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Reactions of Heterocyclic Compounds with Nitrilimines and Their Precursors

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Contents

I. Introduction

A large and valuable store of review literature on many aspects of the chemistry of heterocyclic compounds has grown up over the last few decades.[1] However, the dipolarophilicity of these compounds has not yet been discussed in the available reviews, monographs, and modern treatises. Furthermore, it is worthwhile noting that although there are several comprehensive summaries on the 1,3-dipolar cycloaddition reactions of nitrilimines 1 with various

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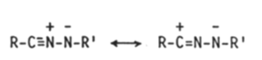
dipolarophiles,[2-7] their reactions with heterocyclic compounds were not included.

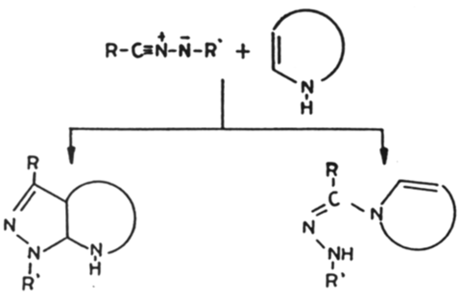


$$R-C\equiv\overset{+}{N}-\overset{-}{N}-R' \longleftrightarrow R-\overset{+}{C}=N-\overset{-}{N}-R'$$

1

R/R' : a, Ar/Ar'; b, Alkyl/Ar'; c, H/Ar'; d, ArCH=CH/Ar'; e, CH_3CO/Ar; f, ArCO/Ar'; g, ROCO/Ar'; h, ArNHCO/Ar'; i, Het/Ar'; j, HetCO/Ar'; k, $ArSO_2$/Ar'; l, Ar/Alkyl; m, Ar/Ar'CO; n, Ar/COOEt; o, Ar/Het; p, Ar/SO_2Ar'

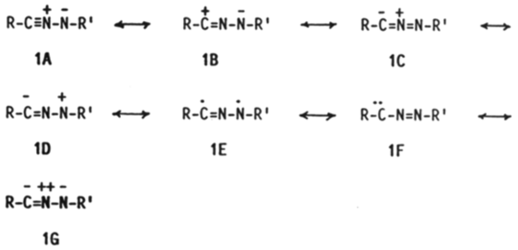
In general, nitrilimines react with heterocyclic dipolarophiles with two modes, namely the 1,3-dipolar cycloaddition and the 1,3-electrophilic addition, as indicated below. Significant amounts of the 1,3-addition product are usually formed when the dipolarophilic activity of the heterocyclic reactant is remarkably decreased as in the case of the more heteroaromatics like imidazole (section III.D.2) and benzimidazoles (section III.I.2).



1,3-Cycloadduct 1.3 -Adduct

The present article will outline these reactions. It will emphasize the issues of reactivity and regiochemistry in the 1,3-dipolar cycloadditions of nitrilimines to heterocyclic dipolarophiles. It is not intended to document all compounds prepared by such reactions or to review the reactions of nitrilimines with compounds bearing the heterocycle as simply a substituent. The literature is covered up to the mid-1993. The reactions are cited according to the size and number of rings in the heterocyclic reactant, and within each group the order of citation is according to the type and number of the heteroatoms present.

Basically a nitrilimine is a flexible system of three atoms over which four π-electrons are distributed. Although one can write the seven possible structures **1A–G** for such a system, theoretical calculations[2] have indicated that the all-octet–zwitterionic structure **1A** is the most stable contributor to the resonance hybrid. Therefore, this formula is the one that is used throughout this review. The sextet structure **1B** with its complementary nucleophilic and electrophilic centers is the classical 1,3-dipolar formula which expresses the 1,3-dipolar cycloaddition properties of nitrilimines.



$$R-C\equiv\overset{+}{N}-\overset{-}{N}-R' \longleftrightarrow R-\overset{+}{C}=N-\overset{-}{N}-R' \longleftrightarrow R-\overset{-}{C}=\overset{+}{N}=N-R' \longleftrightarrow$$

1A 1B 1C

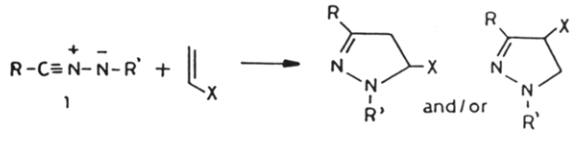
$$R-\overset{-}{C}=N-\overset{+}{N}-R' \longleftrightarrow R-\dot{C}=N-\dot{N}-R' \longleftrightarrow R-\ddot{C}-N=N-R' \longleftrightarrow$$

1D 1E 1F

$$R-\overset{-}{C}=\overset{++}{N}-\overset{-}{N}-R'$$

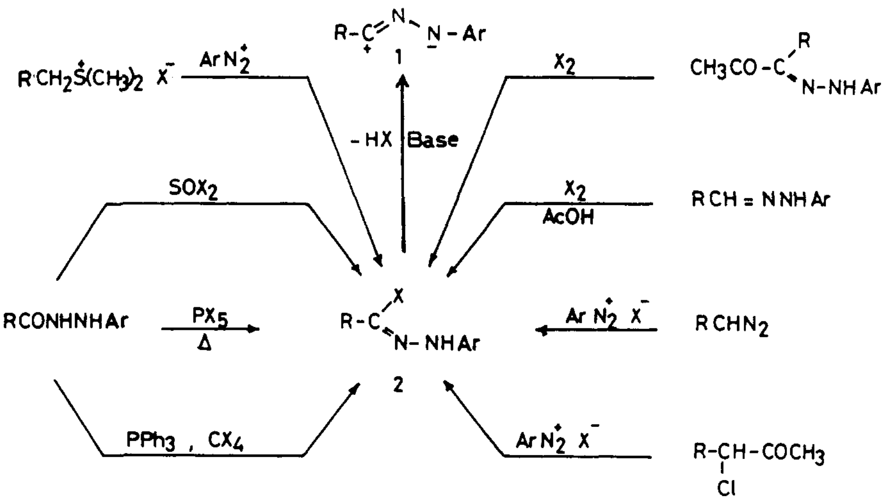
1G

The 1,3-dipolar cycloaddition reactions of nitrilimines are generally $[\pi_s^4 + \pi_s^2]$ thermally allowed pericyclic reactions. Use of a dipolarophile having nonidentical terminal π-centers such as monosubstituted ethylenes in such reactions with nitrilimines can lead theoretically to two orientationally different cycloadducts (referred to as regioisomers), namely the 5- and 4-substituted 2-pyrazolines. Experimentation showed, however, that the orientation observed for alkenes substituted with electron-donor, conjugating, and moderate electron-acceptor substituents is the 5-substituted regioisomers.[8] Sometimes the cycloadditions of nitrilimines to very electron-deficient alkenes give significant amounts of the 4-substituted 2-pyrazolines.[9]



The rationalization of such regiochemical results became evident in terms of the frontier molecular orbital (FMO) theory of Fukui[10] and its applications by the groups of Sustmann,[11] Houk,[12] and Bastide.[13] According to this theory, the 1,3-dipolar cycloaddition of a given 1,3-dipole can be controlled by either HOMO(dipole)–LUMO(dipolarophile) interaction or HOMO(dipolarophile)–LUMO(dipole) interaction according to the relative dispositions of the HOMOs and LUMOs of the 1,3-dipole and the dipolarophile. The dominant interaction is the one that involves orbitals which are much closer in energy. When the energy differences between the two HOMO–LUMO pairs are equal, the cycloaddition process is said to be controlled by both types of HOMO–LUMO interactions. In each of these

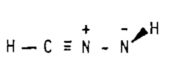
Scheme I



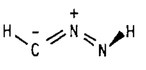
three cases, the reactivity increases as the HOMO–LUMO energy distance decreases.

Prediction of the regiochemistry of the cycloaddition necessitates the knowledge of the orbital coefficients in the FMOs of both the nitrilimine and the dipolarophile and the application of the so-called Fukui's rule which states that the cycloaddition takes place in the direction of maximal HOMO–LUMO overlap. The latter will result only when orbitals of similar magnitudes overlap with each other, i.e. large with large and small with small.

The relative magnitudes of the coefficients of the FMOs of a nitrilimine depend on its geometry. Being a flexible species, a given nitrilimine can adopt two possible geometries, namely the planar and the bent structures **1H** and **1I**, respectively.[14] Although, it is not clear what precise geometry nitrilimines adopt at equilibrium, theoretical calculations on formonitrilimine revealed that the planar form has the large HOMO and LUMO coefficients at the N- and C-termini, respectively.[14] In the bent structure the relative coefficient magnitudes at the C- and N-termini are reversed.[14] As bending must occur to some extent in the transition state for a concerted cycloaddition, it could be speculated, on the basis of the foregoing results, that bending of a nitrilimine increases the nucleophilicity of the carbon terminus at the expense of that of the nitrogen end and a change of the regiochemistry of the cycloaddition to very electron-deficient dipolarophiles may result.[14]



1H



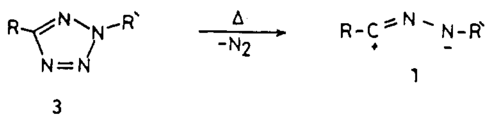
1I

Also, it is worthy to mention that the cycloaddition of nitrilimines proceeds with retention of configuration at the terminal centers of the dipolarophile, provided the latter is configurationally stable under the reaction conditions. This stereospecifity is usually considered as evidence for the concertedness of the cycloaddition process.[2]

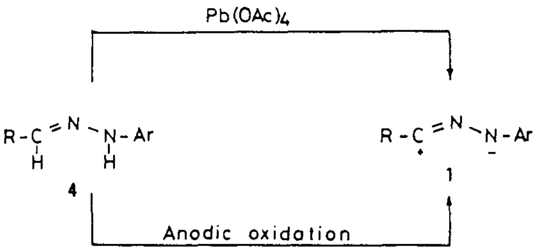
II. Precursors of Nitrilimines

Due to their instability, the reactions of nitrilimines **1** are always performed by their in situ generation from the appropriate precursors. Of these, the hydrazonyl halides **2** are the most widely used precursors of **1**, as they are readily accessible from different sources (Scheme I).[15] Generation of nitrilimines **1** from the halides **2** is usually effected by the treatment of the latter with a base such as triethylamine in an inert solvent.[16-18] The mechanism of this base-induced elimination reaction has been studied.[16-22] Dehydrohalogenation of **2** to give **1** can also be effected by silver nitrate.[23-25]

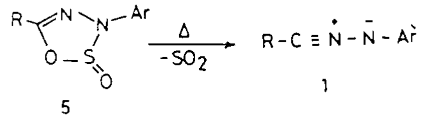
The second most commonly used precursors of **1** are the 2,5-disubstituted tetrazoles **3**. Some of these precursors are easily available; however, they all involve preparation and handling of somewhat hazardous azides.[17] Both thermolysis[26-28] and photolysis[29-32] of **3** proved to be convenient methods for generation of **1**.



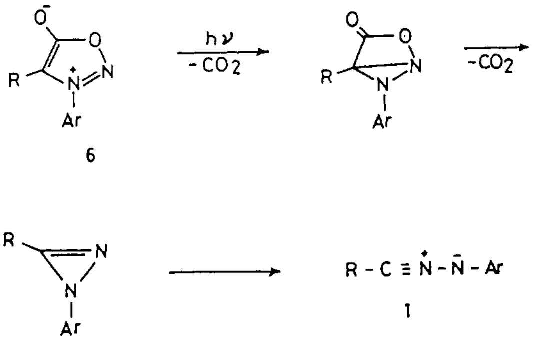
Aldehyde arylhydrazones **4**, which are easily prepared by condensation of aldehydes with arylhydrazines, are also used as nitrilimine precursors. Generation of **1** from **4** can be effected either chemically by their dehydrogenation with lead tetraacetate[33-35] or electrolytically by their anodic oxidation.[36-40]



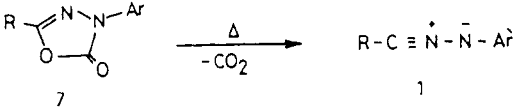
3*H*-1,2,3,4-Oxathiadiazole *S*-oxides **5** are usually prepared by treatment of the corresponding hydrazides with a thionyl chloride–pyridine mixture in anhydrous ether. Thermolysis of **5** in toluene results in the elimination of sulfur dioxide and the formation of the corresponding nitrilimines **1**.[41]



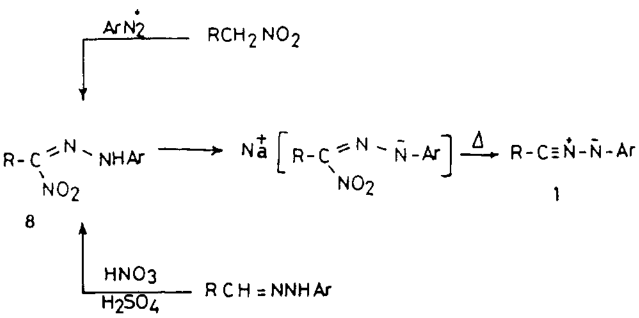
3,4-Disubstituted sydnones **6** are also used as nitrilimine precursors. They are usually prepared from *N*-nitroso derivatives of *N*-alkyl- (or *N*-aryl-) α-amino acids.[42] Photolysis of **6** leads to the corresponding nitrilimines **1**.[43-50]



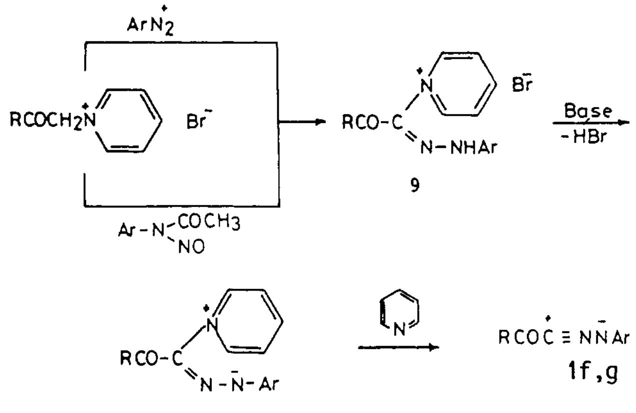
Δ²-1,3,4-Oxadiazolin-5-ones **7** were shown to afford **1** upon flash vacuum thermolysis.[51,52] The major route to such precursors is the thermal cyclization of acylhydrazinecarboxylic acid derivatives. Acid chlorides of the latter acids are conveniently prepared from acylhydrazines and phosgene and they are usually cyclized in situ.



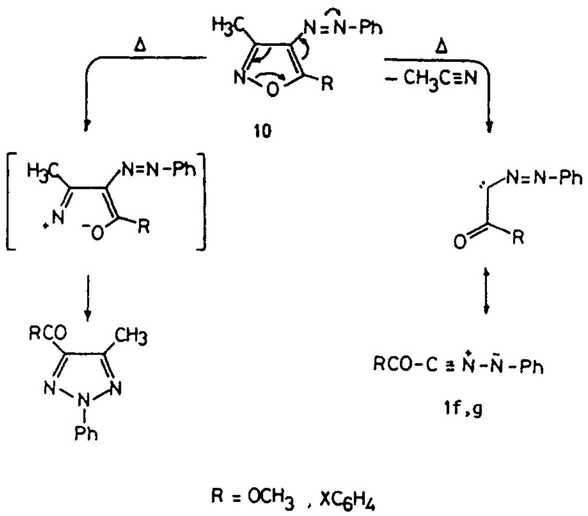
α-Nitrohydrazones **8** have also been used as precursors for nitrilimines **1**. They are usually prepared by either direct nitration of the corresponding aldehyde arylhydrazones[19,53] or azo coupling of the corresponding nitroalkanes with diazotized anilines.[54-56] Thermolysis of the sodium salts of **8** yields the corresponding nitrilimines **2**.[54,55]



N-(α-Arylhydrazoacyl)pyridinium bromides **9** are usually prepared by the azo coupling of *N*-(acylmethyl)pyridinium bromides with diazotized anilines[57] or *N*-nitrosoacetanilides.[58] Thermolysis of the pyridinium betaines, generated by the action of bases on **9**, leads to the corresponding nitrilimines **1f,g**.[59]



The thermal decomposition of 5-aryl-4-arylazoisoxazoles **10** leads to two competitive reactions.[33] The cleavage of the N–O bond gives a triazole derivative via the known Wittig rearrangement, where the 1,3-dipolar cycloreversion gives nitrilimines **1f,g**.[60,61]

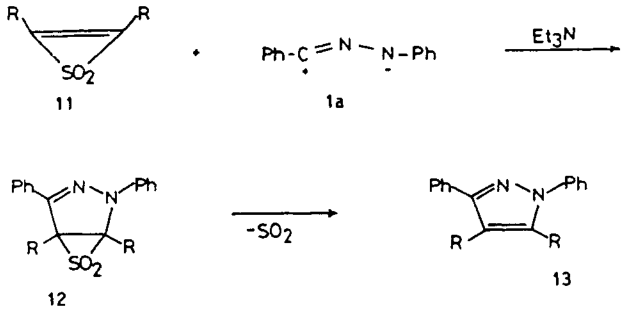


III. Reactions

A. Reactions of Three-Membered Heterocycles with One Heteroatom

1. Thiirene 1,1-Dioxides

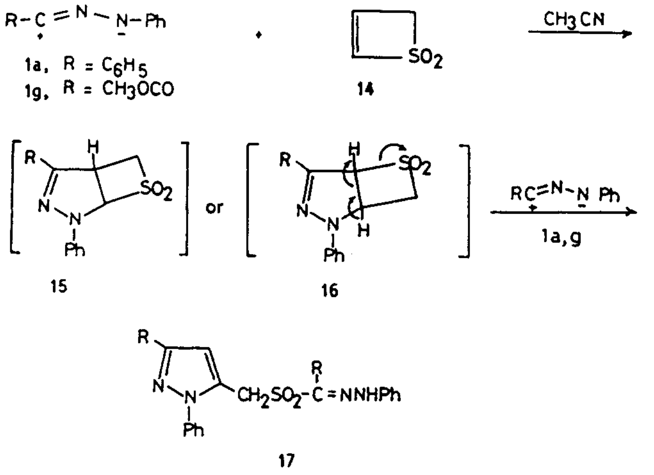
So far only one report has dealt with the behavior of three-membered heterocycles toward nitrilimines. Thus, reaction of diphenylnitrilimine (**1a**) with 2,3-disubstituted thiirene dioxides **11** in benzene affords the pyrazole derivatives **13**, probably via loss of sulfur dioxide from the intermediate cycloadducts **12**.[62] This reaction is similar to the reaction between thiirene dioxides and diazomethane that also leads to pyrazole derivatives.[63]



B. Reactions of Four-Membered Heterocycles with One or More Heteroatoms

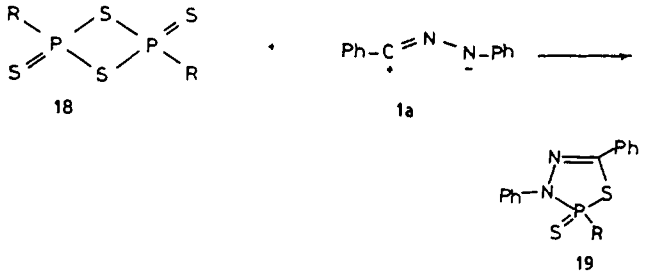
1. Thiete 1,1-Dioxide

Thiete 1,1-dioxide reacts with nitrilimines **1a** and **1g** in acetonitrile to give the pyrazole derivatives **17a** and **17b**, respectively.[64,65] It was assumed that the reaction involves the formation of the bicyclic intermediate **15** or **16** which reacts then with another molecule of nitrilimine by splitting the C–SO_2 bond to yield the corresponding pyrazole derivative **17**.



2. 2,4-Diphospha-1,3-dithietanes

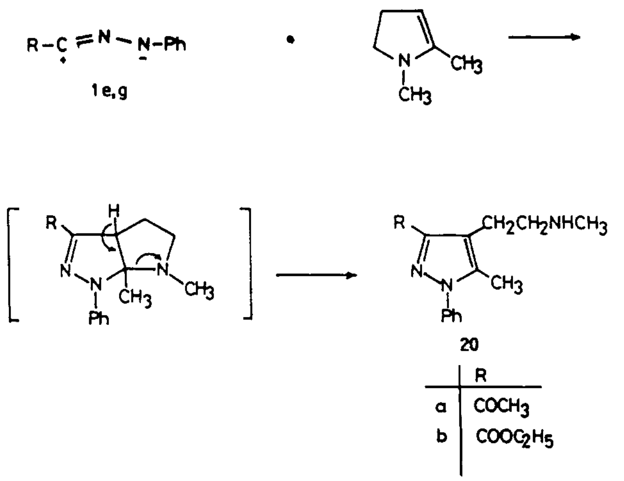
Perthiophosphonic anhydrides **18** react with diphenylnitrilimine (**1a**) in benzene and yield the corresponding 1,3,4,2-thiadiazaphospholine-2-thiones **19**.[66]



C. Reactions of Five-Membered Heterocycles with One Heteroatom

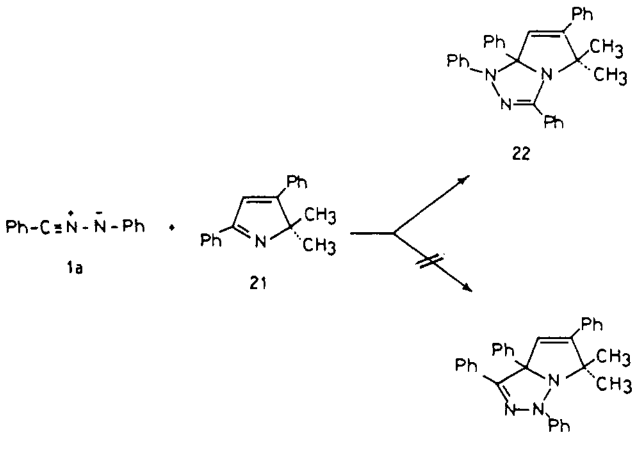
1. Pyrroles

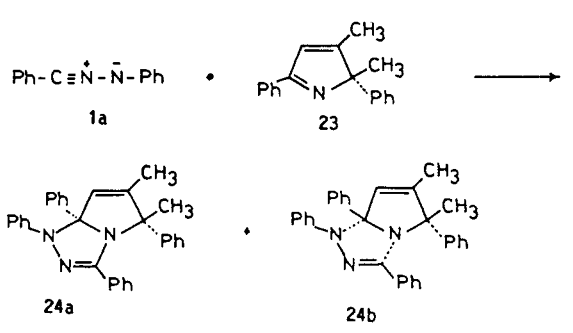
Reactions of 1,2-dimethyl-4,5-dihydropyrrole with the nitrilimines **1e** and **1g** were reported to yield 1-phenyl-5-methyl-4-[2-(methylamino)ethyl]pyrazoles **20a** and **20b**, respectively.[67]



	R
a	$COCH_3$
b	$COOC_2H_5$

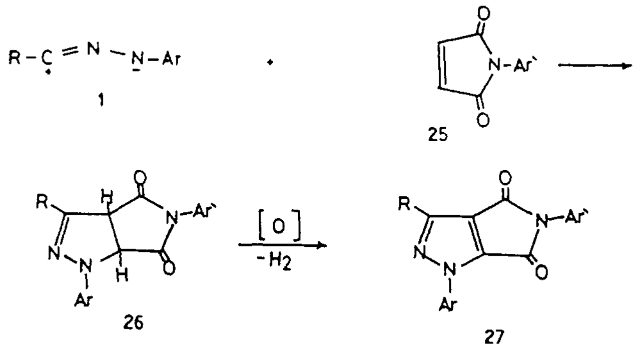
The reaction of diphenylnitrilimine **1a** with 2,2-dimethyl-3,5-diphenyl-2*H*-pyrrole (**21**) was reported to be completely regioselective, yielding the cycloadduct **22**.[68] However, the reaction of **1a** with 2,3-dimethyl-2,5-diphenyl-2*H*-pyrrole (**23**) yielded a mixture of the two diastereoisomers **24a** and **24b** in a ratio of 16:84, respectively.[68]

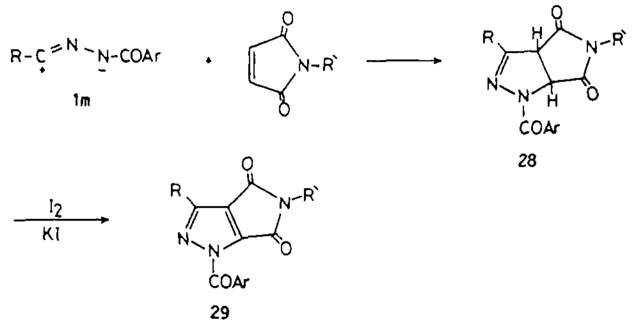




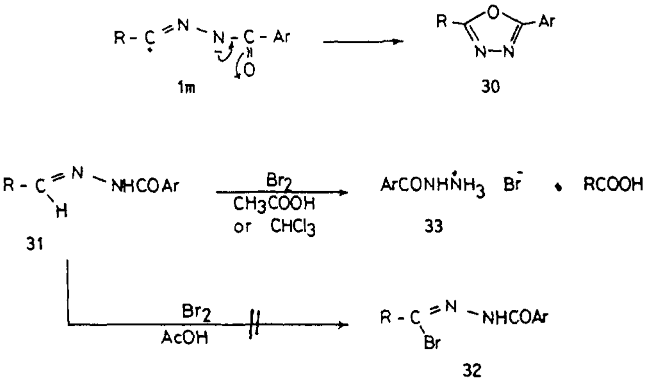
N-Arylnitrilimines **1a** cycloadd to *N*-arylmaleimides (**25**) in benzene, chloroform, or ethanol to give the corresponding pyrrolo[3,4-*c*]pyrazoline derivatives **26**, which can be dehydrogenated with chloranil in refluxing xylene to afford the pyrrolo[3,4-*c*]pyrazole-4,6-diones **27**.[69-78]

Recently, it was reported that maleimide and *N*-phenylmaleimide react with *N*-aroylnitrilimines **1m** to yield the cycloadduct **28**, which was converted into the





pyrrolopyrazole derivatives **29** upon treatment with iodine and potassium iodide.[79] This result seems surprising, as nitrilimines of type **1m** are known to undergo intramolecular cyclization as soon as they are generated to give the oxadiazole derivatives **30**.[80–83] Furthermore, the precursors of the nitrilimines **1m**, namely *N*-(2,4-dichlorobenzoyl)hydrazonyl bromides **32**, which were claimed to be formed by bromination of the corresponding hydrazones **31**, were not characterized.[79] In addition, all previous attempts to prepare hydrazonyl bromides of type **32** by direct bromination of **31** with bromine in acetic acid or in chloroform led to the cleavage of the hydrazone and yield the hydrobromide salts of aroylhydrazines **33**.[84]

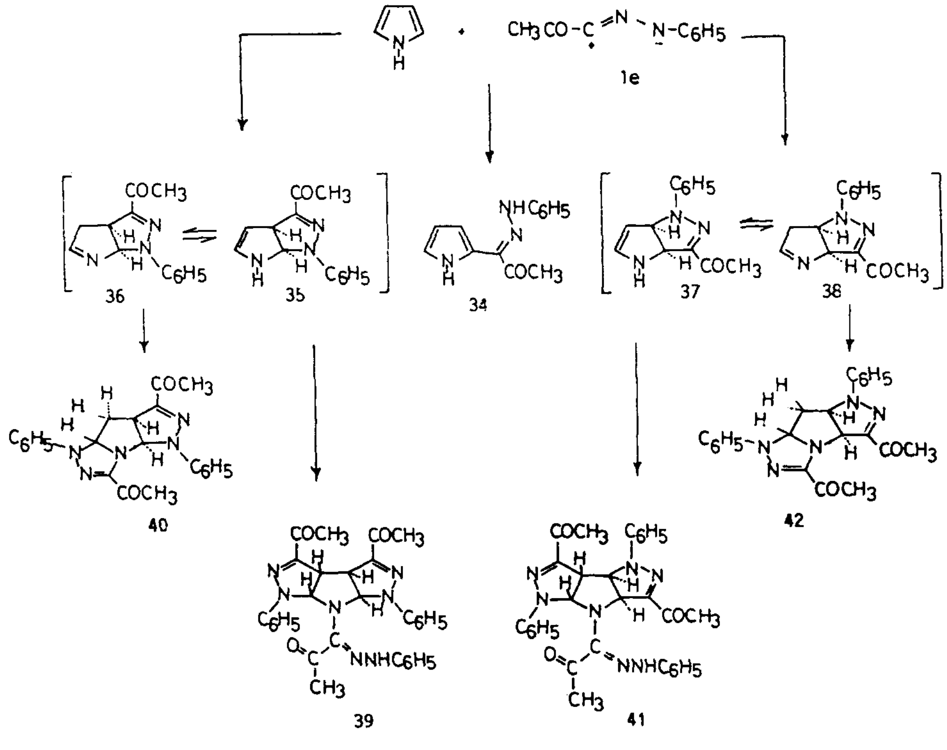


The reaction of **1e** with unsubstituted pyrrole was reported to give a mixture of the 1,3-addition product **34** and the biscycloadducts **39–42**.[85] The intermediate monocycloadducts **35–38** that lead to the biscycloadducts **39–42** were not isolated, however (Scheme II).

