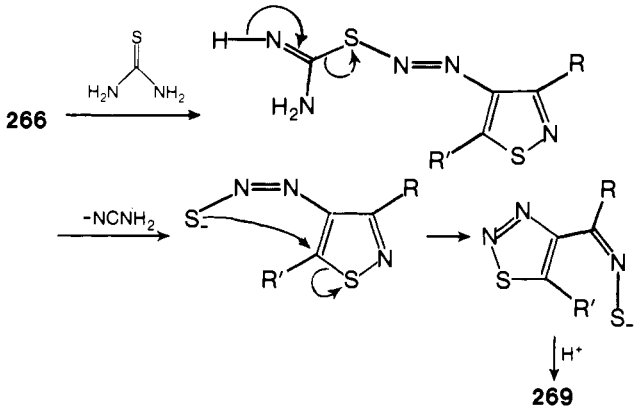
263 264

Diazotization of 4-aminoisothiazoles **265** and reaction of the resulting diazonium salts **266** with thiourea did not afford the expected 4-mercaptoisothiazoles **267.** Instead 1,2,3-thiadiazoles

SCHEME XXIV



SCHEME XXV



269 are formed in fair yields.[107] Two possible mechanisms which are compatible with the experimental observations were proposed to rationalize the formation of **269** (Schemes XXIV and XXV). The first pathway (Scheme XXIV) involves 1,5-dipolar cyclization of the intermediate thiocarbonyldiazomethane **268.**

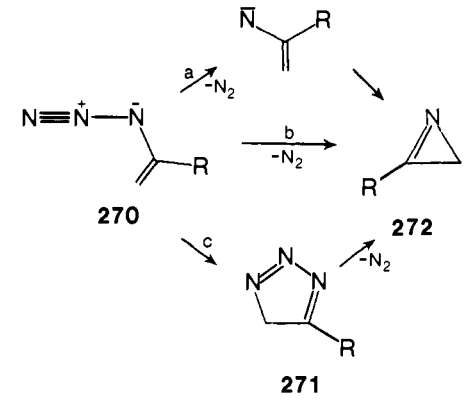
D. Azides

Organic azides enjoy a remarkably rich chemistry as is evidenced by the large volume of review material published in the last 15 years on various aspects of azide synthesis and reactivity. Organic azides can be transformed into a variety of other functional groups including amines, nitriles, isocyanates, and azo compounds to name a few.[108] They are ubiquitous in heterocyclic chemistry, serving as precursors for such systems as aziridines, azirines, oxazoles, isoxazoles, oxadiazoles, and triazoles along with those discussed below.[108]

1. *Vinylazides (4H-1,2,3-Triazoles)*

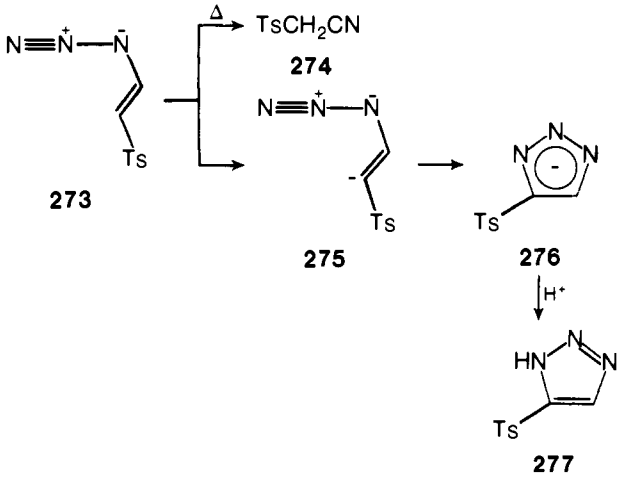
Until recently vinylazides were mere curiosities. The pioneering work of Hassner and his collaborators[109] and Smolinsky (see G. Smolinsky and C. A. Pryde, in ref 108, p 555) among others[108,110] was instrumental in the development of new technology for the synthesis of vinylazides which facilitated the study of these species. One of the most useful reactions of vinylazides is their thermal and photochemical decomposition to 1-azirine derivatives.[111,112] The mechanism of this process remains in doubt. Smolinsky postulated three mechanisms as outlined in Scheme XXVI.[112] While little is known concerning the mechanism of the photoprocess, the vinyl nitrene mechanism (path a) for the thermal process can be discounted on the basis of kinetic arguments.[80,111] The concerted pathway (path b) appears to be the most likely but the available experimental evidence does not completely exclude the 1,5-dipolar cyclization of vinylazide **270** to 1,2,3-triazolenine **271** followed by nitrogen elimination to afford 1-azirine **272** (path c).[80,113] The activation

SCHEME XXVI



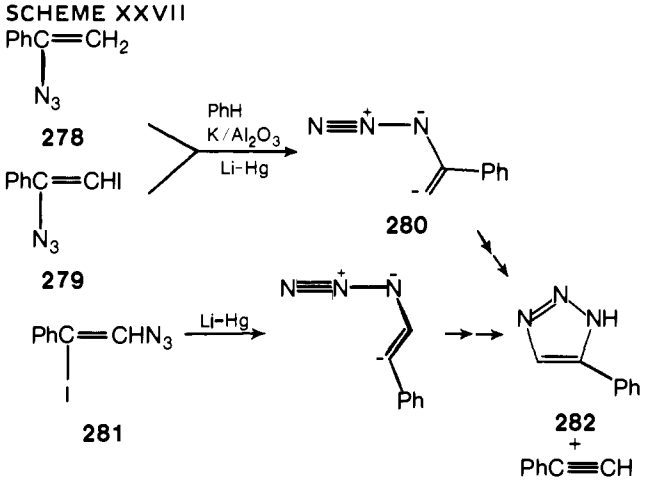
energy for the vinylazide–1,2,3-triazolenine isomerization has been estimated to be 30–40 kcal/mol by ab initio MO methods.[114] The experimentally determined activation energy for the vinylazide–azirine interconversion is 26–30 kcal/mol.[111] Thus this mechanistic pathway is not rigorously excluded on the basis of these theoretical considerations.

1-Azido-2-(*p*-toluenesulfonyl)ethylene (**273**) upon thermolysis in aqueous ethanol affords tosylacetonitrile (**274**) in 53% yield.[115] In sharp contrast to this result is the observation that vinylazide **273** gives 4-tosyl-1,2,3-triazole (**277**) when allowed to stand in $(CH_3)_2SO$ solution in the presence of a base (sodium *p*-toluenesulfinate gives the best results).[116] In the absence of



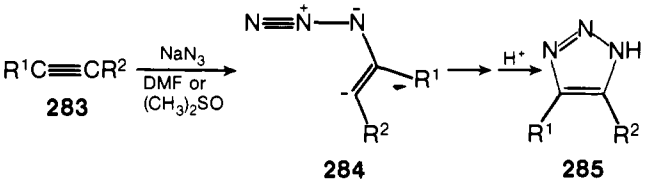
base there is no detectable conversion of **273** to **277.** Thus it was postulated that it is the azidovinyl anion **275** which cyclizes to triazolyl anion **276** which upon work-up yields **277.** Support for this proposal is derived from the results of Woerner and Reimlinger who observed the formation of 1,2,3-triazoles **282** in the reaction of vinylazide **278** with potassium/alumina in benzene.[117] Likewise **282** is isolated when a mixture of iodoazides **279** and **281** is treated with lithium amalgam (Scheme XXVII).

SCHEME XXVII



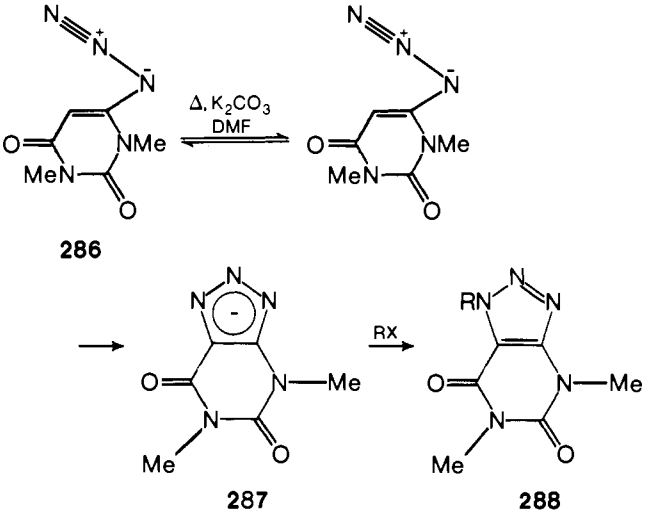
Moreover, Russian chemists have prepared triazoles **285a–e** in good yield from the reaction of sodium azide with acetylenes **283a–e** by what is believed to be a nucleophilic addition of azide ion to the acetylene to furnish azidovinyl anions **284** followed by ring closure.[118] Woerner and Reimlinger have extended this reaction to include the triazoles **285f–l.**[117] Circumstantial evidence led these workers to favor the two-step mechanism (i.e., nucleophilic addition–cyclization) as opposed to the 1,3-dipolar cycloaddition of azide ion to the acetylene for the pathway of triazole formation.

Recently, considerable interest has been shown in 1,2,3-triazolo[4,5-*d*]pyrimidines **288** as potential purine antagonists.



	R^1	R^2	yield, %
a	C_3H_7CO	H	86
b	PhCO	H	82
c	CO_2Et	Ph	92
d	CN	Ph	80
e	$CONH_2$	Ph	53
f	H	H	11
g	Ph	Ph	16
h	CO_2Me	H	49
i	CO_2Me	CO_2Me	54

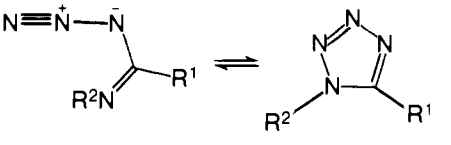
A novel route to these compounds involving cyclization of 6-azido-1,3-dimethyluracil **286** has been developed by Senga et al.[119] Here again a base (K_2CO_3) is required for the success of this reaction. The initially formed triazolyl anion **287** can be intercepted by alkyl halides to afford products **288** (R = alkyl) in 21–77% yield. When the alkyl halide is absent, **288** (R = H) is obtained in 30% yield.



2. *Iminoazides (Tetrazoles)*

Over the last 25 years the iminoazide–tetrazole 1,5-dipolar cyclization (Scheme XXVIII) has attracted considerable attention.

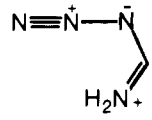
SCHEME XXVIII



Three recent reviews concerning this process which cover the literature up to 1976 have appeared[120-122] (also see ref 108, W. Lwowski, p 503; M. E. C. Biffin, J. Miller, and D. B. Paul, p 57). Because of such extensive review coverage, our concern in this section is to update the previous reviews.

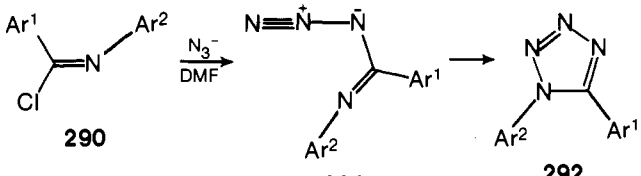
The vast amount of data amassed on the iminoazide–tetrazole isomerism allowed Tisler and Butler to make some generalizations about the factors governing the species which predominates (azide or tetrazole) in the equilibrium. In general the tetrazole is favored by electron-donating R^1 and R^2 substituents, lower temperatures, basic and polar, aprotic media. Ab initio MO calculations (STO-3G) on the iminoazide cyclization suggest an educt-like transition state.[123] The calculated activation energy

and heat of reaction are 12.3 and −66.1 kcal/mol (STO-3G), respectively.[123] More importantly, the calculations reveal that a 90° rotation of the imino π system is a higher energy pathway than the approach of the in-plane imino lone pair to the terminal azide nitrogen in passing to the cyclization transition state. In agreement with this reasoning, an activation barrier of 42.9 kcal/mol was calculated for the cyclization of the protonated iminoazide **289**.[114] Furthermore, as was pointed out above, formation of anions of the type **284** facilitates cyclization of vinylazides to 1,2,3-triazoles.



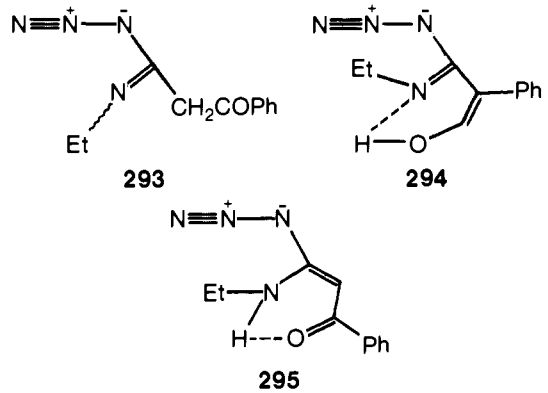
289

The advantages of utilizing polar aprotic rather than protic solvents in the preparation of tetrazoles **292** by the reaction of azide salts with imidoyl halides **290** have been outlined.[124]



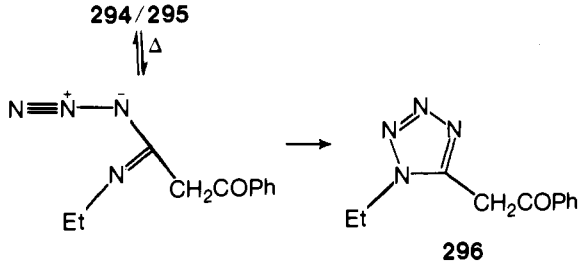
290 **291** **292**

Another factor which should influence the iminoazide–tetrazole electrocyclization is the configuration about the imino moiety; i.e., a trans arrangement of the azido group and the imino nitrogen lone pair should prohibit cyclization. Isolation of iminoazide **293** is presumably made possible because of hydrogen bonding to the imino nitrogen (**294**) and/or rapid tautomerism to **295**.[125a] Cyclization to tetrazole **296** occurs upon heating in



293 **294** **295**

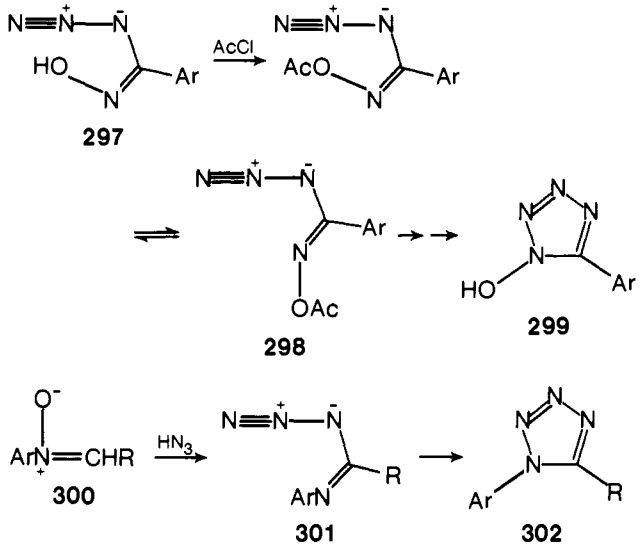
an inert solvent or at room temperature in water. The reaction is catalyzed by both acids and bases. Similarly, acetyl chloride



296

catalyzes the cyclization of hydroxamoyl azides **297** to 1-hydroxytetrazoles **299** presumably by promoting *E*–*Z* isomerization to **298**.[125b]

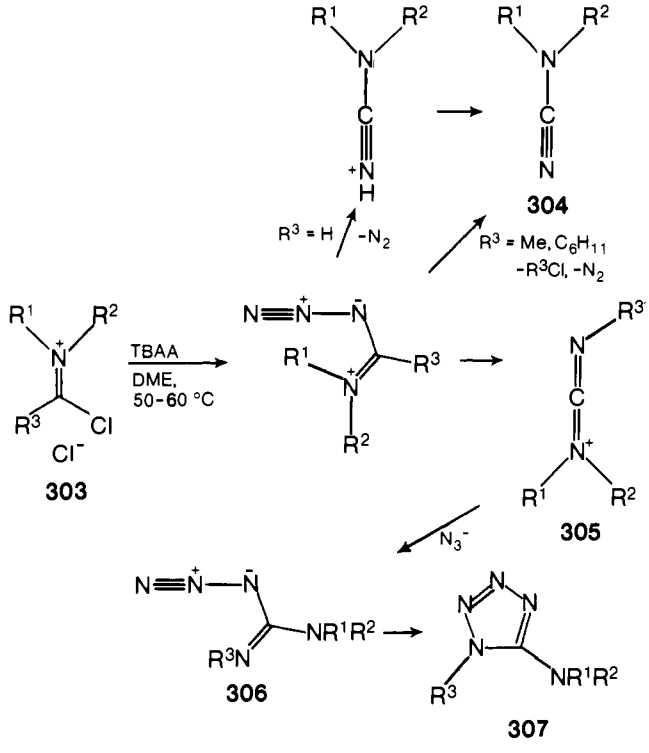
N-Arylnitrones **300** furnish 1-aryltetrazoles **302** (5–62%) among other products when allowed to react with hydrogen azide in methylene chloride–benzene.[126] The reaction is thought to involve iminoazide **301**.



297 **298** **299** **300** **301** **302**

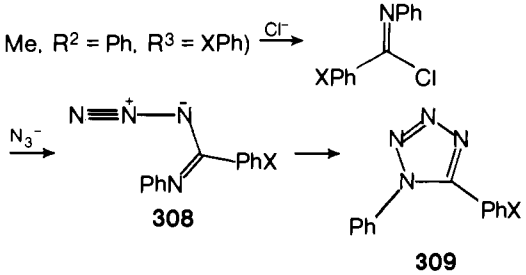
The course of the reaction of chloroiminium chlorides **303** with tetrabutylammonium azide (TBAA) is controlled by the nature of the substituents R^3.[127] When R^3 = H, Me, C_6H_{11}, cyanamides **304** are isolated. When R^3 = XPh, phenyl migration ensues to give the unstable carbodiiminium salt **305** which suffers attack by azide ion (present in excess) to provide iminoazide **306** and ultimately 1-aryl-5-aminotetrazoles **307**

SCHEME XXIX



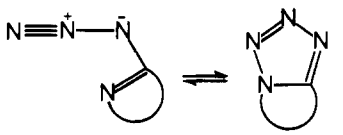
303 **304** **305** **306** **307**

(10–76%). These processes are outlined in Scheme XXIX. Minor amounts of tetrazoles **309** are also formed presumably via iminoazide **308**.



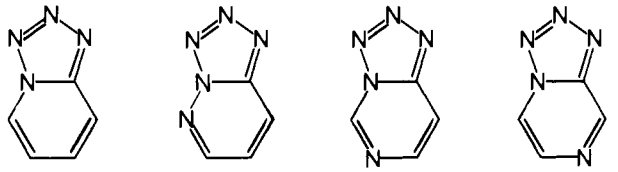
308 **309**

A useful and well-documented method for preparing tetrazoles fused to other heterocycles (i.e., **311**) is by 1,5-dipolar cyclization



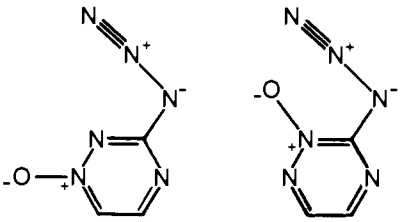
310 **311**

of nitrogen-containing azido heterocycles of the type **310**.[120-122,128] In $(CH_3)_2SO$ solution, **312–315** exist exclusively as the tetrazoles.[129]



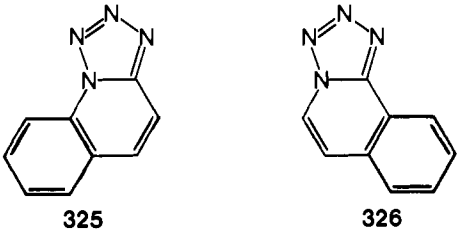
312 **313** **314** **315**

2-Azidopyrimidine and 2-azido-1,2,4-triazine exist in the azido form in $(CH_3)_2SO$ to the extent of 10 and 100%, respectively.[129] 3-Azido-1,2,4-triazines **316** cyclize spontaneously to tetrazolo[1,5-*b*]-1,2,4-triazines **317** rather than the isomeric N-4 cyclized products **318** as revealed by spectral and X-ray crystallographic data.[129] Similarly, nitrous acid oxidation of 3-hydrazino-2,5-dihydro-5-oxo-1,2,4-triazines (**319**, R^1 = H) leads to 7,8-dihydro-7-oxotetrazolo[1,5-*b*]-1,2,4-triazines (**321**, R^1 = H) via 3-azido-2,5-dihydro-5-oxo-1,2,4-triazines (**320**, R^1 = H).[130] Treatment of N-2 alkylated **319** (R^1 = Me, R^2 = H) with nitrous acid effects cyclization at N-4 of iminoazide **320** (R^1 = Me, R^2 = H) to give 4,7-dihydro-4-methyl-7-oxotetrazolo[5,1-*c*]-1,2,4-triazine (**322**). In contrast, 3-azido-1,2,4-triazine-1- and -2-oxides **323** and **324** have been shown by ^{13}C, ^1H, and IR spectroscopic methods to exist entirely in the azide form in the solid state and in solution ($CHCl_3$ or $(CH_3)_2SO$).[131]

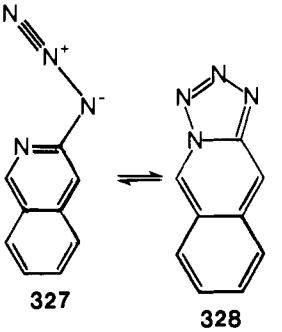


323 **324**

Whereas the iminoazide–tetrazole equilibrium lies completely on the side of the tetrazole for the angular tetrazoloquinoline **325** and tetrazoloisoquinoline **326**, a small amount of the azide **327** exists with the previously unreported linear tetrazolo[1,5-*b*]-isoquinoline **328** in the solid state.[132] In chloroform **327** is the major tautomer (60%).

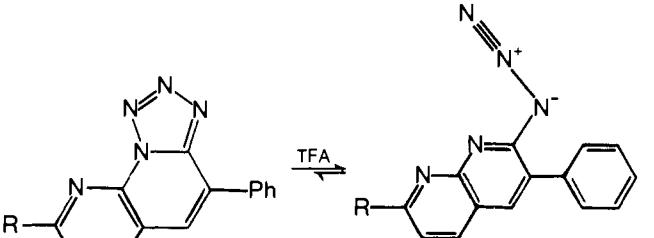


325 **326**

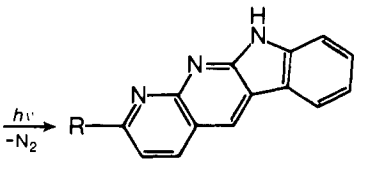


327 **328**

The high yield synthesis of some compounds related to ellipticine and olivacine, the 6*H*-indolo[2,3-*b*][1,8]naphthyridine derivatives **331**, has been effected by photolysis of 4-phenyltetrazolo[1,5-*a*][1,8]naphthyridines **329** in trifluoroacetic acid



329 **330**



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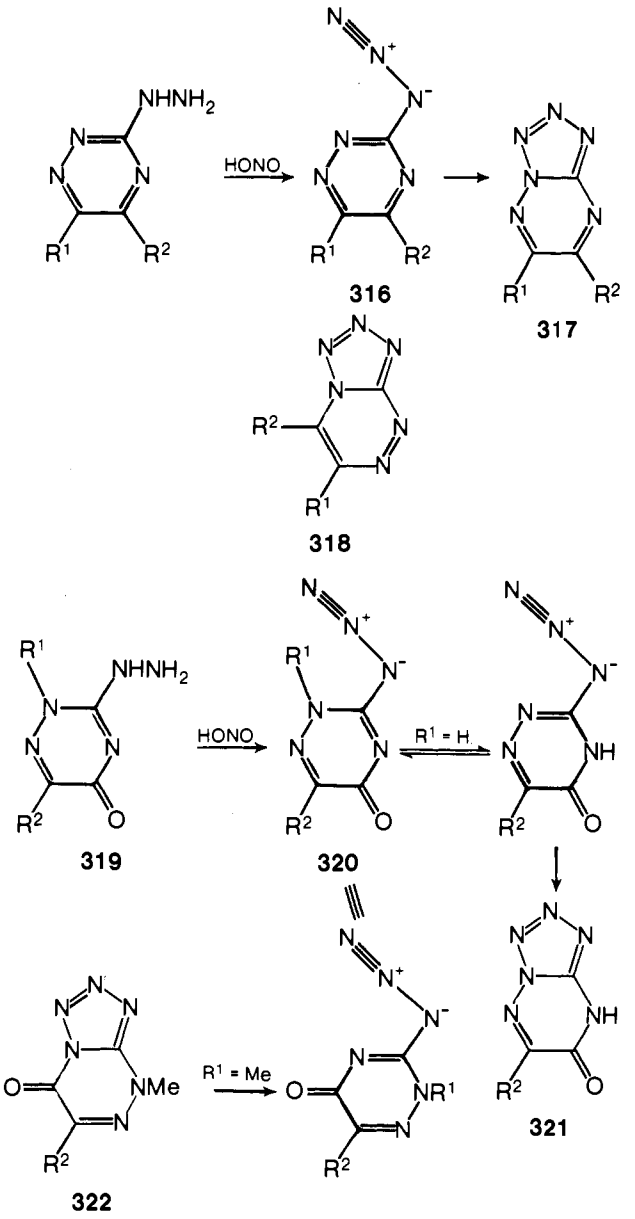
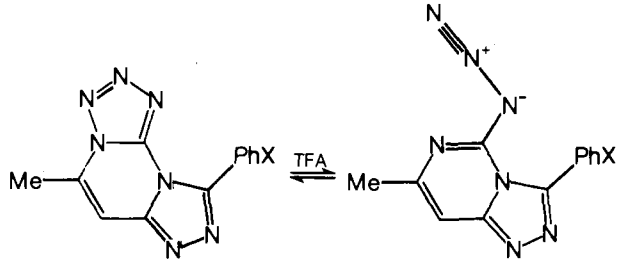


316 **317** **318** **319** **320** **321** **322**

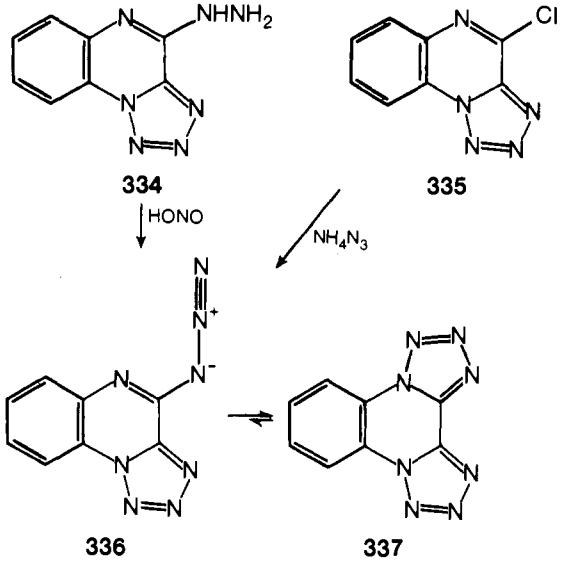
(TFA).[133] In acid solution the iminoazides **330** predominate, and it is believed to be the latter which suffer nitrogen elimination and C–H insertion to furnish the observed products.