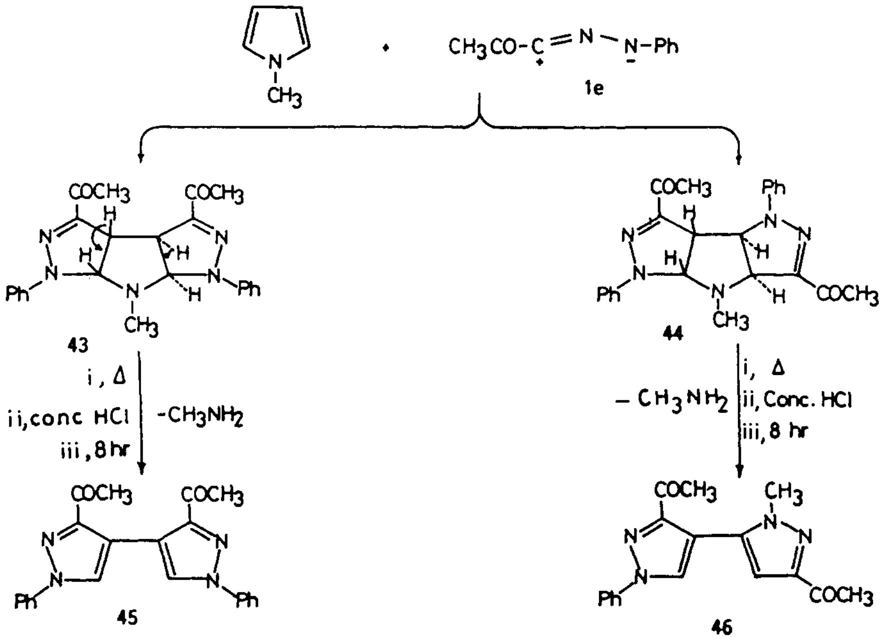
N-Methylpyrrole reacts with *C*-acetyl-*N*-phenylnitrilimine (**1e**) to give a complex reaction mixture from which the double addition products **43** and **44** in 3:1 ratio, respectively, were isolated.[86] Dissolution of **43** in ethanol followed by treatment with concentrated hydrochloric acid yields methylamine and 4,4′-bipyrazolyl derivative **45**. Similarly, the biscycloadduct **44** was converted into **46** when boiled in concentrated hydrochloric acid[86] (Scheme III).

1,2-Dimethylpyrrole reacts with **1e** to give four different products, namely the biscycloadducts **47** and **48**, the spirocycloadduct **49**, and the acyclic bisadduct **50**.[87] The other expected spirocycloadduct **51** was not formed, however. The product **50** arises probably through ring–chain tautomerism of **47**, whereas **49** results from the cycloaddition to the C=C double bond

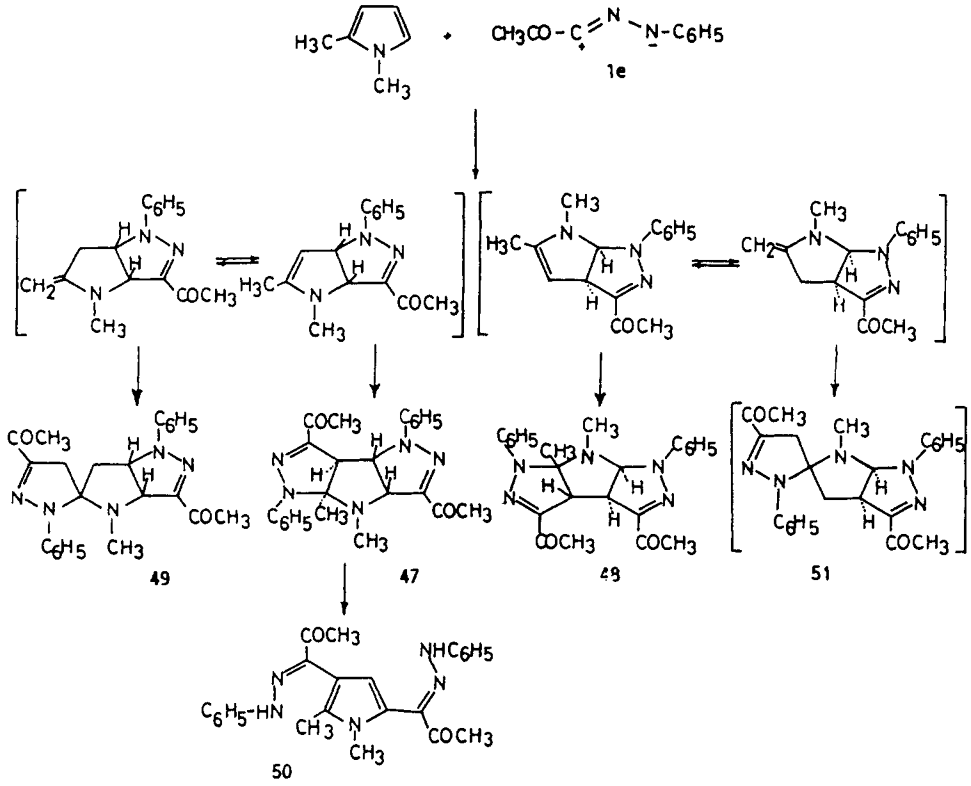
Scheme II



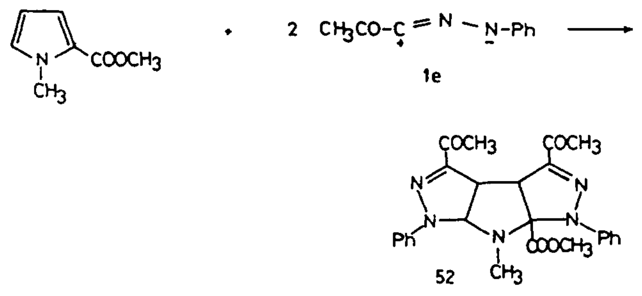
Scheme III



Scheme IV



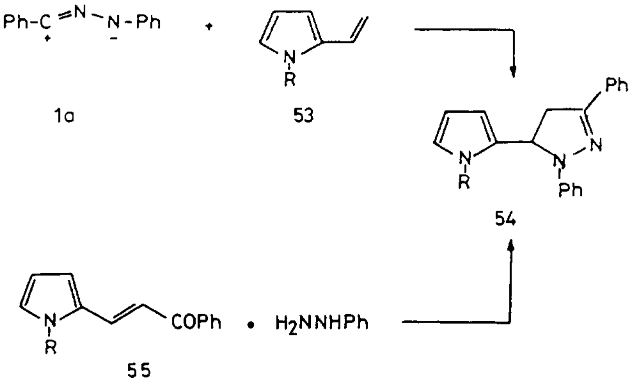
of the methylene tautomer of the preceeding monocycloadduct[87] (Scheme IV).



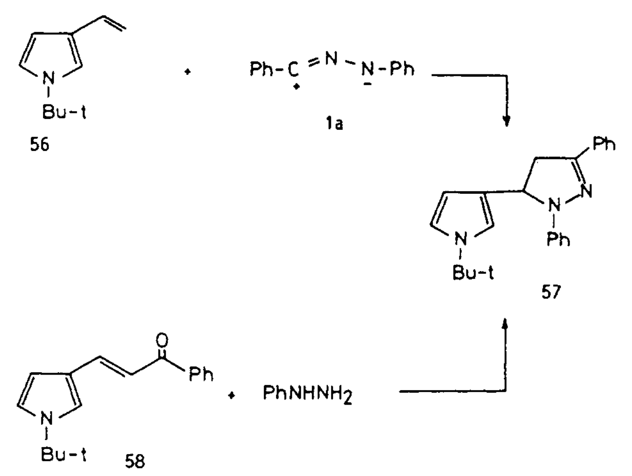
The reaction of methyl 1-methylpyrrole-2-carboxylate with **1e** leads only to a single bicycloadduct, **52**.[87]

Diphenylnitrilimine (**1a**) adds regioselectively to 1-substituted 2-vinylpyrrole derivatives **53** (R = CH_3, C_6H_5) and yields the cycloadducts **54** in high yields.[88] The structure of the latter cycloadducts was identified by their synthesis from the ketones **55** (R = CH_3, C_6H_5) and phenylhydrazine.[88]

Similarly, the 2-pyrazoline derivative **57** was obtained from the reaction of 1-*tert*-butyl-3-vinylpyrrole (**56**) with diphenylnitrilimine (**1a**).[88] The same product **57**

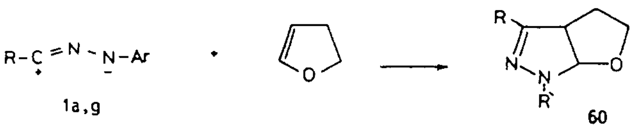


was also produced by the reaction of phenylhydrazine with the ketone **58**.[88]

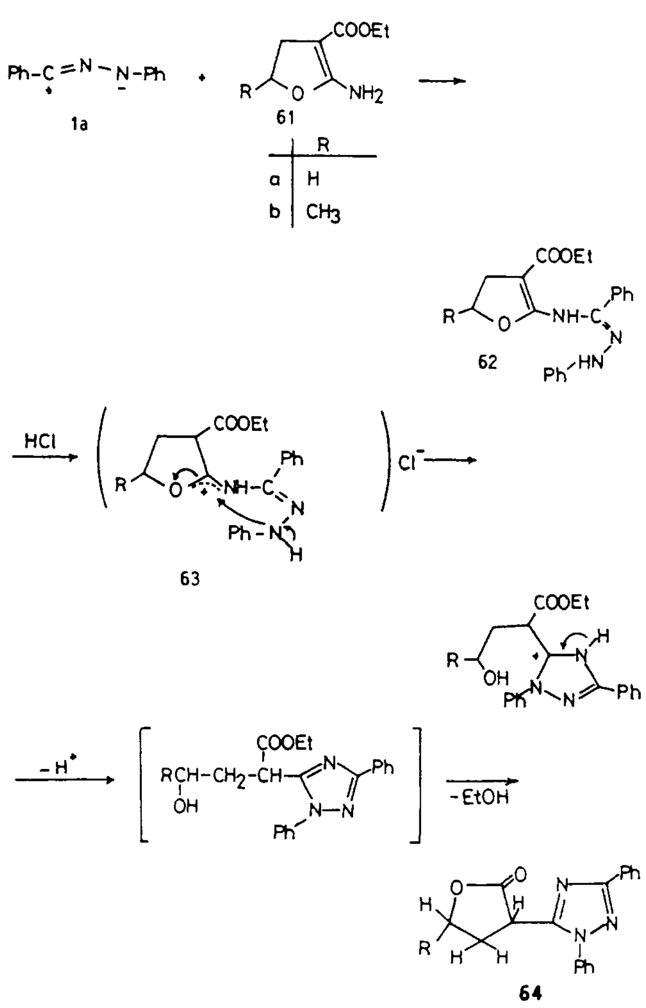


2. Furans

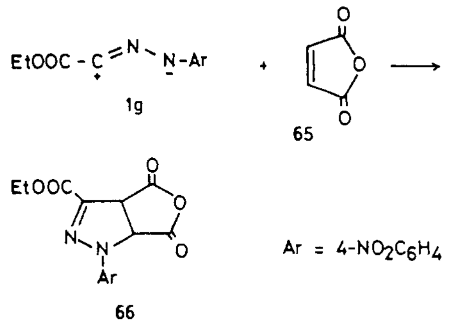
Reactions of 2,3-dihydrofuran with the nitrilimines **1a** and **1g** yielded regioselectively only 2,4-diaryl-2,3-diaza-8-oxacyclo[3.3.0]-3-octene derivatives **60a** and **60b**, respectively.[89]



2-Amino-3-(ethoxycarbonyl)-4,5-dihydrofuran (**61a**) and its 5-methyl derivative **61b** react with the nitrilimine **1a** to yield the corresponding α-triazolyl-γ-butyrolactones **64a** and **64b**, respectively.[90] The latter products were assumed to result from ring cleavage and rearrangement of the intermediate 1,3-adduct **62**.

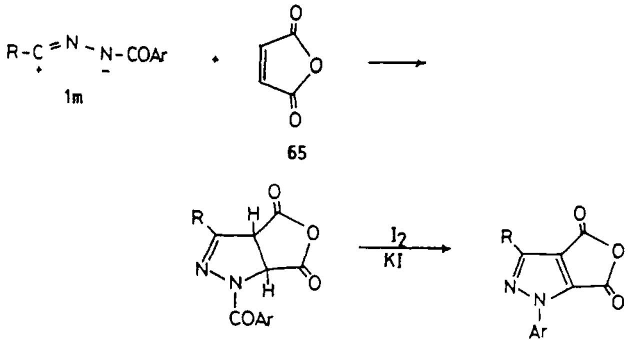


C-(Ethoxycarbonyl)-*N*-arylnitrilimines **1g** cycloadd to maleic anhydride and yield the corresponding cycloadducts **66** in 40% yield.[91]

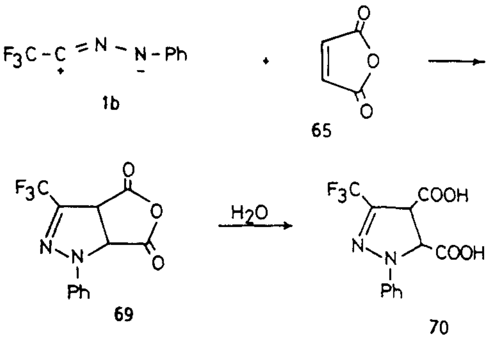


Recently, it was reported that *N*-acylnitrilimines **1m** react similarly with maleic anhydride (**65**) to give the corresponding 1-acylfuro[3,2-*c*]pyrazoline-4,6-diones **67**, which underwent dehydrogenation upon treatment with iodine and potassium iodide to give the furopyrazole derivatives **68**.[79] Such a result should be accepted with some reservations due to the fact that the precursors of **1m** were not characterized and it is well-known that nitrilimines of type **1m** undergo intramolecular cyclization as soon as they are formed to give the corresponding oxdiazole derivatives.[80-83]

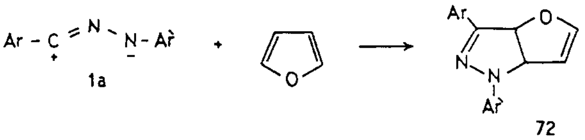
The reaction of *C*-(trifluoromethyl)-*N*-phenylnitrilimine (**1b**) with maleic anhydride yields the dicarboxylic acid **70** directly.[92] It was postulated that the initially

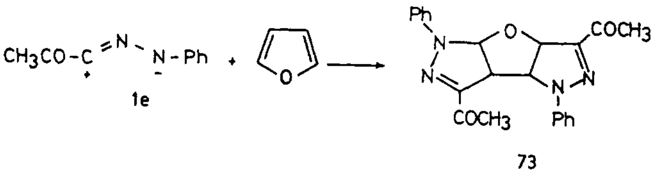


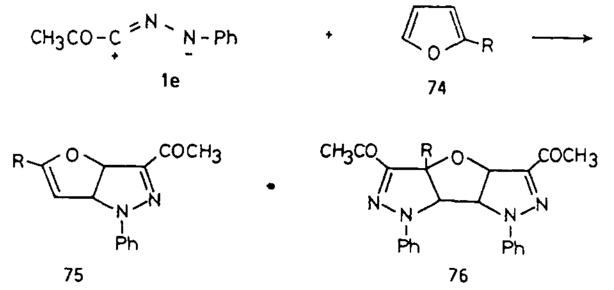
formed cycloadduct **69** underwent hydrolysis during the workup procedure.



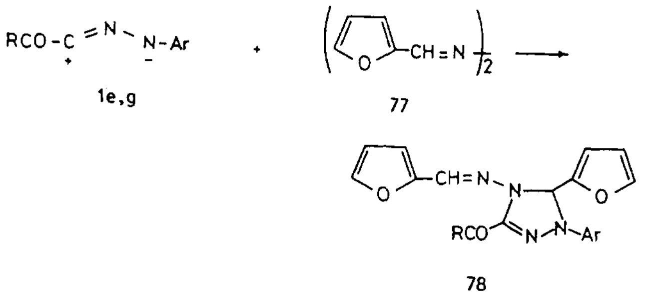
Unsubstituted furan reacts with diarylnitrilimines **1a** and *C*-acetyl-*N*-phenylnitrilimine (**1e**) to give the monocycloadduct **72** and the biscycloadduct **73**, respectively.[93,94] On the other hand, mixture of the mono- and bis-cycloadducts **75** and **76** was isolated from the reaction of 2-alkylfurans and *C*-acetylnitrilimines **1e**.[94]



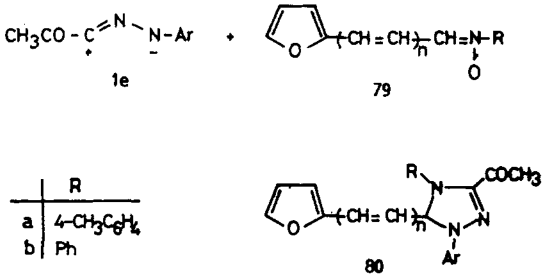




The C=N double bond of the azomethine derivatives of furfuraldehyde seems to be more reactive than the furan ring C=C double bond. Thus, *C*-acetyl- and *C*-(ethoxycarbonyl)nitrilimines **1e** and **1g** react with furfuraldehyde azine and yield the 1:1 cycloadducts **78a** and **78b**, respectively.[95]



Similarly, the nitrone derivatives of furfuraldehyde and furfurylideneacetaldehyde **79a,b** react with *C*-acetyl-*N*-arylnitrilimines (**1e**) to yield the corresponding triazoline derivatives **80**.[95]

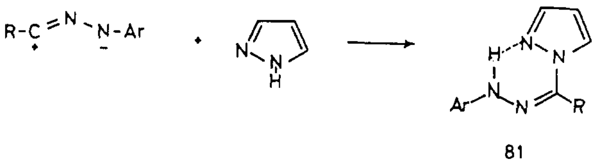


	R
a	4-$CH_3C_6H_4$
b	Ph

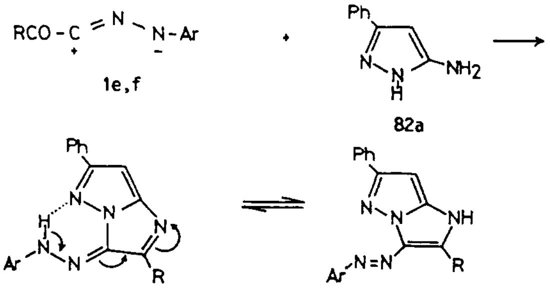
D. Reactions of Five-Membered Heterocycles with Two Heteroatoms

1. Pyrazoles

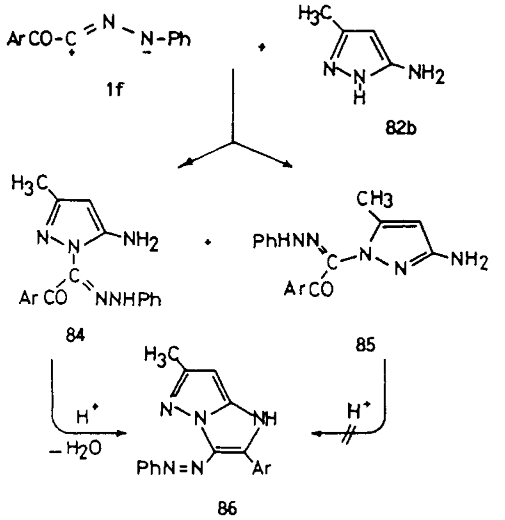
Unsubstituted pyrazole reacts with nitrilimines **1a** to give mainly the arylhydrazone derivatives **81** of the corresponding 1-acylpyrazoles.[96,97]



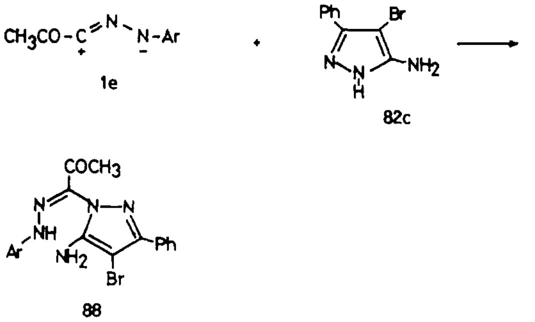
Much controversy on the products of the reactions of 5-aminopyrazole derivatives with nitrilimines was reported. Thus, whereas the reactions of 5-amino-3-phenylpyrazole (**82a**) with *C*-acyl-*N*-arylnitrilimines **1e** and **1f** were reported to give the corresponding imidazo[1,2-b] pyrazoles **83a** and **83b**, respectively,[98–102] it was indicated that reaction of nitrilimines **1f** with 5-amino-3-methylpyrazole (**82b**) yielded a mixture of the 1,3-

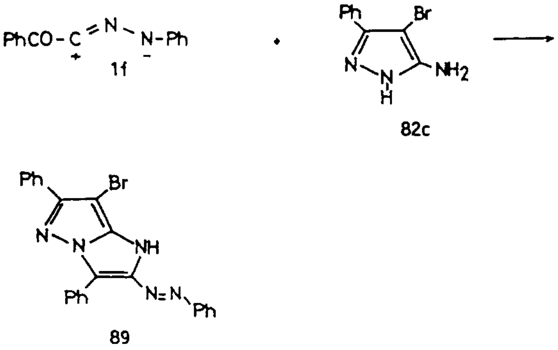


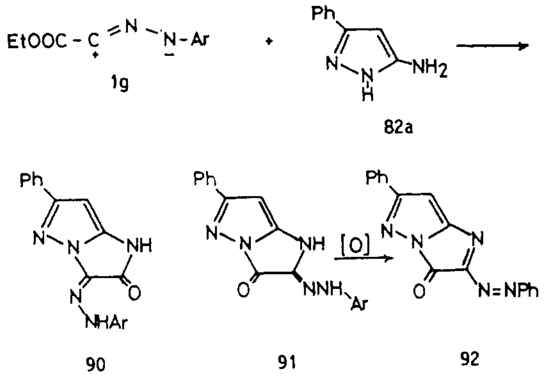
adducts **84** and **85**.[103] The treatment of **84** with acid resulted in the elimination of water to give the imidazo[1,2-*b*]pyrazole derivative **86**. The adduct **85** was recovered unchanged after similar acid treatment.

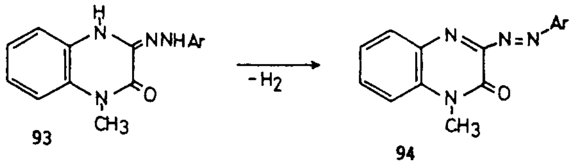


Contrary to these findings, it was claimed that the reaction of 5-amino-4-bromo-3-phenylpyrazole (82c) with *C*-acetyl-*N*-arylnitrilimines (**1e**) yields the amidrazone derivatives **88**.[107] In another report[108] the reaction of **82c** with *C*-benzoyl-*N*-phenylnitrilimine (**1f**) yields the imidazo[1,2-*b*]pyrazole derivatives **89**.