The infrared spectra of *s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]-pyrimidines **332** in KBr show no evidence of azide absorption nor are iminoazides **333** detectable in the NMR spectra of **332** in $(CH_3)_2SO$-d_6 or DMF-d_7.[134] In TFA solution, however, the equilibrium **332** ⇌ **333** occurs at room temperature. Electron-withdrawing X substituents favor the azido isomers in agreement with general trends.



332 **333**

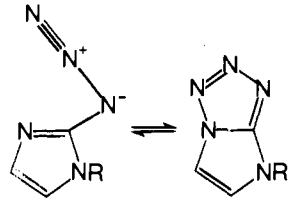
The synthesis of ditetrazolo[1,5-*a*:5,1-*c*]quinoxaline **337** was effected by nitrous acid oxidation of 3-hydrazinotetrazoloquinoxaline **334** or alternatively by treatment of 3-chlorotetrazoloquinoxaline **335** with ammonium azide.[135] The 3-azidotetrazoloquinoxazine **336**, while not present in the solid state, arises to a small extent in $(CH_3)_2SO$ solution.



334 **335**

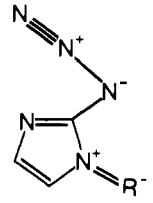
336 **337**

2-Azidoazoles generally exist as such in contrast to the 2-azidoazines. Recently, however, it was demonstrated that 1-acetyl-2-azidoimidazole **338** (R = MeCO) coexists with the isomeric tetrazole **339** (R = MeCO).[136-138] In $(CH_3)_2SO$ solution,



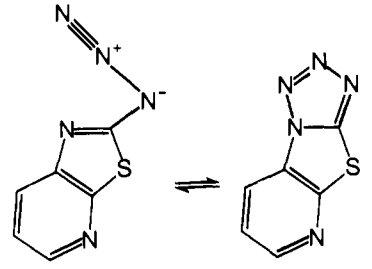
338 **339**

the tetrazole form becomes increasingly favored as the bulk of the R group is increased from COMe to CO-*t*-Bu.[136] The position of the equilibrium is determined by the $T\Delta S$ term since ΔH remains nearly constant in a given series. From this observation it was inferred that the bulky R group forces the azide moiety into the proper conformation for cyclization. Moreover, the decrease in entropy upon cyclization is partially offset by the increase in entropy of the tetrazole in which less hindered rotation of the group CO-*t*-Bu is possible. Groups R, which are mesomerically electron withdrawing (+*E*), favor formation of tetrazole **339**, while inductively electron-withdrawing groups (+*I*) R exhibit the opposite effect.[137] A possible rationale is that +*E* groups reduce the aromaticity of the imidazole ring (cf. **340**); thus the enthalpy increase for cyclization is smaller.[137]

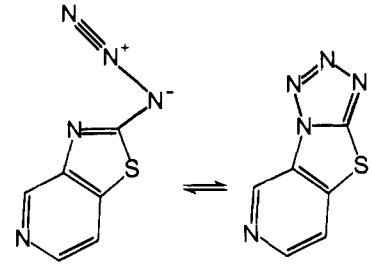


340

Crystallization of 2-azidothiazolo[5,4-*b*]pyridine (**341**) from water gives a new compound, the isomeric tetrazole **342**.[139] When **342** is sublimed in vacuo, it is reconverted to **341** which is again isomerized to **342** at its melting point. Similar behavior is exhibited by azide **343** and the isomeric tetrazole **344**.[139] NMR spectroscopy reveals an equilibrium between the isomer pairs **341/342** and **343/344**.[139] As expected, higher temperatures favor the azide tautomer.

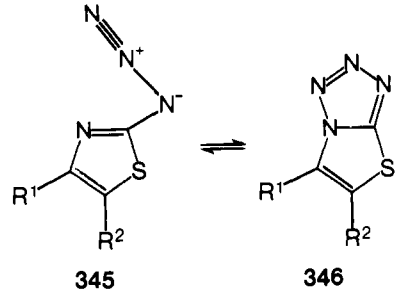


341 **342**



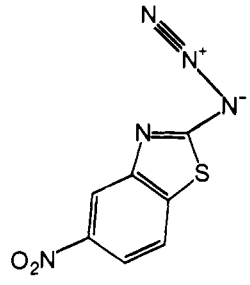
343 **344**

Faure et al. have conducted a quantitative NMR study of the iminoazide–tetrazole cyclization for various azoles.[140] The above generalizations concerning substituent and solvent effects apply to the azole series. Methyl groups at either the 4 or 5 position of the thiazole derivatives **345** and **346** favor the tetrazoles **346** while halogens at these positions favor the azide **345**.[140]



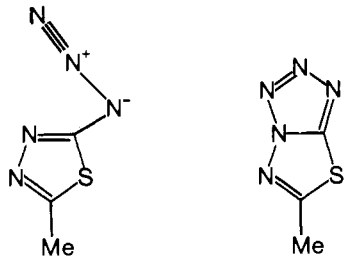
345 **346**

When R^1 = 4-NO_2Ph only the azide **345** can be detected. 2-Azido-5-nitrobenzothiazole (**347**) exists alone either in chloroform or $(CH_3)_2SO$ solution.[140] The NMR spectra of a mixture of

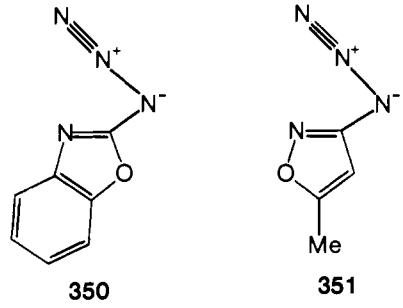


347

2-azido-5-methyl-1,3,4-thiadiazole (**348**) and the isomeric tetrazole **349** in various solvents disclose that increasing solvent polarity displaces the equilibrium toward **349.**[140] 2-Azidobenzoxazole (**350**) and 3-azido-5-methylisoxazole (**351**) show no tendency toward 1,5-dipolar cyclization to the corresponding tetrazoles either in chloroform or $(CH_3)_2SO$.[140]

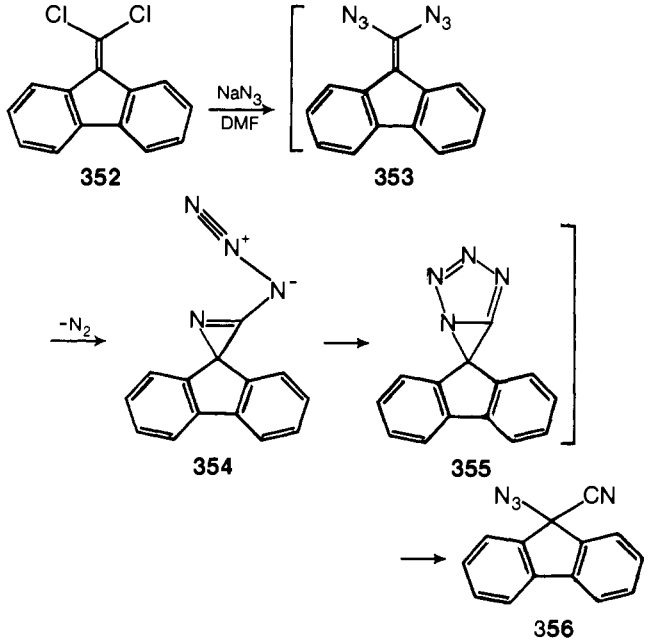


348 349



350 351

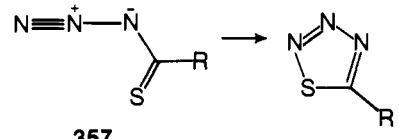
A curious transformation occurs when 9,9-dichloromethylenefluorene (**352**) is treated with sodium azide in DMF.[141] The product, 9-azido-9-fluorenecarbonitrile (**356**), is postulated to arise by cyclization of the initially formed 9-bisazidomethylenefluorene (**353**) to the 1-azido-1-azirine **354.** The latter is an example of an iminoazide which is capable of undergoing a 1,5-electrocyclization to give the strained tetrazoloaziridine **355.** This high-energy intermediate is stabilized by ring opening to the product **356** in 34% yield.



352 353 354 355 356

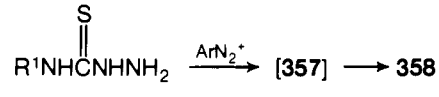
3. *Thiocarbonylazides (1,2,3,4-Thiatriazoles)*

Whereas carbonylazides are isolable species which demonstrate no inclination to undergo 1,5-dipolar cyclization to the isomeric 1,2,3,4-oxatriazoles,[108] thiocarbonylazides **357** have to date never been obtained. They very likely exist as transient intermediates in the formation of 1,2,3,4-thiatriazoles **358.**



357 358

Methods of generating thiocarbonylazides and the chemistry of 1,2,3,4-thiatriazoles have been the subject of two reviews which provide literature coverage up to 1975.[142,143] The usual methods for preparing 1,2,3,4-thiatriazoles **358** involve either nitrous acid oxidation of thionhydrazides or reaction of azide salts with active thiocarbonyl derivatives (e.g., thioacyl chlorides).[142,143] Both of these procedures probably lead to thiocarbonylazides **357** initially. Recently, thiosemicarbazides **359** have been converted to 5-amino-1,2,3,4-thiatriazoles **358** (R = NHR^1) in 35–71% yield by treatment with benzenediazonium tetrafluoroborate or diazotized sulfanilic acid in what is termed an aza transfer reaction.[144]



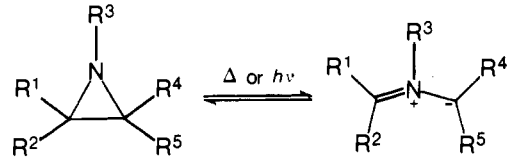
359

R = NHR^1

III. Allyl 1,3-Dipoles

A. Azomethine Ylides

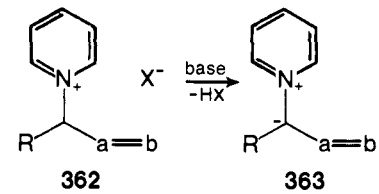
Azomethine ylides,[145,146] a class of 1,3-dipoles isoconjugate with the allyl anion, possess a trisubstituted nitrogen atom as the central atom, flanked by two trisubstituted carbons, i.e., **361.**



360 361

These species can often be generated by thermally or photochemically induced carbon–carbon bond cleavage of aziridines **360.** Whether C–C or C–N bond cleavage occurs is highly substituent dependent. Carbonyl groups activate aziridines toward azomethine ylide formation. As will be seen in the ensuing discussion, aziridines may be involved in various reactions where some nitrogen-containing heterocycles afford products derived from azomethine ylides.

Quaternary salts derived from the alkylation of π-deficient nitrogen heterocycles (such as pyridine, quinoline etc.), e.g., **362,**



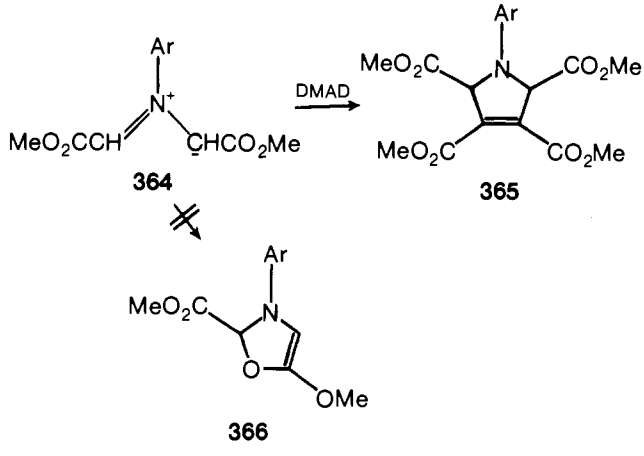
362 363

can be deprotonated under mild, basic conditions to give azomethine ylides of the type **363.**[145]

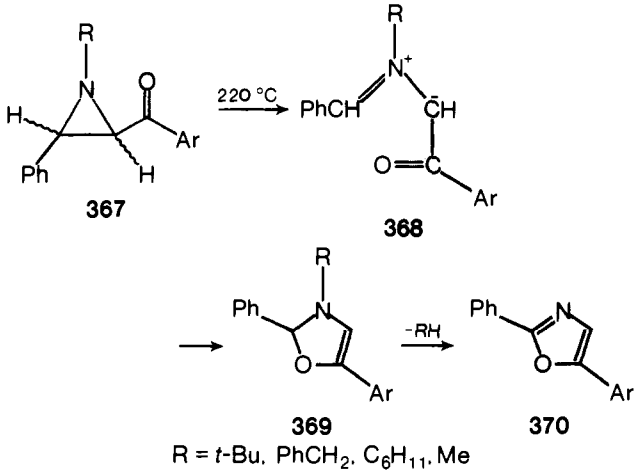
In contrast to nitrile ylides as discussed above, 1,5-dipolar cyclization of carbonyl, vinyl, imino, and thiocarbonyl substituted azomethine ylides appears to be the exception rather than the rule. The mode of stabilization of azomethine ylides is substituent dependent. In most cases they can be trapped quite effectively by dipolarophiles. In the absence of dipolarophiles, other modes of stabilization such as reactions with electrophiles or nucleophiles, [3 + 3]cyclodimerizations, and rearrangements can and often do compete effectively with the 1,5-dipolar cyclization pathway. Nevertheless, many of the above types of azomethine ylides are useful as intermediates in the preparation of five-membered nitrogen heterocycles via the latter pathway.

1. *Carbonylazomethine Ylides (4-Oxazolines)*

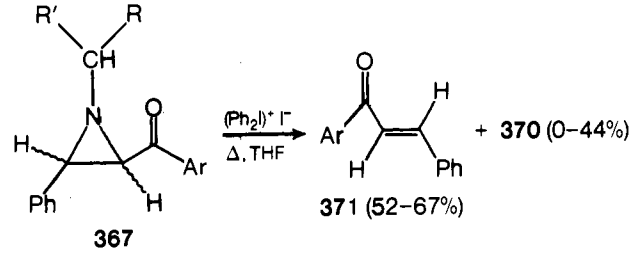
The thermal and photochemical valence isomerization of aziridines leading to azomethine ylides has been investigated by several groups of researchers.[145-148] The classic experiments of Huisgen et al.,[23,147] which demonstrated that the aziridine ring opening was governed by orbital symmetry considerations, involved the carbonylazomethine ylide **364.** This ylide enters into a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to afford 3-pyrroline derivatives **365,** the stereochemistry of the adducts being dictated by the Woodward–Hoffmann rules. No 1,5-dipolar cyclization product, i.e., the 4-oxazoline **366,** was detected.



Subsequently Padwa and Eisenhardt observed that 2,5-diaryloxazoles **370** arise in high yields when 1-alkyl-2-aroyl-3-arylaziridines **367** are pyrolyzed (220 °C) in the injector port of a gas chromatograph.[149] Aroylazomethine ylides **368,** implicated as intermediates in this process, undergo a 1,5-dipolar cyclization to the 4-oxazolines **369** which eliminate the alkyl substituent in a subsequent step presumably by a radical mechanism.

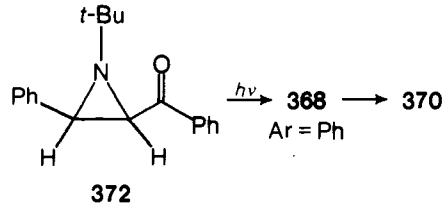


The same aroylaziridines **367** suffer ring opening reactions catalyzed by Lewis acids such as diphenyliodonium iodide in refluxing THF.[150] In this case oxazoles **370** are minor products arising from the above pathway. The major products, however, are benzalacetophenones **371** which are formed by C–N bond cleavage of the aziridine ring. The product distribution appears



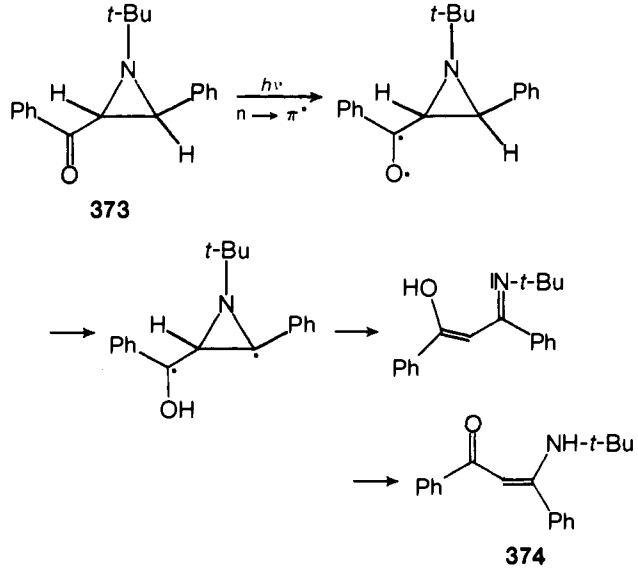
highly dependent upon the nitrogen substituent and the stereochemistry of the aziridine.

The photochemistry of aroylaziridines **367** has been exhaustively studied by Padwa and co-workers. The results of their investigation into the nature of this highly complex process have been reviewed[151] and for the most part lie outside the scope of the present review. The photochemical reactions of aroylaziridines in many cases do not give products derived from aroylazomethine ylides, but lead to products resulting from C–N bond cleavage. *cis*-1-*tert*-Butyl-2-benzoyl-3-phenylaziridine (**372**),



however, affords upon irradiation 2,5-diphenyloxazole in 51% yield, while *trans*-1-*tert*-butyl-2-benzoyl-3-phenylaziridine (**373**) gives both oxazole **370** and (β-*tert*-butylamino)-*trans*-benzalacetophenone (**374**) in approximately equal amounts.[151,152] 1,5-Hydrogen transfer from the ring to the carbonyl substituent in the trans aziridine **373** followed by ring opening serves as a rationale for the formation of **374** (Scheme XXX). 1,5-Electrocyclization of the photochemically generated aroylazomethine ylide **368** (Ar = Ph), followed by loss of isobutane as described above for the thermal case, provides a reasonable pathway for oxazole formation. The absence of the benzalacetophenone **374**

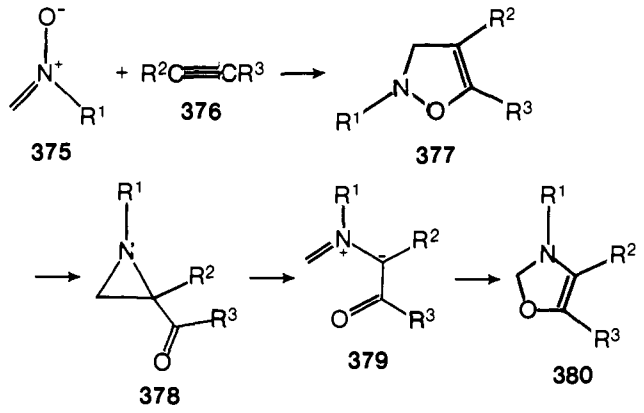
SCHEME XXX



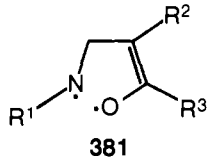
in the photolysis of the *cis*-aziridine **372** supports the above mechanistic contention since **372** cannot undergo the initial 1,5-hydrogen transfer because of steric constraints.

4-Isoxazolines, the products obtained from 1,3-dipolar cycloaddition of nitrones with acetylenes, undergo a fascinating thermal rearrangement leading to 4-oxazolines.[153] The mechanism appears to involve ring contraction of the isoxazoline **377** to the acylaziridine **378** followed by ring opening of **378** generating the carbonylazomethine ylide **379** which affords 4-oxazoline **380** via a 1,5-electrocyclization (Scheme XXXI). The

SCHEME XXXI

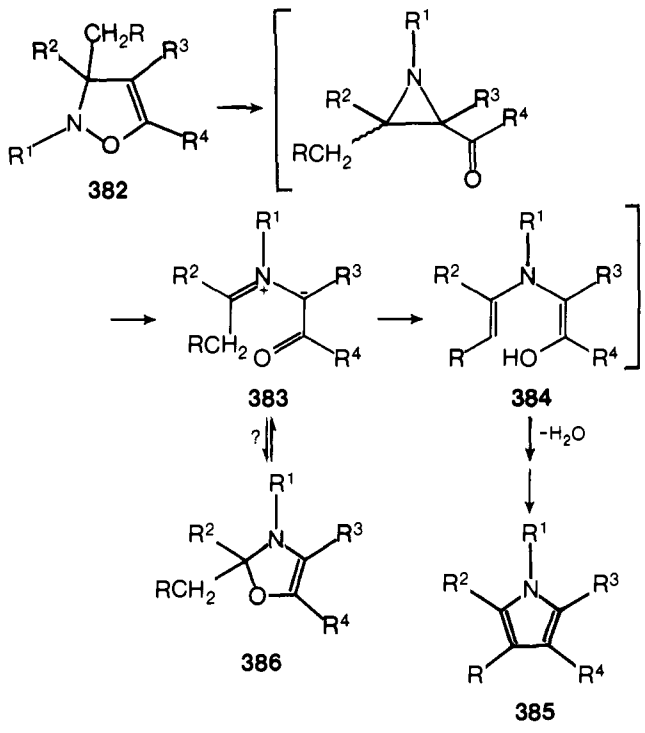


isoxazole–azirine–oxazole rearrangement involving a carbonylnitrile ylide (section II.A) constitutes a photochemical analog. By proper choice of substituents, R^1, R^2, and R^3 on the 4-isoxazoline, Baldwin et al.[153] and Niklas and Huisgen[154] were able to stop the reaction at various stages and study the thermal behavior of the intermediates. Thus when *N*-alkylnitrones **375** (R^1 = Me, *t*-Bu) are allowed to react with the acetylenic esters **376** (R^2 = CO_2Me; R^3 = CO_2Me, Ph), the corresponding 4-isoxazolines are isolated in good yields. Thermolysis of **377** gives the 4-oxazolines **380** (R^1 = Me; *t*-Bu, R^2 = CO_2Me; R^3 = CO_2Me, Ph) without isolation of the aziridine intermediates. The ring contraction of the 4-isoxazolines to the acylaziridines is believed to proceed via the diradical intermediate **381**.[153,154] As predicted, *N*-aryl substituents on **377** greatly enhance the rate of ring contraction.[153] When *N*-arylnitrones **375** (R^1 = Ph, 2,4,6-Me_3Ph) combine with acetylenic esters **376** (R^2 = CO_2Me; R^3 = CO_2Me, Ph) at room temperature, the initial 1,3-dipolar cycloadduct, the 4-isoxazoline **377**, is not obtained but the reaction does stop at the acylaziridine stage **378** (R^1 = Ph; 2,4,6-Me_3Ph; R^2 = CO_2Me; R^3 = CO_2Me, Ph). Thermolysis of the latter, however, provides the corresponding 4-oxazoline **380.** Finally, *N*-*tert*-butylnitrone **375** (R^1 = *t*-Bu) reacts at 74 °C for 10 min with 3-methylbutyn-3-ol to produce the 4-isoxazoline **377** (R^1 = *t*-Bu, R^2 = H, R^3 = $(Me)_2COH$).[153] Aziridine **378** is formed in this case only after prolonged heating (78 °C, 2 h). The corresponding 4-oxazoline **380** is not detected under these conditions.



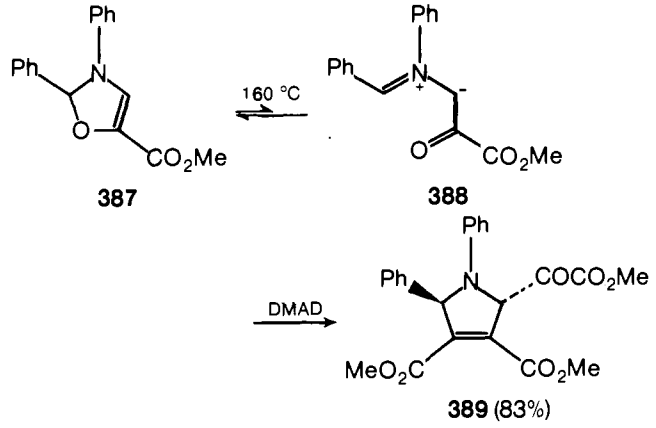
381

The rearrangement outlined in Scheme XXXI takes a detour at the azomethine ylide stage when 4-isoxazolines of the type **382** are thermolyzed.[155-157] Here the acylazomethine ylide **383** undergoes a 1,5-hydrogen migration followed by cyclization of the resulting intermediate **384** to afford the pyrrole derivatives **385.** It is not known whether the equilibrium **383** ⇌ **386** is involved in this example since the 4-oxazoline **386** could not be detected.



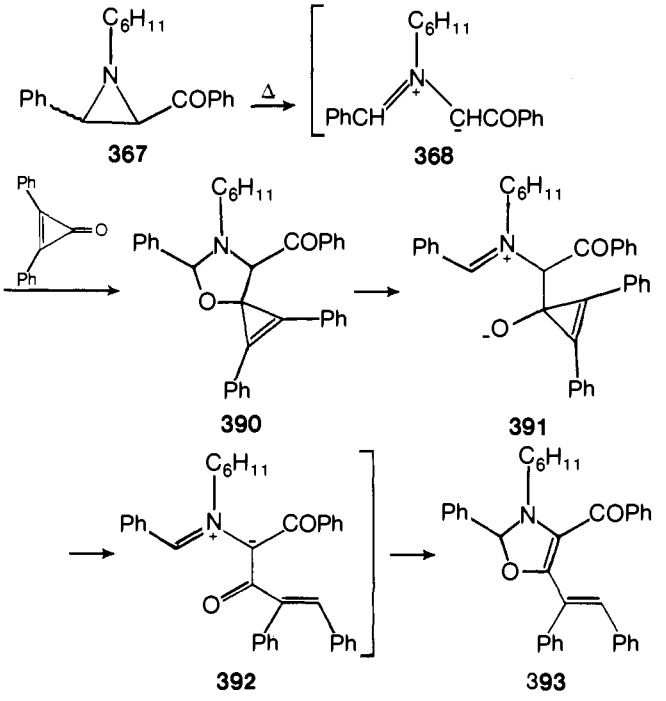
Heterocyclic *N*-oxides,[158] i.e., nitrones in which the azomethine moiety is incorporated into a ring, react as 1,3-dipoles with acetylenes to give 4-isoxazolines; however, these are in general not isolable under the reaction conditions and rearrange to carbonylazomethine ylides via acylaziridine intermediates.[154,159,160] Since the chemistry of this class of azomethine ylides has been the topic of several recent reviews[145,161] and since their chemistry rarely involves 1,5-dipolar cyclization reactions,[162] they will not be considered here.