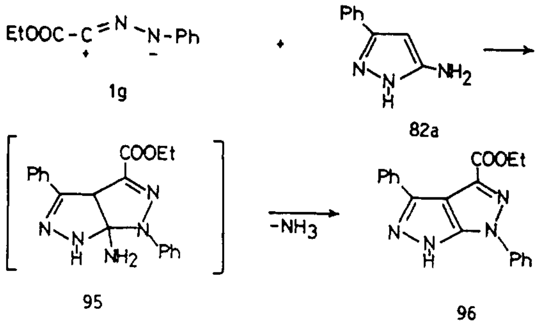




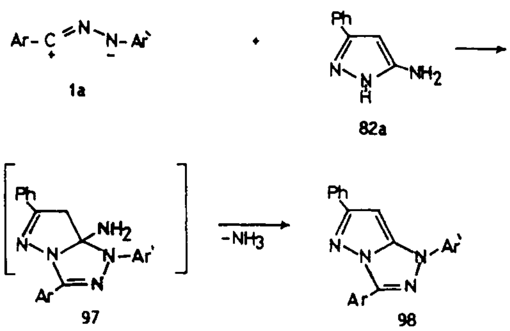


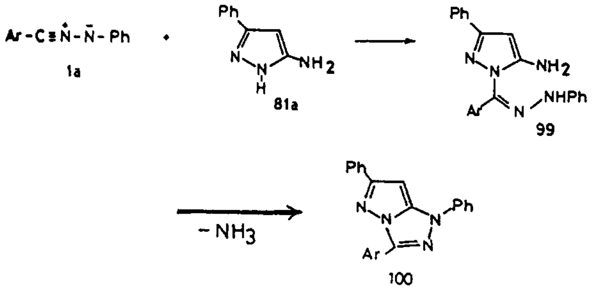
C-(Ethoxycarbonyl)-*N*-arylnitrilimines (**1g**) react with **82a** to give the imidazo[1,2-*b*]pyrazole derivatives **90**.[98] The other isomeric structure **91** was discarded on the basis that the isolated reaction product was recovered unchanged after oxidation treatment.[98] Structures of type **91** are expected to be oxidized to give **92** by analogy with 1-methyl-3-(phenylhydrazono)-1,4-dihydroquinoxalin-2-one (**93**), which yields **94** upon oxidation.[104]

Contrary to this, it was claimed that the pyrazolo[3,4-*c*]pyrazole derivative **96** was the product of the reaction of **82a** with *C*-(ethoxycarbonyl)-*N*-phenylnitrilimine (**1g**).[105]

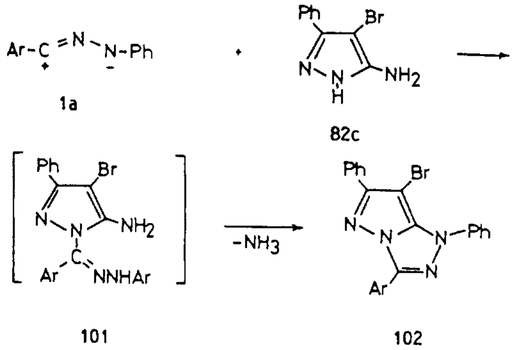


Diarylnitrilimines **1a** were reported to react with 5-amino-3-phenylpyrazole (**82a**) in ethanol to give the pyrazolo[3,4-*c*]pyrazoles **98** via elimination of ammonia from the intermediate cycloadducts **97**.[99,100] Recently, this same reaction was reported to yield pyrazolotriazole **100**.[106]

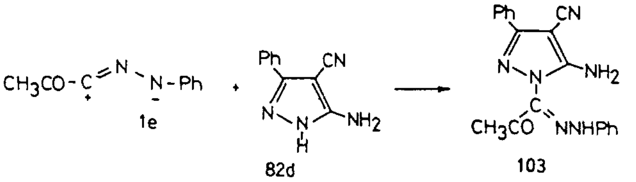


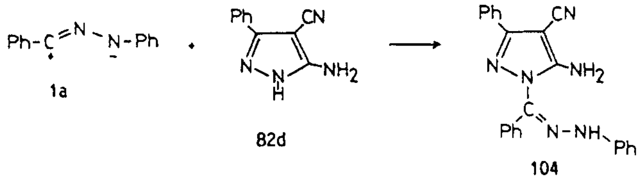


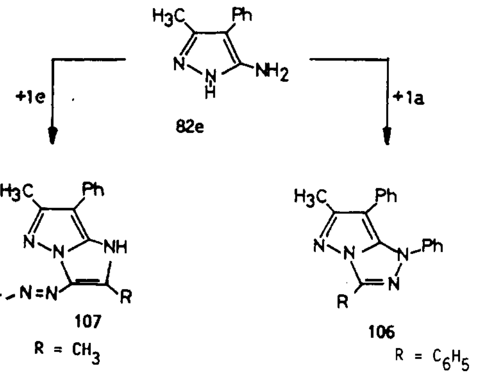
Diarylnitrilimines (**1a**) react with 5-amino-4-bromo-3-phenylpyrazole (**82c**) and yield the pyrazolo[5,1-*c*]-1,2,4-triazoles **102** via elimination of ammonia from the intermediate 1,3-adducts **101**.[106,107]



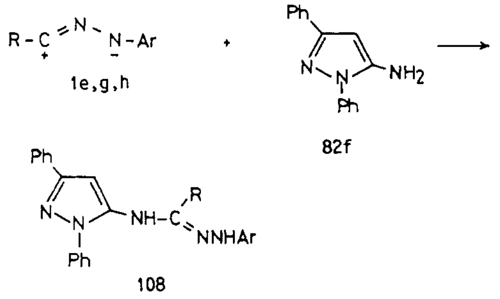
5-Amino-4-cyano-3-phenylpyrazole (**82d**) yielded the 1,3-addition products **103** and **104** when reacted with *C*-acetyl- and *C*-phenyl-*N*-arylnitrilimines (**1e** and **1a**), respectively.[107] Reactions of both **1a** and **1e** with 5-amino-3-methyl-4-phenylpyrazole (**82e**) were reported to give the corresponding pyrazolo[5,1-c]-1,2,4-triazoles **106** and **107**, respectively.[106,107]





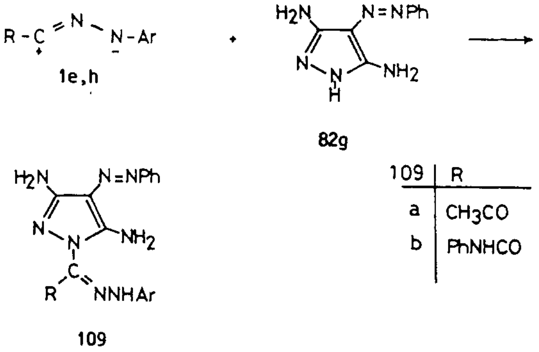


1,3-Diphenyl-5-aminopyrazole (**82f**) reacts with nitrilimines of type **1e**, **1g**, and **1h** and yields the 1,3-addition products **108a**, **108b**, and **108c**, respectively.[99,100,106,109]

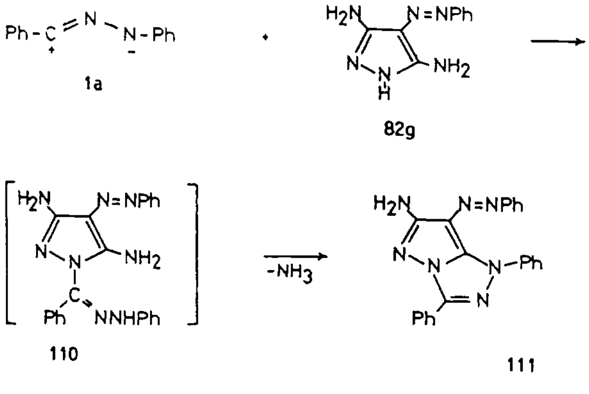


a, R = CH_3CO ; b, R = C_2H_5OCO ; c, R = C_6H_5NHCO

3,5-Diamino-4-phenylazopyrazole (**82g**) reacts with *C*-acetyl- and *C*-(phenylcarbamoyl)nitrilimines **1e** and **1h** and yields the corresponding 1,3-addition products **109a** and **109b**, respectively.[106,107,109] Contrary to this, it was indicated that the reaction of diphenylnitrilimine (**1a**) with **82g** yielded the pyrazolo[5,1-*c*]-1,2,4-triazole **111** probably via elimination of ammonia from the 1,3-addition product **110**.[110]

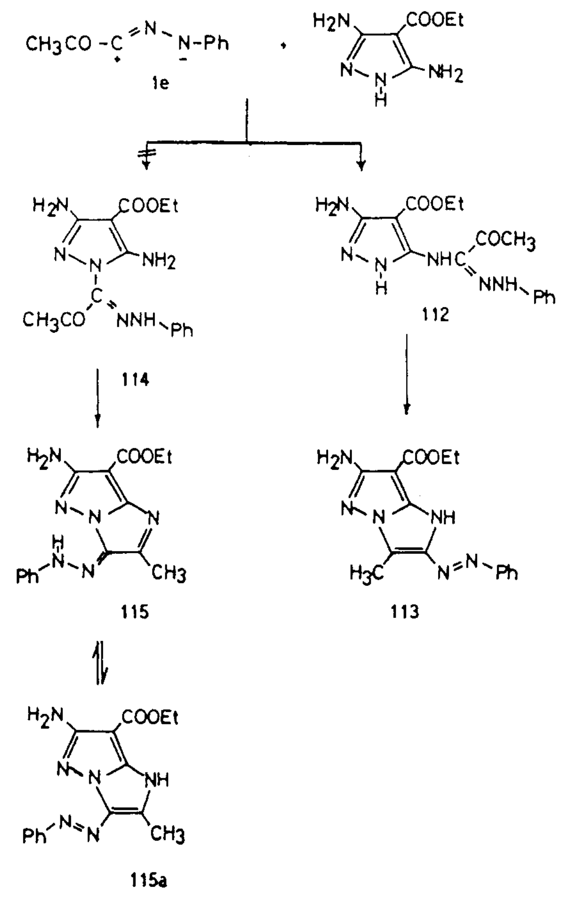


109	R
a	CH_3CO
b	PhNHCO

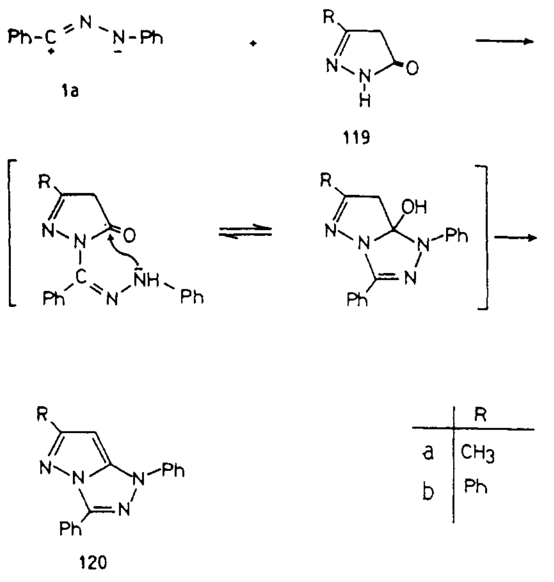


3,5-Diamino-3-(ethoxycarbonyl)pyrazole (**82i**) reacts with nitrilimine **1e** in ethanol and gives the imidazopyrazole derivative **113**.[112] The formation of the latter product was assumed to proceed via the amidrazone **112**, which undergoes cyclization to give **113**. The other isomeric structure **114** and in turn its cyclized product **115** or its tautomer **115a** were discarded although the pyrazole NH is more basic than the exocyclic 5-amino group.

5-Amino-4-mercapto-3-phenylpyrazole (**82j**) reacts with *C*-acyl-*N*-phenylnitrilimines (**1e** and **1f**) in ethanol

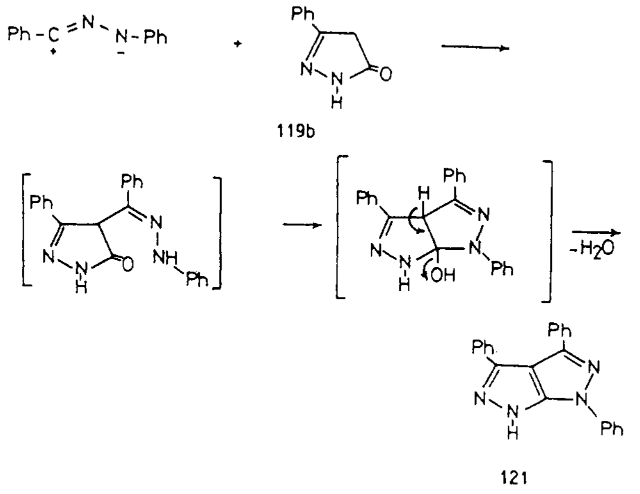


5-Amino-4-mercapto-3-phenylpyrazole (**82j**) reacts with *C*-acyl-*N*-phenylnitrilimines (**1e** and **1f**) in ethanol and yields 2-(phenylazo)-3-substituted-6-phenylpyrazolo[4,3-*b*]-1,4-thiazines **116a** and **116b**, respectively.[108] The other possible reaction products **117** and **118** were discarded. Compound **117b** was prepared by treatment of **89** with sodium sulfide[108] (Scheme V).



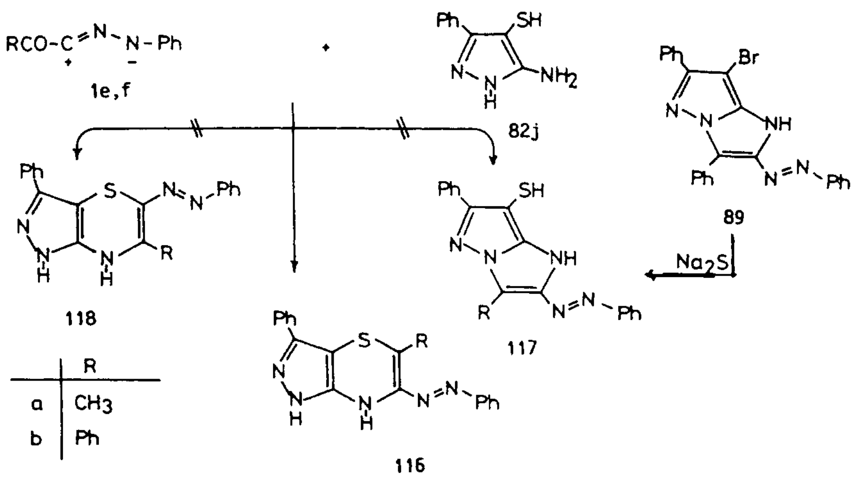
	R
a	CH_3
b	Ph

There are conflicting reports concerning the reactions of 3-substituted 5-pyrazolones with nitrilimines. For example, while diphenylnitrilimine (**1a**) was reported to react with 3-methyl- and 3-phenyl-5-pyrazolones (**119a** and **119b**) and yields the pyrazolo[5,1-*c*]-1,2,4-triazoles **120a** and **120b**, respectively,[99,100] it was indicated in another report that reaction of **1a** with **119b** yields the pyrazolo[3,4-*c*]pyrazole **121**.[100]

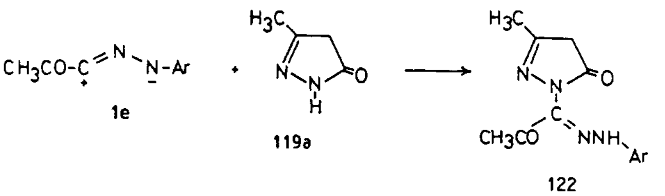


Contrary to this, reaction of **119a** with *C*-acetyl-*N*-arylnitrilimines (**1e**) was reported to give the 1,3-adducts **122**.[106,107]

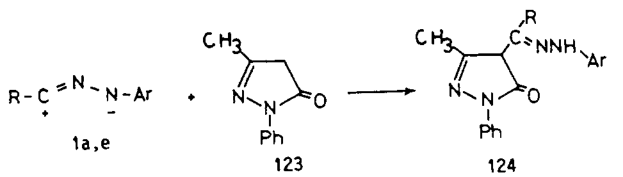
Scheme V

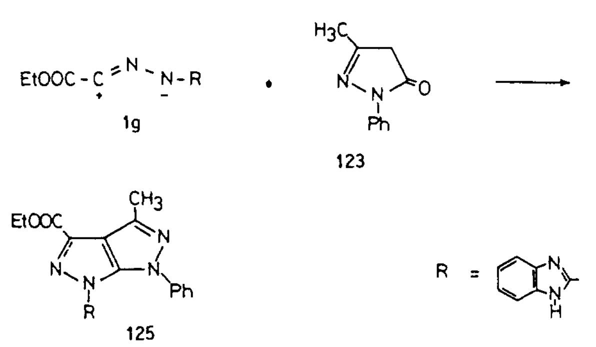


	R
a	CH_3
b	Ph

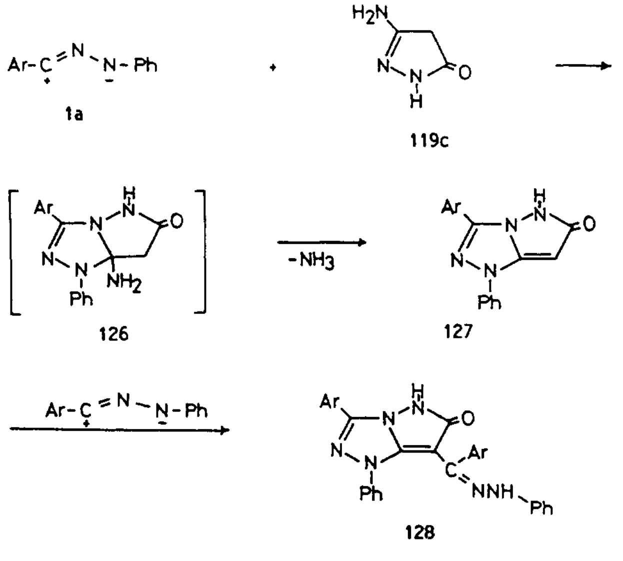

1e
119a
122

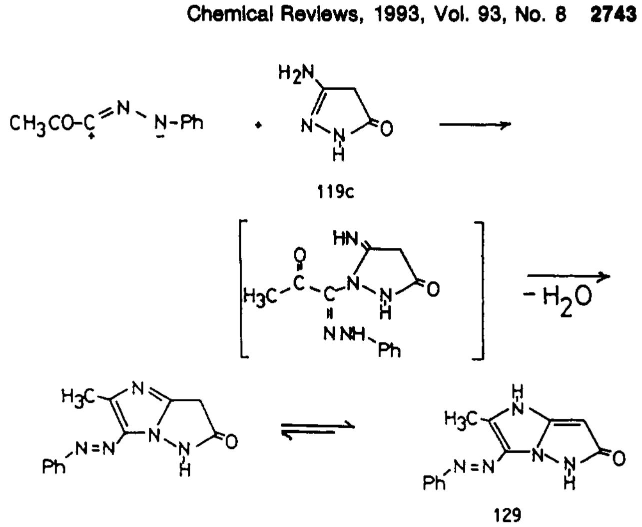
Furthermore, reactions of 3-methyl-1-phenyl-5-pyrazolone (**123**) with diarylnitrilimines (**1a**) and *C*-acetyl-*N*-phenylnitrilimines (**1e**) were reported to give the acyclic 1,3-adducts **124**,[100,106] while the reaction of *C*-(ethoxycarbonyl)nitrilimine **1g** was claimed to give the pyrazolo[5,4-*c*]pyrazole derivative **125**.[113]


1a,e
123
124

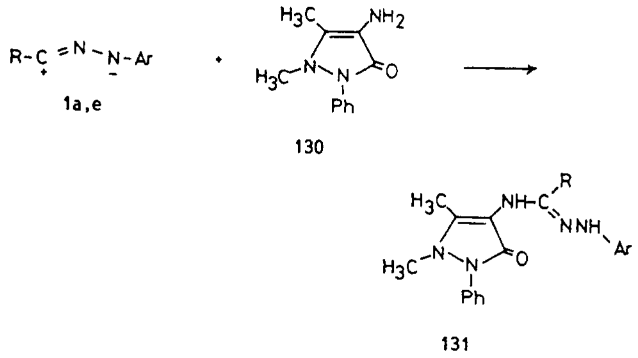

1g
123
125

3-Amino-5-pyrazolone **119c** was reported to give **128** when reacted with diarylnitrilimines (**1a**).[106,107] It was assumed that the reaction involves **126** as an intermediate which eliminates ammonia to give **127**, which reacts in turn with another molecule of nitrilimine **1a** to yield **128**.[107] In contrast to this finding, it was indicated that the reaction of **119c** with *C*-acetyl-*N*-phenylnitrilimine (**1e**) yields the imidazo[1,2-*b*]pyrazole derivative **129**.[107]

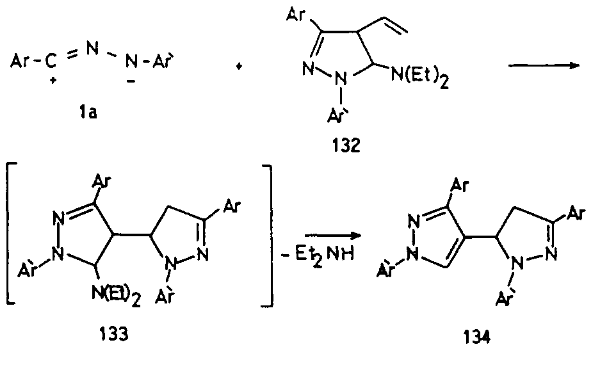

1a
119c
126
127
128


119c
129

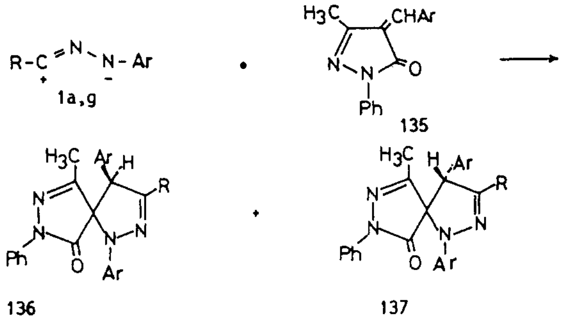
4-Amino-2,3-dimethyl-1-phenyl-5-pyrazolone (**130**) reacts with nitrilimines of types **1a** and **1e** and affords the corresponding amidrazones **131**.[99,100,106]

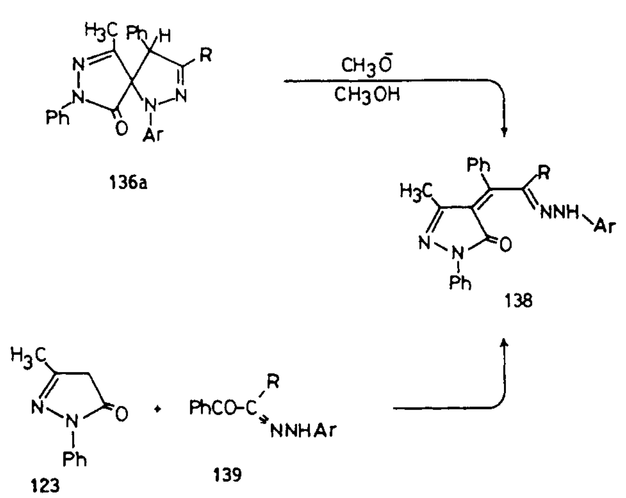

1a,e
130
131

Diarylnitrilimines (**1a**) react with 4-vinyl-1,3-diaryl-5-(*N*,*N*-diethylamino)-2-pyrazolines (**132**) to give 1,3-diaryl-4-(1,3-diaryl-2-pyrazolin-5-yl)pyrazoles (**134**).[114] It was assumed that the products are produced via regioselective 1,3-addition of **1a** to the C=C double bond to give **133** and subsequent release of diethylamine.[114]

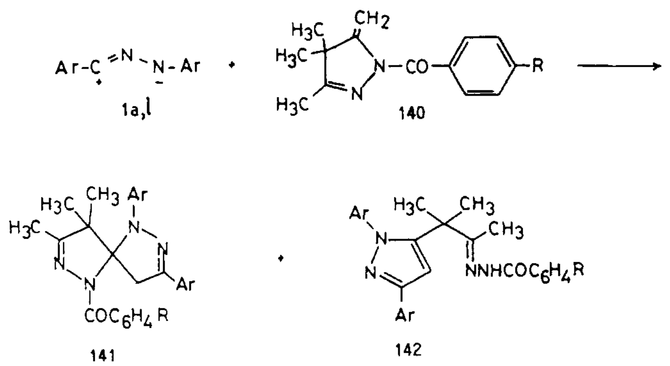

1a
132
133
134

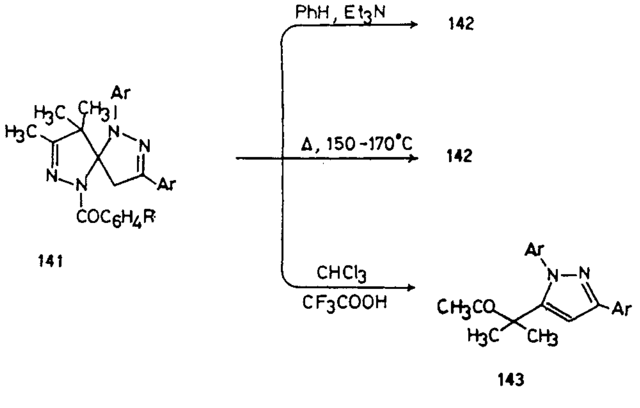
4-Arylidene-1-phenylpyrazolin-5-ones **135** react with diarylnitrilimines (**1a**) and *C*-(alkoxycarbonyl)-*N*-phenylnitrilimines (**1g**) at room temperature in chloroformand give in each case a mixture of two diastereomeric 5,4′-spiro[5,4′-pyrazolin]-5′-ones **136** and **137**.[115] On treatment with sodium methoxide in methanol, the products **136** and **137** gave the same equilibrium mixture, thus indicating their diastereomeric relation. Both products **136** and **137** are cleaved with sodium methoxide in refluxing methanol to give the acyclic product **138**.[115]



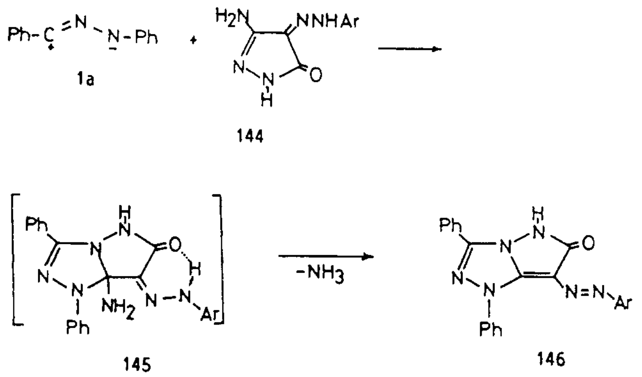


Diarylnitrilimines **1a** cycloadd to 1-aroyl-4,5-dihydro-3,4,4-trimethyl-5-methylene-1*H*-pyrazoles **140** to give the spirocycloadducts **141** as the major products.[116] In addition the acyclic products **142** were produced as minor products (20–40% yield). Reaction of **140** with *C*-aryl-*N*-methylnitrilimines (**1l**) did not yield the expected spirocycloadduct **141d** but yielded the corresponding acyclic product **142**.[116] The spirocycloadducts **141** undergo ring cleavage to give **142** upon thermolysis or refluxing in benzene in the presence of triethylamine.[116] When refluxed in chloroform in the presence of trifluoroacetic acid, the spirocycloadduct **141** is converted into **143**.[116]