The formation of 4-oxazolines from acylazomethine ylides is reversible and involves an electrocyclic ring opening of the former. Methyl 2,3-diphenyl-4-oxazoline-5-carboxylate (**387**) yields the 1,3-dipolar cycloadduct **389** when heated in the presence of dimethyl acetylenedicarboxylate. The dipolar intermediate is the carbonylazomethine ylide **388.**[154]



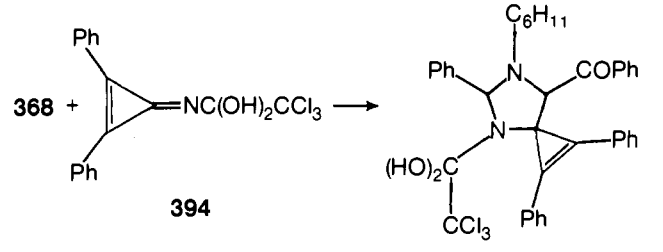
389 (83%)

A particularly intriguing example of 4-oxazoline formation via electrocyclization of carbonylazomethine ylides was observed by Lown et al.[163] These workers were investigating the dipolarophilic behavior of diphenylcyclopropenone (DPP) with azomethine ylides. When 1-cyclohexyl-2-benzoyl-3-phenylaziridine (**367**) was heated in refluxing benzene in the presence of DPP, the initial cycloadduct, the spirooxazolidine **390,** arises. This is not stable under the reaction conditions and suffers ring cleavage to the zwitterion **391.** Subsequent opening of the cyclopropene ring of **391** generates the carbonylazomethine ylide **392** which cyclizes in a 1,5-dipolar fashion affording the observed 4-oxazoline **393** in 46% yield. Although addition of 1,3-dipoles to DPP normally occurs across the C–C double bond rather than to the



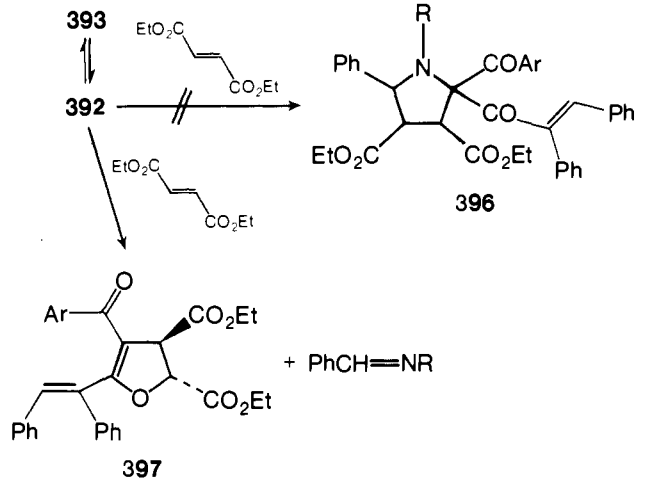
367 368 390 391 392 393

carbonyl group, addition of **368** to the C–C double bond in this case would lead to a severely crowded transition state. Since 1,3-dipolar cycloadditions are sensitive to steric effects, addition to the C–O double bond is favored. The isolation of the spiroimidazoline **395** from the reaction of **368** with the cyclopropenone imine **394** supports these contentions.[163]



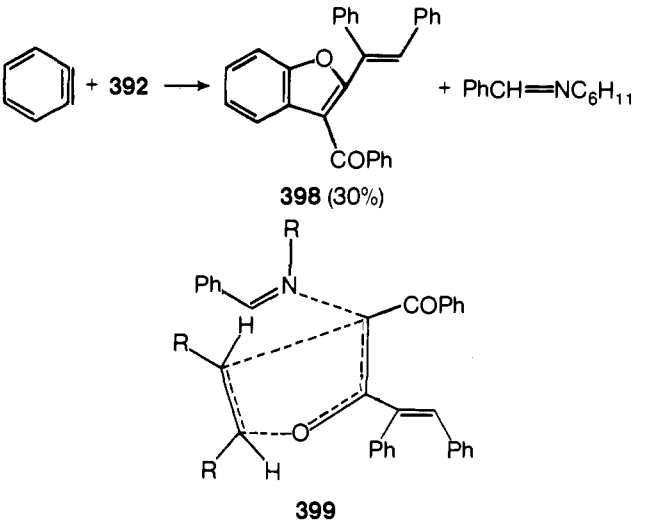
394 395

The 4-aroyl-4-oxazolines **393** exhibit photochromic and thermochromic behavior. This is probably due to the equilibrium **392** ⇌ **393**.[163] Attempts to intercept carbonylazomethine ylide **392** with olefinic dipolarophiles such as diethyl fumarate did not give the adduct **396** but rather 2,3-dihydrofurans **397** and benzalimines.[164] Analogous results were obtained with a variety of



393 392 396 397

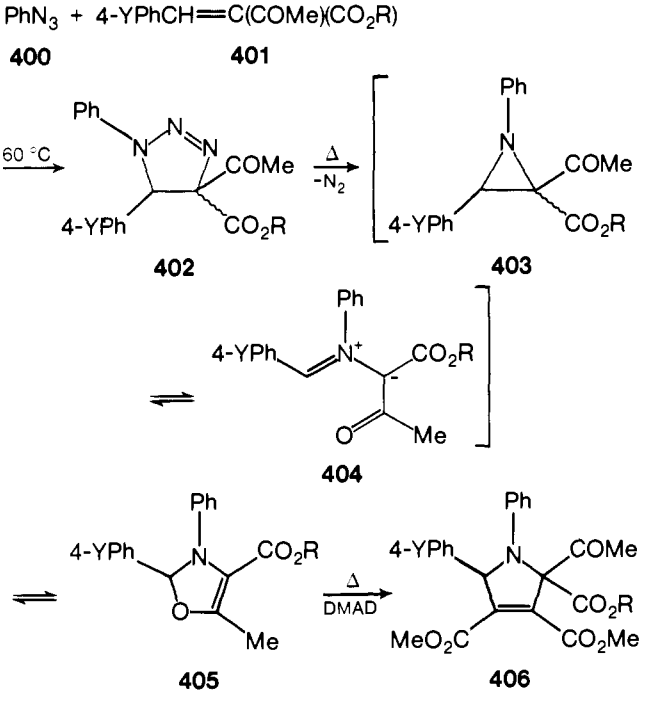
olefinic dipolarophiles, the dihydrofurans arising in moderate to good yields. Acetylenes provide the corresponding furans, e.g., **398** with benzyne. The dihydrofurans appear to be formed via



398 (30%) 399

a transition state resembling **399**. Ketocarbenes react as 1,3-dipoles with various dipolarophiles furnishing oxygen-containing heterocycles.[165] The carbonylazomethine ylide **392** generated by the electrocyclic ring opening of the 4-oxazoline **393** can be considered to be behaving as a masked ketocarbene in its reactions with olefins and acetylenes.

Phenyl azide (**400**) undergoes a 1,3-dipolar cycloaddition to α-acylcinnamic esters **401**.[166] At elevated temperatures, however, the dipolar cycloadduct **402** liberates nitrogen leading to the acylaziridine **403**. The latter is not isolable under the re-

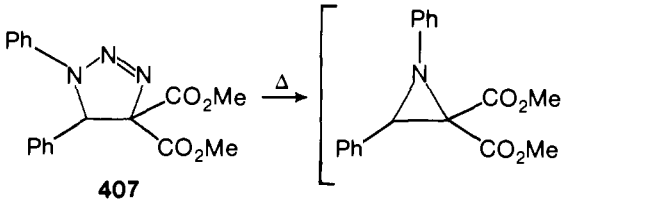


PhN_3 + 4-YPhCH=C(COMe)(CO_2R)

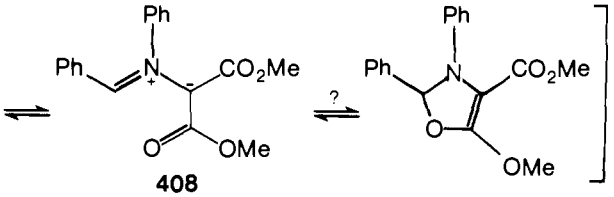
400 401 402 403 404 405 406

action conditions but experiences a subsequent valence isomerization to the acylazomethine ylide **404** which cyclizes to provide the observed 4-oxazoline **405**. Heating **405** in the presence of dimethyl acetylenedicarboxylate causes a 1,5-dipolar cycloreversion to the ylide **404** which is trapped by the acetylenic ester yielding the 3-pyrroline **406**. Similarly, Burger et al. have reported a synthesis of 3-iminoazetidines **409** by the thermolysis of dimethyl 1,5-diphenyl-2-triazoline-3,3-dicarboxylate (**407**) in the presence of isonitriles.[167] The azetidines **409** are formed by a [3 + 1] cycloaddition of the azomethine ylide **408** to the isonitrile.

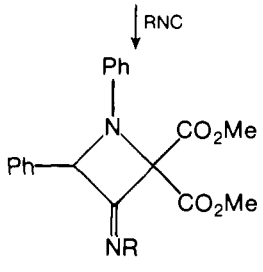
2-Imino-1,3-dithiolanes **410** can be alkylated on nitrogen with various alkyl halides to give aminodithiolium salts. When the alkyl



407

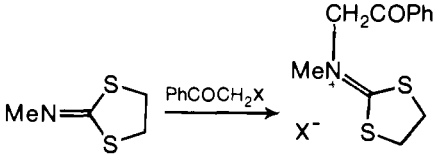


408

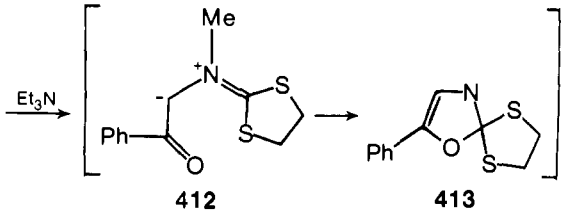


409

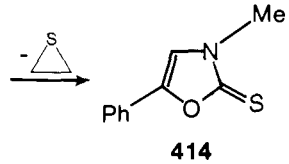
halide is a haloacetophenone, the salt **411** is formed.[168] The product of deprotonation of **411** is the acylazomethine ylide **412** which undergoes a 1,5-dipolar cyclization to **413.** Irreversible



410 411

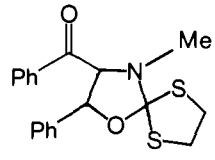


412 413



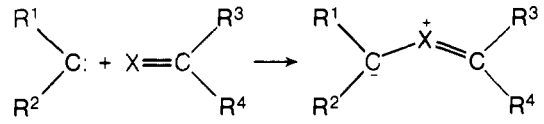
414

elimination of ethylene sulfide then gives 3-methyl-5-phenyl-4-oxazoline-2-thione (**414**) in nearly quantitative yield. When the ylide **412** was generated in the presence of benzaldehyde, the cycloadduct **415** was obtained in 55% yield. Other dipolarophiles such as phenyl isothiocyanate, carbon disulfide, or diethyl fumarate failed to react with the ylide **412;** only the intramolecular cyclization product **414** was obtained.



415

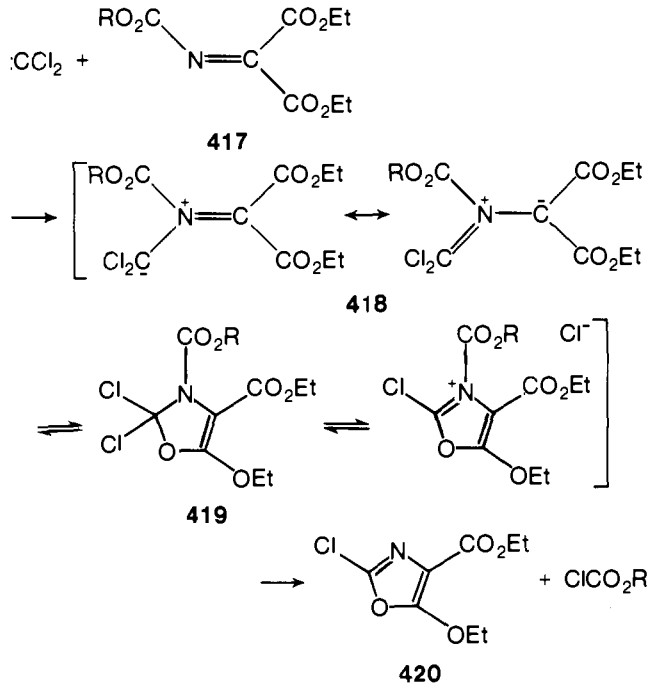
1,3-Dipoles are, at least in principle, accessible via the electrophilic addition of a carbene or carbenoid to the heteroatom of a species such as **416.** Seyferth and Shih have studied the reaction of dichlorocarbene, generated from phenyl trichloromethylmercury, with azomethines of the type **417.**[169] The



416
X = NR, O, S, etc.

observed product, ethyl 2-chloro-5-ethoxyoxazole-4-carboxylate (**420**), is thought to arise by a 1,5-electrocyclization of the initially formed azomethine ylide **418** to give the 4-oxazoline **419** (not isolated) which undergoes a subsequent elimination of an alkyl chloroformate (Scheme XXXII). Intermediate **419** was observed spectroscopically.

SCHEME XXXII



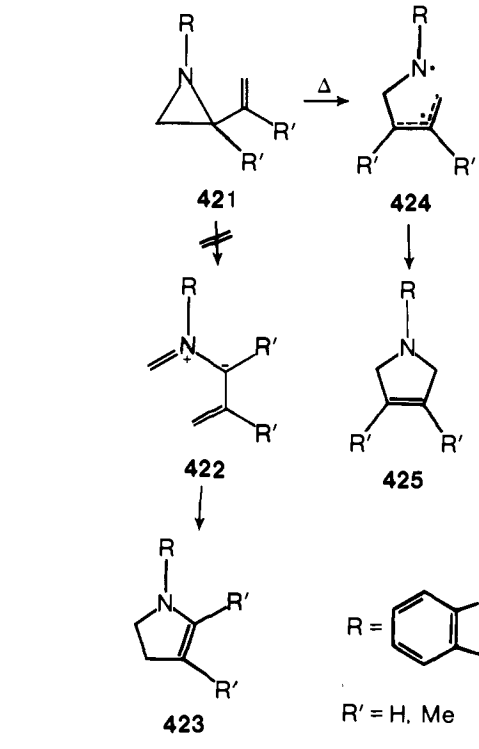
417 418 419 420

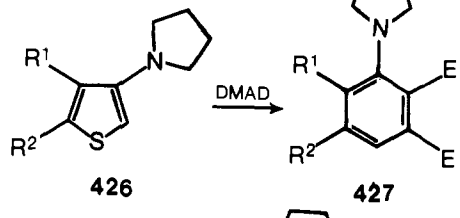
The addition of dihalocarbenes to various azo compounds produces azomethine imines. A discussion of this reaction is deferred to that section.

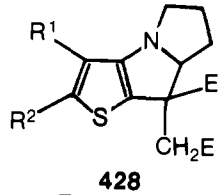
2. *Vinylazomethine Ylides (2-Pyrrolines)*

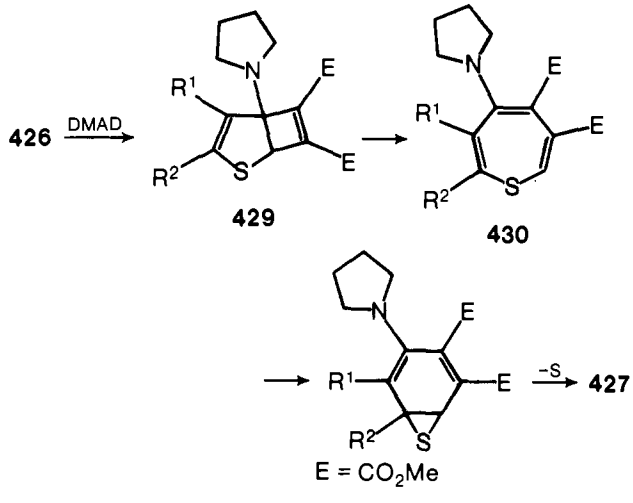
Vinyl substituted azomethine ylides do not appear to be as accessible as their carbonyl substituted counterparts. Whereas acylaziridines often produce acylazomethine ylides upon thermolysis, vinylaziridines **421** suffer a different fate, i.e., carbon–nitrogen bond cleavage leading to the diradicals **424** which close to afford the 3-pyrroline derivatives **425.**[170] None of the isomeric 2-pyrrolines **423,** the products of a 1,5-dipolar cyclization of azomethine ylides **422,** could be detected.

Reinhoudt and his co-workers observed that in nonpolar solvents such as benzene, dimethyl acetylenedicarboxylate (DMAD) adds to 3-pyrrolidinothiophenes **426** to furnish methyl 3-pyrrolidinophthalates **427** along with a minor product, 6,7,7a,8-tetrahydro-5*H*-thieno[3,2-*b*]pyrrolizines **428.**[171] In methanol, on the other hand, **428** becomes the major product and is isolated in yields of 45–64%. The phthalate esters **427** arise by [2 + 2] cycloaddition of DMAD to thiophenes **426**[172] followed by ring opening of the initial adducts **429** and desulfurization of the resulting thiepins **430.** In the polar solvent methanol, however, it is thought that the initially formed 1,4-dipolar species **431** are stabilized by solvation. Prototropic shift leads to the formation of azomethine ylides **432** which tautomerize to the vinylazomethine ylides **433.** Subsequent 1,5-electrocyclization of **433** gives the observed thienopyrrolizines **428.** In the nonpolar medium, formation of the two new σ bonds in the [2 + 2] cycloaddition may be concerted.[171] An analogous sequence of



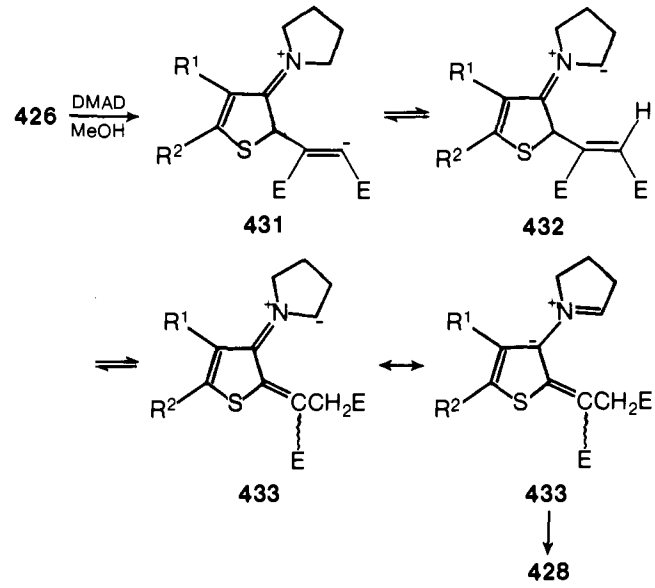


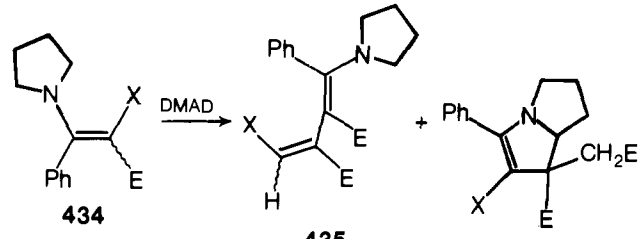




events was invoked to rationalize the formation of dienamines **435** and pyrrolizines **436** in the reaction of enamines **434** with DMAD in methanol.[173]

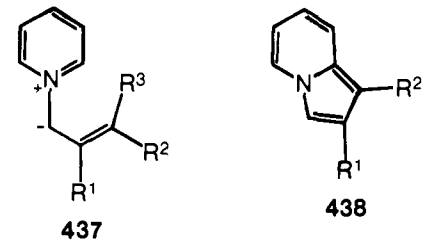
In contrast to the carbonylazomethine ylides of the pyridinium betaine type mentioned in section III.A, vinylpyridinium ylides, i.e., **437**, are more prone toward 1,5-electrocyclizations, and serve as useful precursors to indolizine derivatives **438**. Augstein



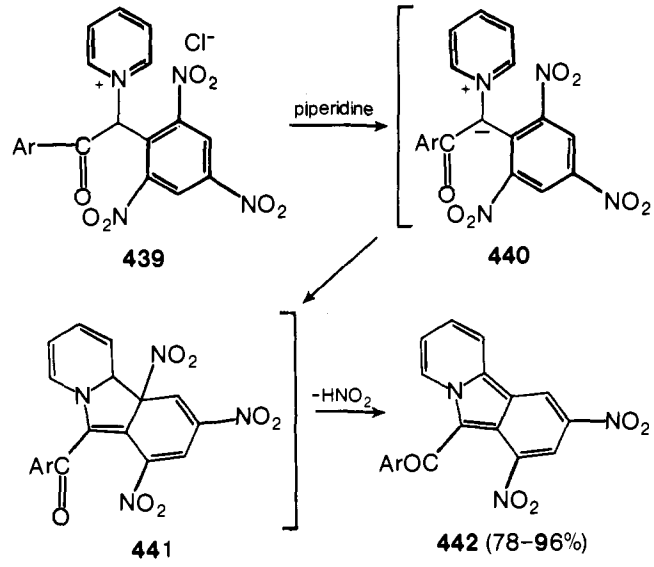


	435	436
X = SPh	30%	52%
= OPh	20%	45%
= Ph	35%	23%

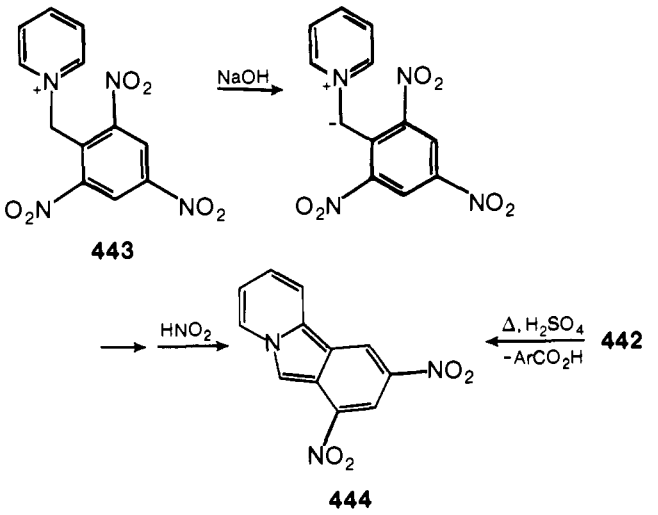
E = CO_2Me



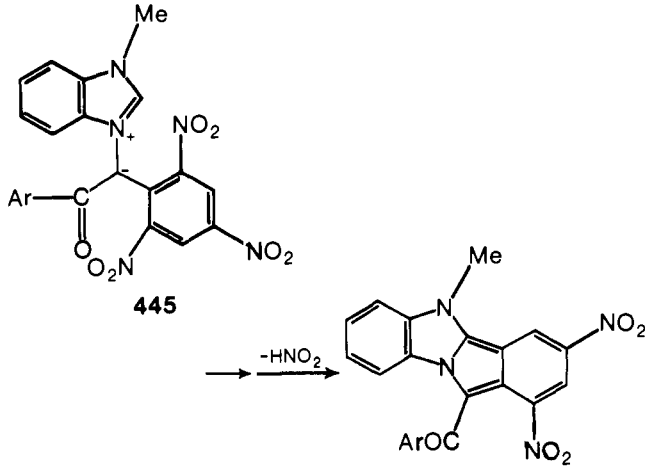
and Kröhnke have observed the 1,5-dipolar cyclization of the azomethine ylide **440** derived from the pyridinium salt **439** when the latter is heated in the presence of piperidine.[174] The dihy-



droindolizine **441** initially formed loses the elements of nitrous acid and furnishes the observed product **442.** Heating **442** in concentrated sulfuric acid affords the dearoylated product **444** which was independently prepared by heating the pyridinium salt **443** with sodium hydroxide. The benzimidazolium betaine system **445** cyclizes in an analogous fashion to the indolizine **446.**[175]

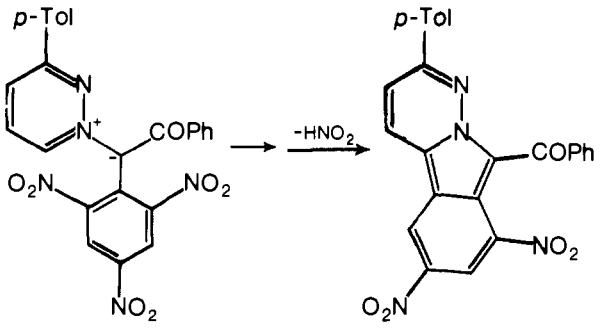


443 **444** **442**



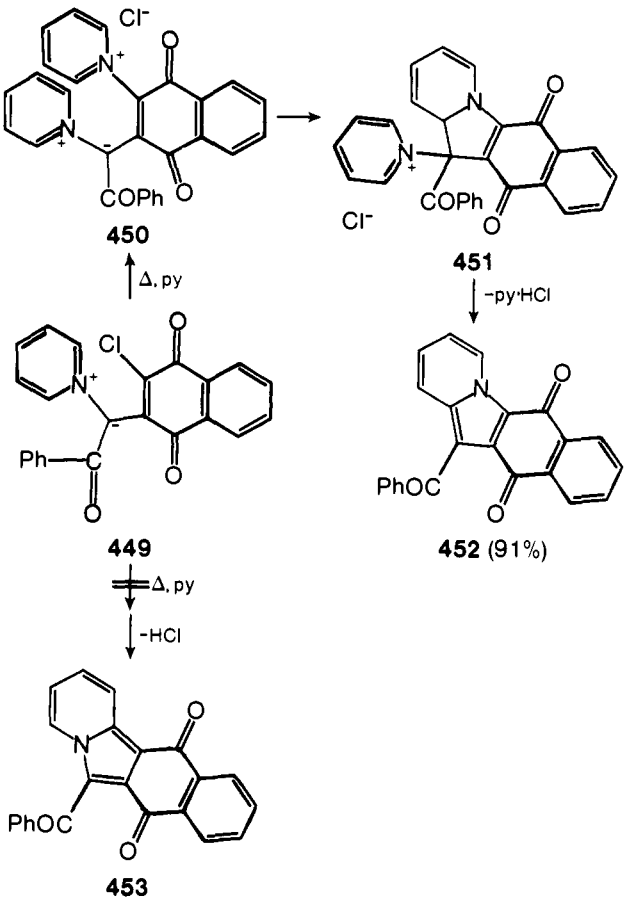
445 **446**
Ar = BrPh

Likewise, pyridazinium ylide **447** undergoes 1,5-dipolar cyclization and elimination of HNO_2 to give indolizine **448.**[175b] An amusing variation on this theme occurs when the betaine **449** is heated in the presence of pyridine.[174] The naphtho[2,3-*b*]-