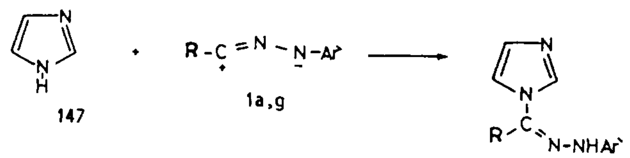


Diphenylnitrilimine (**1a**) reacts with 3-amino-4-(arylhydrazono)pyrazolin-5-ones (**144**) in refluxing ethanol and yields the pyrazolo[3,2-*c*]triazole derivatives **146**.[117]

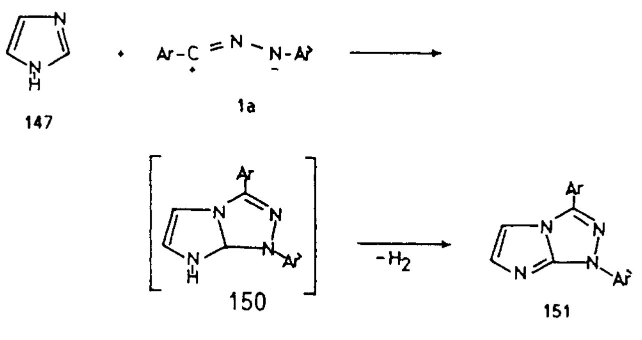


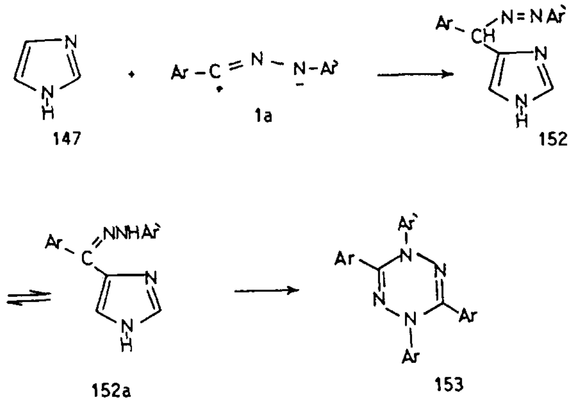
2. Imidazoles

Conflicting results concerning the reactions of imidazole derivatives were reported. For example, unsubstituted imidazole **147** was reported to react with diarylnitrilimines (**1a**) and *C*-(ethoxycarbonyl)-*N*-phenylnitrilimine (**1g**) to give the 1,3-addition products **148** and **149**, respectively.[96,118,119] On the other hand, the electrochemically generated diarylnitrilimines (**1a**) were reported to react with **147** to give the azapentalene derivatives **151**, probably via the in situ oxidation of the intermediate cycloadducts **150**.[120] In another report,[121] it was indicated that reaction of **1a** with **147** affords the electrophilic substitution products **152**. Oxidation of the latter yields the diarylnitrilimine dimers **153**.[121]

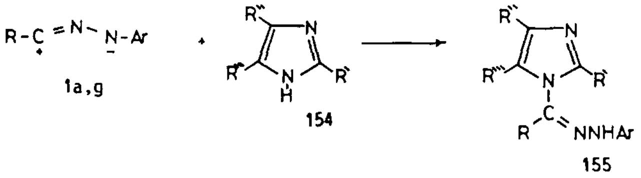


148, $R = XC_6H_4$
149, $R = CH_3CH_2OCO$

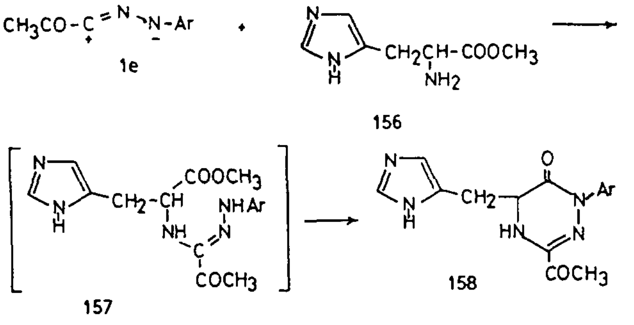




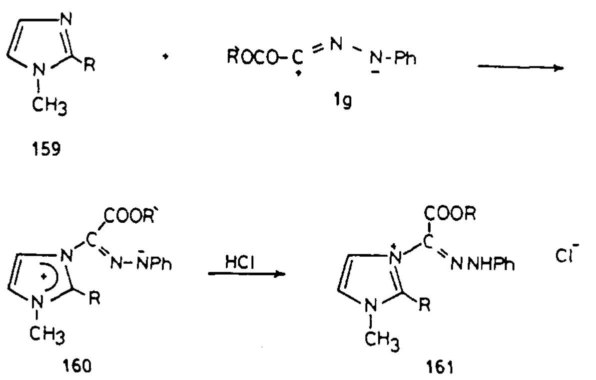
Other 1-unsubstituted imidazole derivatives (**154**) were reported to yield the corresponding 1,3-addition products **155** when reacted with nitrilimines **1a,g**.[118,119]



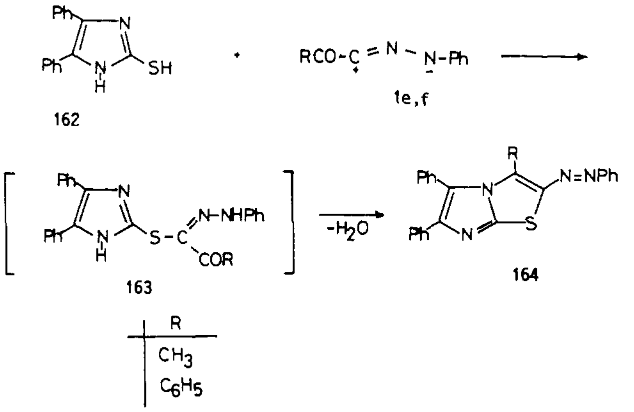
Recently it was reported that *C*-acetyl-*N*-arylnitrilimines (**1e**) react with methyl 2-amino-3-(3-imidazolyl)-propanoate (**156**) and give the cyclized products **158**, probably via the intermediate 1,3-adducts **157**.[122]

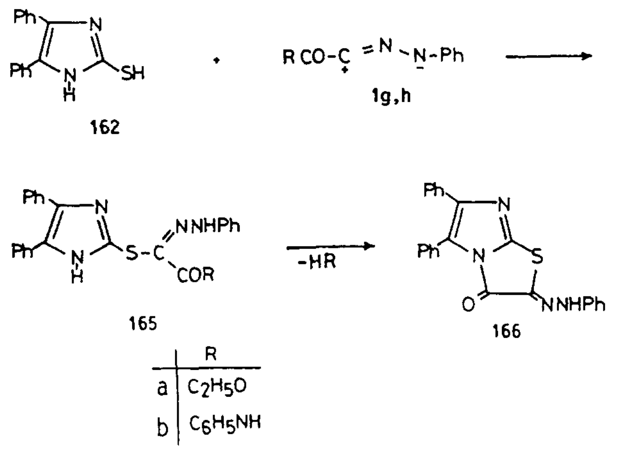


Reactions of 1-substituted imidazole derivatives **159** with nitrilimines **1g** give the betaines **160**, which were isolated in some cases as imidazolium salts **161**.[104,119]

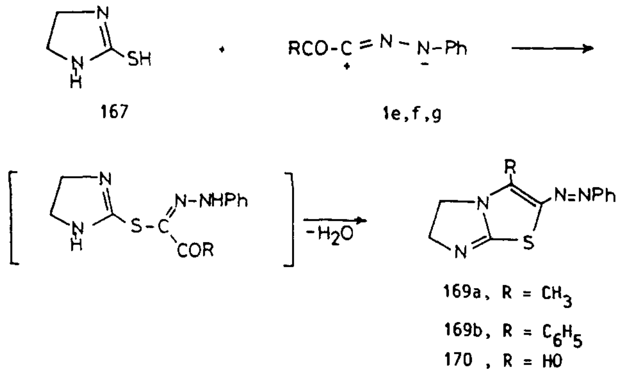


2-Mercapto-4,5-diphenylimidazole (**162**) reacts with the nitrilimines **1e** and **1f** to give the 1,3-adducts **163a** and **163b**, which undergo cyclization to afford **164a** and **164b**, respectively.[123] *C*-(Ethoxycarbonyl)-*N*-phenylnitrilimine (**1g**) reacted similarly with **162** to give **166a**. The intermediate 1,3-addition product **165a** was not isolated, however. The same product was also obtained from the reaction of **162** with *C*-(phenylcabamoyl)-*N*-phenylnitrilimine (**1h**).[123] Recently, however, it was reported that the latter reaction between **1h** and **162** yielded the acyclic 1,3-addition product **165b**.[109]



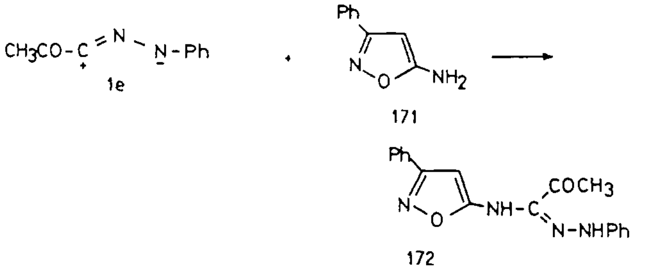


2-Mercapto-4,5-dihydroimidazole (**167**) reacts with *C*-acyl-*N*-phenylnitrilimines (**1e** and **1f**) and *C*-(ethoxycarbonyl)-*N*-phenylnitrilimine (**1g**) and gives the bicyclic products **169a**, **169b**, and **170**, respectively.[108]

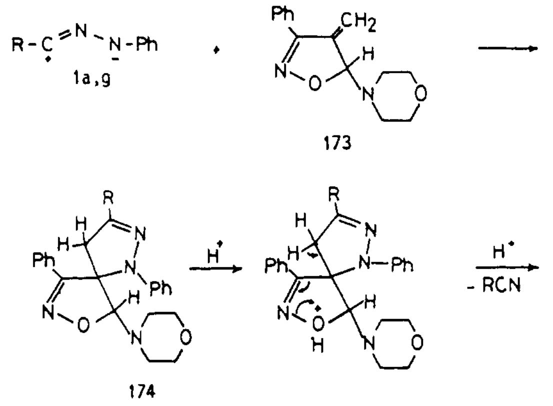


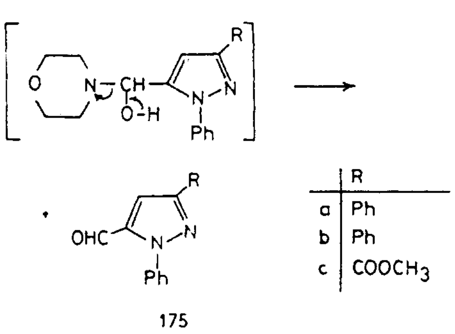
3. Isoxazoles

5-Amino-3-phenylisoxazole (**171**) reacts with *C*-acetyl-*N*-phenylnitrilimine (**1e**) in ethanol to give the amidrazone **172**.[99,100]



Also, 4-methyleneisoxazoline derivative **173** reacts with the nitrilimines **1a** and **1g** to give the corresponding spirocycloadducts **174a** and **174b**, respectively.[124] Treatment of **174a** with a HBr–HOAc mixture yieldedmorpholine, benzoic acid, benzonitrile, and 1,3-diphenylpyrazole-5-carboxaldehyde (**175a**).[124]





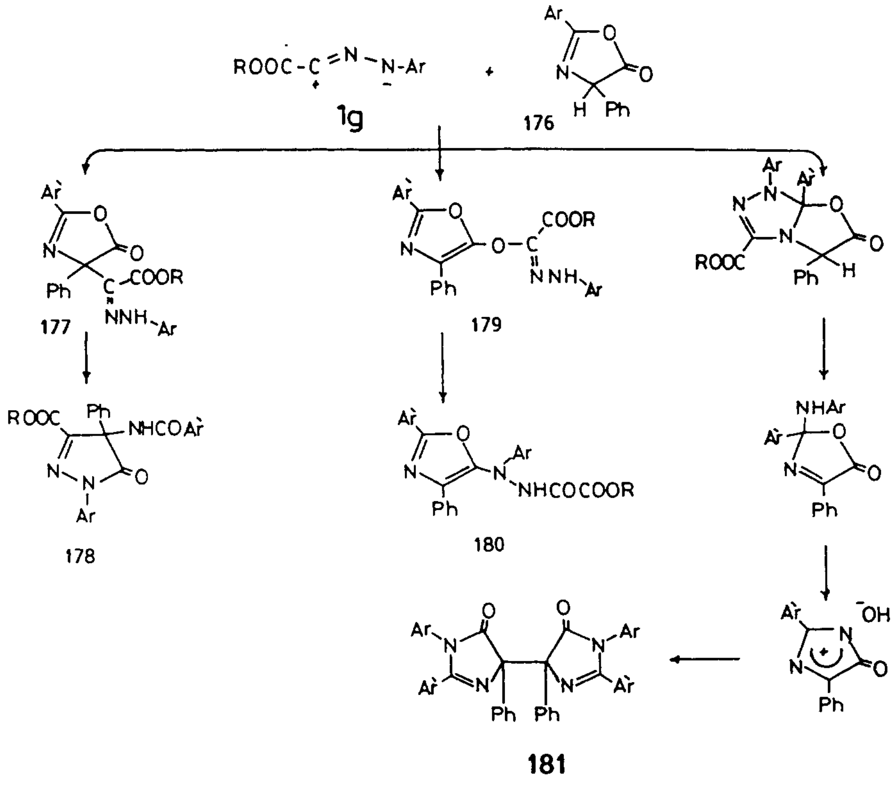
	R
a	Ph
b	Ph
c	COOCH3

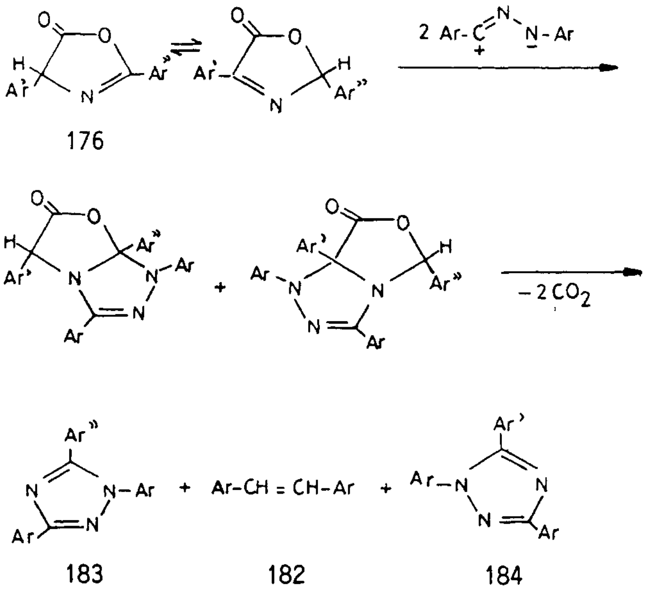
4. Oxazoles

Reaction of 2-(4-methoxyphenyl)-4-phenyl-5(4*H*)-oxazolone (**176**) with nitrilimines **1g** affords the substituted derivative **178** as the main product.[125] In some instances, however, this same reaction yielded the oxazole derivatives **180** and/or the bis-imidazolones **181** were formed in substantial amounts.[125] It was assumed that **178** results from the rearrangement of the initially formed substitution products **177** whereas **180** results from rearrangement of the hydrazonate esters **179**[27,126,127] (Scheme VI).

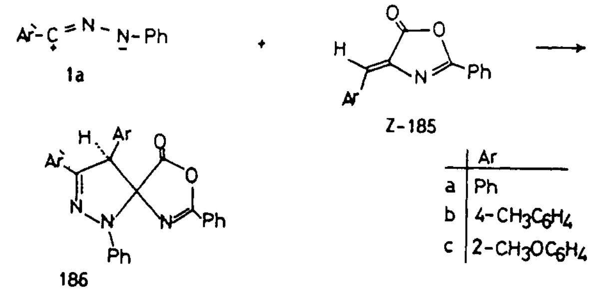
Recently, 5(4*H*)-oxazolones **176** were reported to react with nitrilimines generated from tetrazoles in refluxing anisole to afford 1,2-diarylethylenes **182** and the two isomeric 1*H*-1,2,4-triazoles **183** and **184**.[128]

Scheme VI

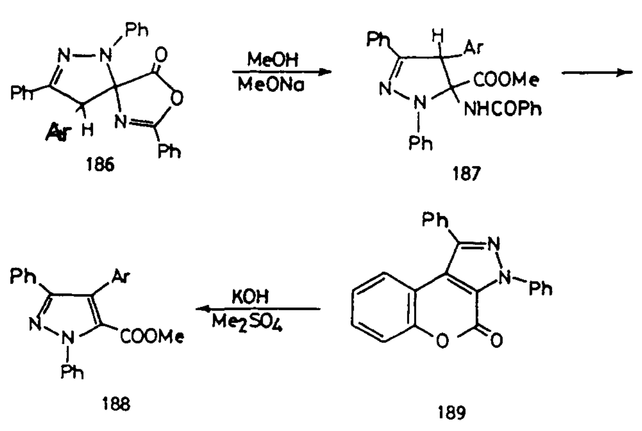




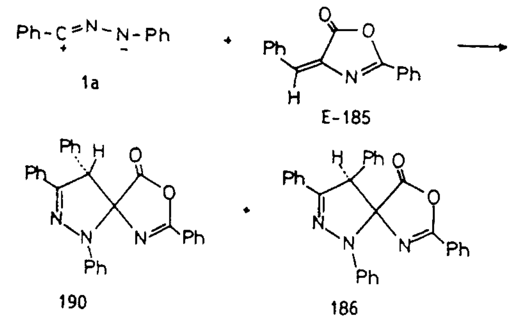
(*Z*)-4-Arylidene-2-phenyloxazol-5(4*H*)ones (**185**) react with diarylnitrilimines (**1a**) to give the spirocycloadducts **186**.[129,130] The reactions were regioselective and in all cases only one regioisomer was isolated. The regiochemistry of the products **186** was confirmed by chemical evidence. Thus, when the cycloadduct **186** was refluxed in methanol in the presence of sodium methoxide, it afforded the ester **188**.[130] The structure of the latter compound **188c** was confirmed by its alternate synthesis by methanolysis of the corresponding chromenopyrazolones **189**.[130]



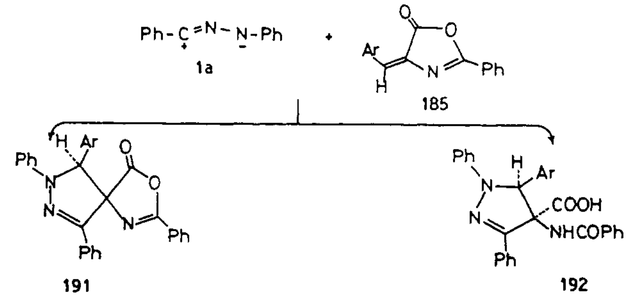
	Ar
a	Ph
b	4-CH$_3$C$_6$H$_4$
c	2-CH$_3$OC$_6$H$_4$



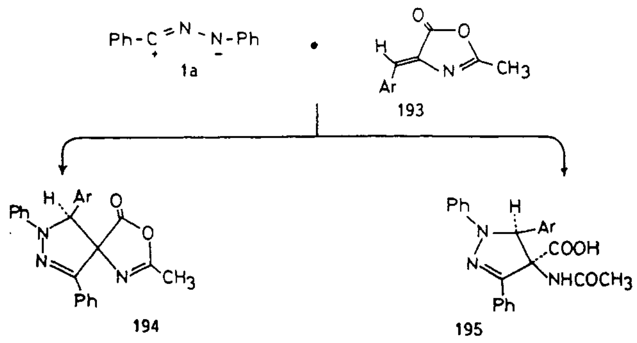
Reaction of diphenylnitrilimine **1a** with the (*E*)-oxazolone derivative *E*-**185** gave, however, a mixture of **186** and **190**.[129,130] The formation of **186** in this reaction was attributed to the known conversion of the (*E*)-**185** into the stable (*Z*)-**185** in the presence of amines.[131]



Recently, the reactions of diphenylnitrilimines (**1a**) with *Z*-**185** were reported to give the other regioisomer products **191** in addition to the 2-pyrazoline derivatives **192**.[132] The ratio of **191**:**192** was found to be solvent dependent. In another report, it was indicated that reaction of **185** with diphenylnitrilimine (**1a**) yielded only the spirocycloadducts **191**.[133]



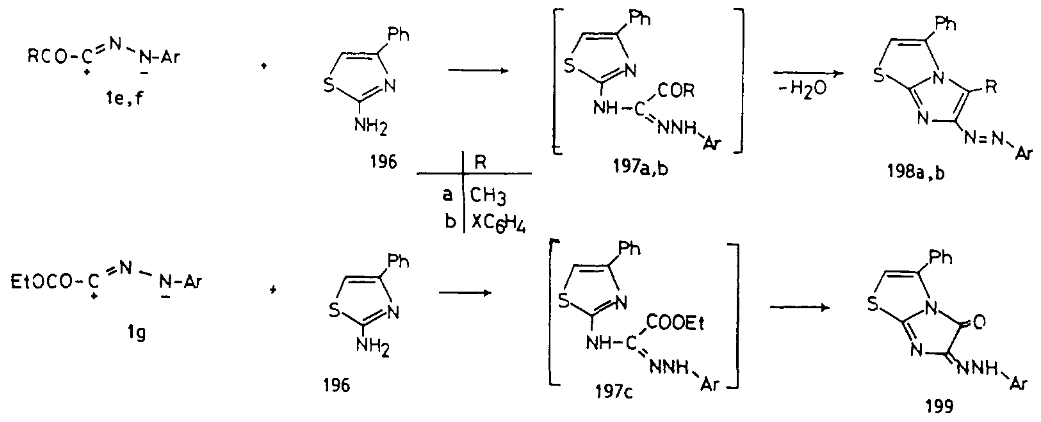
4-Arylidene-2-methyl-5(4*H*)oxazolones (**193**) react with diphenylnitrilimine (**1a**) to give **194** and/or **195** according to the solvent used in the reaction.[132]

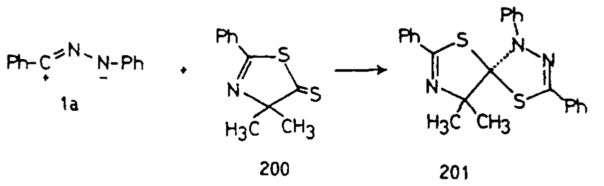


5. Thiazoles

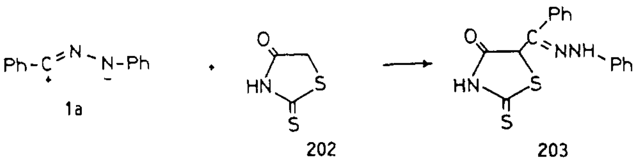
2-Amino-4-phenylthiazole (**196**) reacts with *C*-acylnitrilimines **1e** and **1f** and *C*-(ethoxycarbonyl)nitrilimines **1g** in ethanol and yields the amidrazones **197a**, **197b**, and **197c**, which cyclize to the final bicyclic products **198a**, **198b**, and **199**, respectively[98] (Scheme VII). 2-Thiazoline-5-thione **200** yields the spirocycloadduct **201** when treated with diphenylnitrilimine (**1a**).[134]

Scheme VII

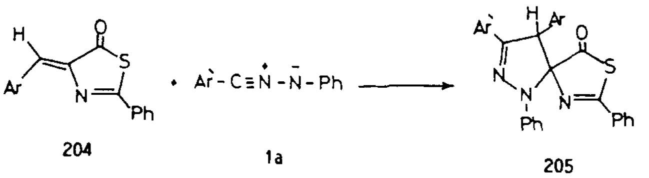


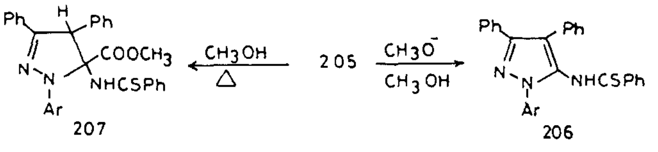


However, the reaction of the same nitrilimine **1a** with 5-oxotetrahydrothiazole-2-thione (**202**) in benzene was reported to give the substitution product **203**.[99,100]



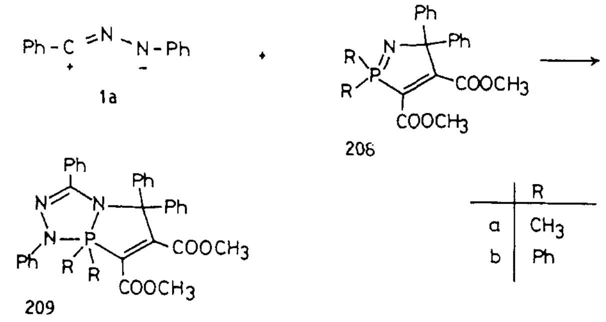
Recently, the reaction of diarylnitrilimines (**1a**) with (*Z*)-4-arylidene-2-phenyl-5(4*H*)thiazolones (**204**) in benzene at room temperature was reported to yield the spiropyrazolines **205** in good yields.[135] The latter products showed greater tendency for aromatization of the pyrazoline ring than nucleophilic ring opening of the thiazoline ring. For example, heating **205** in benzene in the presence of triethylamine or in methanol in the presence of sodium methoxide or in a water–acetone mixture yielded the thioamide **206**. However, heating of **205** in methanol at reflux afforded **207** in 50% yield.[135]

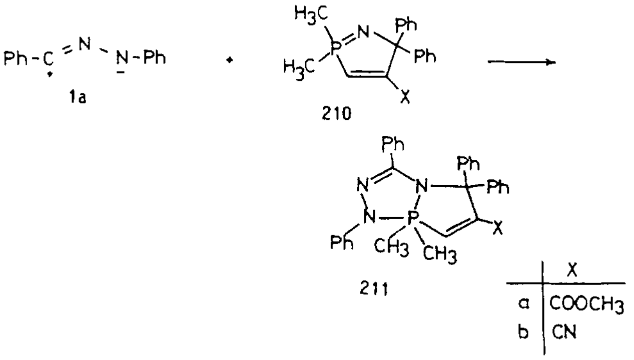




6. 1,2-Azaphospholes

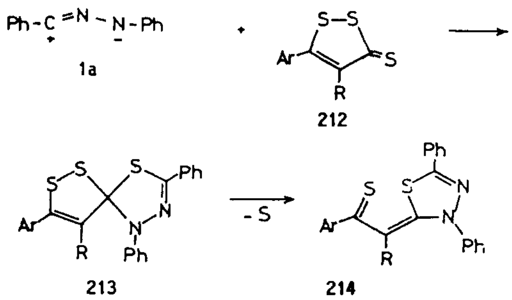
Diphenylnitrilimine (**1a**) cycloadds to the P=N double bond of 3,4-disubstituted **208a,b** and 4-monosubstituted azaphospholine derivatives **210a,b** to give the corresponding cycloadducts **209a,b** and **211a,b** in good yields, respectively.[136]





7. 1,2-Dithiolines

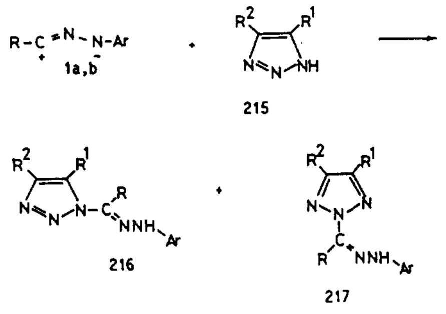
Diphenylnitrilimine (**1a**) reacts with 1,2-dithiole-3-thionenone derivatives **212** to give the 1,3,4-thiadiazoline derivatives **214**, probably via the ring cleavage of the initially formed spirocycloadducts **213**.[137]



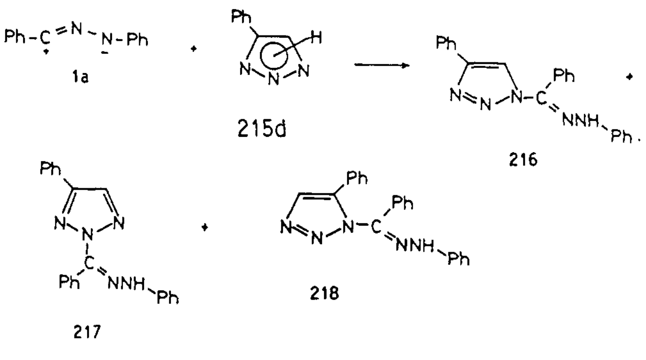
E. Reactions of Five-Membered Heterocycles with Three or More Heteroatoms

1. 1,2,3-Triazoles

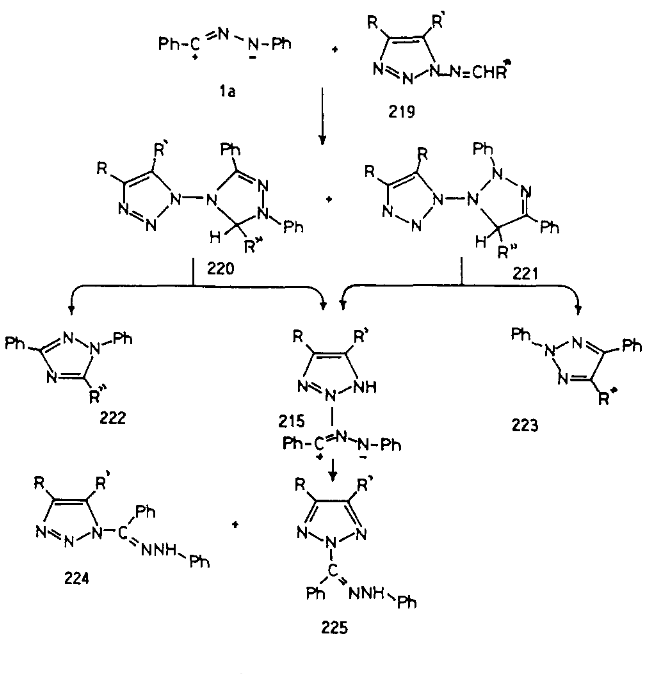
Unsubstituted 1,2,3-triazole (**215a**) and symmetrically substituted 1,2,3-triazoles (**215b**) react with nitrilimines **1a** and **1b** and give in each case a mixture of two 1,3-adducts, namely the arylhydrazone derivatives of 1- and 2-acyl-1,2,3-triazoles **216** and **217**, respectively.[138] 3-(*p*-Chlorophenyl)-1,2,3-triazole (**215c**) reacts similarly with diarylnitrilimines (**1a**) to give a mixture of the corresponding 1,3-adducts **216c** and **217c**.[138] However, reaction of 3-phenyl-1,2,3-triazole (**215d**) with diphenylnitrilimine (**1a**) was reported to give a mixture of the three 1,3-adducts, **216**–**218**.[139]



R^1/R'' : a, H / H; b, CH_3 / CH_3
c, 4-ClC_6H_4 / H ; d, H / C_6H_5

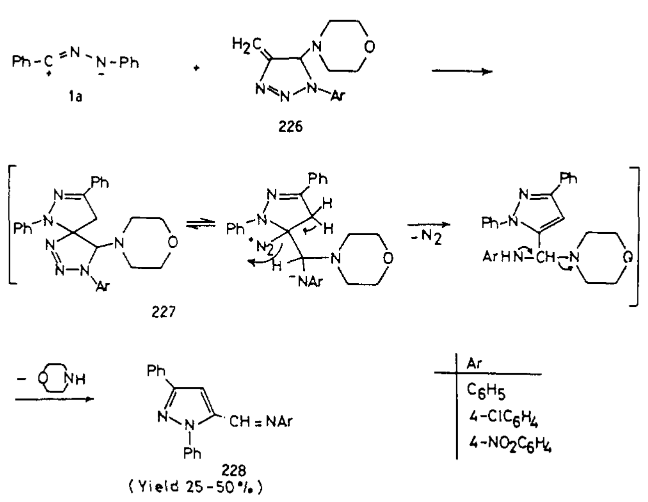


Diphenylnitrilimine (**1a**) reacts with 1-(*N*-arylideneamino)-1,2,3-triazoles **219** and 1-(*N*-phenacylideneamino)-1,2,3-triazoles **219a** and yields in each case a mixture of 1,2,3- and 1,2,4-triazoles **222** and **223** together with the phenylhydrazone derivatives of 1- and 2-benzoyl-1,2,3-triazoles **224** and **225**, respectively.[139,140] The formation of the latter products occurs through the cycloaddition of the nitrilimine **1a** to the C=N double bond to the give the two regioisomeric cycloadducts **220** and **221**, which upon elimination of 1,2,3-triazole **215** give **222** and **223**, respectively. Reaction of the resulting 1,2,3-triazole with diphenylnitrilimine (**1a**) leads in turn to **224** and **225**.[139,140]



219, $R^* = XC_6H_4$
219a, $R^* = XC_6H_4CO$
$R/R' = CH_3/CH_3$, Ph/H

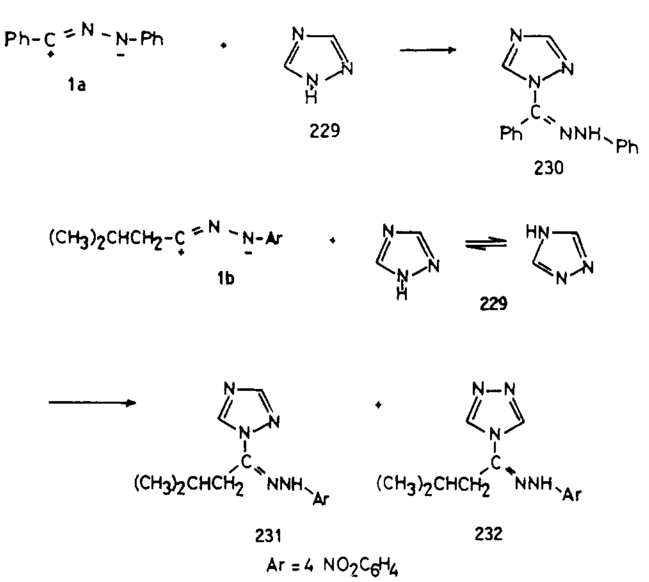
4-Methylene-4,5-dihydro-1,2,3-triazole derivatives **226** react with diphenylnitrilimine (**1a**) at room temperature to yield the anil derivatives **228** of 1,3-diphenylpyrazole-5-carbaldehyde via a reaction sequence involving the spirocycloadduct **227** as intermediate.[141]



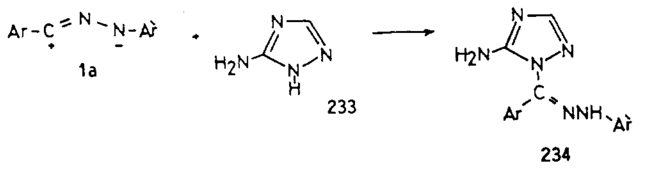
2. 1,2,4-Triazoles

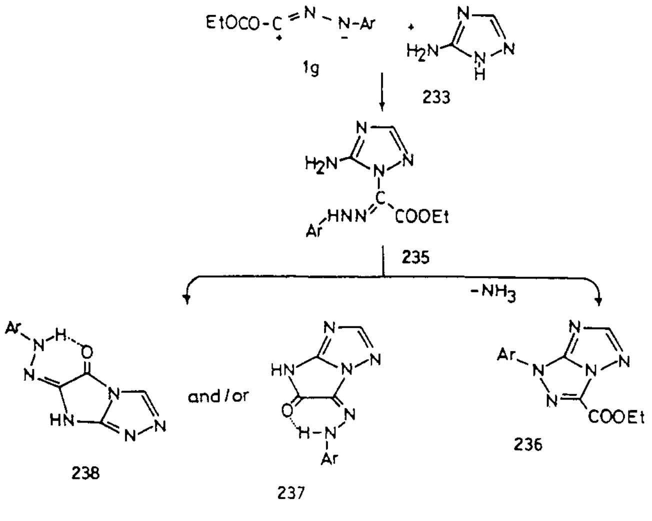
Unsubstituted 1,2,4-triazoles **229** was reported to react with diphenylnitrilimine (**1a**) and gives only a single 1,3-adduct **230**.[96] However, similar reaction of *C*-alkylnitrilimines **1b** with **229** was reported to give in each case a mixture of the 1- and 4-substituted 1,2,4-triazoles **231** and **232**.[97]

Different results were reported for the reactions of 5-amino-1,2,4-triazole (**233**). For example, Diarylni-

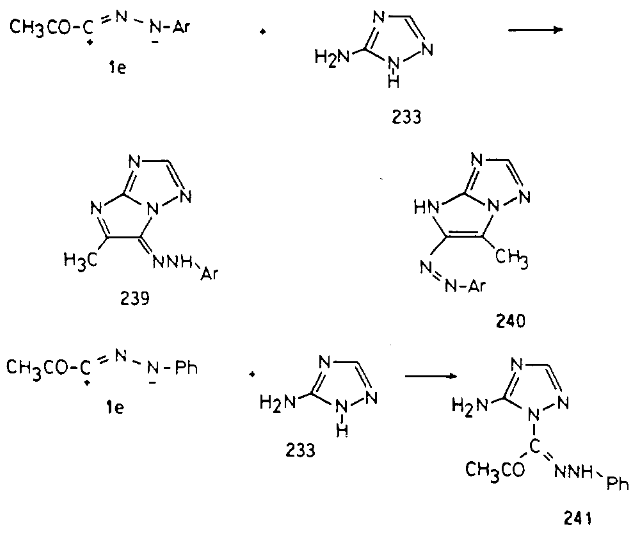


trilimines (1a) were reported to react with **233** and givethe corresponding amidrazones **234**.[99,106] Similar reaction of **233** with *C*-(ethoxycarbonyl)nitrilimines **1g** was reported to give the triazolotriazole derivatives **236**, probably via elimination of ammonia from the corresponding 1,3-adducts **235**.[105] The other possible products **237** were excluded, however.[105] Contrary to this, it was indicated in another report[98] that such a reaction affords imidazotriazole derivatives which can be formulated as **237** or **238**.[98]

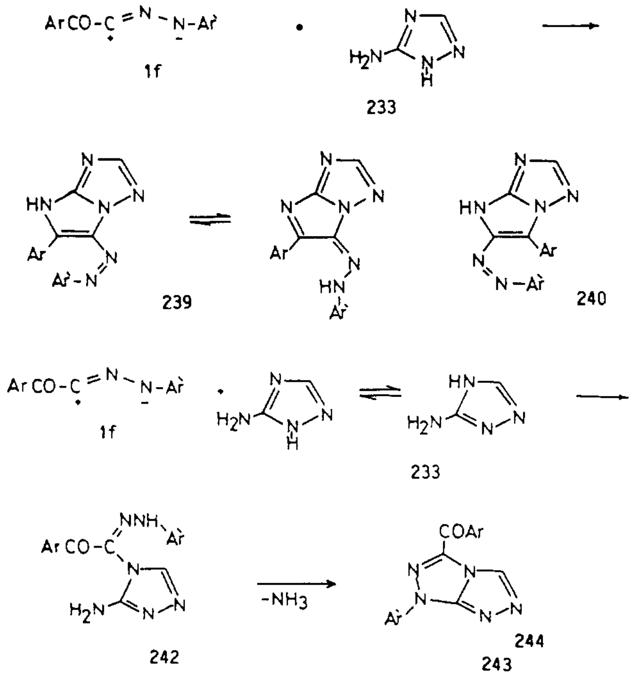




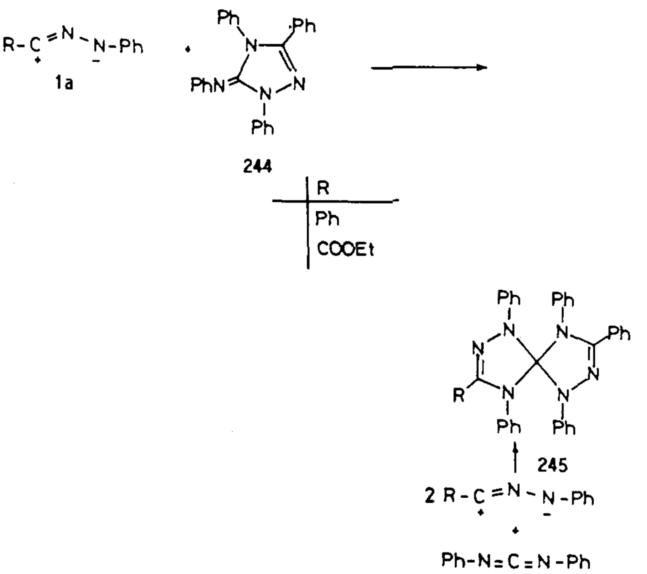
Reaction of *C*-acetylnitrilimines **1e** with **233** were indicated in one report[98] to give **239** and not **240**, and in another report[99] the reaction product was claimed to be the 1,3-adduct **241**.



There is a similar contradiction concerning the products of the reaction of **233** with **1f**.[98,103] Thus, whereas such a reaction was reported to give **239** and not **240**,[98] it was indicated in another report that the product of this reaction was **243**.[103]

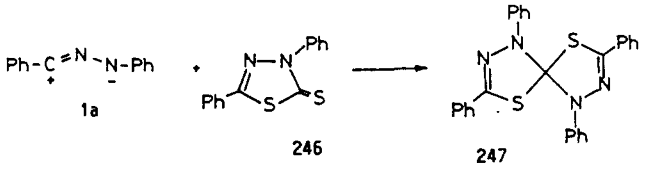


Reactions of the nitrilimines **1a,g** with 1,3,4-triphenyl-1,2,4-triazol-5-one anil **244** afforded the corresponding spirocycloadducts **245**.[142] The structure of the latter products was confirmed by their alternate synthesis from *N,N*-diphenylcarbodiimide to the corresponding nitrilimines.[142]



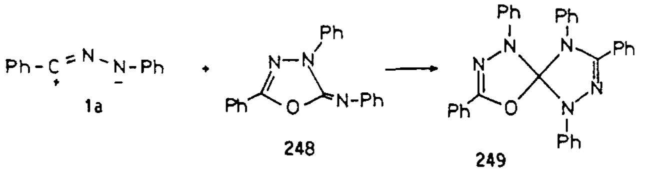
3. 1,3,4-Thiadiazoles

Diphenylnitrilimine (**1a**) reacts with 3,5-diphenyl-1,3,4-thiadiazole-5-thione (**246**) and gives the spirocycloadduct **247**.[143]



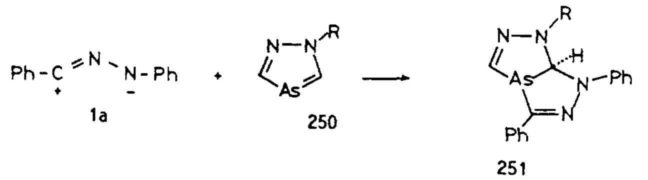
4. 1,3,4-Oxadiazoles

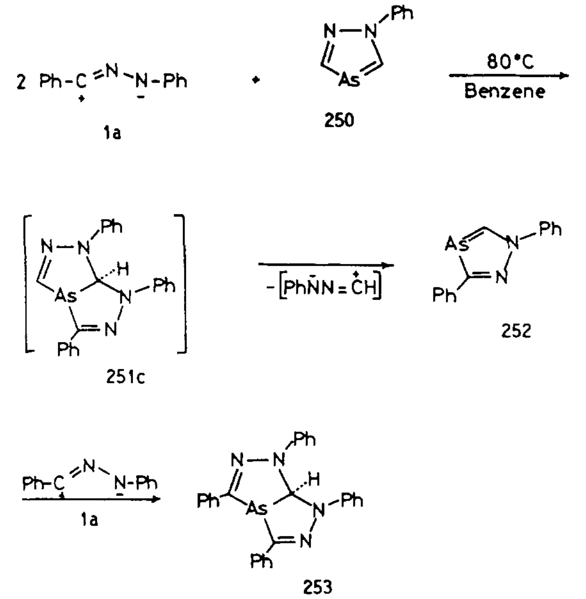
Reaction of 2,4-diphenyl-1,3,4-oxadiazol-5-one anil **248** with diphenylnitrilimine (**1a**) yields the spirocycloadduct **249**.[142]

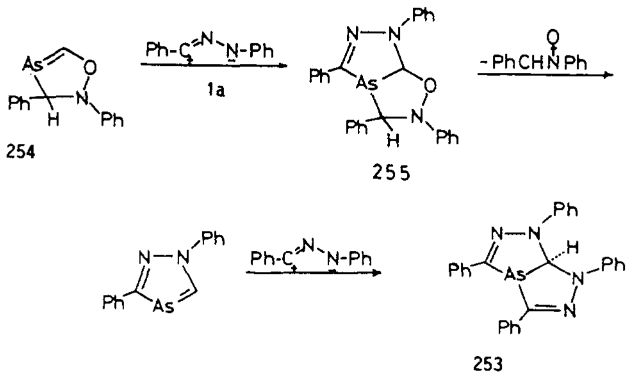


5. 1,3,4-Arsadiazoles

Diphenylnitrilimine (**1a**) reacts with 1,3,4-arsadiazole and its 3-substituted derivatives **250** to give the cycloadducts **251**.[144] However, reaction of 3-phenyl-1,3,4-arsadiazole with diphenylnitrilimine **1a** was reported to give the bicyclic product **253**.[144] It was assumed in this case that the initially formed cycloadduct **251c** underwent cycloreversion to give 3,5-diphenyl-1,3,4-arsadiazole (**252**), which reacted with another molecule of diphenylnitrilimine to give **253** as the end product.[144] The latter product was also obtained from the reaction of **254** with excess diphenylnitrilimine **1a**.[144]

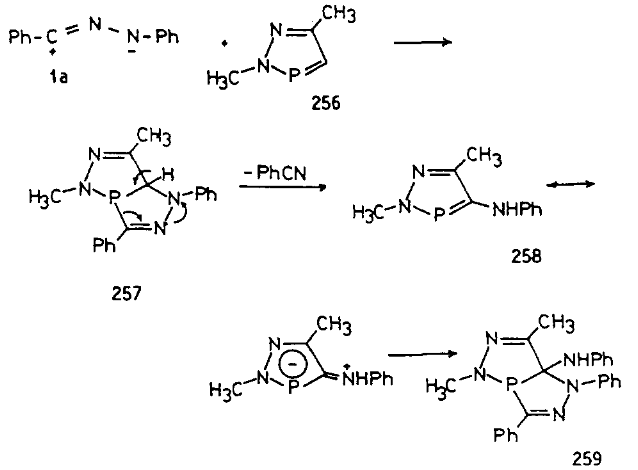






6. 1,2,3-Phosphadiazoles

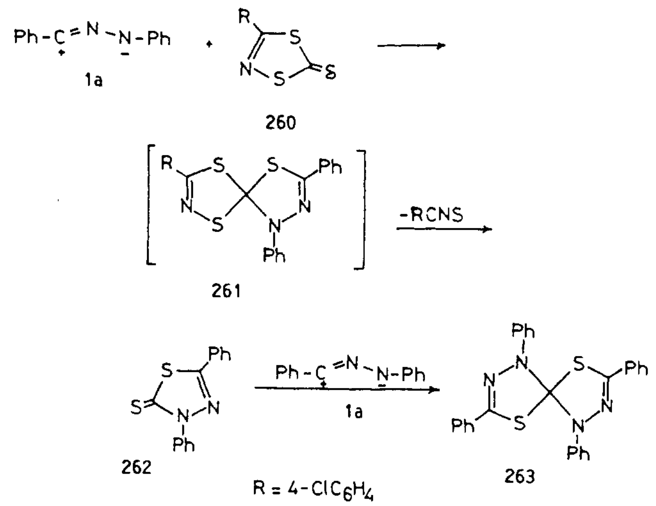
Reaction of diphenylnitrilimine (**1a**) with 2,5-dimethyl-1,2,3-diazophosphole (**256**) was reported to give **259**.[145] It was assumed the reaction involves cycloaddition of the nitrilimine to the C=P double bond of **256** to give **257** which in turn eliminates benzonitrile to yield **258**. Reaction of the latter with another molecule of **1a** afforded the final product **259**.



7. 1,4,2-Dithiazoles

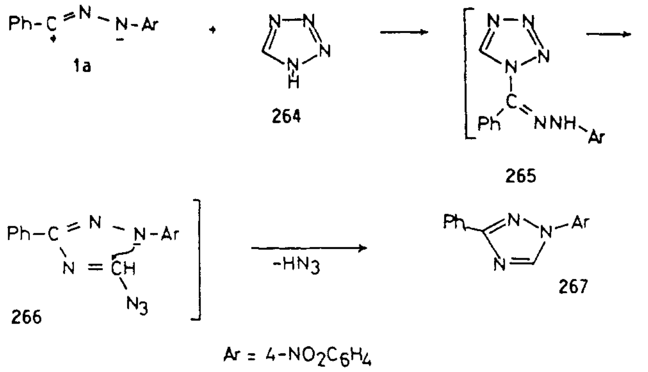
Reaction of diphenylnitrilimine (**1a**) with 3-substituted 1,4,2-dithiazol-5-thione (**260**) was reported to yield

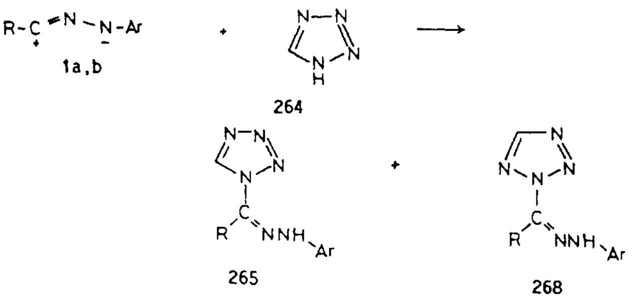
1,3-diphenylthiadiazole-5-thione (**262**) and the spirothiadiazole derivative **263**.[146] The latter products were characterized by comparison with authentic samples prepared by reaction of diphenylnitrilimine with carbon disulfide.[143]



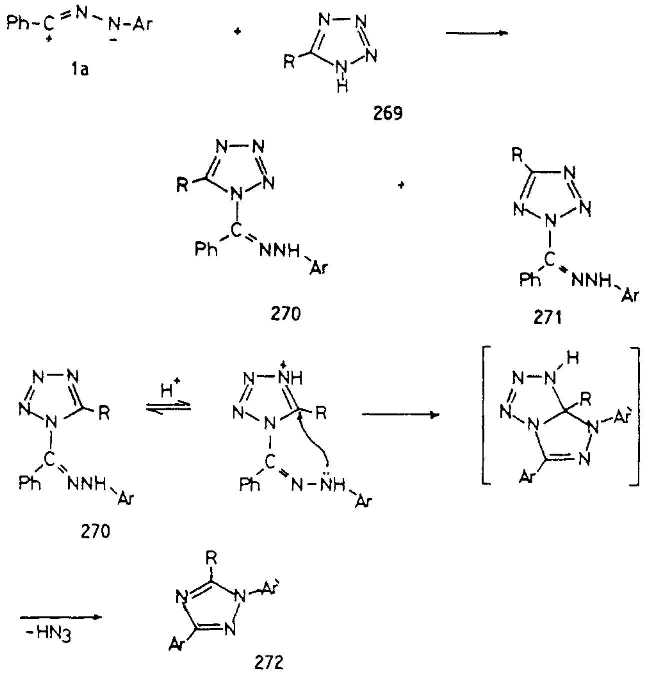
8. Tetrazoles

Unsubstituted tetrazole **264** reacts with diarylnitrilimines (**1a**) to give 1-hydrazonyltetrazoles **265**, which fragmented and recyclized to yield 1,3-diaryl-1,2,4-triazoles (**267**).[147] Attempts to isolate the acyclic hydrazone derivatives **265** failed, however, even at 20 °C.[147] However, Plenkiewicz et al.[97] reported that reactions of **264** with both *C*-aryl- and *C*-alkylnitrilimines **1a** and **1b** yielded in most cases a mixture of the isomer 1- and 2-hydrazonyltetrazoless **265** and **268**, respectively.