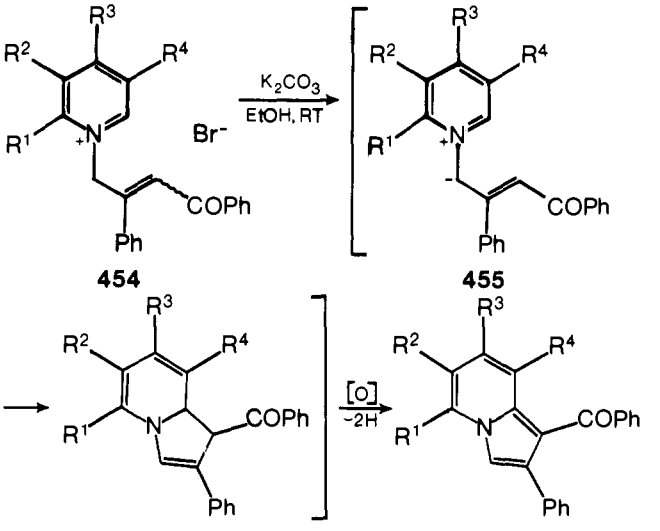
447 **448**

indolizine **452** was obtained in good yield instead of naphtho[2,3-*a*]indolizine **453,** the product expected from a 1,5-dipolar cyclization. Attack of pyridine at the quinone ring displaces chloride ion affording the new vinylazomethine ylide **450.** 1,5-Electrocyclization of **450** followed by loss of pyridine hydrochloride provides a pathway leading to the product **452.**



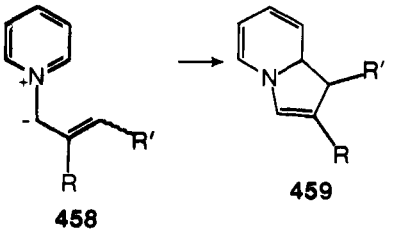
450 **451** **449** **452** (91%) **453**

The 1-benzoyl-2-phenylindolizines **457** have been prepared via 1,5-dipolar cyclization of vinylazomethine ylides **455** generated by base-induced elimination of HBr from the pyridinium bromides **454.**[176]



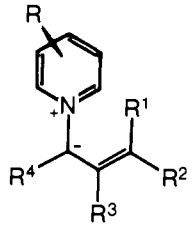
454 **455** **456** **457** (42-95%)

It was later demonstrated that in some cases the initial product of the 1,5-cyclization, the dihydroindolizines **459,** could be isolated depending upon the substituents R and R^1.[177]



458 **459**

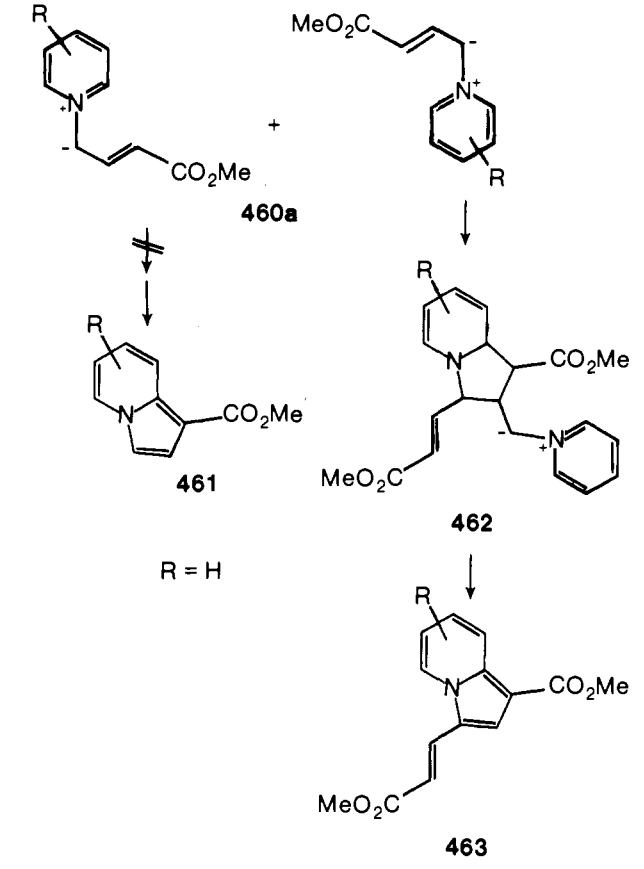
Independent studies by two groups of Japanese workers on the effect of the substituents R^1–R^4 present on the pyridinium ylides **460** have served to outline the possible reaction pathways open to this intermediate.[178-181] For the ylide **460a** a 1,5-dipolar cyclization does not occur to give the indolizine **461.** Instead the



460

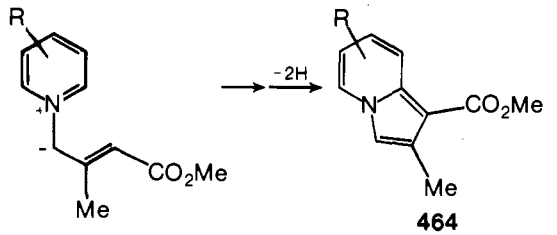
carbon–carbon double bond of **460a** acts as a dipolarophile and adds to the dipolar part of another molecule of **460a** to afford a 1,3-dipolar adduct with the structure **462.** This initially formed adduct ultimately leads to the observed indolizine **463** (Scheme XXXIII).[178] Ylide **460b,** on the other hand, furnishes only the in-

SCHEME XXXIII



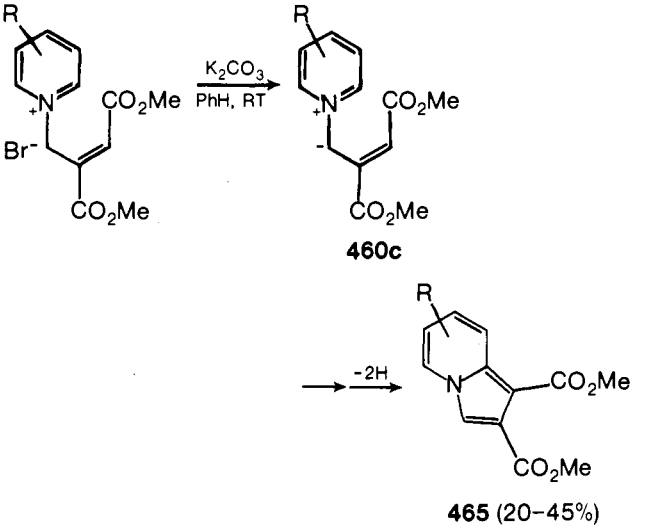
460a **461** **462** **463**

tramolecular cyclization products **464** in moderate yield.[178] In this case the methyl substituent, R^3, would hinder the approach of a second molecule of **460b.** Consequently the rate of the



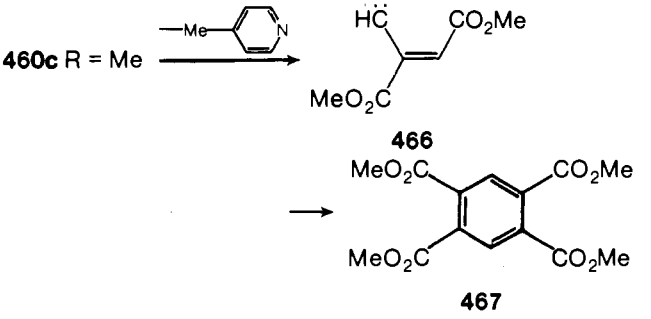
460b **464**

1,3-dipolar cycloaddition (which gives **462** in the first case above) is slowed relative to the rate of 1,5-electrocyclization. In a similar light, for vinylazomethine ylide **460c** 1,5-dipolar cyclization obtains affording the indolizines **465.**[179] Interestingly, when the pyridine ring of **460c** is substituted with a 4-methyl group, no



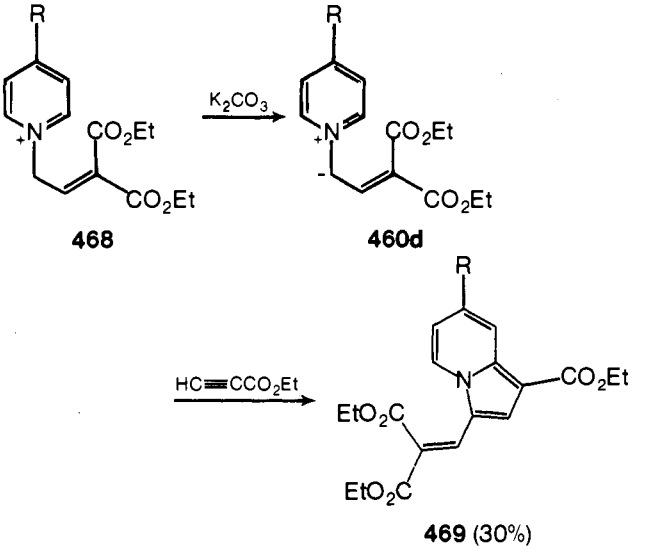
460c **465** (20–45%)

indolizine **465** could be obtained, but instead only tetramethyl benzene-1,2,4,5-tetracarboxylate (**467**) was isolated.[179] A possible intermediate involved in the formation of **467** is the vinyl carbene **466.** Traces of **467** have also been found along with the indolizines **465** when a methyl group is present at the 3 position of the pyridine ring.



466 **467**

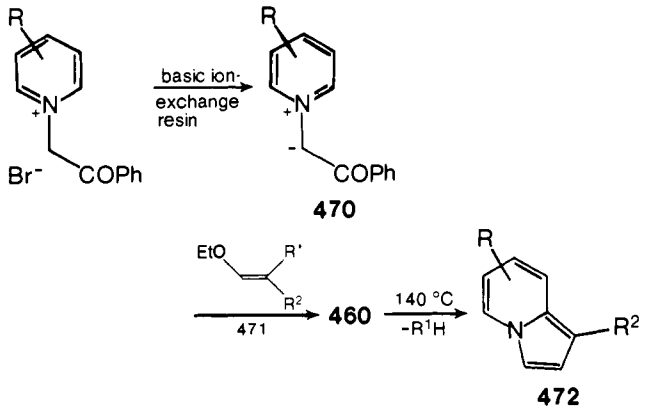
Treatment of the salt **468** with potassium carbonate in benzene or chloroform resulted only in extensive decomposition, with no detectable quantities of indolizines arising.[179] The ylide **460d** could be trapped with ethyl propiolate to afford the corresponding 1,3-dipolar adduct **469.**



468 **460d** **469** (30%)

Pyridinium ylides **460** ($R^1 = R^2$ = COMe or CO_2Et, R^3 = H, R^4 = COPh) have been prepared by the reaction of various pyridinium phenacylides **470** with enol ethers **471.**[180,181] Ther-

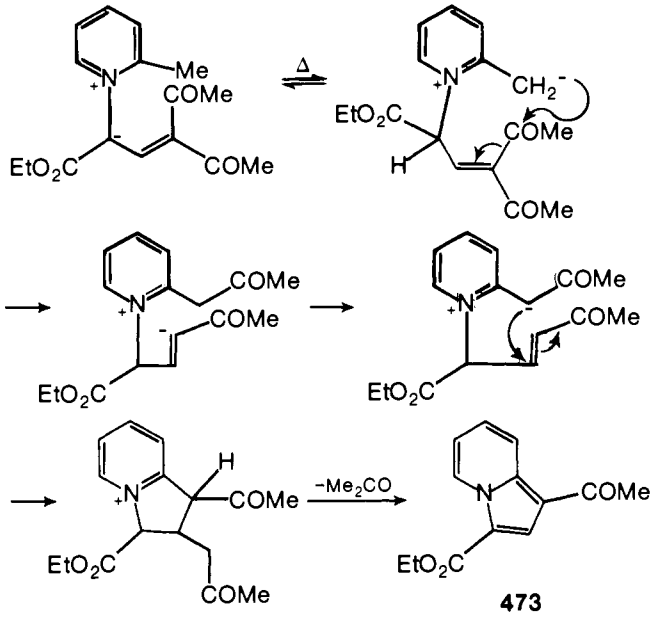
molysis of **460** ($R^1 = R^2 = COMe, CO_2Et$; $R^3 = H$; $R^4 = COPh$) in refluxing xylene gave large quantities of intractable material along with the indolizine derivatives **472** in low (~20%) yield.



$R^1 = R^2 = COMe, CO_2Et$
$R^3 = H, R^4 = COPh$

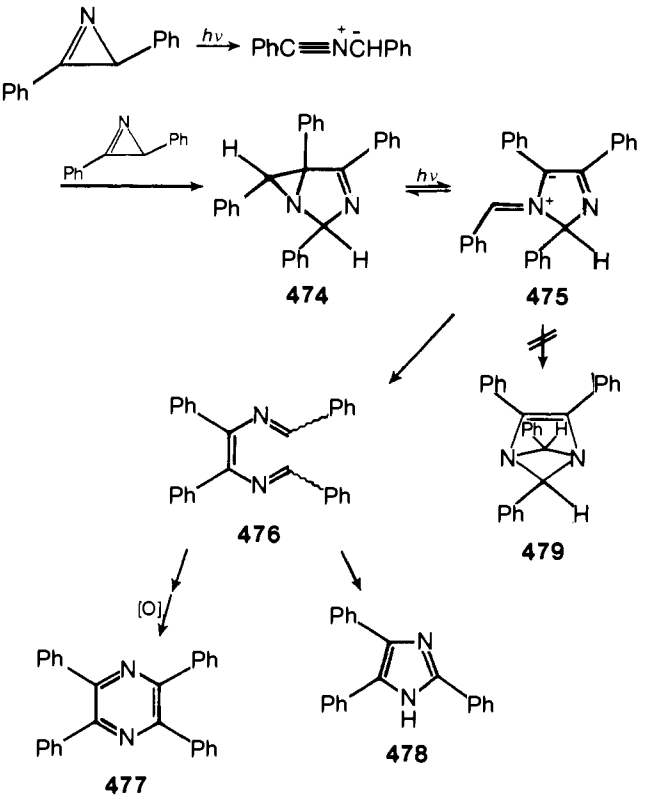
Introduction of a methyl group in the 2 position of the pyridine ring in **460** ($R^1 = R^2 = COMe, R^3 = H, R^4 = CO_2Et, R = 2\text{-Me}$) allows a new reaction pathway. The only isolable product, the indolizine **473** (obtained in 3% yield), is apparently formed as outlined in Scheme XXXIV.[181] 1,5-Electrocyclization was not observed.

SCHEME XXXIV

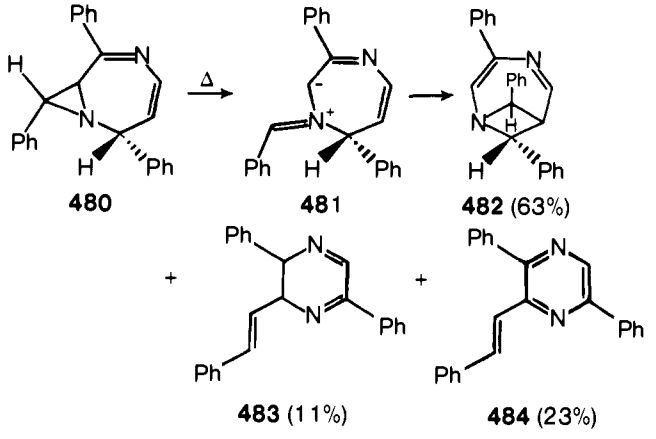


3. *Iminoazomethine Ylides (4-Imidazolines)*

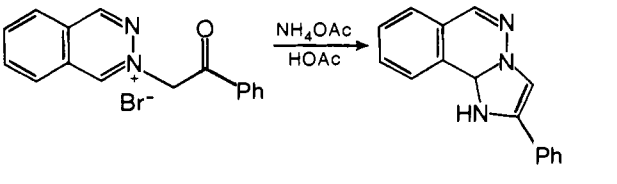
As discussed previously, the photochemical ring opening of azirine derivatives affords nitrile ylides. In the absence of other modes of stabilization these ylides add to the carbon–nitrogen double bond of the azirine ring to give 1,3-diazabicyclo[3.1.0]-hex-3-enes, e.g., **474.**[182,183] These adducts possess an iminoaziridine moiety which upon further irradiation produces an iminoazomethine ylide **475.** The ylide **475** chooses to follow a pathway involving opening of the imidazoline ring to give the diazahexatriene intermediate **476** which cyclizes to the observed heterocyclic products, 2,3,5,6-tetraphenylpyrazine (**477**) and 2,4,5-triphenylimidazole (**478**).[182-184] Electrocyclization of **475** to the [2.1.1] diazabicyclohexene system **479** does not occur presumably because of steric considerations. The iminoazomethine ylide **481** derived from the thermally induced carbon–carbon bond cleavage of the aziridine ring of 2,6,8-triphenyl-1,5-diazabicyclo[5.1.0]octa-3,5-diene (**480**), however, does



provide the novel [4.1.1] diazabicyclooctadiene **482** in 63% yield via a *1,7-dipolar cyclization* along with smaller amounts of the pyrazine derivatives **483** and **484.**[185]



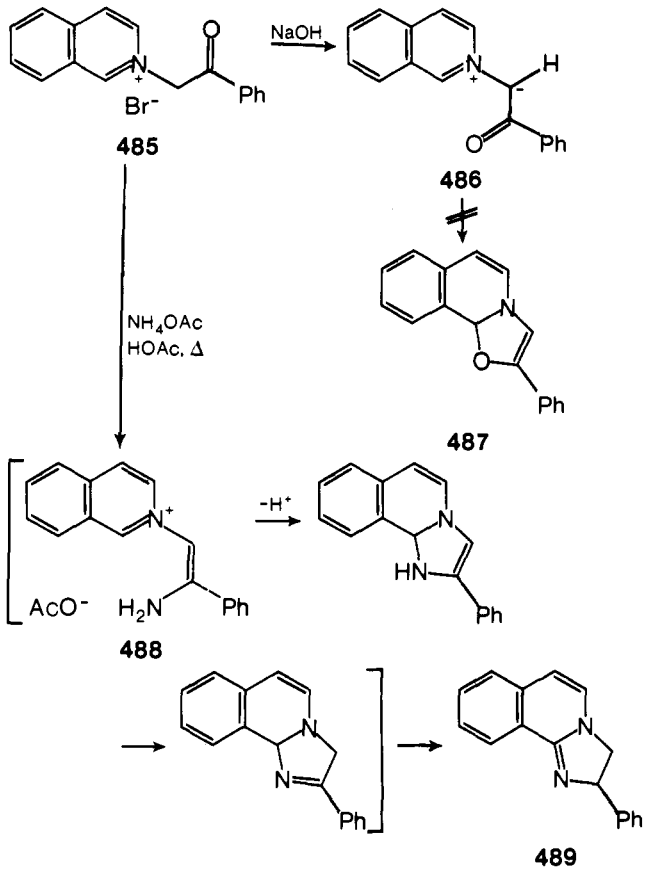
Dehydrohalogenation of the isoquinolinium salt **485** gives the carbonylazomethine ylide **486.**[162] While **486** does not appear to undergo a 1,5-dipolar cyclization to the 4-oxazoline **487,** the salt **485** gives the imidazoline **489** in 70% yield when allowed to react with ammonium acetate in acetic acid. The postulated mechanism involves cyclization of the conjugate acid of the intermediate iminoazomethine ylide **488** as outlined in Scheme XXXV. The corresponding phthalazine system acts analogously under the same conditions.[186]



4. *Thiocarbonylazomethine Ylides (4-Thiazolines)*

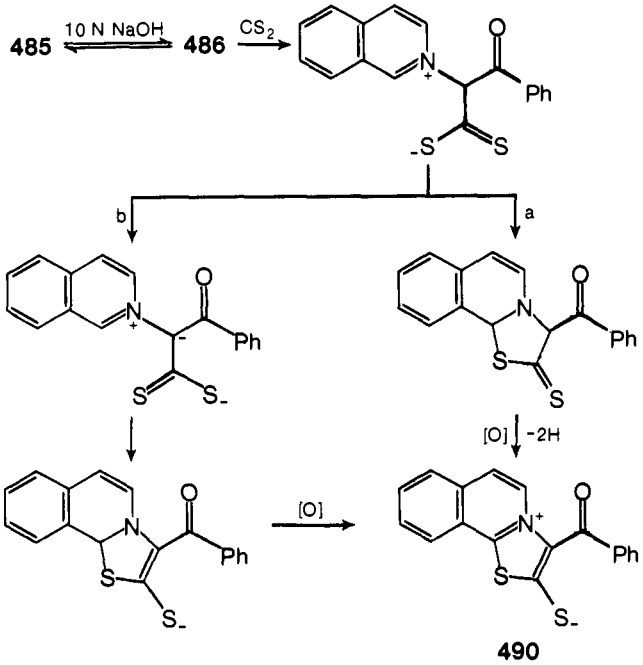
The mesoionic thiazolium-5-sulfide **490** has been obtained in 17% yield by the reaction of **485** with carbon disulfide in the presence of 10 N sodium hydroxide.[187] Although a mechanism

SCHEME XXXV



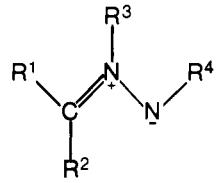
not involving a 1,5-dipolar cyclization can be invoked to rationalize the formation of **490** (path a), a second mechanism (path b) which appears equally likely, does entail such an electrocyclization step (Scheme XXXVI).

SCHEME XXXVI



B. Azomethine Imines

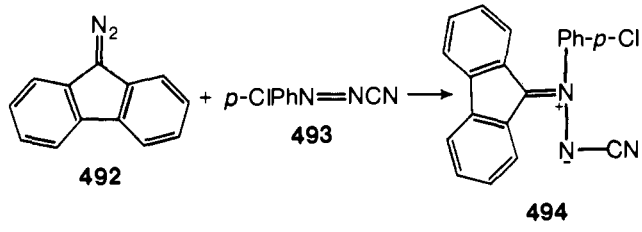
A review covering methods of generation and some reactions of azomethine imines **491** has appeared.[188]



1. Carbonylazomethine Imines

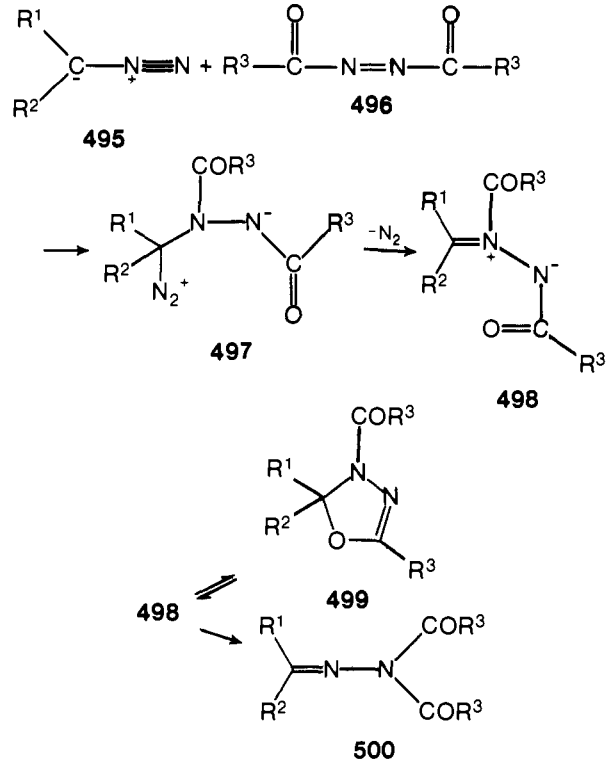
a. *N*-Carbonyl (1,3,4-Δ^2-Oxadiazolines)

The stable, isolable *N*-cyanoazomethine imine **494** has been prepared by the reaction of diazafluorene (**492**) with the azocyanide **493**.[189] Fahr and co-workers[190-195] and others[196-198]

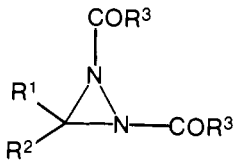


have undertaken extensive studies of the reaction of diazo compounds **495** with carbonyl substituted azo compounds **496**. The proposed intermediates, *N*-carbonylazomethine imines **498**, are not isolable but undergo a 1,5-dipolar cyclization to the oxadiazolines **499** or an acyl group migration to provide hydrazones **500** (Scheme XXXVII).