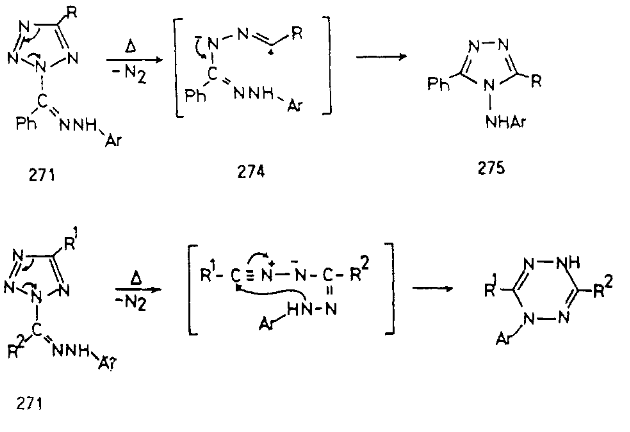


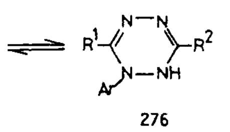
Reactions of diarylnitrilimines (**1a**) with 5-alkyl- and 5-aryltetrazole derivatives **269a** and **269b** were reported to give in each case a mixture of the corresponding the hydrazonyl tetrazole derivatives **270** and **271**.[97,147,148]



The latter products were stable, as they did not fragment on being heated in solution or treated with a base.[147] However, treatment of **270** with trifluoroacetic acid readily gives high yield of the triazoles **272**, with the exception of compound **270** (R = 2,6-$Cl_2C_6H_3$).[148] Thermolysis of **270** (R = H or Cl) afforded the corresponding triazoles **272** (R = H or N_3).[148]

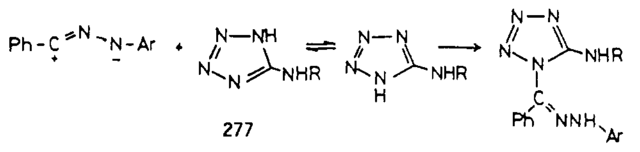
Thermolysis of **271** was reported to give the corresponding substituted 1,2,4-triazoles **275** via the intermediate formation of **274**. Thermolysis of 2,5-disubstituted tetrazoles is now a standard route to nitrilimines.[148–150] However, thermolysis of **271** (R^1 or R^2 = alkyl) yields different products, namely the dihydrotetrazine or its tautomers.[97]





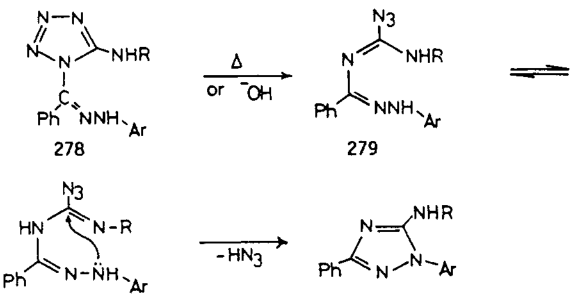
R^1	R^2	Ar
Ph	$(CH_3)_2CH$	4-$NO_2C_6H_4$
$(CH_3)_2CH$	Et	4-$NO_2C_6H_4$

Diarylnitrilimines (**1a**) react with both 5-amino- and 5-(*N*-alkylamino)tetrazoles **277a,b** in ethanol at 0–5 °C and yield the corresponding 1-hydrazonyltetrazoles **278**.[97,147,148] Heating the latter products in refluxing ethanol or in ethanolic sodium hydroxide solution



277

278

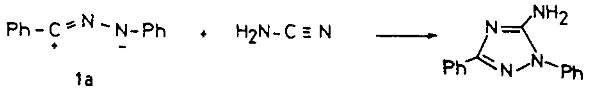


278

279

280

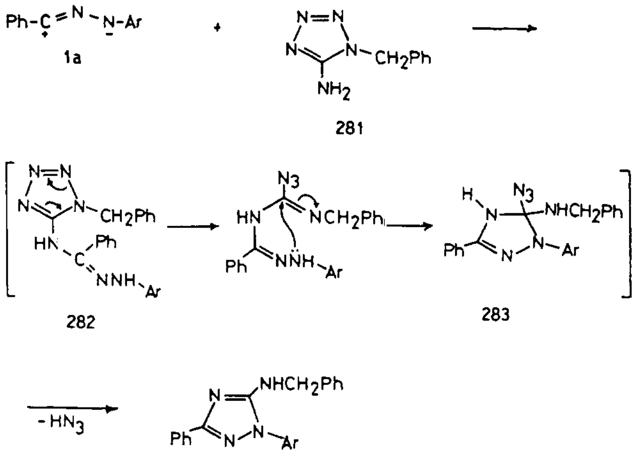
converted them to the triazoles **280**.[97,147,148] Compound **280** (R = H, Ar = C_6H_5) was confirmed by its alternate formation from the addition of diphenylnitrilimine (**1a**) to cyanamide.[147]



1a

280

5-Amino-1-benzyltetrazole (**28**) reacts similarly with diarylnitrilimines (**1a**) in boiling ethanol and yields **284**.[147,148] In another report[103] it was indicated that *C*-aroylnitrilimine **1f** reacts with 5-aminotetrazole **285** to yield a mixture of the aminotriazoles **288** and **289**. The latter products were assumed to result from the loss of hydrazoic acid from the initially formed cycloadducts **286** and **287**, respectively.



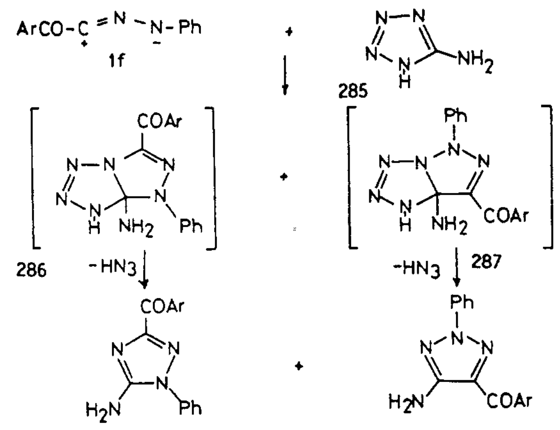
1a

281

282

283

284



1f

285

286

287

288

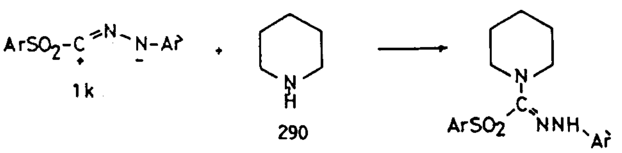
289

Ar = 2,4-$Cl_2C_6H_3$

F. Reactions of Six-Membered Heterocycles with One Heteroatom

1. Piperidines and Pyridines

Piperidine **290** adds to *C*-(arenylsulfonyl)nitrilimines **1k** to give the corresponding amidrazones **291**.[151]

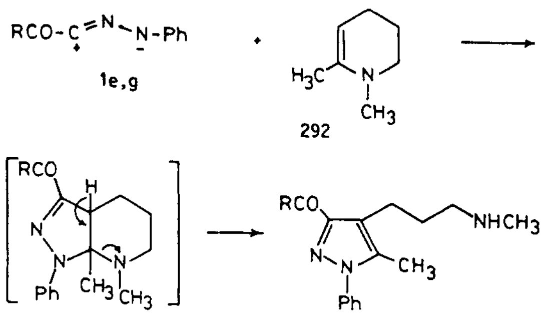


1k

290

291

C-Acetyl- and *C*-(ethoxycarbonyl)nitrilimines **1e** and **1g** react with 1,2-dimethyl-1,4,5,6-tetrahydropyridine (**292**) to give 3-acetyl (**294a**) and 3-(ethoxycarbonyl) (**294b**) derivatives of 4-[3-(*N*-methylamino)propyl]-5-methyl-1-phenylpyrazoles, respectively.[67] The latter products seem to result from ring cleavage of the corresponding 1,3-cycloaddition intermediates **293a** and **293b**, respectively.



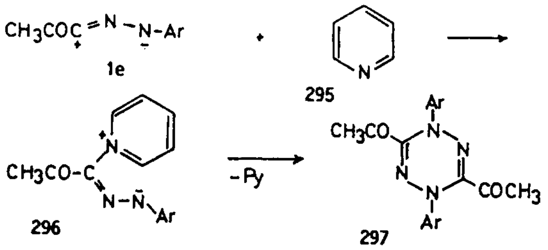
1e,g

292

293

294

Unsubstituted pyridine reacts with *C*-acetylnitrilimine **1e** and gives the betaine **296**, which yields the tetrazine derivative **297** upon heating the ethanol.[152,153]



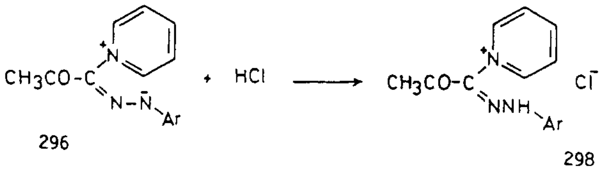
1e

295

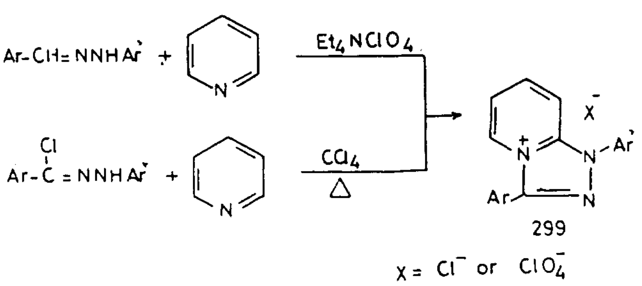
296

297

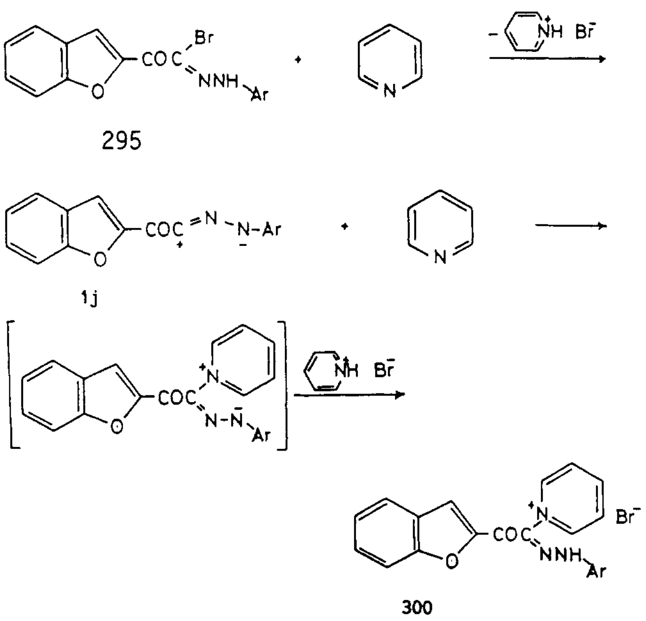
The betaine **296** reacts also with hydrogen chloride to give the pyridinum salt **298**. Salts of the latter type **298** had also been obtained by coupling acetonylpyridinium halides with diazotized anilines.[57]



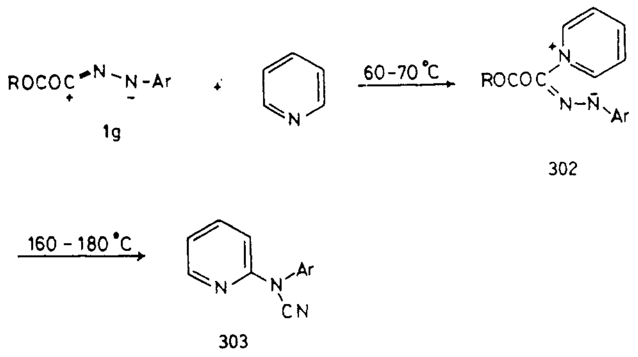
Diphenylnitrilimine (**1a**), generated from the corresponding hydrazonyl chloride, reacts with pyridine in refluxing carbon tetrachloride to give the bicyclic salt **299**.[154] Also, *s*-triazolo[4,3-*a*]pyridinium perchlorates were obtained by reaction of diarylnitrilimines, generated by anodic oxidation of the corresponding aldehyde arylhydrazones, with pyridine in the presence of perchlorate salt as electrolyte.[36,39]

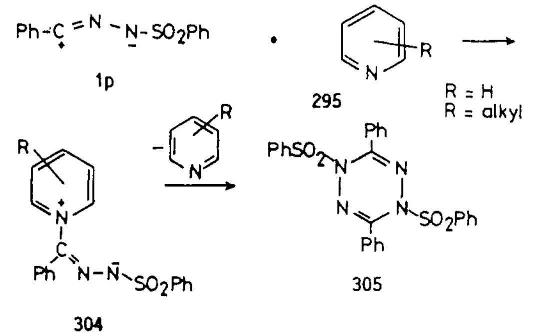


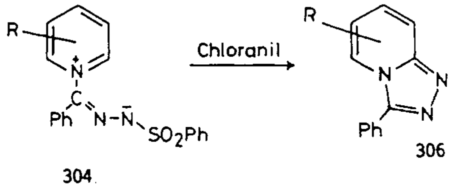
Hydrazonyl halides of type **295**, which are the precursors of heteroaroylnitrilimines **1j**, forms the pyridinium salts **300** when treated with pyridine.[155]



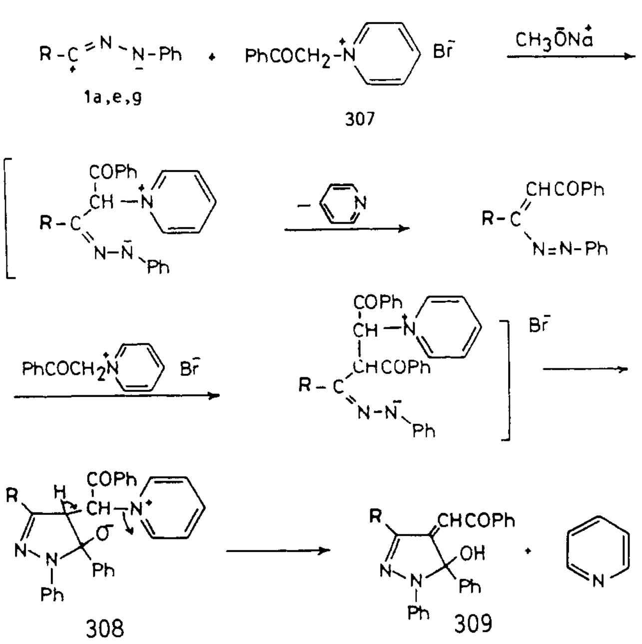
Fusco et al.[156] reported, however, that the betaine **302** obtained from the reaction of pyridine with *C*-(ethoxycarbonyl)nitrilimine **1g** underwent a complex transformation process upon heating to give the cyanamide derivatives **303**. Earlier, it was indicated that the betaines **304** isolated from the reaction of pyridine and alkylpyridines with *N*-(phenylsulfonyl)benzonitrilimine (**1p**) yields the corresponding tetrazine **305** when dissolved in dichloromethane or tetrahydrofuran.[157] On the other hand, treatment of **304** with chloranil in benzene or dioxane afforded the triazolo[4,3-*a*]pyridine derivatives **306** together with small amounts of tetrazine **305**.[157]



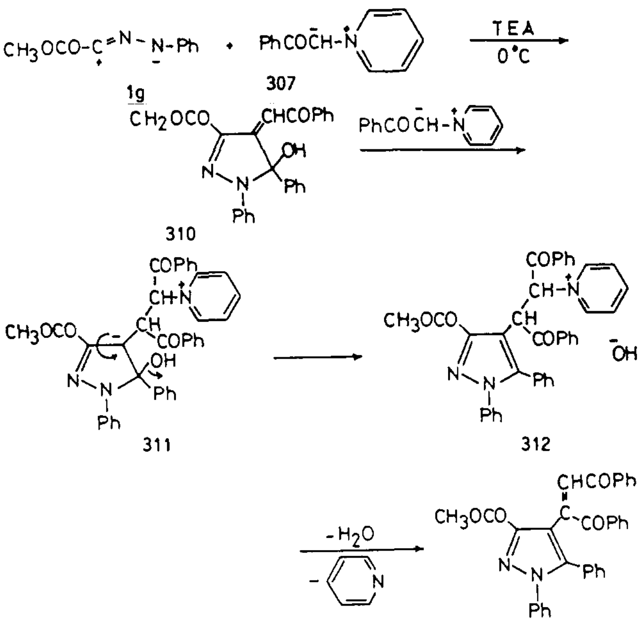




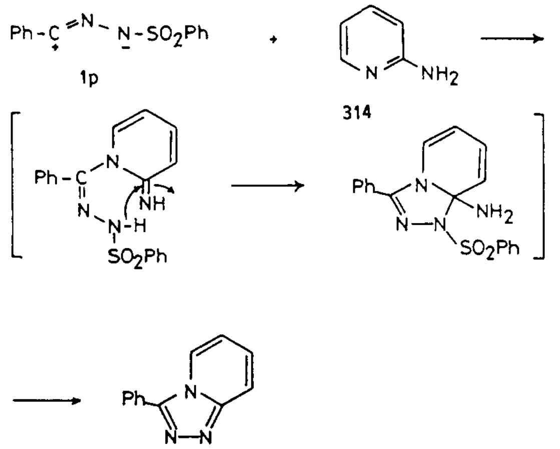
N-Phenacylpyridinium bromide (**307**) was reported to react with nitrilimines of types **1a**, **1e** and **1g** and gives the corresponding 2-pyrazoline derivatives **309a**, **309b**, and **309c**, respectively.[158-160] However, reaction



of *C*-(methoxycarbonyl)nitrilimine **1g** with **307** was reported to give a mixture of **310** (R = CH_3OCO) and **313**.[159] The formation of the latter product **313** was assumed to result from Michael addition of the betaine, derived from **307**, to **310** to give **311**, which underwent elimination of water and pyridine to yield **313** as the end product.



2-Aminopyridine (**314**) yields 1,3,4-triazolo[4,3-*a*]-pyridine **315** when treated with *N*-(phenylsulfonyl)-nitrilimine **1p**.[161] However, its reaction with *C*-acylnitrilimines **1e,f** was reported to give the corresponding 2-substituted-3-arylazoimidazo[1,2-*a*]pyridines **317**.[77,98,101,102,162] *C*-(Ethoxycarbonyl)nitrilimines **1g** react with 2-aminopyridine (**314**) to yield 2-oxo-3-arylhydrazonoimidazo[1,2-*a*]pyridines (**319**).[98] When the precursor of the *C*-(ethoxycarbonyl)-*N*-heteroarylnitrilimine **1q** was treated with 2-aminopyridine (**314**), it underwent intramolecular cyclization to give the pyrazolo[5,1-*c*]-1,2,4-triazole derivative **320**, however.[163]



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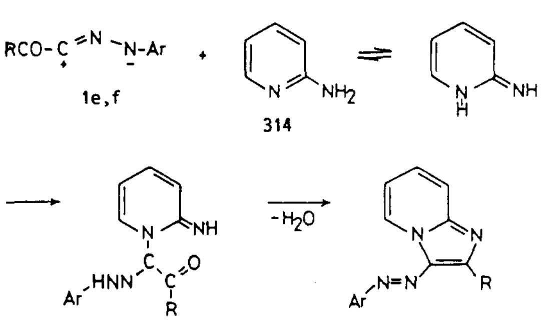

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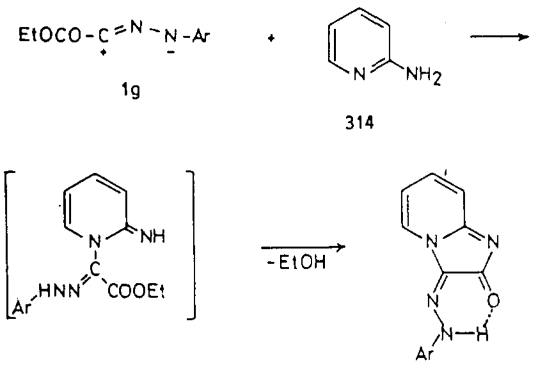
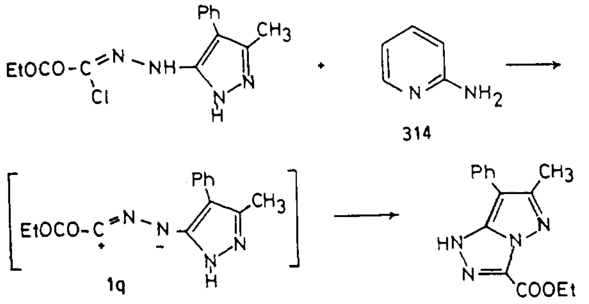


319



320

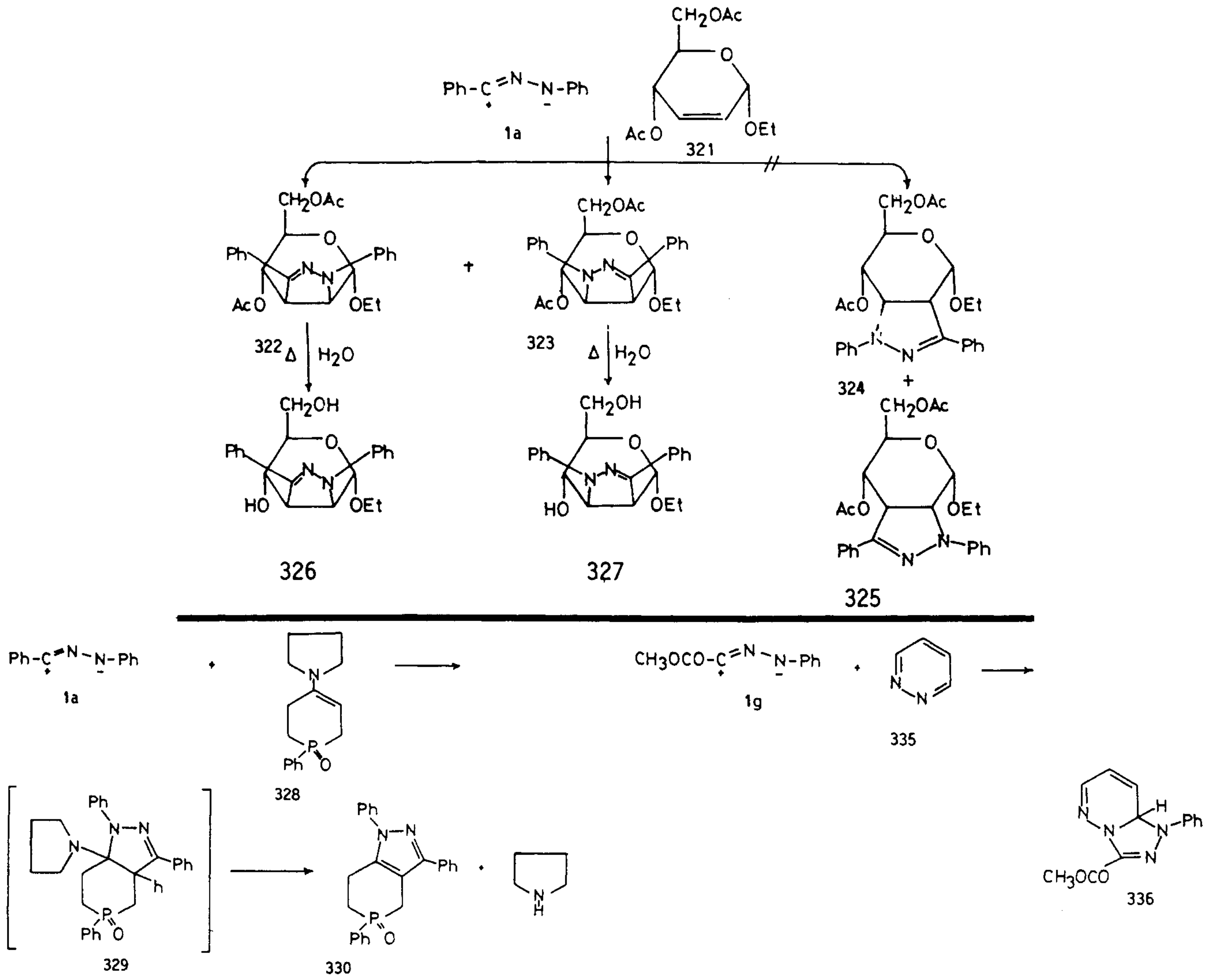
2. Pyrans

Diphenylnitrilimine (**1a**) cycloadds to the pyranoside derivative **321** and yields a mixture of the two regioisomeric cycloadducts **322** and **323**.[164] The other diastereomeric cycloadducts **324** and **325** were not produced. Heating of the cycloadducts **322** and **323** in water in the presence of triethylamine leads to the formation of **326** and **327**, respectively[164] (Scheme VIII).