SCHEME XXXVII

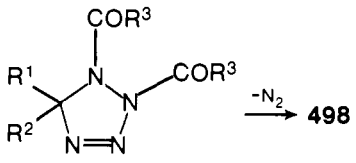


The fate of azomethine imine **498** is dependent upon reaction conditions and the nature of the substituents R^1-R^3. Since Fahr has reviewed his work in this area,[199] we do not discuss these processes in detail. However, several points are worth mentioning. (1) It was originally believed that the product of the reaction of **495** and **496** was the diaziridine **501**.[200] In no case could **501** be detected. (2) The zwitterionic intermediate **497** was postulated to be the precursor of azomethine imine **498**.[192,199] The available evidence does not exclude a 1,3-dipolar addition of the diazo compound to the azo compound to give the tetra-



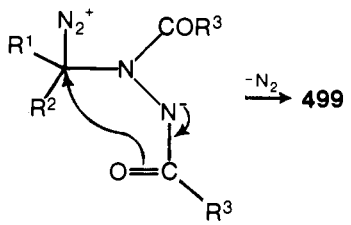
501

zoline intermediate **502** which suffers elimination of nitrogen under the reaction conditions. (3) A less likely mechanism for



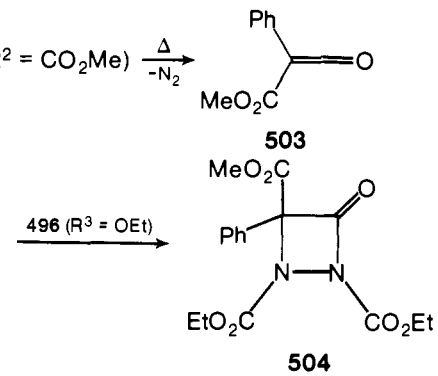
502

the formation of 1,3,4-oxadiazolines **499** which does not require the intermediacy of *N*-acylazomethine imines **498** is cyclization of the zwitterion **497.** (4) α,α'-Dicarbonyl diazo compounds are



497

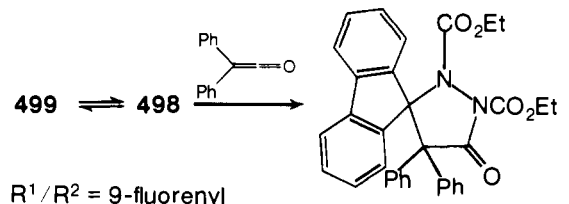
not reactive toward azo compounds. At elevated temperatures decomposition of the diazo compound ensues to afford the corresponding carbene which undergoes a Wolff rearrangement to the corresponding ketene.[192,195] In the case of methyl benzoyldiazoacetate **495** (R^1 = PhCO, R^2 = CO_2Me), the ketene **503** formed reacts with diethyl azodicarboxylate to produce 1,2-dicarboethoxy-3-phenyl-3-carbomethoxydiazetidinone (**504**).[192]



503

504

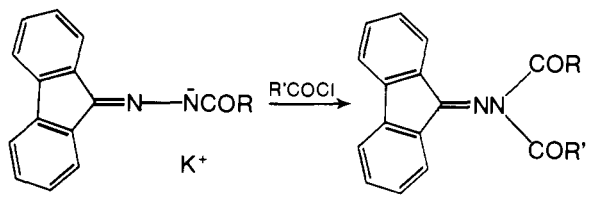
(5) Diazoacetic esters **495** (R^1 = H, R^2 = CO_2R) and azodicarboxylic esters **496** (R^3 = OR′) afford 1,3,4-oxadiazolines **499** (R^1 = H, R^2 = CO_2R, R^3 = OR′) below 80 °C.[191] The same reactants at >100 °C lead to the isomeric hydrazone dicarboxylic esters **500** (R^1 = H, R^2 = CO_2R, R^3 = OR′).[191] (6) 1,3,4-Oxadiazolines **499** (R^1 = H, R^2 = CO_2R, R^3 = OR′) are not in equilibrium with the corresponding azomethine imines **498** in solution either at room temperature or at elevated temperatures.[191] On the other hand, 1,3,4-oxadiazolines **499** (R^1/R^2 = 9-fluorenyl, R^3 = OR), the products of the reaction of 9-diazafluorene with azodicarboxylic esters, are in equilibrium with the azomethine imine **498** (R^1/R^2 = 9-fluorenyl, R^3 = OR) in solution as shown by IR spectroscopy.[193] As the temperature and/or dielectric constant of the medium increases, the position of the equilibrium shifts toward the dipolar species. At temperatures above 50 °C, irreversible rearrangement of **498** to the hydrazone **500** (R^1/R^2 = 9-fluorenyl, R^3 = OR) occurs. (7) Azomethine imine **498** (R^1/R^2 = 9-fluorenyl, R^3 = OEt) is intercepted by diphenylketene to afford pyrazolidinone **505** via 1,3-dipolar cycloaddition when the ketene is added to a solution of 1,3,4-oxadiazoline **499.**[193] (8) Diazo ketones react with azodibenzoyl to provide *N,N*-dibenzoylhydrazones **500** (R^1 = H, R^2 = COR, R^3 = Ph) exclusively, while diazoacetic esters[195,196] and diazomethane[196] give only 1,3,4-oxadiazolines **499** (R^1 = H, R^2 = CO_2R or H, R^3 = Ph) with azodibenzoyl. (9) The 1,3,4-oxadiazoline **499** (R^1/R^2 = 9-fluorenyl, R^3 = Me) formed in the reaction of diazofluorene with azodiacetyl is converted to hydrazone **500** (R^1/R^2 = 9-fluorenyl, R^3 = Me) upon heating above its melting point.[195] The latter is in equilibrium with the above-mentioned 1,3,4-oxadiazoline **499** in cyclohexane solution. This is the only case where the equilibrium **500** ⇌ **499** has been observed.



R^1/R^2 = 9-fluorenyl
R^3 = OEt

505

In their attempts to prepare 1,3,4-oxadiazolines **499** and hydrazones **500** independently, Fahr et al. found that the potassium salt of the monoacylhydrazone **506** affords only *N,N*-diacylhydrazone **500** when treated with acetyl or benzoyl chloride.[194]



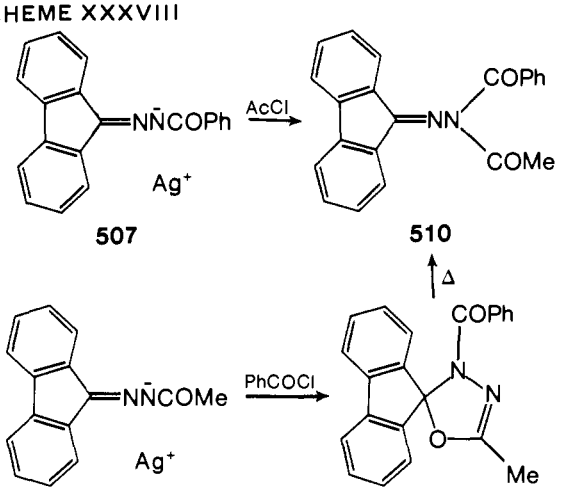
506

500

R = Me or Ph, R′ = Me or Ph

With acetyl chloride, the silver salt of the hydrazone **507** gives *N,N*-diacylhydrazone **510** while the silver salt **508** with benzoyl chloride provides 1,3,4-oxadiazoline **509** exclusively (Scheme XXXVIII).[194] When heated, **509** rearranges to **510** presumably

SCHEME XXXVIII



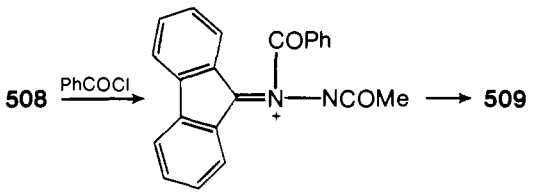
507

510

508

509

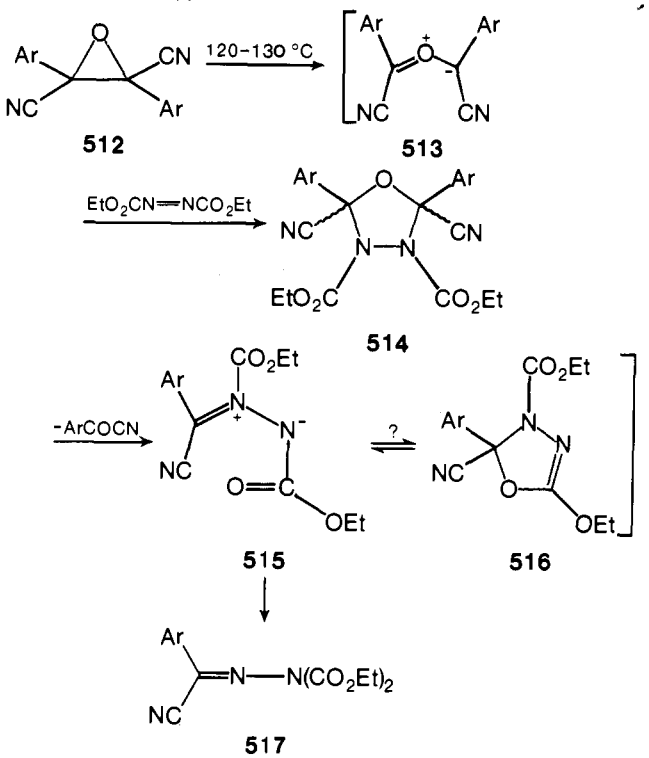
via electrocyclic ring opening followed by benzoyl group migration. The proposed mechanistic interpretation of the above observations[194] is unsatisfactory and the following point (among others) requires clarification. The formation of oxadiazoline **509** is postulated to proceed by aroylation of the silver salt **508** at the central (nitrogen) atom yielding azomethine imine **511** which undergoes the usual 1,5-electrocyclization. Why the silver salt **507** behaves differently to furnish the hydrazone **510** directly is not clear.



511

In a related process, azomethine imine **515** is implicated as an intermediate in the formation of hydrazone **517** when the oxirane **512** is heated in the presence of diethyl azodicarboxylate (Scheme XXXIX).[201] Carbon–carbon bond cleavage of **512** to

SCHEME XXXIX

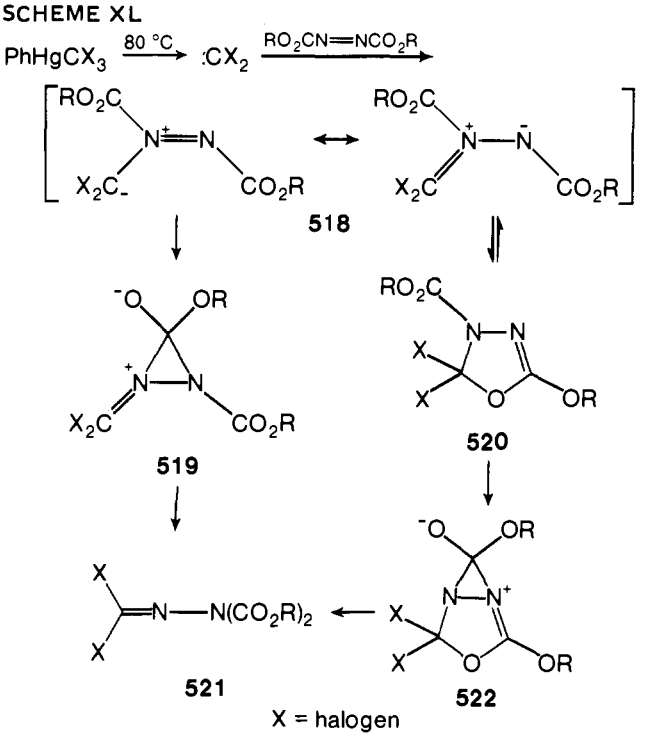


give the carbonyl ylide **513** (vide infra) followed by 1,3-dipolar cycloaddition of **513** to the azo compound affords the 1,3,4-oxadiazolidine **514** (not isolated). A 1,3-dipolar cycloreversion of the latter results in the formation of **515** and an aroyl cyanide. Azomethine imine **515** can cyclize to form 1,3,4-oxadiazoline **516**; however, this product is not isolated under the reaction conditions, and only hydrazone **517** is obtained in 50–54% yield.

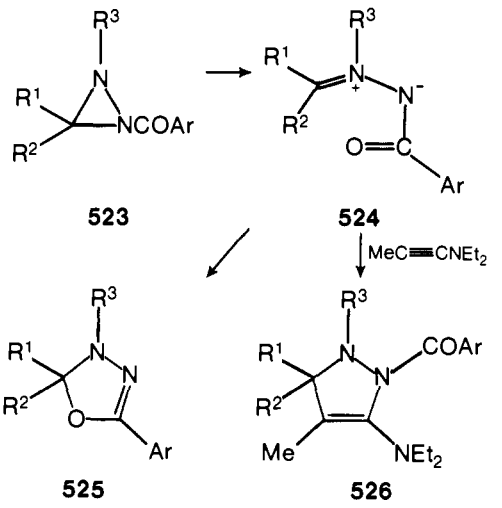
The reaction of azodicarboxylic esters with phenyltrihalomethylmercury (or sodium trichloroacetate) at 80 °C gives hydrazones of the type **521** in 15–87% yield.[202] This process (Scheme XL) appears at least formally to be analogous to those discussed above. In this case as in those reported by Fahr, *N*-carbonylazomethine imines **518** are thought to be intermediates. Here, however, **518** arises by electrophilic attack of free dihalocarbene on the azo ester. In the case of diazo compounds reacting with azo compounds, it was demonstrated that the former do not decompose to carbenes but combine with the latter as such. The proposed intermediates **518** could not be isolated or trapped by dipolarophiles but undergo electrocyclization to 2,2-dihalo-1,3,4-oxadiazolines **520** which were observed by IR and NMR spectroscopy and in one case isolated. The activation parameters obtained for the ester group migration **520** → **521** favor a process involving either intermediate **519** or **522**. Here again no diaziridine intermediate could be detected.

Nevertheless, *N*-aroyldiaziridines **523** have been prepared by the reaction of N-unsubstituted diaziridines with aroyl chlorides and can be converted to 1,3,4-oxadiazolines **525** in high yield by dissolution in suitable solvents.[203,204] This interconversion most likely occurs via electrocyclic ring opening of **523** followed by 1,5-dipolar cyclization of the resulting *N*-aroylazomethine imines **524**. The 1,3-dipole **524** is captured by 1-(*N*,*N*-diethylamino)propyne to give the pyrazoline **526**.[204]

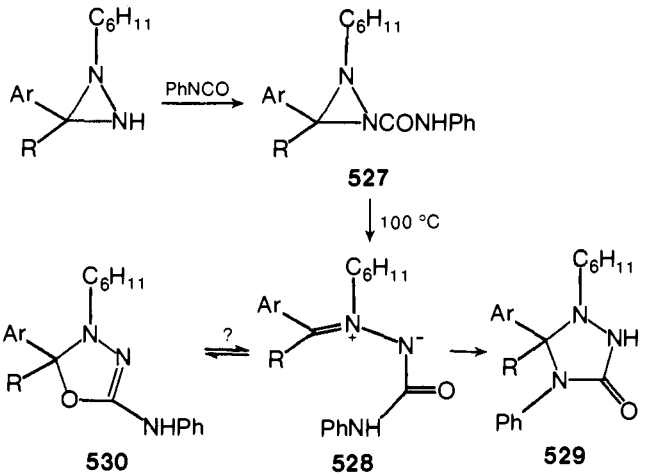
SCHEME XL



X = halogen

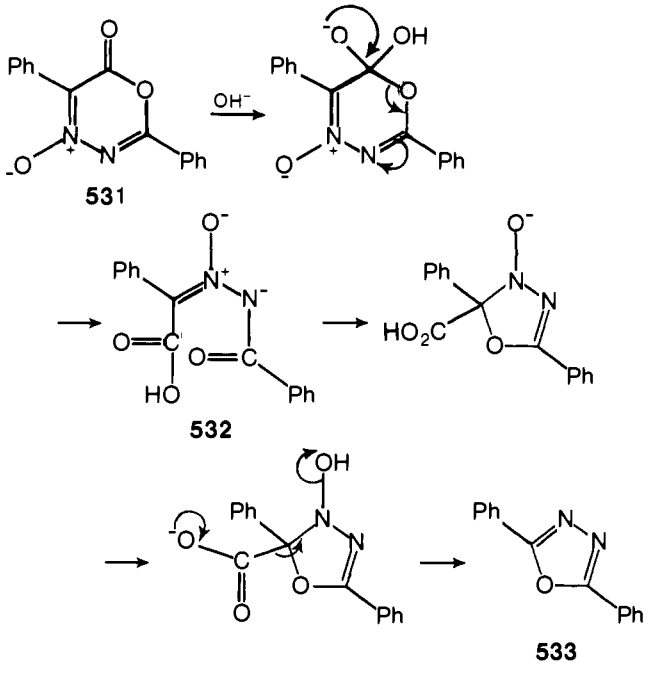


The condensation of N-unsubstituted diaziridines with phenyl isocyanate yields diaziridines **527**.[205] Thermolysis of **527** (100

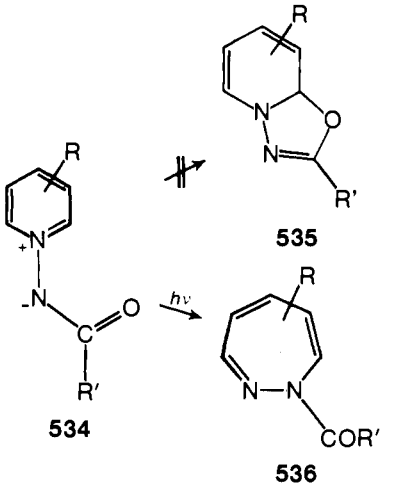


°C, 1 h) does not provide 1,3,4-oxadiazolines **530** by 1,5-electrocyclization. The products are 1,2,4-triazolidin-5-ones **529** obtained in 65% yield by intramolecular 1,3-addition of NHPh to the *N*-acylazomethine imine **528.**

2,5-Diphenyloxadiazole **533** arises in high yield in the base hydrolysis of 1,3,4-oxadiazin-6-one **531.** A 1,5-dipolar cyclization of *N*-carbonylazomethine imine *N*-oxide **532** has been invoked to explain the formation of **533.**[206]



N-Carbonylpyridinium *N*-imines **534** appear to be stable with respect to their 1,3,4-oxadiazoline valence isomers **535.**[145,207-209] Photolysis of **534** affords diazepine derivatives **536.**[207]

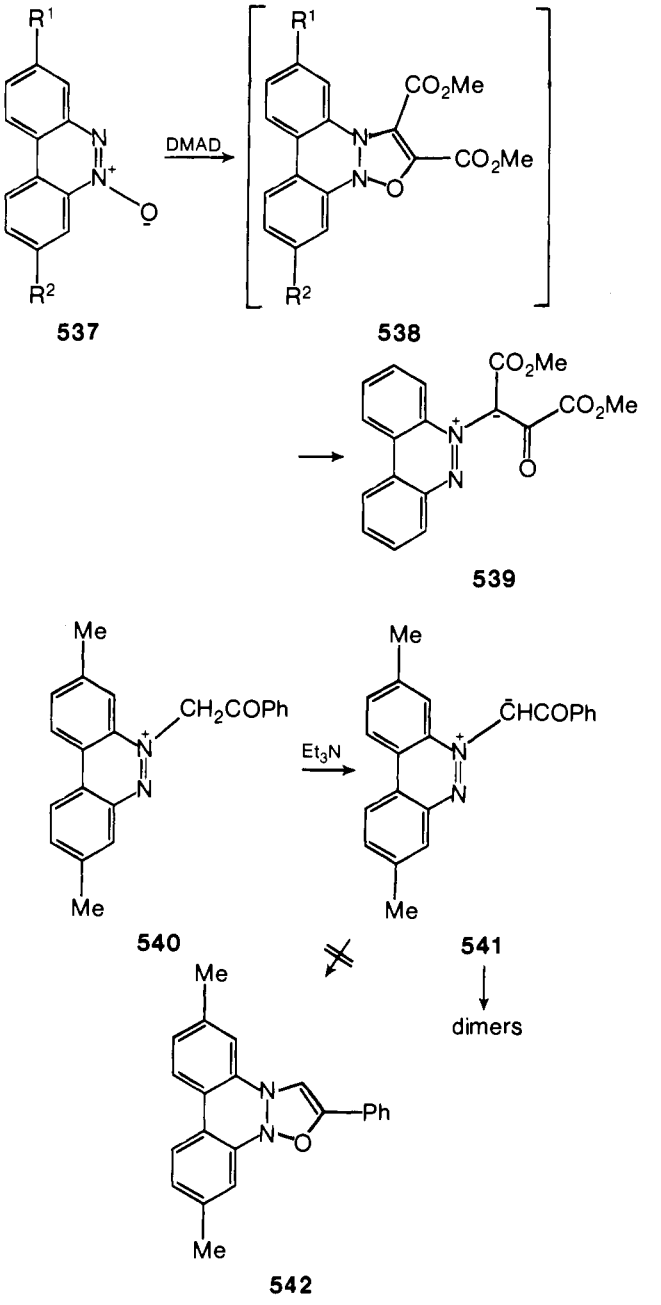


b. *C*-Carbonyl (1,2,3-Δ^4-Oxadiazolines)

1,2,3-Oxadiazolines **538** are likewise unstable relative to their *C*-acylazomethine imine valence isomers **539.** The 1,3-dipolar adduct is not isolated when benzocinnoline *N*-oxides **537** are allowed to react with dimethyl acetylenedicarboxylate; instead, **538** is thought to undergo electrocyclic ring opening to the *C*-acylazomethine imine **539.**[210]

C-Acylazomethine imines **541** derived from deprotonation of the benzocinnolinium salts **540** can be trapped by various dipolarophiles; in the absence of dipolarophiles, dimers rather than products of 1,5-dipolar cyclization (**542**) are isolated.[211]

C-Acylazomethine imines **544** have been generated by thermolysis of azines **543.**[212] Imines **544** do not provide 1,5-



electrocyclization products **545** but rather N-substituted pyrazoles **546** are obtained in fair to good yields by prototropic rearrangement of **544** or alternatively by isomerization of the unstable 1,5-dipolar cyclization products **545** (Scheme XLI).

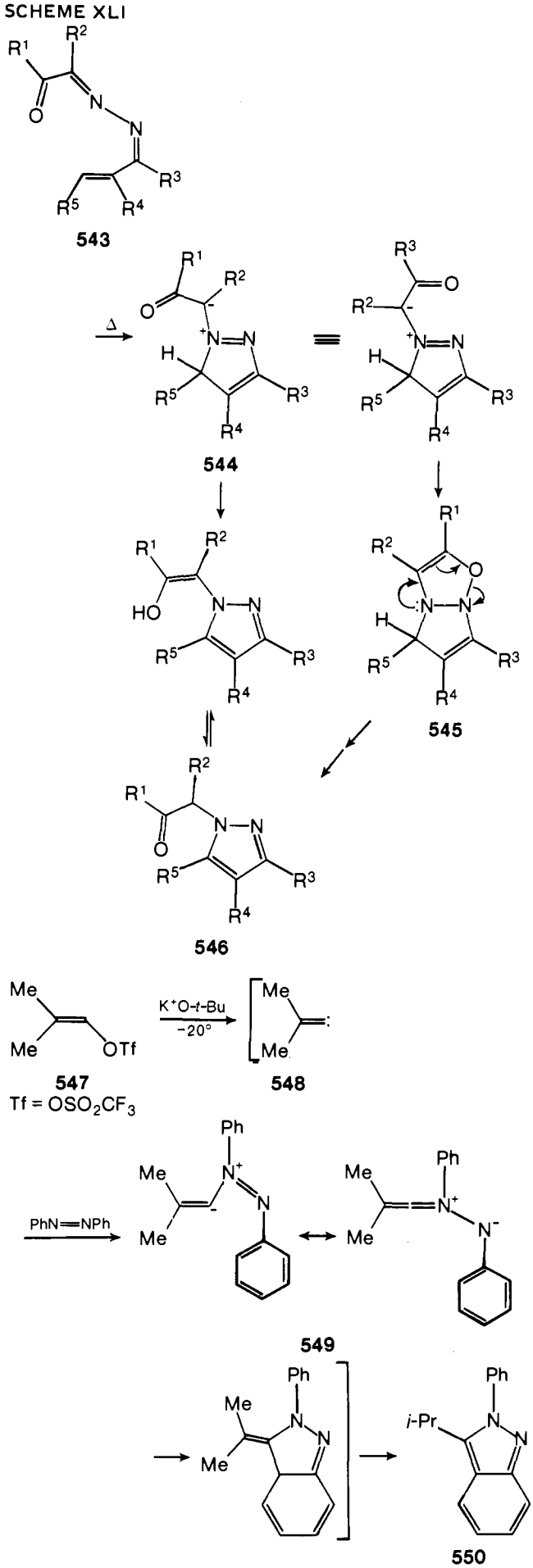
2. *Vinylazomethine Imines*

a. *N*-Vinyl (2-Pyrazolines)

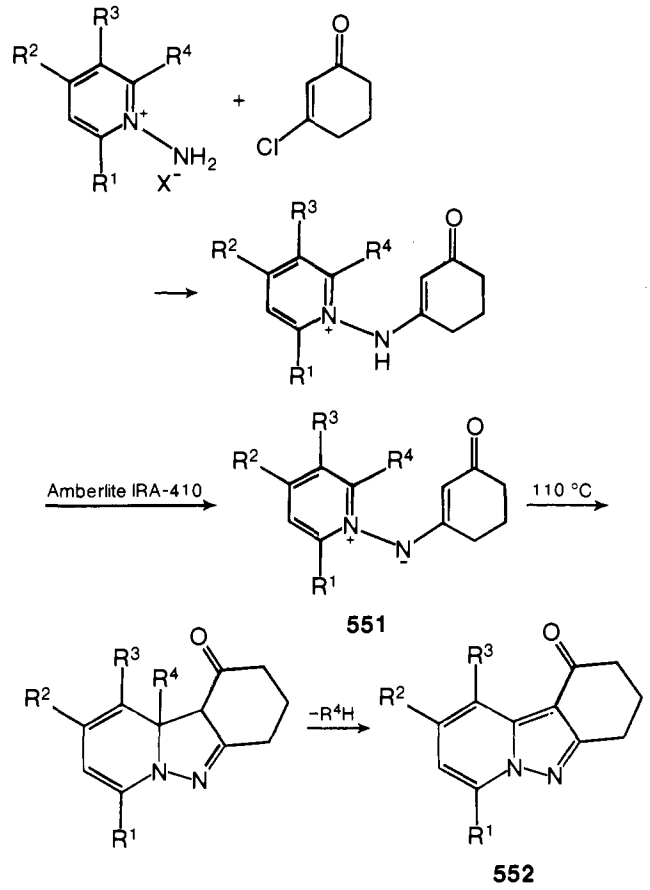
Stang and Mangum showed that isopropylidene carbene **548,** derived from the primary vinyl triflate **547** and potassium *tert*-butoxide in glyme at −20 °C, gives 2-indazole **550** in 63% yield when generated in the presence of azobenzene.[213] Several mechanisms were considered but the authors favored a process involving electrophilic attack of the carbene on the azo compound to produce *N*-phenylazomethine imine **549.** 1,5-Electrocyclization of **549** followed by prototropic rearrangement gives the observed product **550.** Mechanistic pathways involving direct 1,4-addition of the carbene to the azo compound or diaziridine formation and subsequent rearrangement were discounted.