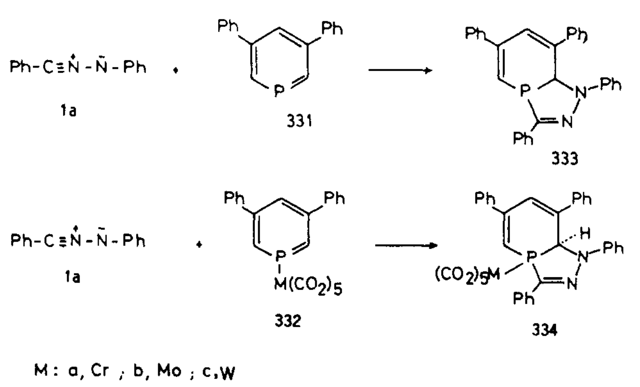
3. Phosphorans

Reaction of phosphorinanone enamine **328** with diphenylnitrilimine (**1a**) gives the cycloadduct **329**, which eliminates pyrrolidine to give the bicyclic product **330**.[165]

Scheme VIII



3,5-Diphenylphosphinine (**331**) and its metal carbonyl complexes **332** react with diphenylnitrilimine (**1a**) and yield the corresponding cycloadducts **333** and **334**, respectively.[166]



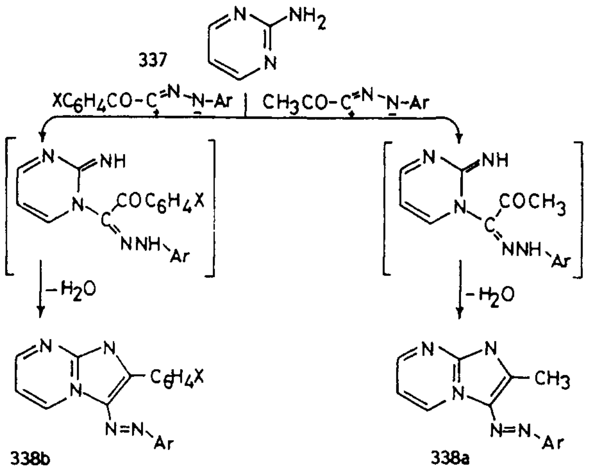
G. Reactions of Six- and Seven-Membered Heterocycles with Two or More Heteroatoms

1. Pyridazines

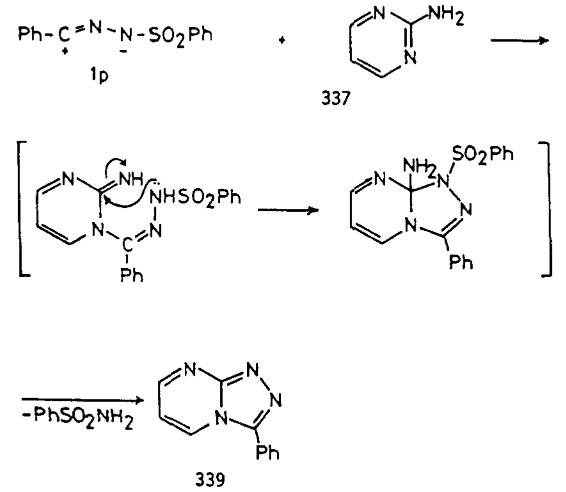
Reaction of *C*-(methoxycarbonyl)nitrilimine **1g** with pyridazine (**335**) was reported to give the 1,3-cycloadduct **336**.[167]

2. Pyrimidines

2-Aminopyrimidine (**337**) reacts with *C*-acylnitrilimines **1e** and **1f** to give the corresponding imidazo[1,2-*a*]pyrimidines **338a** and **338b**, respectively.[98] How-

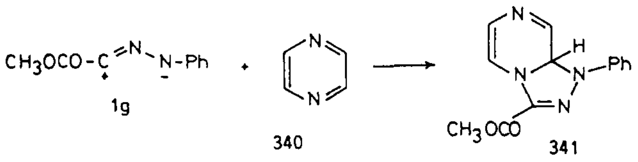


ever, reaction of **337** with *N*-(phenylsulfonyl)nitrilimine **1p** afforded the triazolo[4,3-*a*]pyrimidine **339** via the reaction sequence indicated below.[161]

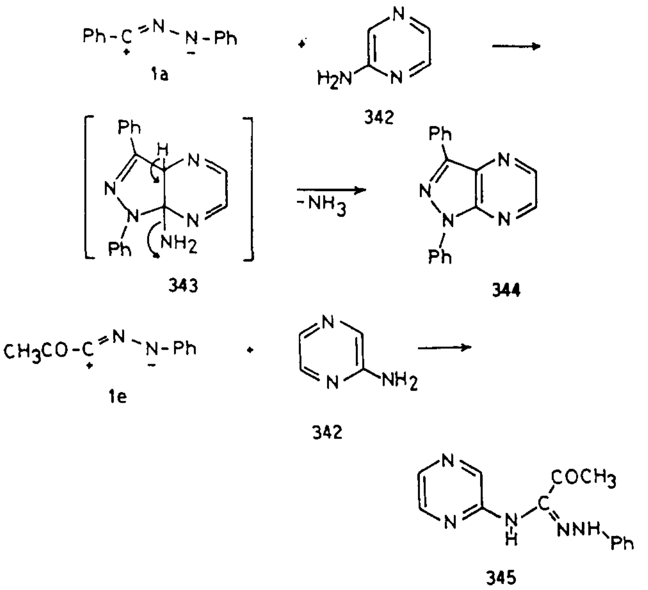


3. Pyrazines

Unsubstituted pyrazine **340** reacts with *C*-(methoxycarbonyl)nitrilimine **1g** and yields the correspondng 1,3-adduct **341**.[167]

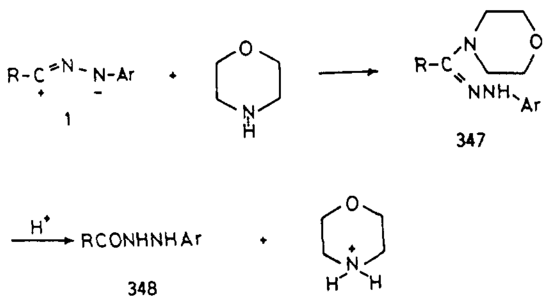


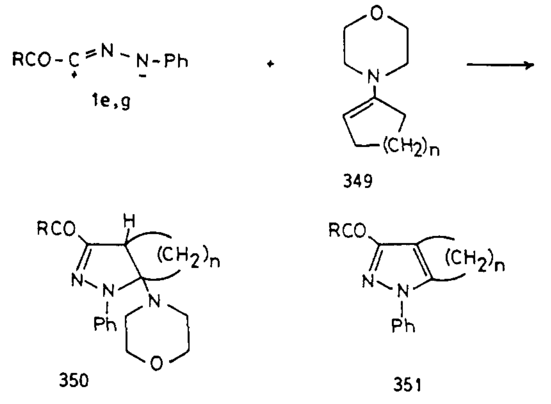
Reaction of 2-aminopyrazine (**342**) with diphenylnitrilimine (**1a**) yields the pyrazolo[3,4-*b*]pyrazine derivative **344** via elimination of ammonia from the intermediate cycloadduct **343**.[106,107] However, the reaction of **342** with *C*-acetylnitrilimine **1e** was reported to yield the amidrazone **345**.[107]



4. Morpholines

The reaction of morpholine with various nitrilimines was extensively studied.[151,168-170] In all cases the reaction yields the corresponding 1,3-adduct **347**, which hydrolyzes readily when refluxed in acetic acid to give the corresponding hydrazide **348**. However, reaction of morpholino enamine **349** with nitrilimines of type **1e** and **1g** was reported to give the cycloadducts **350**, which eliminate morpholine to yield the cycloalkanopyrazole derivatives **351a** and **351b** respectively.[67]



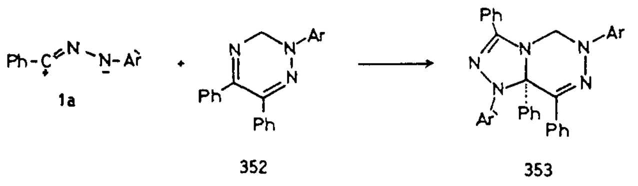


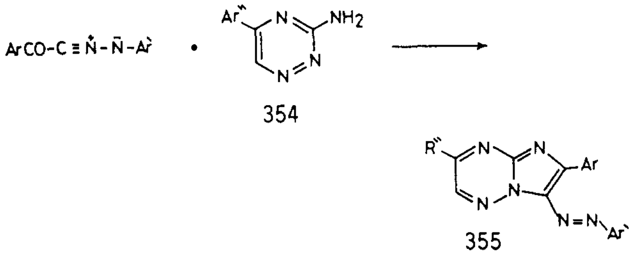
	R
a	CH_3
b	OEt

n = 3, 4, 5

5. 1,2,4-Triazines

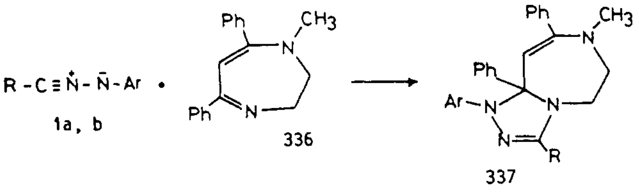
Diarylnitrilimines (**1a**) react with 1,2,4-triazine derivatives **352** and yield the triazolo[4,3-*d*]-1,3,4-triazine derivatives **353**.[171] However, reaction of *C*-aroylnitrilimines **1f** with 3-amino-1,2,4-triazine derivatives **354** afforded 7-arylazoimidazo[1,2-*b*]1,2,4-triazines **355**.[172]





6. Diazepines

Treatment of the diazepine derivative **356** with nitrilimines **1a,b** afforded 1,2,4-triazolo[4,3-*d*]diazepines **357**.[173] The reaction proved to be peri-selective and regioselective.

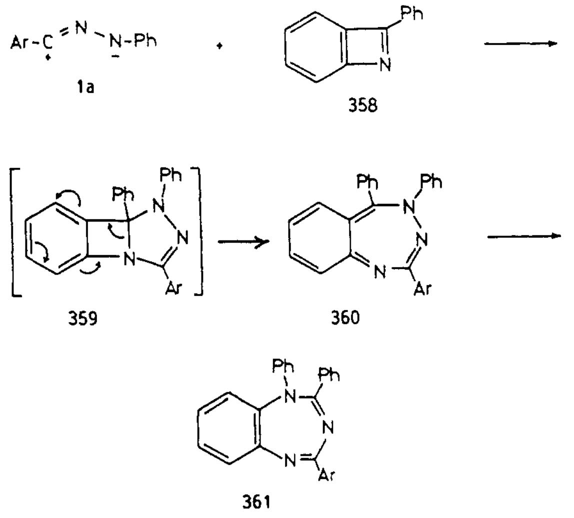


R / Ar : Ph / Ph ; CF_3 / Ph ; CF_3 / 4-BrC_6H_4

H. Reactions of Two-Ring Heterocycles with One Heteroatom

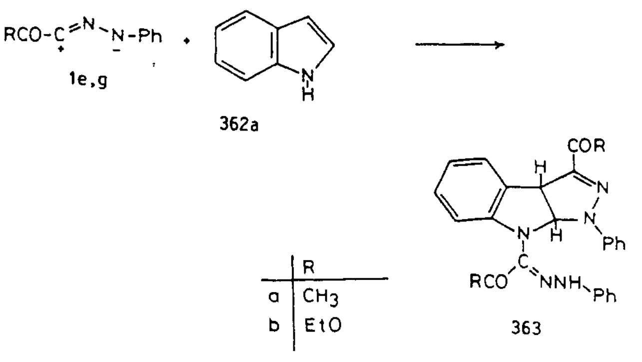
1. Benzazete

Addition of diarylnitrilimines (**1a**) to 2-phenylbenzazete (**358**) gives the cycloadducts **359**, which undergo ring opening to the corresponding benzo[*e*]-1,2,4-triazepines **360**.[174] The latter products rearrange to give benzo[*f*]-1,3,5-triazepines **361** by electrocyclic ring closure to diaziridine, a 1,5-*N*-aryl shift, and ring opening. In some cases the latter rearrangement occurs spontaneously so that **360** was not isolated.[174]

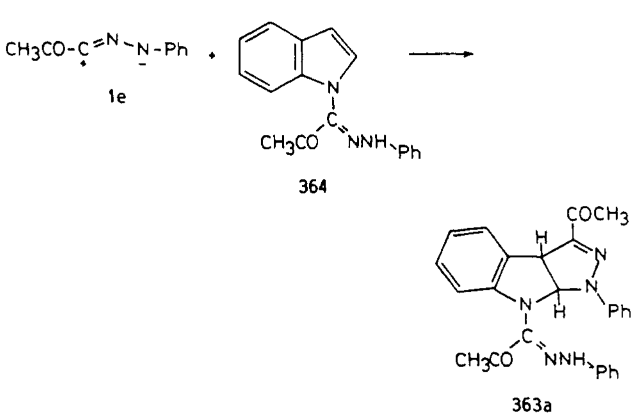


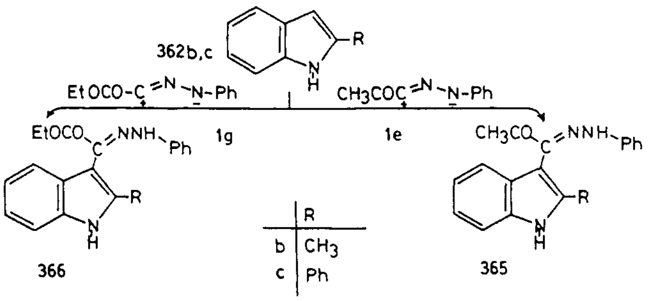
2. Indoles

Unsubstituted indole **362a** reacts with the nitrilimines **1e** and **1g** and gives the corresponding bis-adducts **363a** and **363b**, respectively.[175] Compound **363a** was also produced by the reaction of *N*-indolylpyruvaldehyde phenylhydrazone **364** with *C*-acetylnitrilimine **1e**.[175] However, reactions of 2-substituted indoles **362b** and **362c** with the nitrilimines **1e** and **1g** were reported to give the 3-hydrazonylindole derivatives **365** and **366**, respectively.[175]



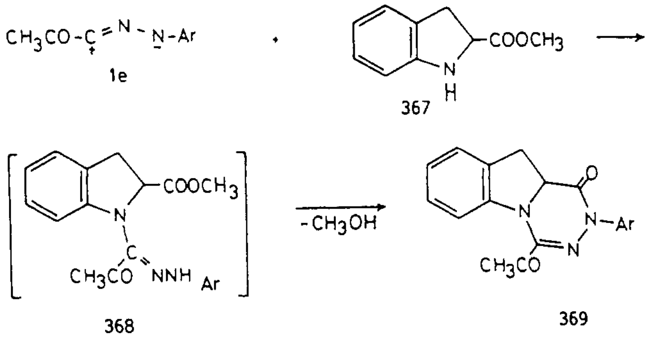
	R
a	CH_3
b	EtO





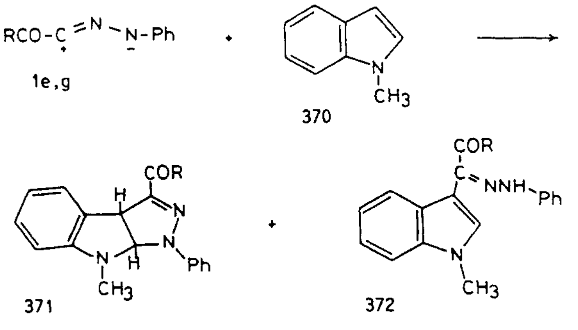
	R
b	CH_3
c	Ph

Very recently, it was indicated that 2-(methoxycarbonyl)-2,3-dihydroindole (**367**) reacts with *C*-acetylnitrilimine **1e** to yield the 1,3-adduct **368**, which cyclized readily to the tricyclic products **369**.[122]

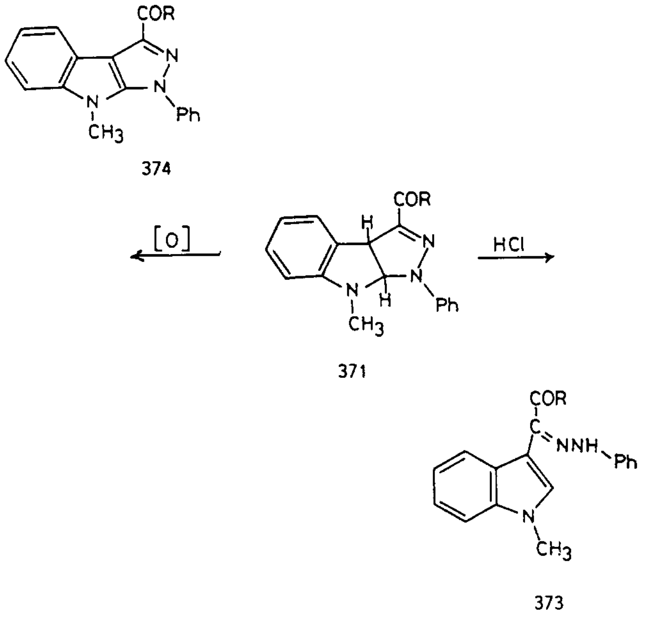


Ar = C_6H_4 , 4-FC_6H_4 , 4-ClC_6H_4

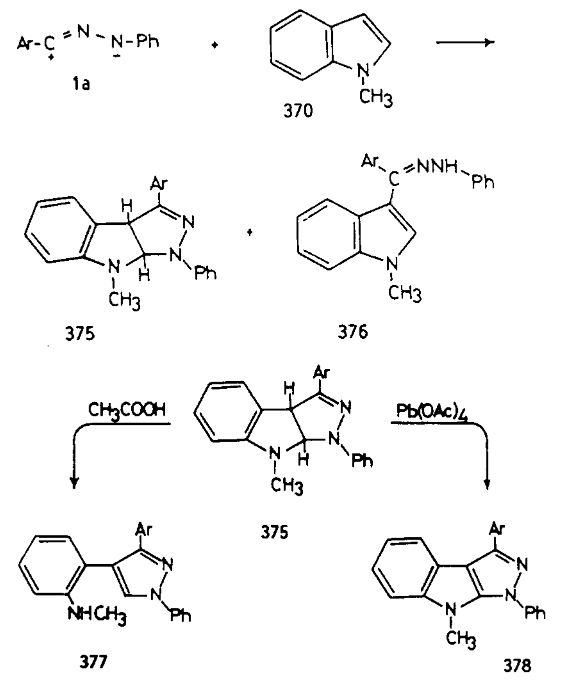
N-Methylindole (**370**) reacts with the nitrilimines **1e** and **1g** and gives in each case a mixture of the products **371** and **372** in 35% and 8–13% yields, respectively.[175,176]



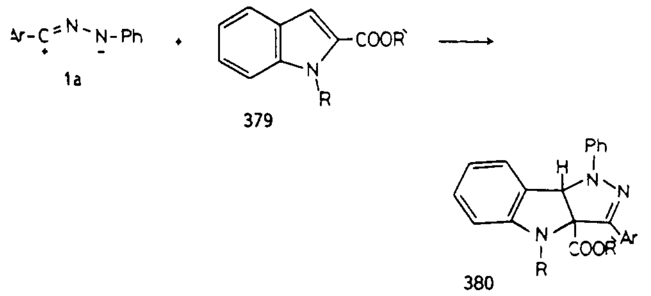
In another report it was indicated that this same reaction yields only the cycloadducts **371**.[177] The treatment of the former product **371** with hydrochloric acid converts it to **373**.[175,176] This may invalidate the previous assumption that the products **373** result from the 1,3-addition of nitrilimine to **370** to give **373** followed by proton transfer.[175] Also, compound **371** undergoes aromatization when treated with chloranil in refluxing xylene.[176]

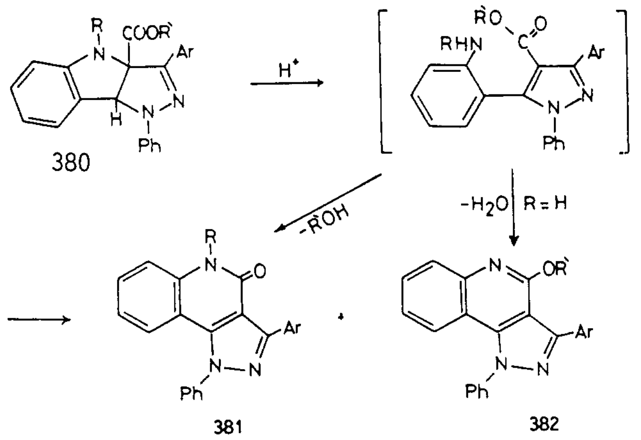


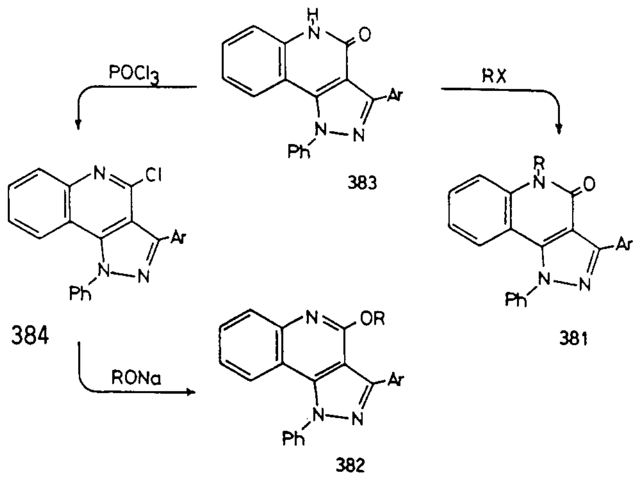
Diarylnitrilimines (**1a**) react similarly with *N*-methylindole (**370**) and give in each case a mixture of the products **375** and **376**.[177] Unlike **371**, the cycloadducts **375** yielded **377**, when refluxed in acetic acid, and **378**, when treated with lead tetraacetate.[175]



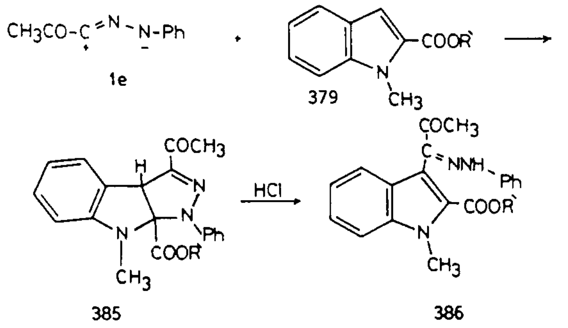
Reaction of 2-(alkoxycarbonyl)-1-substituted-indoles **379** with diarylnitrilimines (**1a**) afforded only one regioisomeric cycloadduct in each case, identified as **380**.[178] Acid treatment of the latter yielded a mixture of the pyrazoloquinolines **381** and **382**.[178] The structures of the products **381** and **382** were confirmed by their alternate syntheses from the pyrazoloquinoline derivative **383**[178] using Friedlander's condensation.[179]



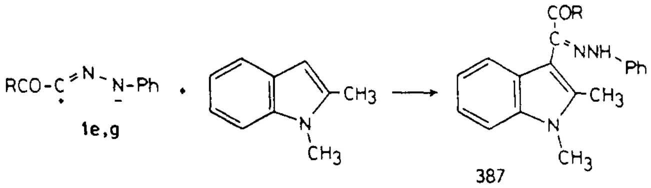




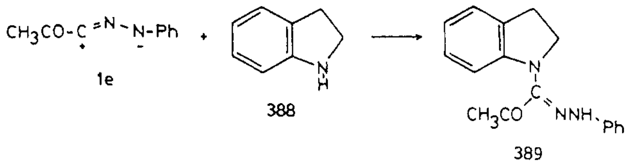
C-Acetylnitrilimines **1e** react similarly with indole derivatives **379** and yield the cycloadducts **385**.[175] The products undergo hydrolytic cleavage when treated with acid and give the phenylhydrazone adducts **386**.[175]



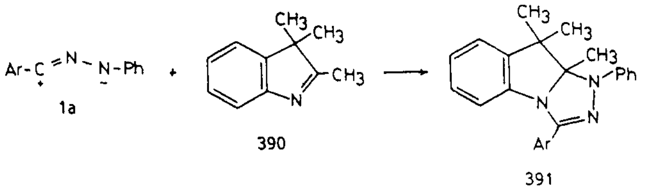
1,2-Dimethylindole reacts with the nitrilimines **1e,g** and yields only the 1,3-adducts **387**.[175,180]



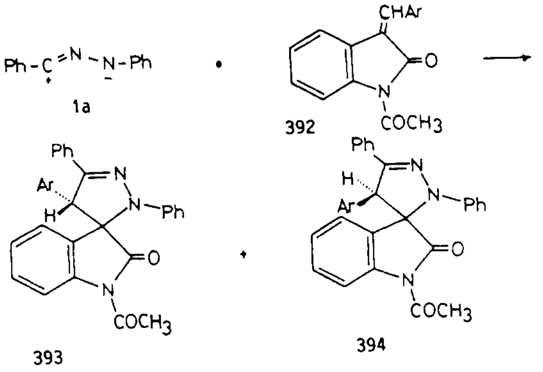
Indoline **388** yields the amidrazone **389** when treated with the *C*-acetylnitrilimine **1e**.[175]



1,2,4-Triazolo[4,5-*a*]indoles **391** were produced in almost quantitative yields when diarylnitrilimines (**1a**) reacted with 2,3,3-trimethyl-3*H*-indole (**390**).[181]

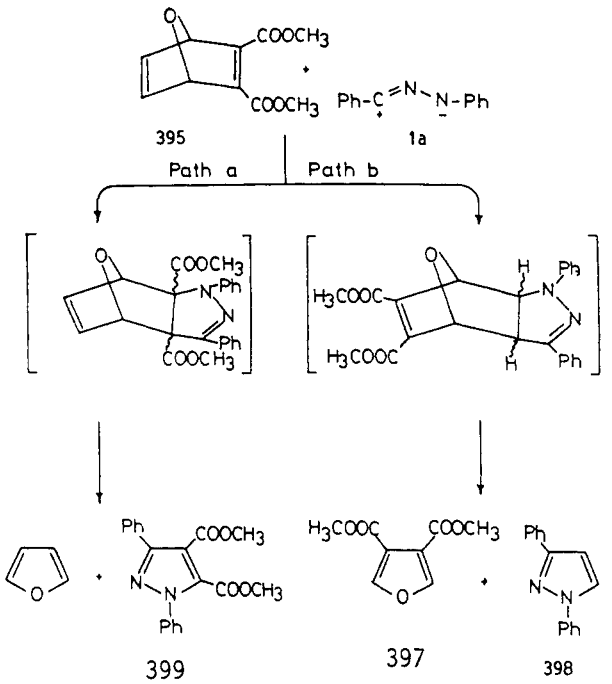


Reaction of diphenylnitrilimine (**1a**) with 1-acetyl-3-arylideneindolin-2-ones (**392**) afforded in each case a pair of diastereoisomeric spiro[pyrazole-5,3′-indolin]-2′-ones **393** and **394**.[115]



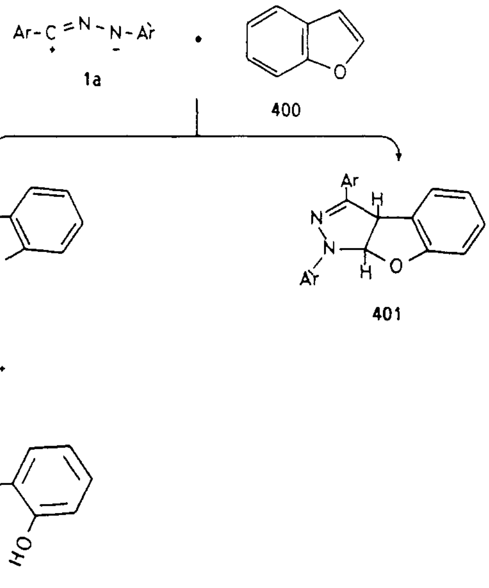
3. 7-Oxabicyclo[2.2.1]hepta-2,5-dienes

The reaction of diphenylnitrilimine (**1a**) with 2,3-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene (**395**) was investigated to determine the site selectivity and stereoselectivity.[182] The results showed that this reaction yielded furan and the pyrazole derivative **399** as major products and **397** and **398** as minor products. Such results indicate that the cycloaddition occurs preferentially at the more substituted double bond (path a).[182]