N-Vinylpyridinium *N*-imines have proven to be useful intermediates for the synthesis of indazole derivatives.[209] Several

SCHEME XLI

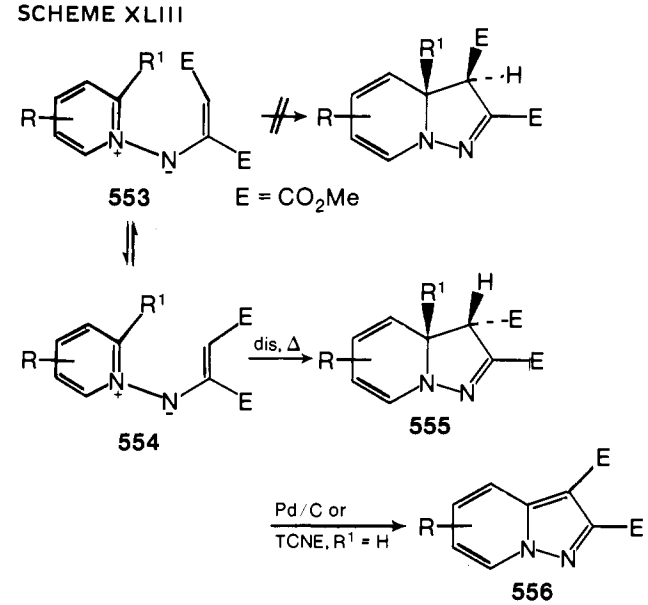


SCHEME XLII



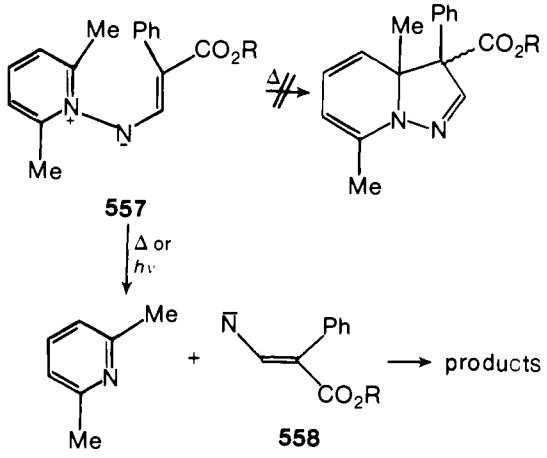
groups of Japanese workers have independently reported 1,5-dipolar cyclization of these intermediates. Thus Tamura et al. have prepared indazoles **552** via the insolable *N*-vinylazomethine imines **551** as outlined in Scheme XLII.[176] Sasaki et al. studied the dipolar cyclization of the *N*-vinylpyridinium *N*-imines **553.**[214] Although they are stable in the solid state, dissolution in chloroform, methylene chloride, or carbon tetrachloride leads to the formation of dihydroindazoles **555.** A *Z* configuration for the *N*-vinylimino group was assigned by spectral analysis. Since the R^1 and carbomethoxy groups are trans in the dihydroindazoles **555,** 1,5-electrocyclization of **553** is presumably slow owing to steric crowding in the transition state for thermal, disrotatory cyclization. As a consequence, isomerization to imines **554**

SCHEME XLIII

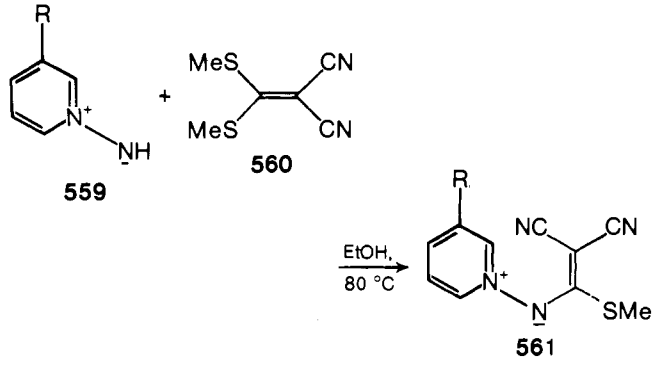


possessing the *E* configuration competes effectively with 1,5-dipolar cyclization, and these latter isomeric azomethine imines **554** cyclize rapidly in a disrotatory mode to **555**, since steric interactions in this transition state are minimal (Scheme XLIII).[214] Dehydrogenation of **555** to indazoles **556** occurs smoothly with Pd/C or TCNE.

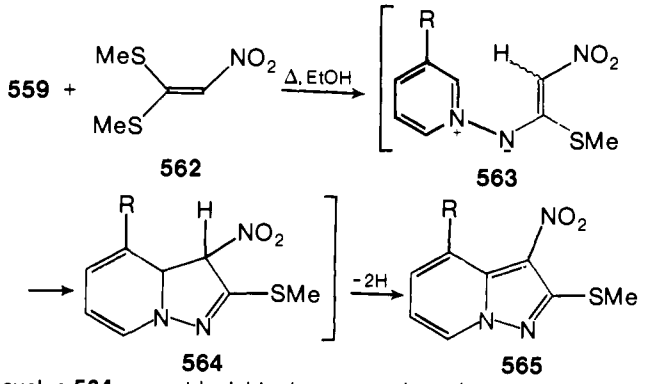
In contrast, thermolysis or photolysis of *N*-vinylazomethine imines **557** does not lead to 1,5-dipolar cyclization.[215] Owing to steric factors, imines **557** decompose to 2,6-lutidine and vinyl nitrenes **558** which go on to give other products.



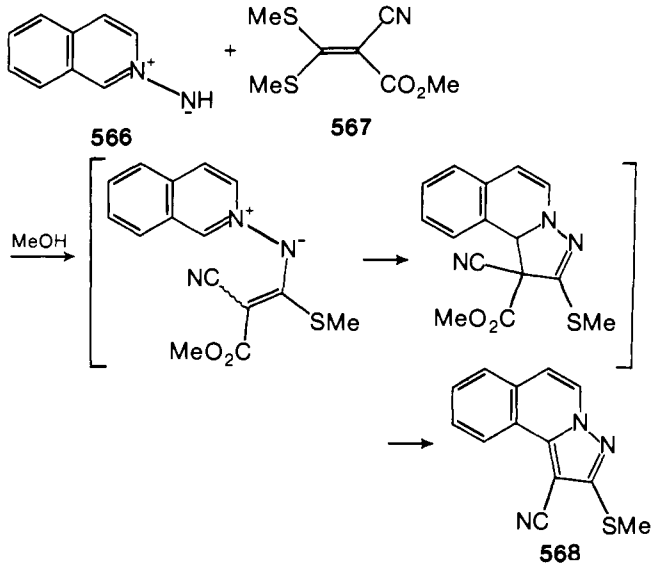
Pyridine *N*-imines **559** react with 2-cyano-3,3-bis(methylthio)acrylonitrile (**560**) to produce the stable *N*-vinylazomethine imines **561** in low yield.[216] Although **561** appears to be stable,



the same report discloses the instability (in refluxing ethanol) of the closely related *N*-vinylazomethine imines **563**, derived from **559** and 2,2-bis(methylthio)-1-nitroethylene (**562**), with respect to their dihydroindazole valence isomers **564**. Hetero-



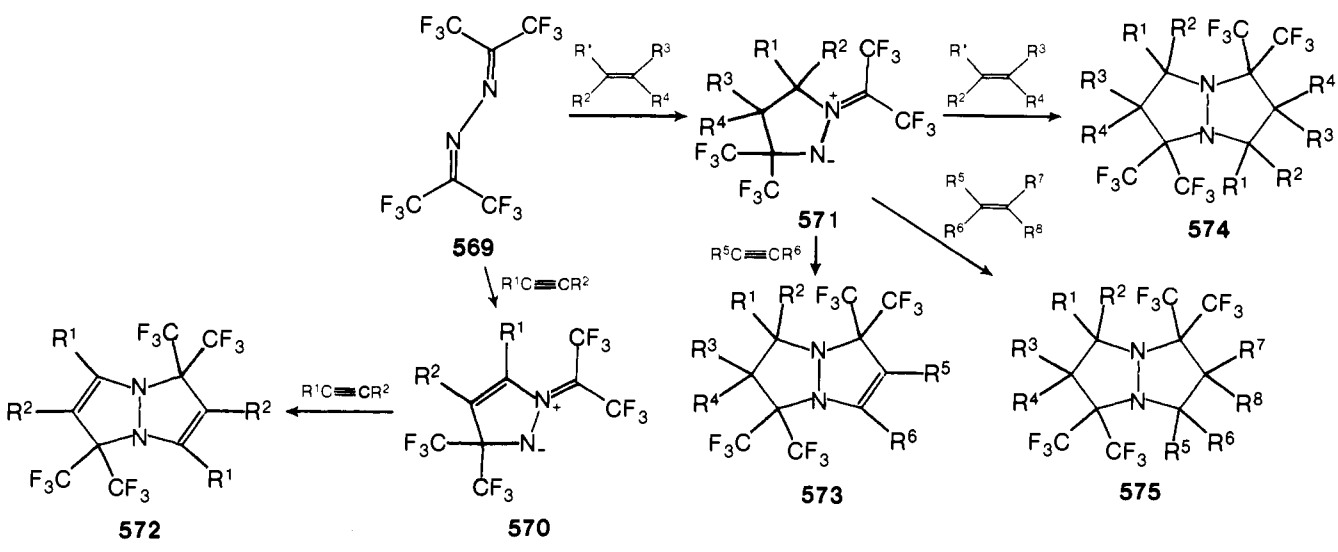
cycles **564** are not isolable, however, since they undergo rapid oxidation to provide indazoles **565** in moderate yields. Similarly isoquinoline *N*-imine **566** furnishes the pyrazolo[2,3-*a*]isoquinoline **568** in 29% yield with methyl 2-cyano-3,3-bis(methylthio)acrylate (**567**).[216]



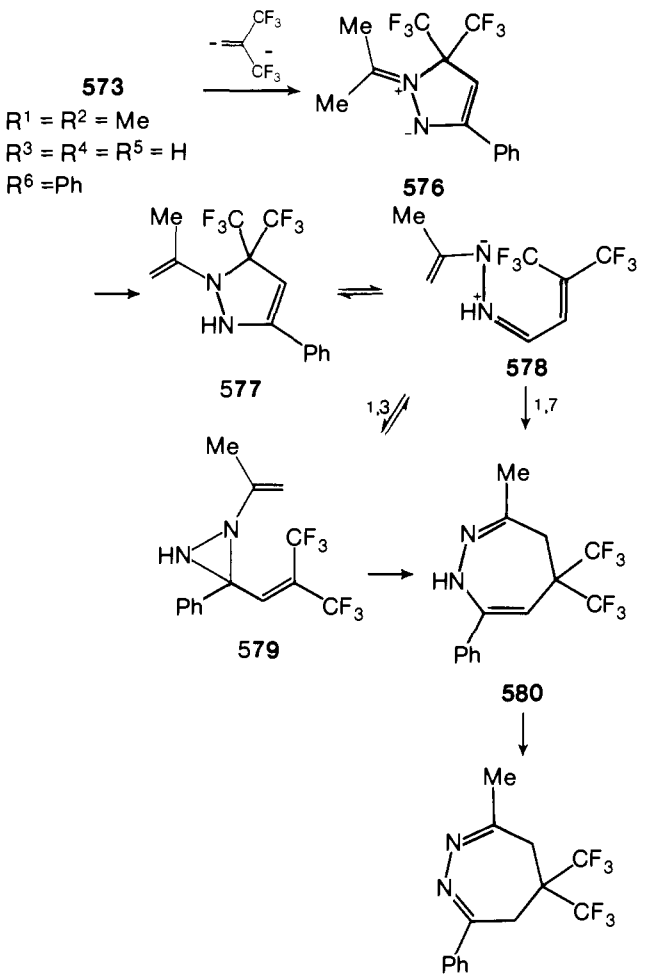
b. *C*-Vinyl (3-Pyrazolines)

Burger and co-workers have extensively studied the so-called criss-cross cycloaddition reaction of hexafluoroacetone azine **569** with a variety of olefins and acetylenes (Scheme XLIV).[217-219] The properties of the intermediate azomethine imines **571** (when isolable) and the thermal behavior of the products **572–575** were also investigated. At 200 °C the 1,5-diazabicyclo[3.3.0]oct-2-enes **573** ($R^1 = R^2 = Me$, $R^3 = R^4 =$

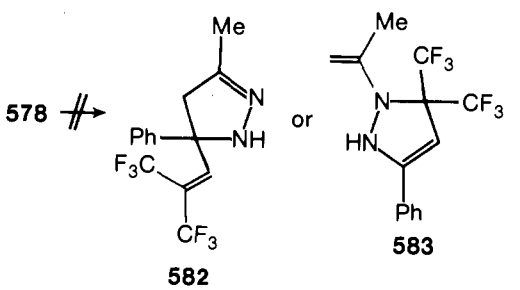
SCHEME XLIV



SCHEME XLV

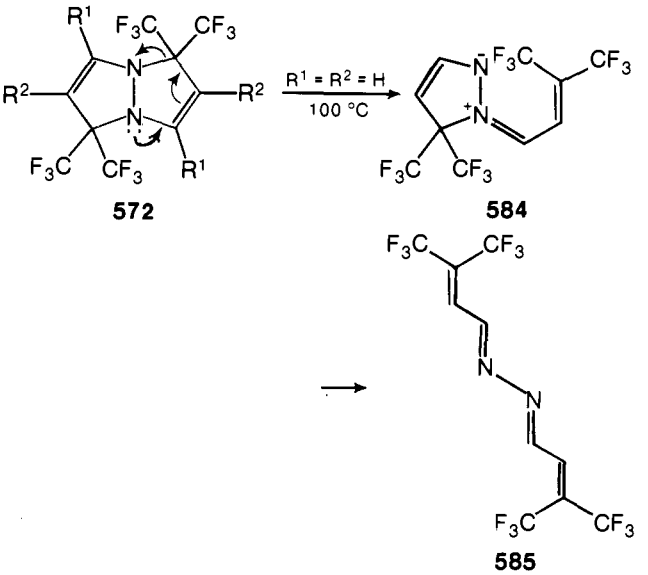


R⁵ = H, R⁶ = Ph) afford 1,2-diazacycloheptadiene **581** in 78% yield.[220] The proposed mechanism is outlined in Scheme XLV. 1,3-Dipolar cycloreversion of 1,1-bistrifluoromethylethylene leads to azomethine imine **576** which undergoes a 1,4-hydrogen shift to **577.** Pyrazoline **577** suffers a 1,5-electrocyclic ring opening to give the acyclic azomethine imine **578** which may undergo a 1,7-electrocyclization to **580,** which then isomerizes to give the observed product **581.** Alternatively **578** may cyclize to diaziridine **579** which ultimately can give **581** via a Cope rearrangement and subsequent isomerization. Pyrazolines **582** or **583** from a 1,5-dipolar cyclization of **578** were not detected.

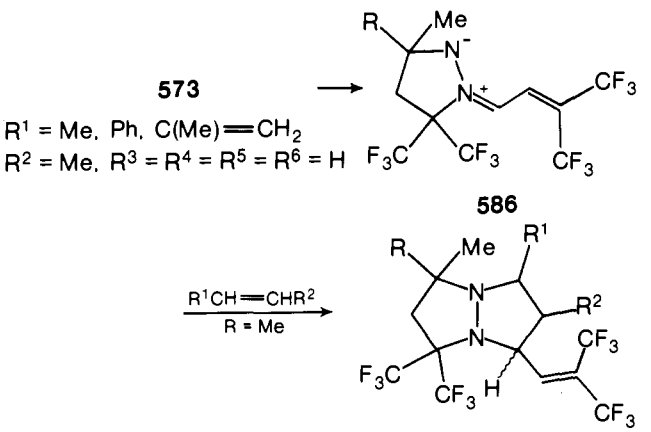


Two successive electrocyclic ring opening processes are responsible for the formation of azine **585** when 1,5-diazabicyclo[3.3.0]octa-2,6-diene **572** ($R^1 = R^2 = H$) is heated to 100 °C; the *C*-vinylazomethine imine **584** is proposed as the intermediate.[221]

At 140 °C, 1,5-diazabicyclo[3.3.0]oct-2-enes **573** (R^1 = Me, Ph, $C(CH_3)=CH_2$, R^2 = Me, $R^3 = R^4 = R^5 = R^6 = H$) furnish azomethine imines **586** (R = Me, Ph, $C(CH_3)=CH_2$) in quantitative yield via an electrocyclic ring opening.[222] Azomethine

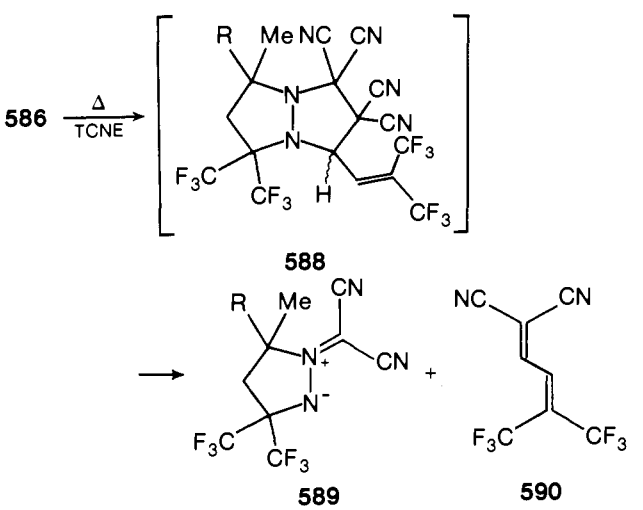


imine **586** (R = Me) combines with a variety of olefinic dipolarophiles to afford 1,3-dipolar cycloadducts **587.**[223]

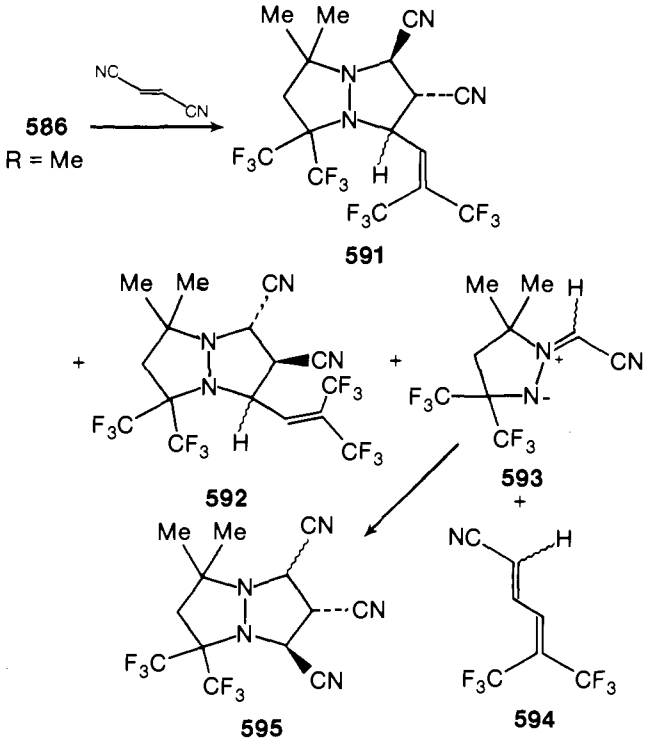


R^1	R^2	yield (%)
H	CO_2Me	93
H	CO_2Et	69
H	CO_2-*n*-Bu	76
Me	CO_2Et	22
H	CH_2CN	55

The reaction of **586** with tetracyanoethylene affords the stable azomethine imine **589** and diene **590** by 1,3-dipolar cycloreversion of **590** from the initial adduct **588.**[224] With fumaronitrile

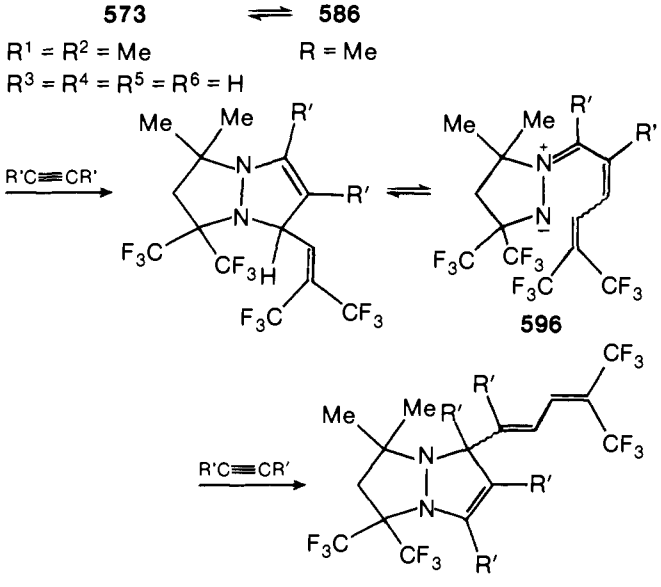


586 (R = Me) gives a mixture of cycloadducts **591** and **592** along with azomethine imine **593**, diene **594**, and adduct **595**. Adduct **595** becomes the major product when higher temperatures or an excess of fumaronitrile are utilized.



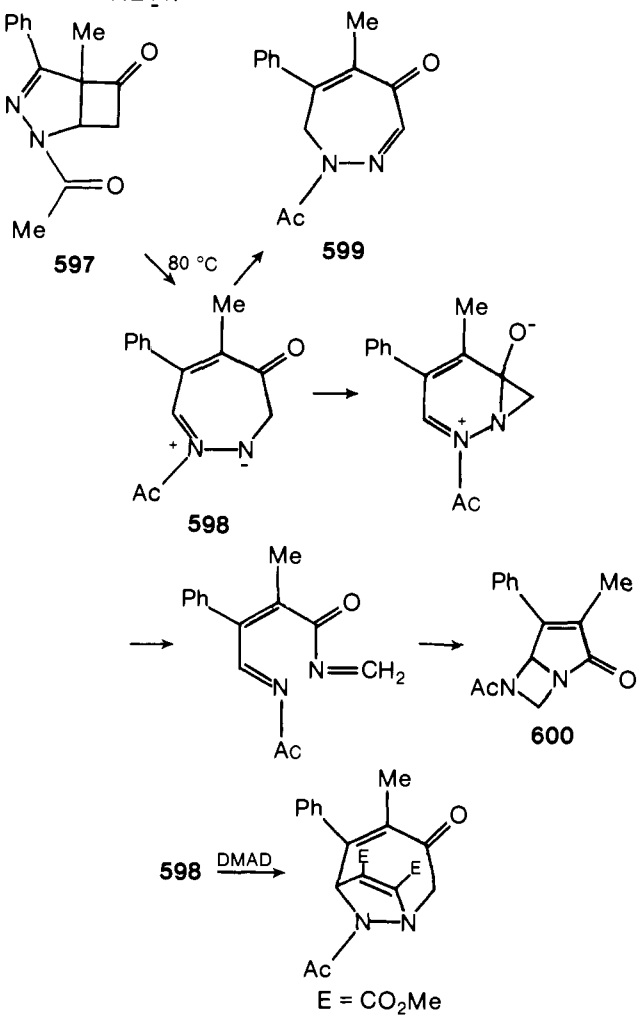
A procedure for generating conjugated 1,*x*-azomethine imines **596** by repeating the sequence of electrocyclic ring opening of **573** ($R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = R^6 = H$) and 1,3-dipolar cycloaddition of an acetylene to the resulting C-vinylazomethine imine **586** (R = Me) has been reported (Scheme XLVI).[225] This sequence can be considered as a new type of acetylene oligomerization.

SCHEME XLVI



Thermal rearrangement of 1,2-diazabicyclo[3.2.0]hept-3-ene **597** to the isomeric pyrrolinone **600** and dihydrodiazepinone **599** has been studied by Moore et al.[226] A possible mechanistic pathway rationalizing the formation of **599** and **600** is outlined in Scheme XLVII. The intermediate cyclic *C*-vinylazomethine imine **598**, which arises by electrocyclic ring opening of **597**, can be trapped by dimethyl acetylenedicarboxylate.[227]

SCHEME XLVII



3. *Iminoazomethine Imines*

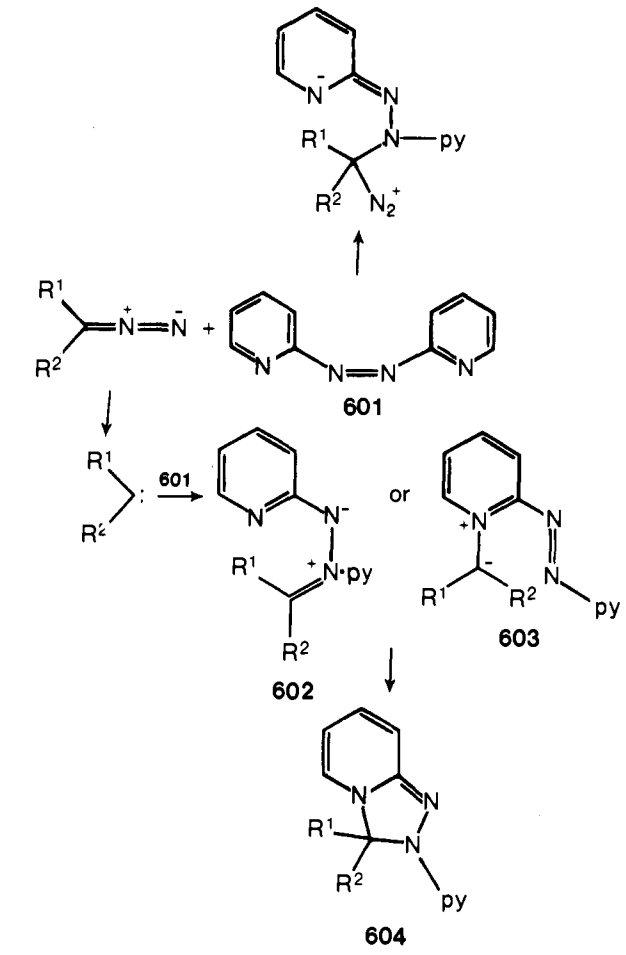
a. *N*-Imino (1,2,4-Δ^2-Triazolines)

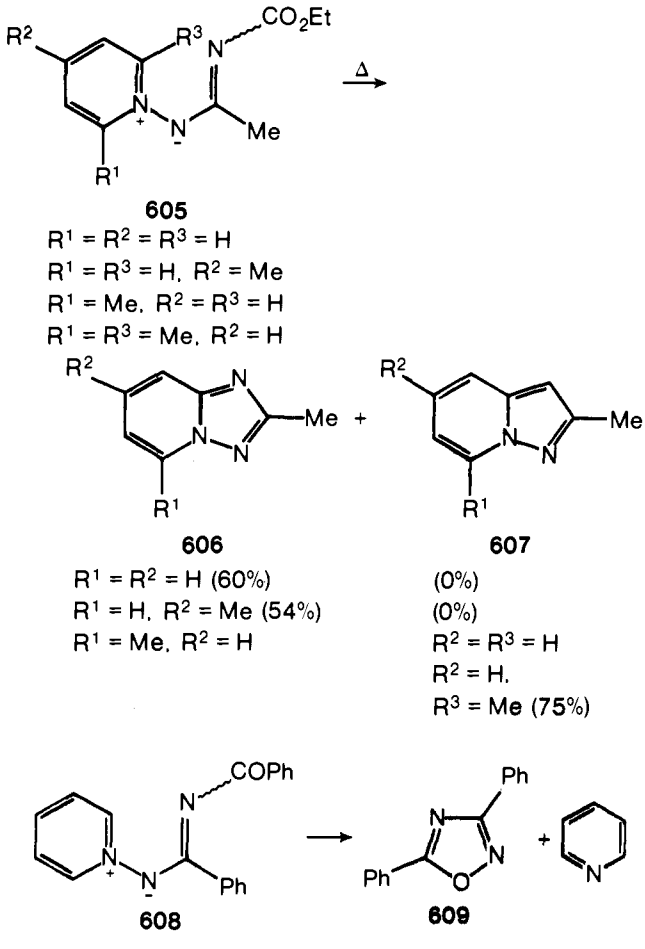
Triazolines **604** arise from the reaction of diazoalkanes with 2,2′-azopyridine (**601**).[228,229] Fahr et al. demonstrated that in contrast to the results described above for the reaction of diazo compounds with azodicarbonyl compounds, the free carbene rather than the diazo compound combines with **601**. This is probably due to the lower reactivity of **601** as an electrophile (or dipolarophile) compared with the azodicarbonyl compounds. The site of electrophilic attack of the carbene on **601**, i.e., on the nitrogen of the azo linkage to generate the *N*-iminoazomethine imines **602** or on the pyridine nitrogen to produce ylides **603**, has not been ascertained. 1,5-Dipolar cyclization of **602** or ring closure of ylides **603** furnishes the observed products **604**.

Studies by Kakehi et al. have shown that thermolysis (140 °C) of the stable *N*-iminoazomethine imines **605** gives triazolopyridines **606** and pyrazolopyridines **607** in varying amounts depending upon the substituents R^1–R^3.[230] Triazolopyridines **606** are products of a 1,5-electrocyclization of **605** followed by elimination of ethyl formate. The authors discuss several possible mechanistic pathways leading to **607**. When *N*-iminoazomethine imine **608** is heated, however, only 3,5-diphenyl-1,2,4-oxadiazole **609** is obtained (79%) along with pyridine.[230]

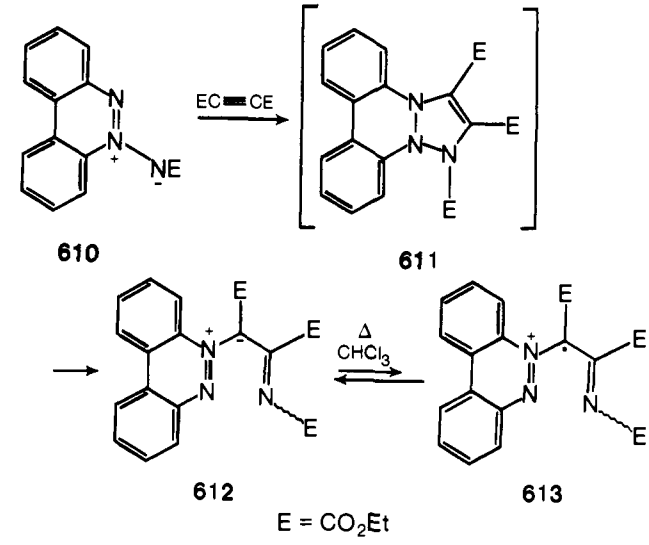
b. *C*-Imino (1,2,3-Δ^4-Triazolines)

Rees et al. have recently described the reaction of a member of a relatively new class of 1,3-dipoles, the azimine **610**, with diethyl acetylenedicarboxylate to provide a 1:1 adduct.[231] The



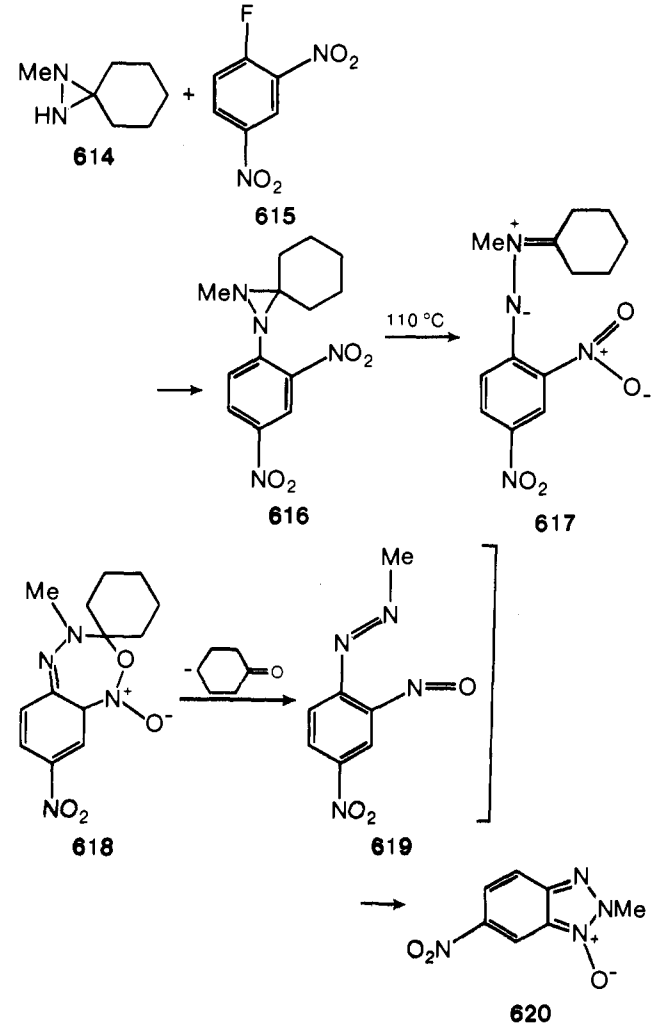


adduct proved to be the *C*-iminoazomethine **612** derived from the initial 1,3-dipolar adduct **611** by an electrocyclic ring opening. Interestingly, azomethine imine **612** is in equilibrium with a small amount of the stabilized radical cation **613** in hot chloroform as confirmed by ESR spectroscopy.[231]



4. *Miscellaneous*

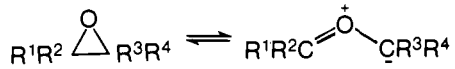
2,4-Dinitrofluorobenzene (**615**) undergoes nucleophilic substitution of fluoride when allowed to react with 1-methyl-3,3-pentamethylenediaziridine (**614**) to yield 1-methyl-2-(2,4-dinitrophenyl)-3,3-pentamethylenediaziridine (**616**). Heating **616**



affords 2-methyl-6-nitrobenzotriazole 1-oxide (**620**, 97%) and cyclohexanone.[232] A mechanism which rationalizes the formation of **620** involves electrocyclic ring opening of diaziridine **616** to the *N*-(2,4-dinitrophenyl)azomethine imine **617** followed by a 1,7-electrocyclic reaction providing intermediate **618**. This collapses with loss of cyclohexanone to give the 2-nitrosoazobenzene **619**, which cyclizes under the reaction conditions to **620**.

C. Carbonyl Ylides

Carbonyl ylides **621** are most conveniently generated by the thermal or photochemical carbon–carbon bond cleavage of oxiranes.[147,148,233] This reaction appears to parallel the aziri-



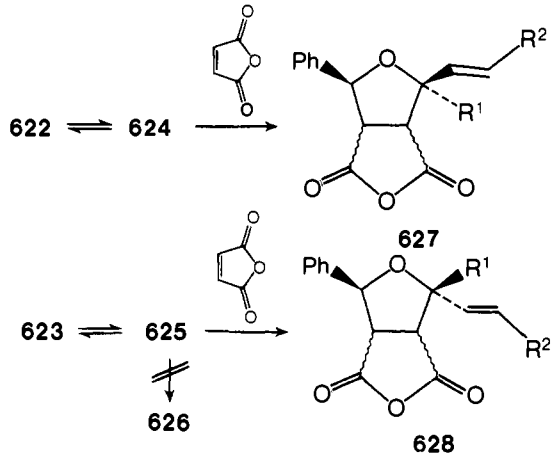
621

dine–azomethine ylide valence isomerization in its stereochemical course, i.e., the thermal process is a conrotatory ring opening while the photochemical one is disrotatory.[233]

1. *Vinylcarbonyl Ylides*[234,235] (*Dihydrofurans*)

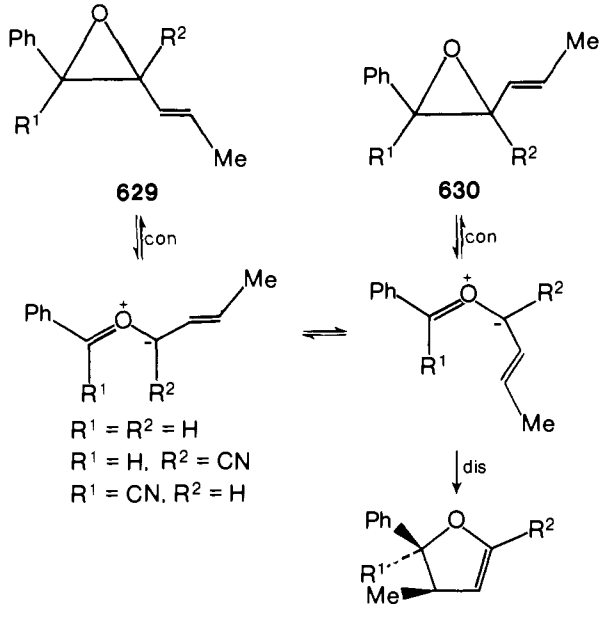
Two further stereochemical points arise in a consideration of 1,5-dipolar cyclizations of vinylcarbonyl ylides, i.e., the conformation of the ylide[233] and the direction (conrotatory or disrotatory) of the ring closure.

When the isomeric vinyl oxiranes **622** or **623** are heated to 150–170 °C in bromobenzene, a cis–trans isomerization occurs along with a slower, irreversible ring expansion to give the *cis*-2,3-dihydrofuran derivative **626**.[236] The reaction course and product stereochemistry are best rationalized by the pathway illustrated in Scheme XLVIII. Conrotatory ring opening of epoxide **622** leads to the vinylcarbonyl ylide **624**, while **623** affords ylide **625**. Ylides **624** and **625** can revert to the starting epoxides or interconvert via rotation around the C–O bond. 1,3-Electrocyclization of the isomerized carbonyl ylide **625** affords isomerized epoxide **623**, while 1,5-electrocyclization of ylide **625**a provides the *cis*-2,3-dihydrofuran **626**. Of the ylides depicted in Scheme XLVIII only **625**a has the proper conformation required for the 1,5-dipolar cyclization. Evidence for the intermediacy of carbonyl ylides **624** and **625** is derived from trapping experiments with maleic anhydride and dimethyl acetylenedicarboxylate. 1,3-Dipolar cycloaddition of these dipolarophiles to carbonyl ylides **624** and **625** is more facile than C–O bond rotation in the ylides since the tetrahydrofuran cycloadducts **627** and **628**



627 **628**

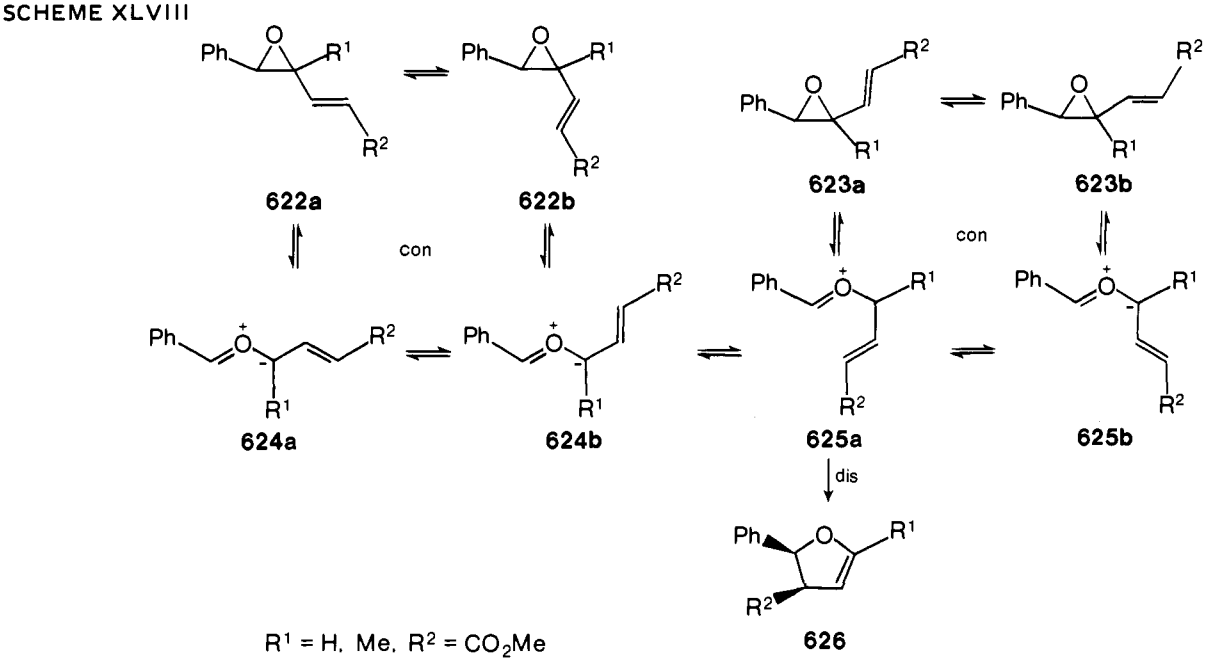
SCHEME XLIX



629 **630**

$R^1 = R^2 = H$
$R^1 = H,\ R^2 = CN$
$R^1 = CN,\ R^2 = H$

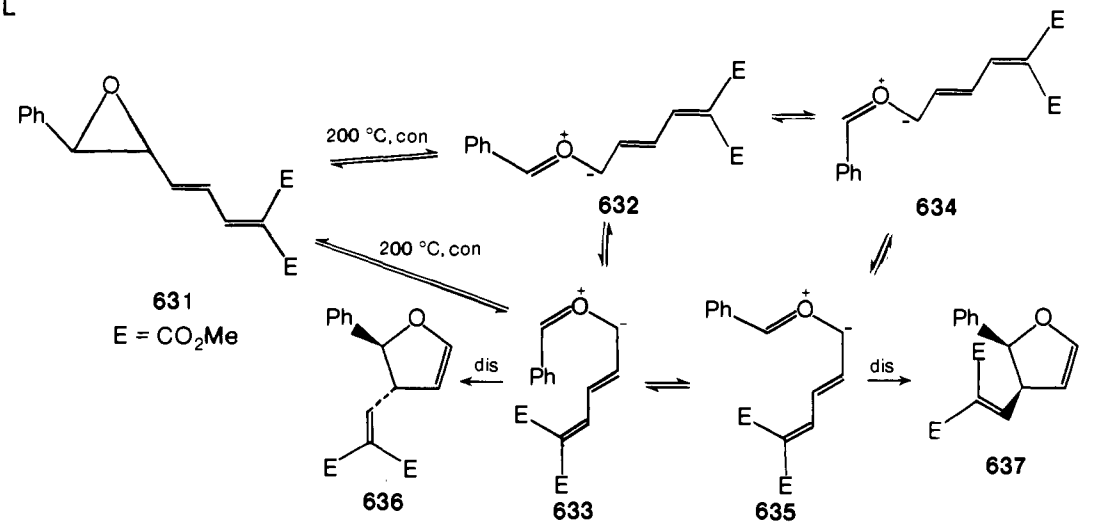
SCHEME XLVIII



622a **622b** **623a** **623b** **624a** **624b** **625a** **625b** **626**

$R^1 = H,\ Me,\ R^2 = CO_2Me$

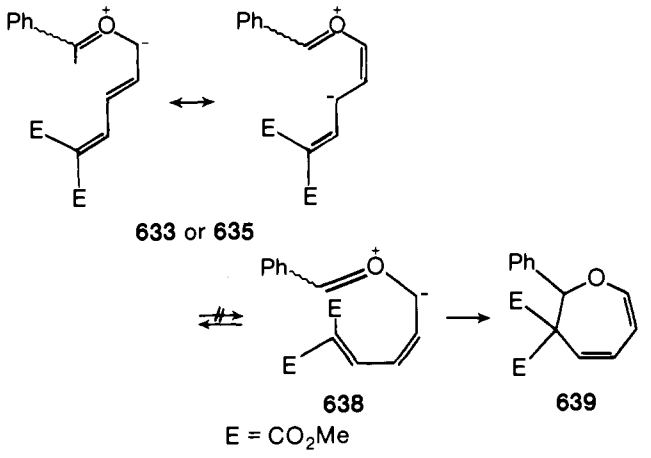
SCHEME L



are formed stereospecifically. Moreover, no 1,5-dipolar cyclization product **626** arises when these dipolarophiles are present. Dihydrofuran **626** can be obtained in preparatively useful yield (80%) by flash vacuum pyrolysis of **622** or **623** at 330 °C.[236] Analogous results were obtained by thermolysis of epoxides **629** and **630** (Scheme XLIX).[237,238]

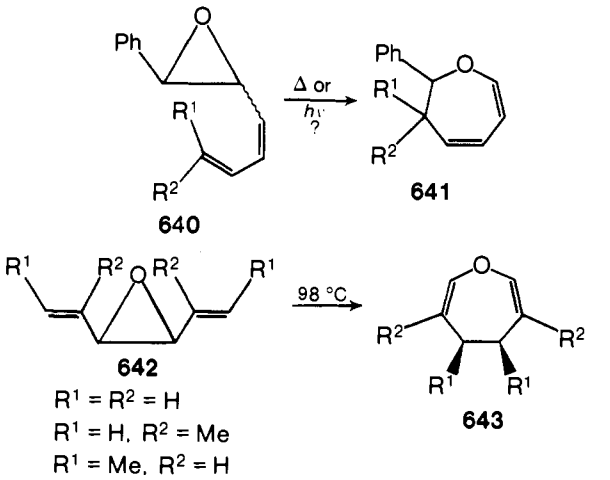
The steric course of the thermolysis of butadienyl epoxide **631** is more complex than that shown in the previous examples.[239] Thus thermal conrotatory carbon–carbon bond cleavage of **631** leads to the formation of butadienylcarbonyl ylides **632** and **633** (Scheme L). Isomerization of **633** or **635** is competitive with 1,5-dipolar cyclization, and both the *cis*- and *trans*-2,3-dihydrofurans **637** and **636** are formed in a ratio of 5:1 (70%).

The *photoinduced* disrotatory ring opening of **631** to carbonyl ylides **634** and **635** followed by 1,5-cyclization of **635** affords *cis*-2,3-dihydrofuran **637** in 30% yield.[239] This is the first example of a photochemical vinyloxirane-2,3-dihydrofuran ring expansion. Thermolysis or photolysis of epoxide **631** in the presence of *N*-phenylmaleimide furnishes only 1,3-dipolar cycloadducts and no 1,5-dipolar cyclization products **637** and **636**.



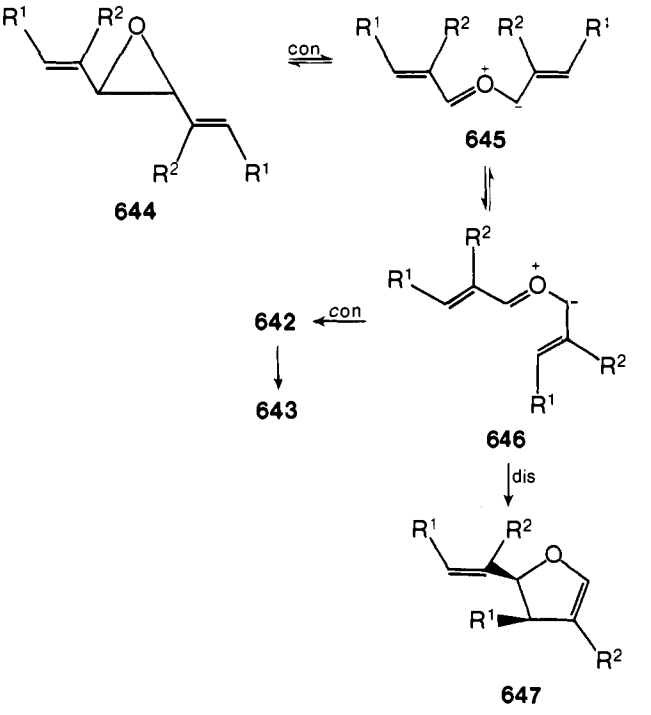
The carbonyl ylides **632–635** are not in the proper conformation for a 1,7-cyclization (cf. **638**). Rotation around the C_4–C_5 bond in **633** or **635** is apparently not competitive with 1,5-cyclization. Of interest would be the thermal or photochemical behavior of the epoxide bearing a cis butadienyl substituent as in **640.** Thus 1,7-electrocyclization to **641** in principle could occur.

Divinyloxiranes follow a different reaction course. Upon thermolysis (98 °C) *cis*-2,3-divinyloxirane derivatives **642** undergo a Cope rearrangement to provide 4,5-dihydrooxepins **643.**[234,240] On the other hand, *trans*-2,3-divinyloxiranes **644**



when heated to 330–380 °C afford both dihydrooxepins **643** and *cis*-2-vinyl-2,3-dihydrofurans **647** in nearly equal amounts.[240] Support for the proposed mechanistic pathways (Scheme LI)

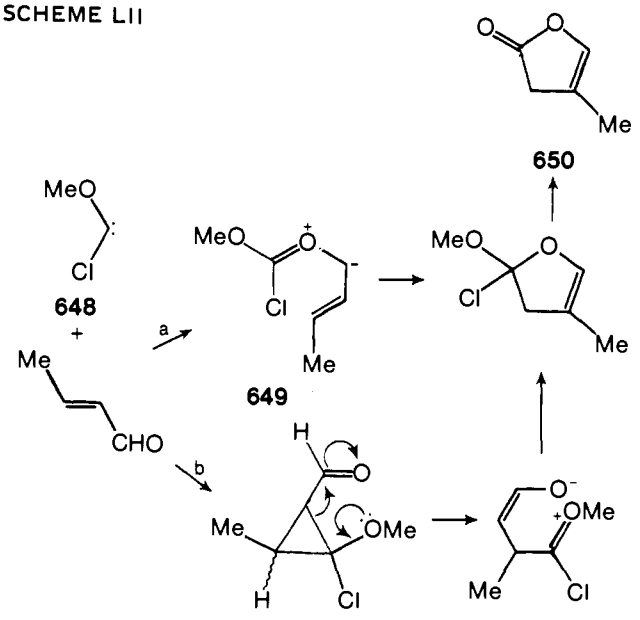
SCHEME LI



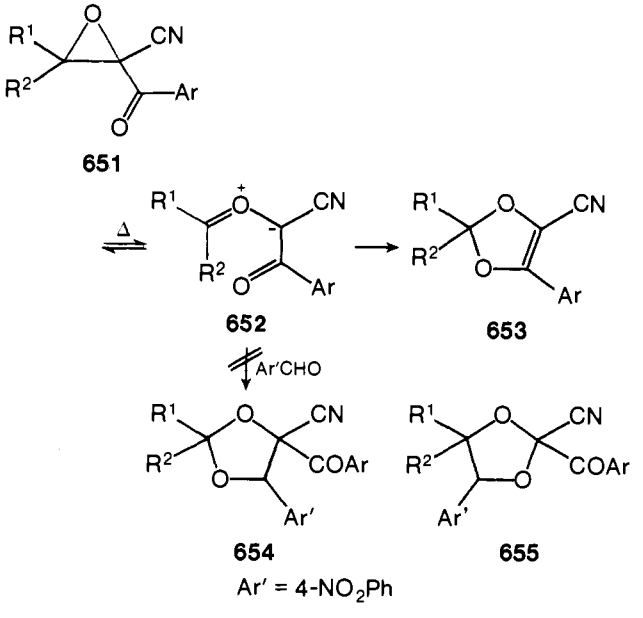
leading to **643** and **647** comes from a kinetic investigation.[241,242] Conrotatory ring opening of **644** gives *exo,exo*-divinylcarbonyl ylides **645.** (Presumably the highly crowded endo,endo ylide is not formed.) Conrotatory closure of **645** affords the starting oxiranes while rotation around the carbon–oxygen bond in **645** produces the exo,endo ylides **646** which are in the conformation required for disrotatory 1,5-electrocyclization leading to **647.** Conrotatory 1,3-cyclization of **646** affords *cis*-divinyloxiranes **642** which undergo the thermal Cope rearrangement to yield **643.** Secondary deuterium isotope effects suggest that the Cope products **643** are derived from carbonyl ylides **646;**[243] however, this conversion is difficult to envisage. Clarification of this point awaits further data.

Recently Smith and Stevens observed the formation of methoxychlorocarbene **648** from the thermal decomposition of 3-methoxy-3-chlorodiazirine and discussed this intermediate in terms of its ambiphilic properties.[244] Carbene **648** gives cyclopropanes with electrophilic olefins such as ethyl acrylate and acrylonitrile. With crotonaldehyde the butenolide **650** is obtained.

SCHEME LII



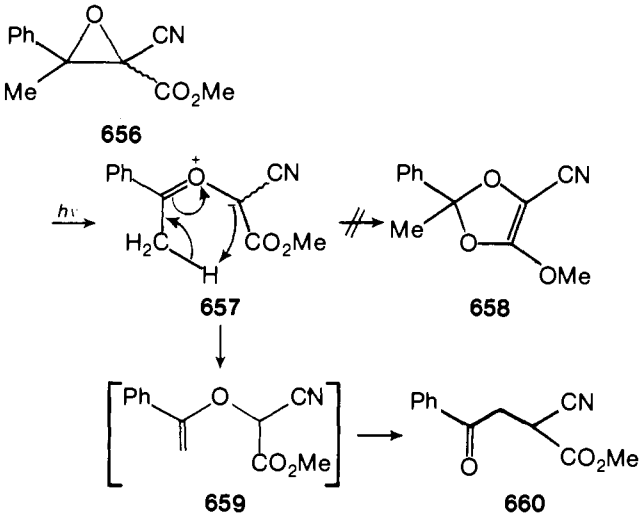
Two reasonable mechanisms for the formation of **650** can be envisioned (Scheme LII). The authors preferred path a which involves 1,5-electrocyclic ring closure of the initially formed vinylcarbonyl ylide **649.**



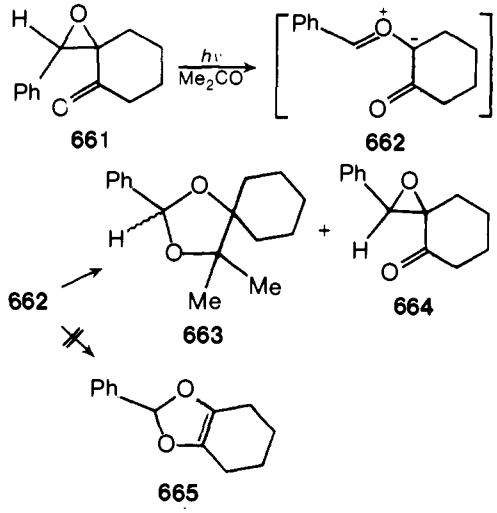
2. Carbonylcarbonyl Ylides (1,3-Dioxolenes)

Carbonyl ylides bearing a carbonyl substituent have been generated by thermal carbon–carbon bond cleavage of carbonyl-substituted epoxides; however, only one such system affords a product derived from a 1,5-dipolar cyclization. Thermolysis of epoxides **651** gives dioxolenes **653** (100%) via a 1,5-electrocyclization of carbonyl ylide **652.**[245] The dipolarophile, 4-nitrobenzaldehyde, failed to intercept the proposed ylide intermediate. The rate of carbonyl ylide formation in the thermolysis of epoxides is highly substituent dependent.[233] In this case the conversion of the monophenyloxirane **651** (R^1 = Ph, R^2 = H) requires 24 h in refluxing toluene for complete conversion to the corresponding dioxolene **653** (R^1 = Ph, R^2 = H), while the diphenyloxirane **651** (R^1 = R^2 = Ph) gives **653** (R^1 = R^2 = Ph), quantitatively after only 1 h under the same conditions.[245]

Carbonylcarbonyl ylide **657,** generated photochemically from the epoxide **656,** does not provide the dioxolene **658;** instead, a prototropic shift ensues to afford enol ether **659** which subsequently rearranges to the keto ester **660.**[246]



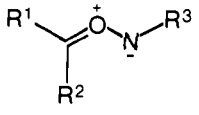
Photolysis of the spiro epoxide **661** in the presence of acetone affords the 1,3-dipolar adduct **663** along with the epimerized oxirane **664.**[247] The product **665** derived from a 1,5-dipolar cyclization of ylide **662** was not detected.



Stereochemical considerations similar to those involved in the vinyloxirane-2,3-dihydrofuran ring expansion probably apply to the carbonyloxirane–dioxolene rearrangement. Little effort has been expended toward an understanding of stereochemical factors which affect these processes, and further study of the scope and stereochemistry of these transformations would appear to be warranted.

D. Carbonyl Imines

Carbonyl imines **666** are among the rarer members of the family of 1,3-dipoles. Little is known concerning methods of their generation and reactivity. While carbonyl imines appear to be reasonable intermediates in the transformations discussed in this section, their intermediacy is nevertheless speculative.

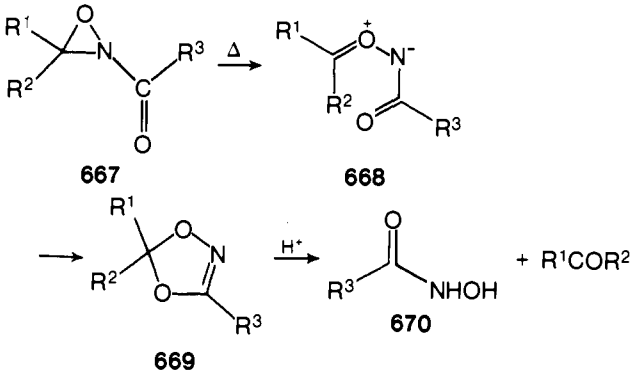


666

1. Carbonylcarbonyl Imines

a. *N*-Carbonyl (1,2,4-Dioxazoles)

Pyrolysis of 2-acyloxaziridines **667** at 80–130 °C causes ring expansion to give 1,3,4-dioxazoles **669** (48–81%) possibly through the *N*-carbonylcarbonyl imine intermediate **668**.[248]



667 **668** **669** **670**

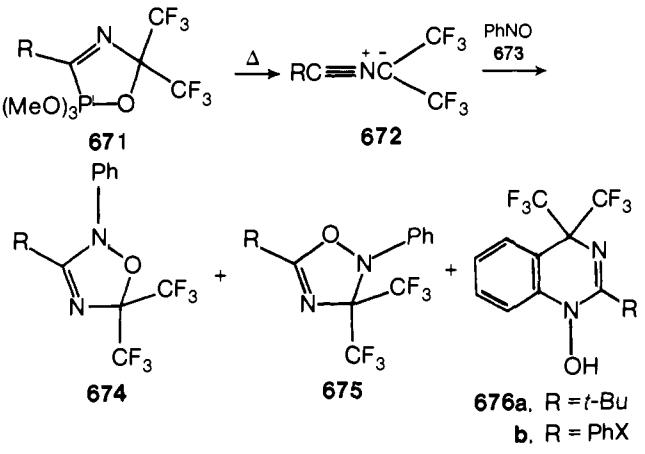
1,3,4-Dioxazoles can be hydrolyzed by aqueous acid to provide the corresponding hydroxamic acids **670**. Whereas 2-alkyloxaziridines give 1,2,4-oxadiazolidin-5-ones when heated in the presence of isocyanates, 2-benzoyl-3,3-pentamethyleneoxaziridine **667** (R^1, R^2 = $-(CH_2)_5-$, R^3 = Ph) affords only the product of ring expansion **669** (R^1, R^2 = $-(CH_2)_5-$, R^3 = Ph) under these conditions.[249]

1,2,4-Dioxazoles **669** (R^1, R^2 = alkyl, R^3 = Ph) are formed in good yield along with minor amounts of phenyl isocyanate and benzamide when benzoyl azide is photolyzed in the presence of dialkyl ketones at wavelengths >300 nm.[250] 2-Benzoyloxaziridines **667** (R^3 = Ph) can be discounted as intermediates in this process, however, since the latter provide 1-benzoyl-5-caprolactams under the photochemical conditions. With light of shorter wavelengths the yield of phenyl isocyanate increases at the expense of **669**.

2. Iminocarbonyl Imines

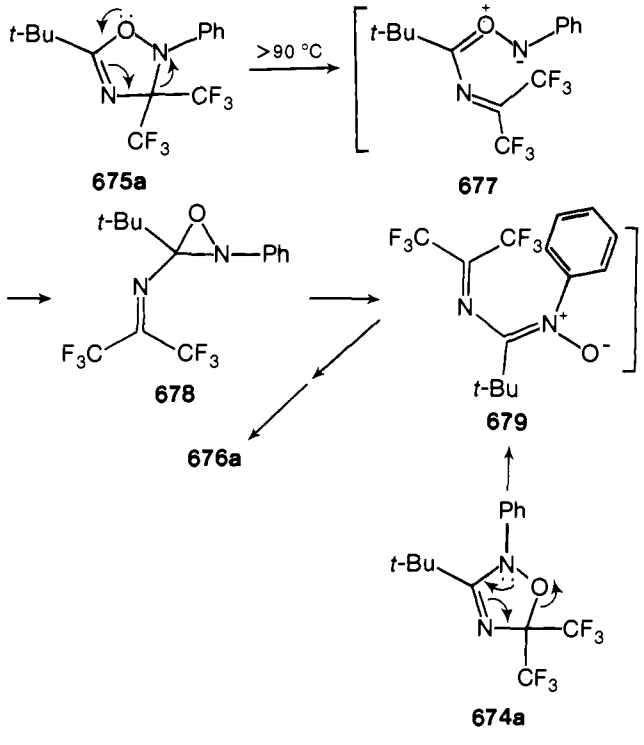
a. *C*-Imino (1,2,4-Δ^4-Oxadiazolines)

Thermolysis or photolysis of 3,3-bis(trifluoromethyl)-Δ^4-1,4,2,λ^5-oxazaphospholines **671** results in the formation of bis(trifluoromethyl)nitrile ylides **672**.[251] When these 1,3-dipolar species are generated thermally in the presence of nitrosobenzene (**673**), the regioisomeric 1,3-dipolar cycloadducts, 2-phenyl-5,5-bis(trifluoromethyl)-Δ^3-1,2,4-oxadiazolines **674** and 2-phenyl-3,3-bis(trifluoromethyl)-Δ^3-1,2,4-oxadiazolines **675**, arise along with 1-hydroxy-4,4-bis(trifluoromethyl)-1,4-dihydroquinazolines **676**.[251] The product distribution is highly dependent upon the reaction temperature. For example, when **671a** and nitrosobenzene are heated to 90 °C in nitrobenzene, the ratio of **674a:675a:676a** is 34:66:0. As the temperature is increased, the yield of **676a** increases with an accompanying decrease in the yield of **675a**. After 2 h at 140 °C no **675a** remains and the ratio of **674a:676a** is 32:68. Thus at temperatures of 90 °C or greater the adduct **675a** isomerizes to the dihydroquinazoline **676a**. The first step in the postulated mechanism for this rearrangement involves electrocyclic ring opening of **675a** to provide the *C*-iminocarbonyl imine **677**. 1,3-Electrocyclization of **677** to the 3-iminooxaziridine **678** followed by thermal carbon–oxygen bond cleavage of **678** gives the *C*-iminonitrone **679**. The product **676a** derives from an electrocyclic ring closure of **679** (Scheme LIII). A further increase in the temperature results in the decomposition of **674a** with a further increase in the yield of **676a**. After 24 h at 220 °C no **674a** remains and only **676a** can be isolated.[251] Adduct **674a** is converted to quinazoline **676a** at the higher temperatures presumably via electrocyclic ring opening to the *C*-iminonitrone **679** (Scheme LIII).



671 **672** **674** **675** **676a**, R = *t*-Bu; **b**, R = PhX

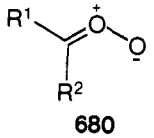
SCHEME LIII



675a **677** **678** **679** **676a** **674a**

E. Carbonyl Oxides

The Criegee mechanism for the ozonolysis of alkenes invokes carbonyl oxides **680** as intermediates in the rearrangement of primary ozonides to ozonides.[252] Controversy still exists concerning the details of this mechanism; however, carbonyl oxides

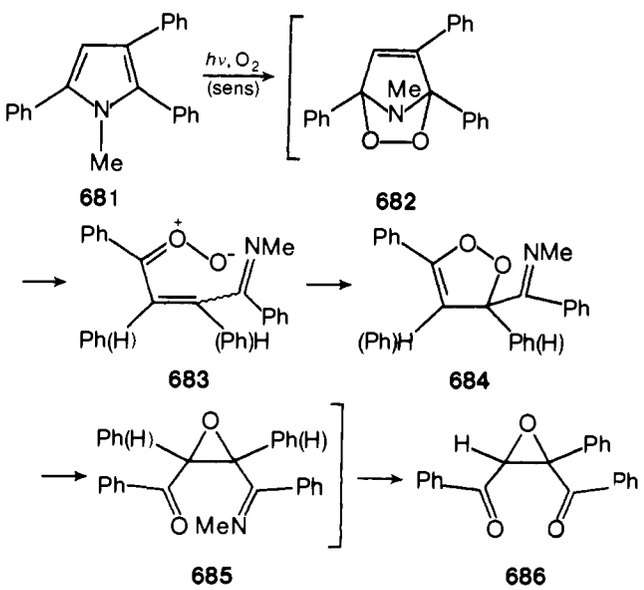


680

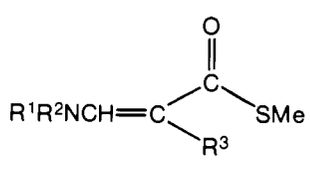
remain as likely intermediates.[253] Besides this little is known about carbonyl oxides.

1. *Vinylcarbonyl Oxides (1,2-Dioxol-4-enes)*

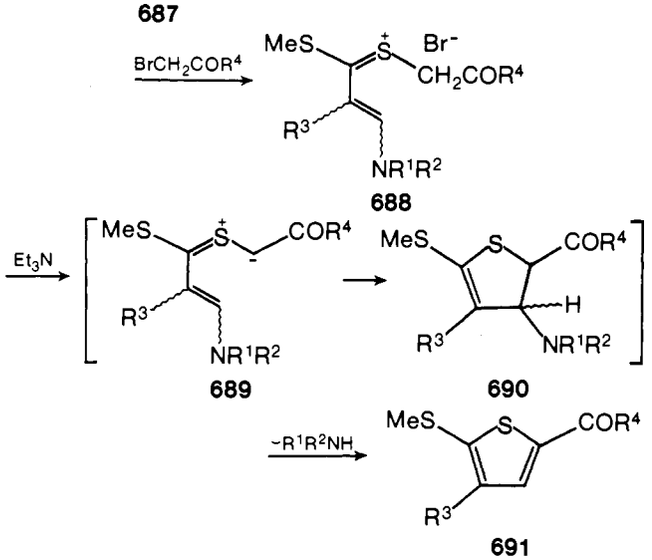
The formation of epoxides from the photooxidation of 1-substituted pyrroles is believed to involve a vinylcarbonyl oxide intermediate.[254] For example, 1-methyl-2,3,5-triphenylpyrrole (**681**) when irradiated using methylene blue as sensitizer affords benzoic acid (12%) and *cis*-dibenzoylstyrene oxide (**686**, 65%). The suggested mechanism for this conversion calls for ring opening of the initially formed bicyclic peroxide **682** to provide the vinylcarbonyl oxide **683** which gives 1,2-dioxol-3-ene **684** by a 1,5-electrocyclization. Rearrangement of **684** and subsequent hydrolysis of the *N*-methylimino functionality in **685** upon work-up leads to the observed product **686**.[254]



681 **682** **683** **684** **685** **686**



687



688 **689** **690** **691**

R^3 = H, R^4 = Me 70%
R^3 = H, R^4 = Ph 70%
R^3 = H, R^4 = 4-NO_2Ph 83%
R^3 = CN, R^4 = Me

F. Thiocarbonyl Ylides

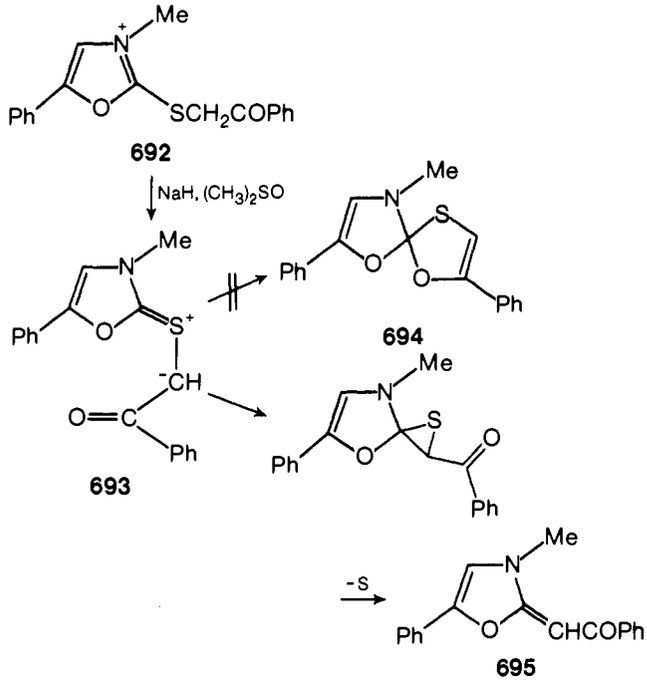
A review surveying the recent literature on azomethine, carbonyl, and thiocarbonyl ylides has appeared.[148]

1. *Vinylthiocarbonyl Ylides (Dihydrothiophenes)*

Methyl 3-aminodithioacrylates **687** are alkylated by α-halocarbonyl compounds to give the thionium salts **688**. Treatment of these salts with triethylamine results in deprotonation affording vinylthiocarbonyl ylides **689**. 1,5-Electrocyclization of **689** followed by elimination of R^1R^2NH from the initially formed dihydrothiophene **690** constitutes a synthesis of 2-acyl-5-methylthiophenes **691**.[255]

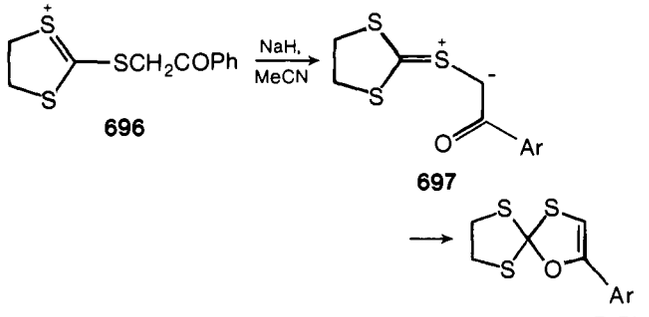
2. *Carbonylthiocarbonyl Ylides (1,3-Oxathiolenes)*

Treatment of the oxazolium salt **692** with base provides 2-phenazylidene-3-methyl-5-phenyl-1,3-oxazoline (**695**) rather than the spirooxathiolene **694**, the product expected from a 1,5-dipolar cyclization of the carbonylthiocarbonyl ylide **693**.[168]



692 **694** **693** **695**

On the other hand, oxathiolene **698** is produced when carbonylthiocarbonyl ylide **697** is generated by treating the salt **696** with sodium hydride in acetonitrile.[168] The factors governing the reactivity difference between the thiocarbonyl ylides **693** and **697** are not clear.



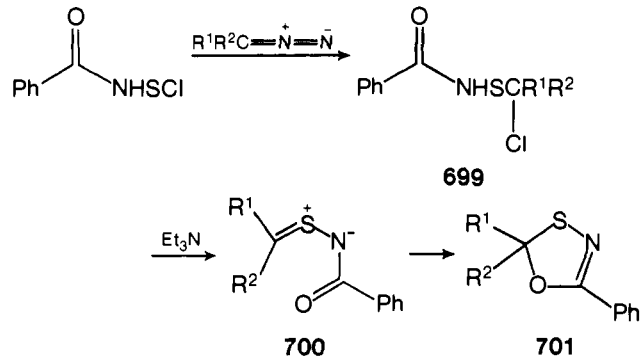
696 **697** **698**, Ar = 4-BrPh

G. Thiocarbonyl Imines

1. *Carbonylthiocarbonyl Imines*

N-Carbonyl (1,3,4-Δ^2-Oxathiazolines). Burgess and Penton have succeeded in generating one of the few reported examples of a thiocarbonyl imine.[256] Treatment of the *N*-benzoylchloro-

SCHEME LIV

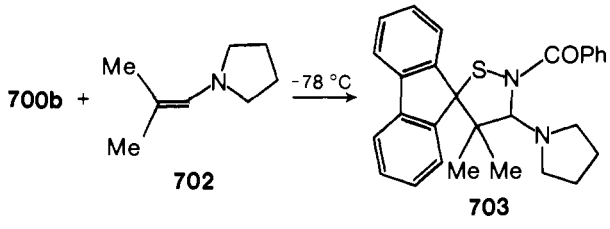


699

700 701

a. $R^1 = R^2 = Ph$, 31%
b. R^1,R^2 = 9-fluorenyl, 46%
c. $R^1 = H$, $R^2 = CO_2Et$

sulfenamides **699** (prepared as outlined in Scheme LIV) with triethylamine results in 1,3-elimination of HCl. The products isolated are 1,3,4-oxathiazolines **701** which derive from 1,5-dipolar cyclization of carbonylthiocarbonyl imines **700** (Scheme LIV). The thiocarbonyl imine **700b** has been isolated as a crystalline solid. It is instantaneously converted to **701b** upon mechanical deformation and reacts with HCl to give the sulfenamide precursor **699b.** When generated at −78 °C in the presence of *N*-isobutenylpyrrolidine **702,** thiocarbonyl imine **700b** yields the dipolar cycloadduct **703** (64%).[256] Attempts to trap **700a** with **702** failed to furnish an adduct; only **701a** could be isolated.

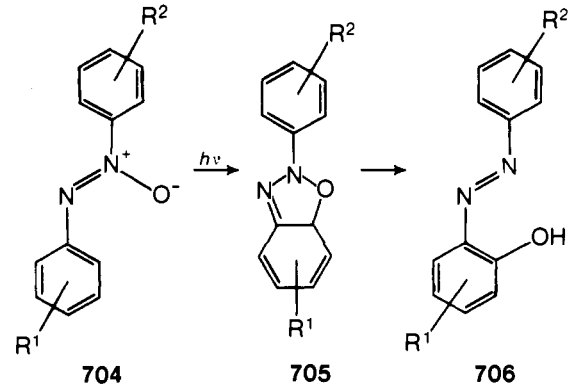


702 703

H. Azoxy Compounds and Azimines

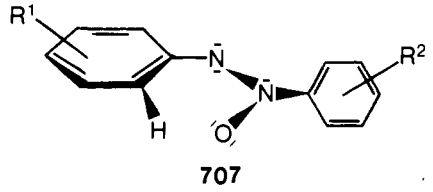
1. *Vinylazoxy Compounds (1,2,3-Δ³-Oxadiazolines)*

The photochemical conversion of azoxybenzenes **704** to hydroxyazo compounds **706** (Wallach rearrangement) most probably occurs by a 1,5-dipolar cyclization of excited **704** to provide the oxadiazoline intermediates **705.** Subsequent ring opening of **705** affords the *o*-hydroxyazo compounds **706.** Reviews of earlier work delineating the scope and gross mechanistic features of this process have appeared.[257,258] Bunce and his co-workers have recently explored the details of the azoxybenzene–hydroxyazobenzene photoisomerization.[259] They found that a low-lying n–π^* singlet excited state of **704** is involved. Substituent effects on the rate of this photoprocess suggest that attack by the azoxy oxygen on the more distant



704 705 706

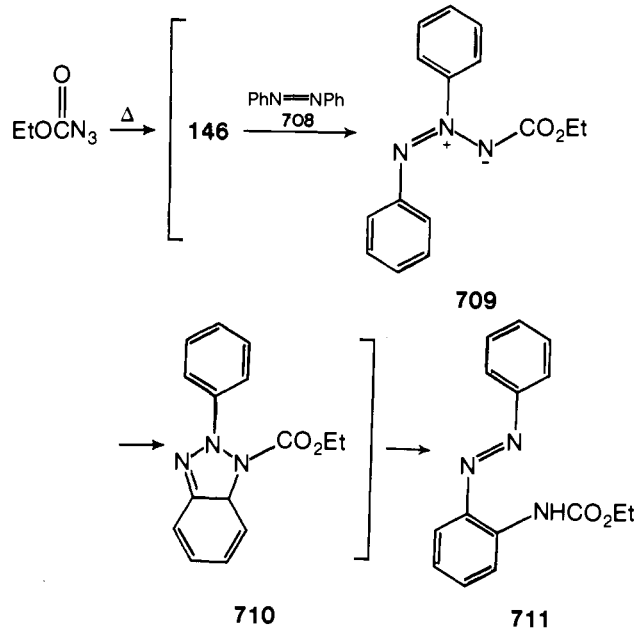
aromatic ring is electrophilic in nature. Furthermore, these workers argued on the basis of their results that the structure of the excited state of **704** responsible for cyclization may be crudely represented by **707.**



707

2. *Vinylazimines (1,2,3-Δ³-Triazolines)*

The major product (formed in 3–10% yield) when ethyl azidoformate is thermolyzed (**117** °C) in the presence of azobenzene **708** is ethyl 2-(phenylazo)carbanilate (**711**).[260] Unchanged **708** was recovered in 78% yield. Under the reaction conditions ethyl azidoformate is believed to decompose to ethoxycarbonyl nitrene (**146**) which combines with **708** to provide azimine **709.** 1,5-Electrocyclization of **709** yields triazoline **710** which suffers ring cleavage to give the observed product **711.** This ground-state process is thus analogous to the photorearrangement of azoxybenzenes to hydroxyazobenzenes described above.



709 710 711

IV. Addendum

Extensive calculations on nitrile ylides[261,262] and other 1,3-dipoles[263,264] have been reported by Houk and co-workers. These investigators and others have developed powerful predictive theories of 1,3-dipolar cycloaddition reactions.[265]

2-Isocyano-*N*-isopropylacetanilide and 4-cyclohexylthio-2,6-dimethylmorpholine combine to provide 2-cyclohexylthio-5-(*N*-isopropylanilino)oxazole in 63% yield. The oxazole is believed to arise by a 1,5-electrocyclization of carbonylnitrile ylide **31** ($R^1 = C_6H_{11}S$, $R^2 = H$, $R^3 = NPh\text{-}i\text{-}Pr$).[266]

The thermal conversion of the (*Z*)-vinyl-1-azirines **74** to the tetraphenyloxazepins **76** has been discussed in terms of a concerted mechanism not involving nitrile ylides **75** (section II.A.3).[267]

Flash vacuum pyrolysis of 2-methyl-4-phenyl-1,3,4-oxadiazolin-5-one gives 3-methylindazole (89%) presumably by a 1,5-dipolar cyclization of *C*-methyl-*N*-phenylnitrile imide followed by tautomerization of the initially formed 3*H*-indazole.[268]

1,5-Diazabicyclo[3.3.0]octadienediones arise upon treatment

of 4-chloropyrazol-5-ones with base. Dehydrochlorination of the latter to give 2,3-diazacyclopentadienones followed by 1,5-electrocyclic ring opening yields 2-diazoketenes. The resulting diazoketones dimerize with elimination of nitrogen to afford the observed syn and anti forms of the diazabicyclooctadienediones.[269]

Anselme et al. reported that the manganese dioxide oxidation of 4,5-diphenyl-1,2-diaminoimidazole gives 3-amino-5,6-diphenyl-1,2,4-triazine (62%) and smaller amounts of other products including the iminodiazomethane **212** ($R^1 = R^2 = Ph$, $R^3 = CN$).[270] These authors stated that this iminodiazomethane could be in equilibrium with 1-cyano-4,5-diphenyl-1,2,3-triazole (**213**, $R^1 = R^2 = Ph$, $R^3 = CN$).

Diazotization of 3-hydrazinoquinoxaline 1-oxide or treatment of 3-chloroquinoxaline 1-oxide with sodium azide produces tetrazolo[1,5-*a*]quinoxaline 45-oxide (46–60%) via 1,5-electrocyclization of 3-azidoquinoxaline 1-oxide.[271]

Thermal electrocyclic ring opening of the tetrazole in 5-(2-quinolyl)-9-methyl-*s*-triazolo[4,3-*c*]tetrazolo[1,5-*a*]pyrimidine (175 °C) leads to the corresponding iminoazide (not isolated) which suffers loss of nitrogen to afford [4-methylquinolino[2,1-*d*]-1,2,4,5,6-pentazacycl[2.3.3]azine (96%).[272]

A kinetic investigation of the thermal decomposition of 5-phenyl-1,2,3,4-thiatriazoles suggests that the products (benzonitrile, N_2, and S) arise by a three-step mechanism involving (*E*)-thiobenzoyl azide.[273]

Further studies on the pyrolytic ring opening of the 1,2-diazabicyclo[3.2.0]hept-3-ene system **597** to the cyclic *C*-vinylazomethine imine **598** (section III.B.2) and its subsequent reactions have been reported.[274]

Eberbach and co-workers have recently described further studies concerning the mechanism and stereochemistry of the vinyloxirane–dihydrofuran ring expansion which occurs via the intermediacy of vinylcarbonyl ylides.[275,276]

Photolysis of 4-methoxychalcone oxide promotes carbon–carbon bond cleavage of the epoxide ring leading to the corresponding carbonylcarbonyl ylide. 1,5-Electrocyclization of this intermediate affords 2-(4-methoxyphenyl)-4-phenyl-1,3-dioxole.[277] On the other hand, chalcone oxide gives dibenzoylmethane upon irradiation which is assumed to arise from cleavage of the C_α–O bond of the epoxide ring.[277]

In refluxing benzene, azibenzil and thiobenzophenone yield 2,2,4,5-tetraphenyl-1,3-oxathiole (31%) and 3,3,4,4-tetraphenylthietan-2-one (8%). The 1,3-oxathiole could be formed in a 1,5-dipolar cyclization of 1,3,3-triphenyl-1-benzoylthiocarbonyl ylide.[278]

N,N'-Dimethylimidazole-2-thione *S*-carbomethoxymethylide does not appear to undergo a 1,5-dipolar cyclization but acts as a quasi-Wittig reagent, affording α,β-unsaturated esters with aldehydes.[279]

Further details of the mechanism of the photochemical azoxybenzene–hydroxyazobenzene rearrangement (section III.H.1) have been elucidated.[280]

V. References

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