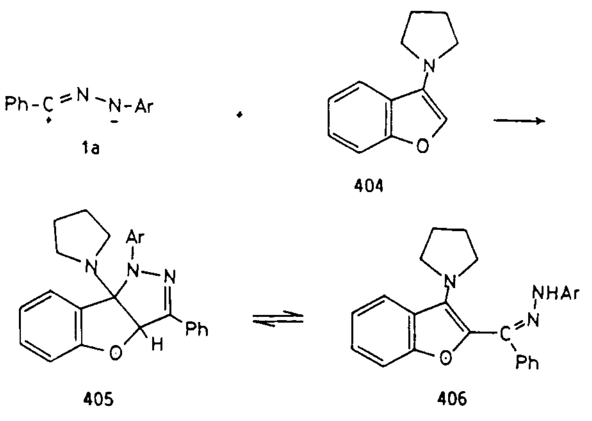


4. Benzo[*b*]furans

Reaction of benzofuran (**400**) with diarylnitrilimines (**1a**) was reported to give the cycloadducts **402**.[178,183] However, it was shown in an earlier report that the products of such a reaction are the other regioisomers **401**.[175,184] Treatment of the cycloadducts **402** with acid afforded the triarylpyrazole derivatives **403**.[183]

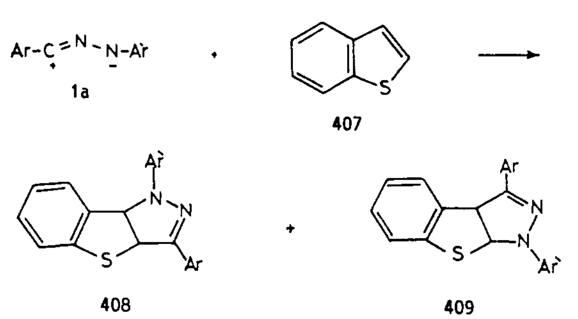


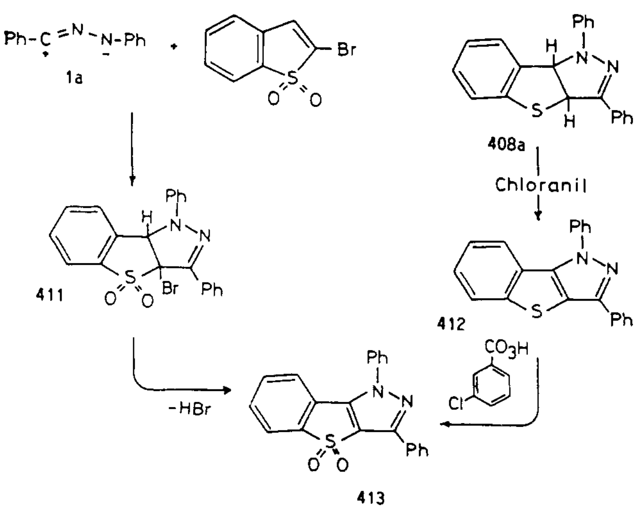
3-(*N*-Pyrrolidinyl)benzofuran (**404**) reacts with diarylnitrilimines (**1a**) to give a mixture of benzofurano[3,2-*c*]pyrazolines **405** and 2-benzoylbenzo[*b*]furan arylhydrazones **406**.[184]



5. *Benzo[b]thiophenes*

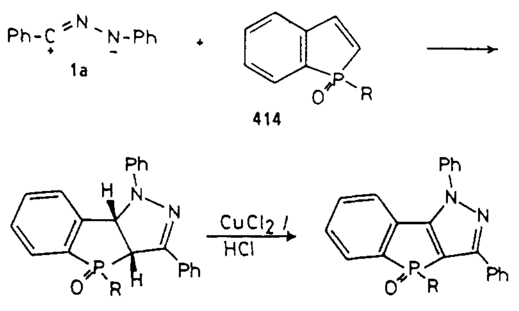
Reactions of diarylnitrilimines (**1a**) with unsubstituted benzo[*b*]thiophene (**407**) yield in each case a mixture of the two regioisomeric 1,3-cycloadducts **408** and **409**.^{178} However, reaction of diphenylnitrilimine (**1a**) with 2-bromobenzo[*b*]thiophene 1,1-dioxide was reported to be regiospecific, yielding only the 1,3-cycloadduct **413**.^{180,185} It was assumed that the cycloadduct **411** formed in the first step underwent dehydrobromination to give **413**. The structure of the latter product **413** was confirmed by its alternate synthesis by dehydrogenation of **408a** to give **412** and oxidation of the latter with *m*-chloroperbenzoic acid.^{180,185}





6. *Benzo[b]phosphindoles*

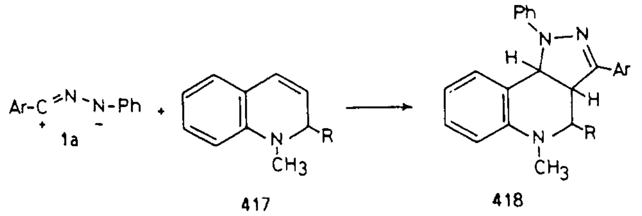
Diphenylnitrilimine (**1a**) reacts with phosphindole oxides **414** to yield the cycloadducts **415**.^{186} This cycloaddition proved to be regiospecific. Oxidation of **415** afforded **416**.^{187}

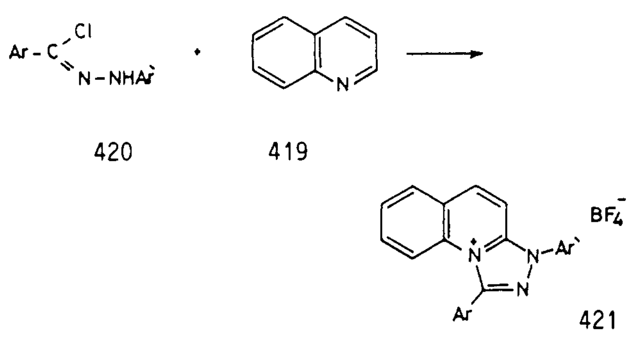


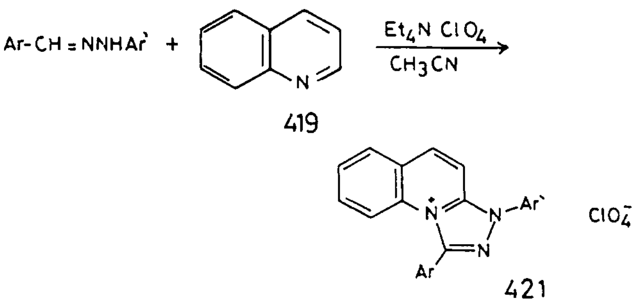
	R
a	CH_3
b	Ph

7. *Quinolines and Isoquinolines*

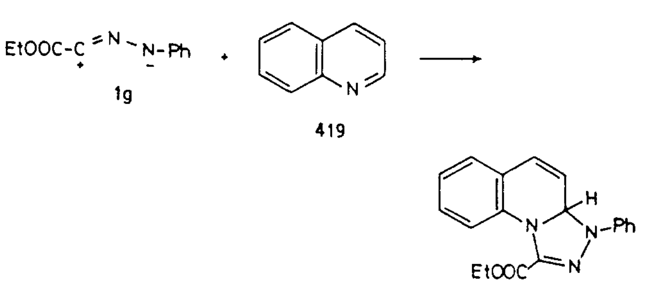
N-Methyl-2-alkyl-1,2-dihydroquinolines (**417**) react with diarylnitrilimines (**1a**) and give a single cycloadduct, **418**, in each case.^{242} Treatment of diarylnitrilimine precursors **420** with quinoline **419** in refluxing carbon tetrachloride followed by treatment with tetrafluoroboric acid afforded the triazolquinolinium salts **421**.^{154} Similarly, the perchlorate salts **421** were obtained by anodic oxidation of aldehyde arylhydrazones in acetone–tetraethylammonium perchlorate in the presence of quinoline.^{39}







A high yield of the triazolo[4,3-*a*]quinoline derivative **422** was isolated from the reaction of quinoline (**419**) with *C*-(ethoxycarbonyl)nitrilimine **1g**.^{91} Contrary to this, it was reported that the reaction of quinoline **419**

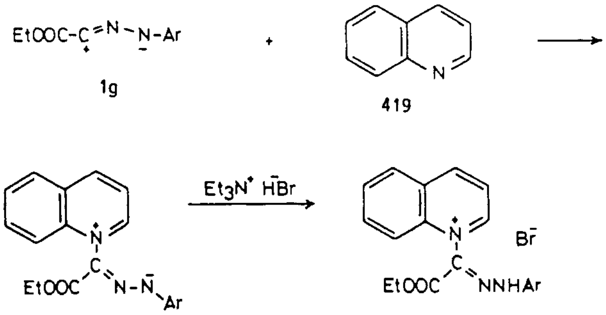


1g

419

422

with **1g** at 40–50 °C in ethanol afforded the 1,3-adduct **424**.[91] If this reaction is carried out at 160 °C, it yields

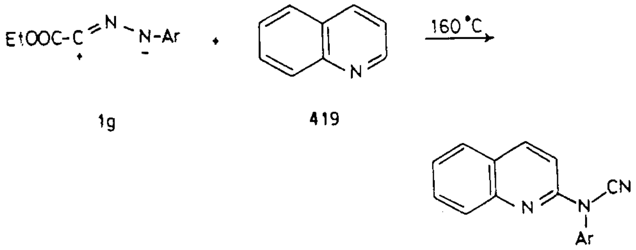


1g

419

424

the 2-quinoline derivative **425**.[91]

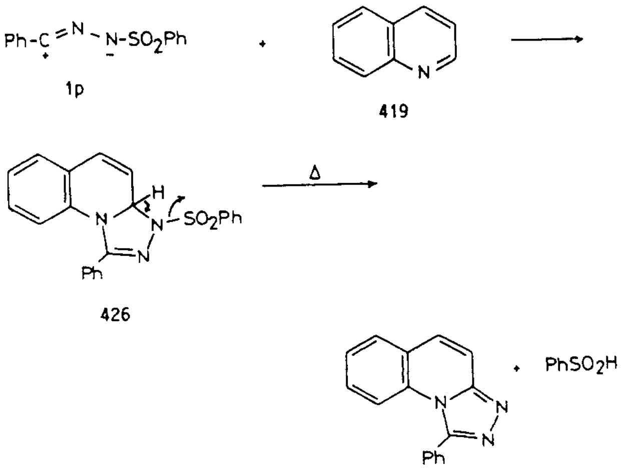


1g

419

425

Reaction of quinoline **419** with *N*-(phenylsulfonyl)nitrilimine **1p** was reported to give the triazolo[4,3-*a*]quinoline **426**.[157] Heating of the latter in dioxane causes elimination of benzenesulfinic acid to give **427**.[157]



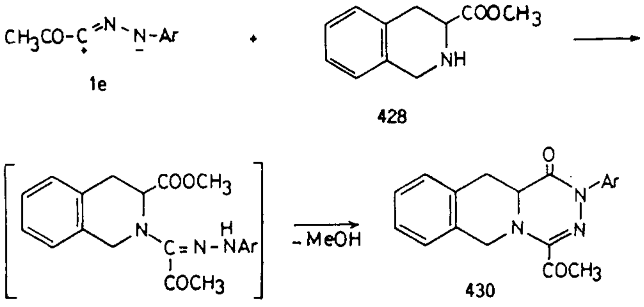
1p

419

426

427

Recently, the reaction of 3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (**428**) with *C*-acetylnitrilimines **1e** was reported to give the 1,3-adducts **429**, which cyclized readily to give the tricyclic products **430**.[122]



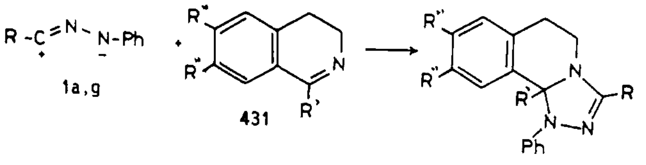
1e

428

429

430

3,4-Dihydroisoquinolines **431** react with the nitrilimines **1a,g** to give the corresponding 1,2,4-triazolo[3,4-*a*]isoquinoline derivatives **432**.[189] Very recently, the cycloadditions of the nitrilimines **1a,g** to the 3,4-dihydroisoquinoline derivatives **431d–g**, having an active methyl or methylene group at C-1, were reported.[188] The reactions afforded good yields of the corresponding cycloadducts **433**.[188] The authors did not exclude the possibility of the formation of the cycloadducts of type **433A**. No evidence was given to confirm or disprove this conclusion, however.[188]

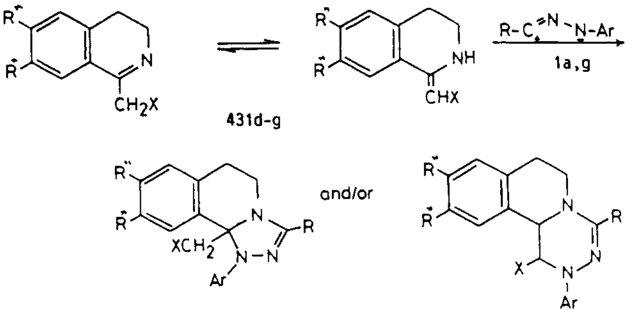


1a,g

431

432

R'/R'' : a,H/H; b, H/CH_3O; c, C_6H_5/CH_3O



431d-g

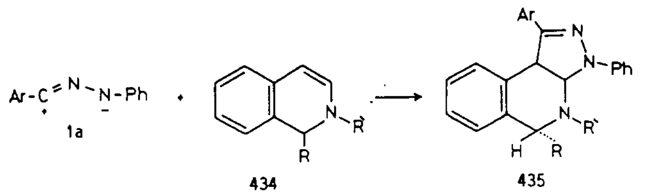
433A

433

X/R'' : d, H/CH_3O ; e, COOEt/CH_3O ;

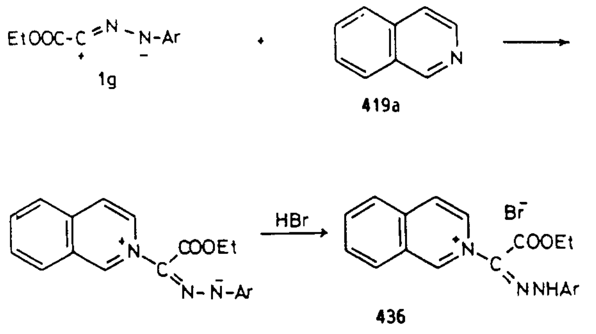
f, CN/CH_3O ; g, 3,4-$(EtO)_2C_6H_3$/EtO

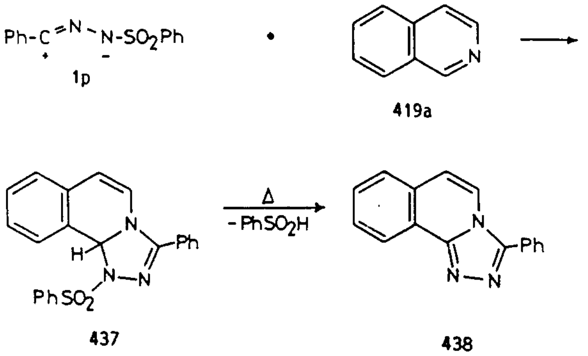
2-Monosubstituted and 1,2-disubstituted 1,2-dihydroisoquinoline derivatives **434a–d**[189] and **434e–l**[190] react with diarylnitrilimines **1a** to yield the corresponding cycloadducts **435**. On the other hand, reaction of 1-*tert*-butyl-2-ethyl-1,2-dihydroisoquinoline (**434m**) with diarylnitrilimines (**1a**) results in the elimination of the *tert*-butyl group as isobutylene and the formation of the cycloadducts **435b**.[190]



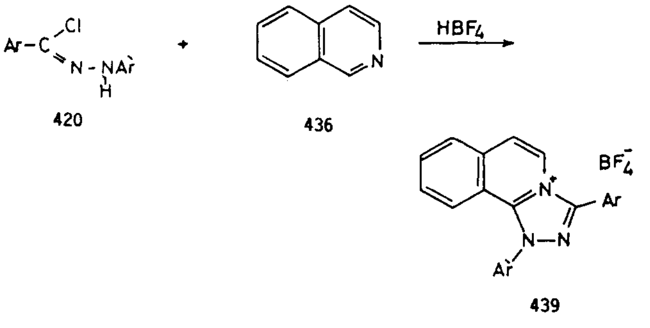
R /R' : a, H/CH_3; b, H/Et; c, H/n-Bu; d, $H/PhCH_2$;
e, CH_3/CH_3; f, CH_3/Et; g, CH_3/i-Pr;
h, Et/CH_3; i, Et/Et; j, i-Pr/CH_3;
k, i-Pr/Et; l, t-Bu/H; m, t-Bu/Et

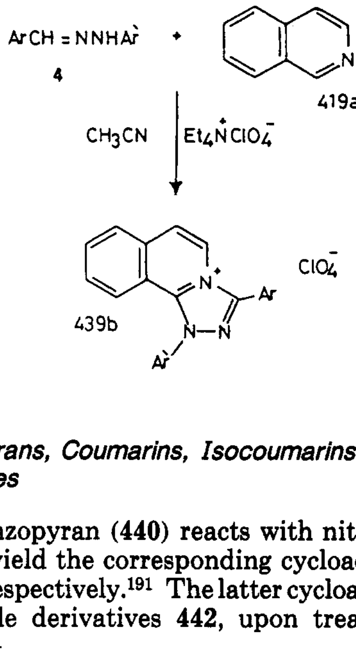
Reactions of unsubstituted isoquinoline with nitrilimines give different products, depending on the type of nitrilimine used. Thus, whereas reaction of **1g** with isoquinoline had been reported to give the 1,3-adducts **436**,[91] its reaction with (phenylsulfonyl)nitrilimine **1p** afforded the 1,2,4-triazolo[3,4-*a*]isoquinoline **437**, which upon thermolysis in dioxane yielded **438**.[157]





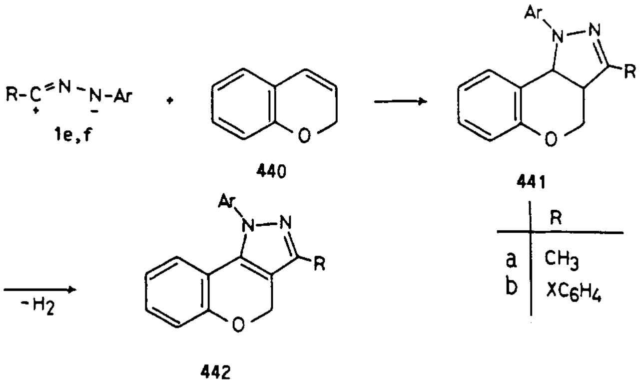
Also, isoquinoline reacts with the diarylnitrilimine precursors **420** in carbon tetrachloride to yield **439** after treatment with tetrafluoroboric acid.[154] Similarly the perchlorate salts **439b** were also obtained by the anodic oxidation of aldehyde arylhydrazones in acetonitrile–tetraethylammonium perchlorate in the presence of isoquinoline **436**.[39]





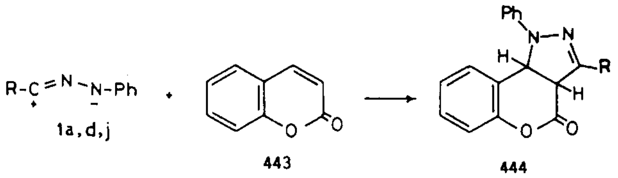
8. Benzopyrans, Coumarins, Isocoumarins, and 4-Chromones

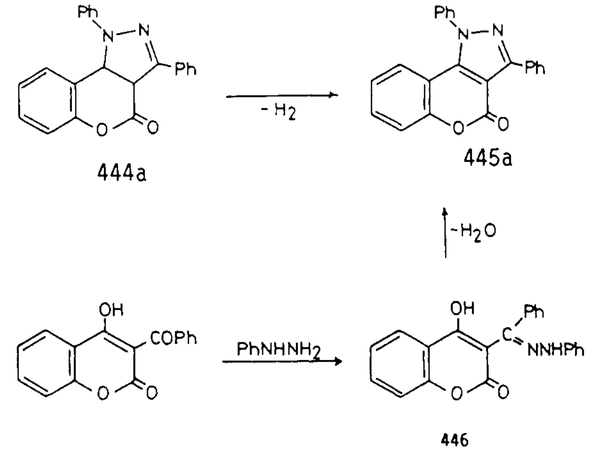
2*H*-1-Benzopyran (**440**) reacts with nitrilimines **1a** and **1b** to yield the corresponding cycloadducts **441a** and **441b**, respectively.[191] The latter cycloadducts yield the pyrazole derivatives **442**, upon treatment with chloranil.[191]



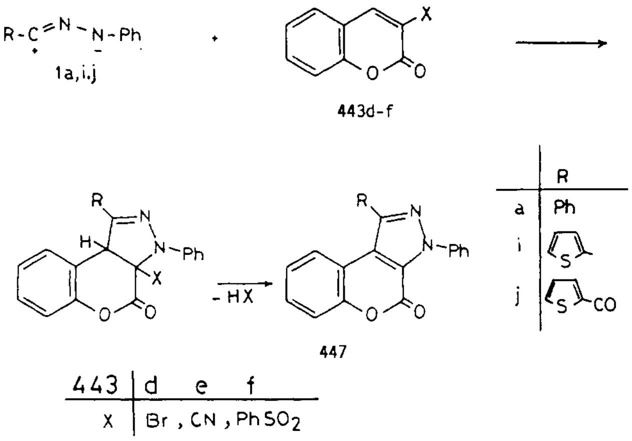
	R
a	CH_3
b	XC_6H_4

Unsubstituted coumarin **443** reacts with nitrilimines of types **1a** and **1i** and yields the corresponding 1,3-disubstituted 4-oxo-1*H*-benzopyrano[4,3-c]pyrazoline derivatives **444a** and **444b**, respectively.[192–194,197] The other possible regioisomers were not produced, however. Dehydrogenation of the latter cycloadducts with chloranil afforded **445**.[193] Compound **445a** was also prepared by heating a mixture of 3-benzoyl-4-hydroxycoumarin with phenylhydrazine and refluxing the resulting hydrazone **446** with ethanolic hydrochloric acid.[193]



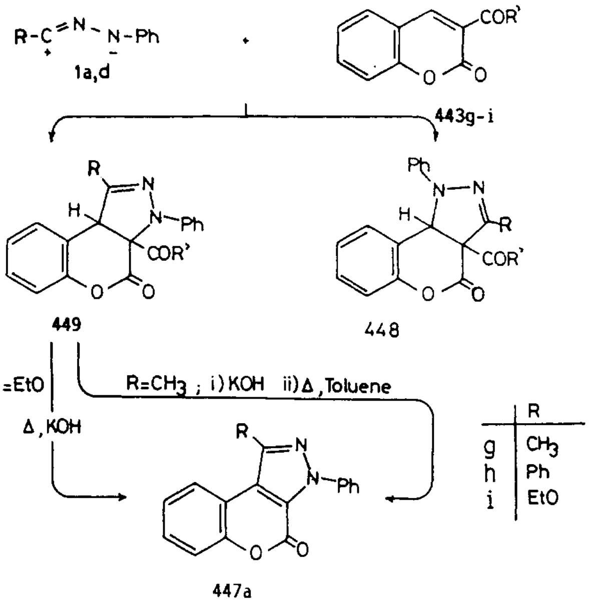


Nitrilimines **1a**, **1i**, and **1j** react with 3-cyano-, 3-bromo-, and 3-(phenylsulfonyl)coumarins **443d**, **443e**, and **443f** to give in all cases the corresponding benzopyranopyrazole derivatives **447a**, **447b**, and **447c**, respectively.[196,197] In such cases, the initially formed cycloadducts seem to undergo the elimination of the elements of an acid (HX) as soon as they are formed, to give **447**.



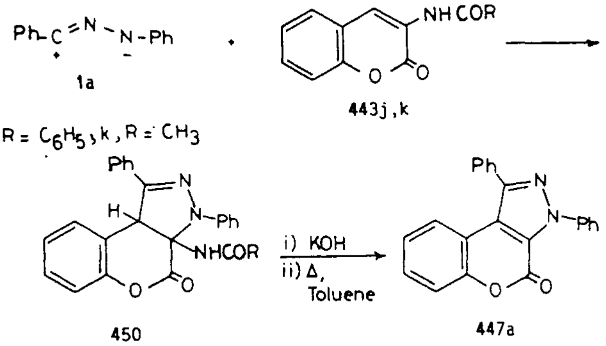
443	d	e	f
X	Br	CN	PhSO2

Different conclusions have been reported on the regiochemistry of the cycloaddition of diphenylnitrilimine **1a** to 3-acyl- and 3-(ethoxycarbonyl)coumarins **443g–i**. In one report, Shawali et al.,[193] on the basis of FMO calculations, assigned structure **448** to the cycloadducts isolated from such reactions. In another report, Fathi et al.[194] indicated that the same reactions afforded the other regioisomeric cycloadducts **449a–c**. This was confirmed by conversion of **449a** into **447a** by heating it in aqueous potassium hydroxide solution followed by heating the resulting crude product in toluene. Also, the thermolysis of **449a** (R = C_2H_5O) in aqueous potassium hydroxide solution afforded **447a**.[194] Reactions of *N*-phenylcinnamonitrilimine **1d** with the coumarin derivatives **443g–i** were reported to give products of type **449** too.[197]

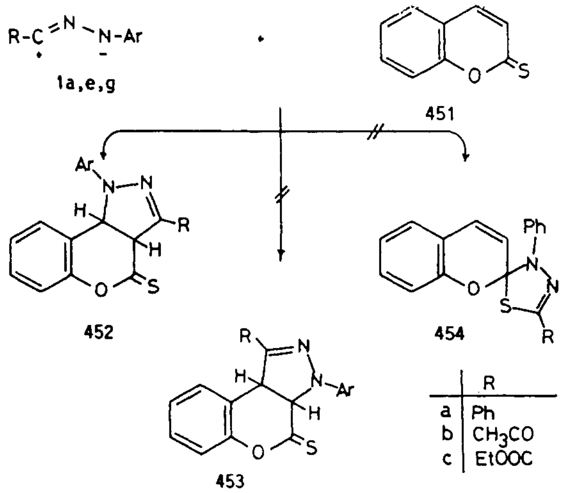


	R
g	CH3
h	Ph
i	EtO

Recently, it was reported that reaction of diphenylnitrilimine (**1a**) with 3-(acylamino)coumarins **443j,k** yielded the cycloadducts **450a,b**. Thermolysis of the product **450a** in toluene in the presence of sodium hydroxide yielded the pyrazolocoumarin **447a**.[198]

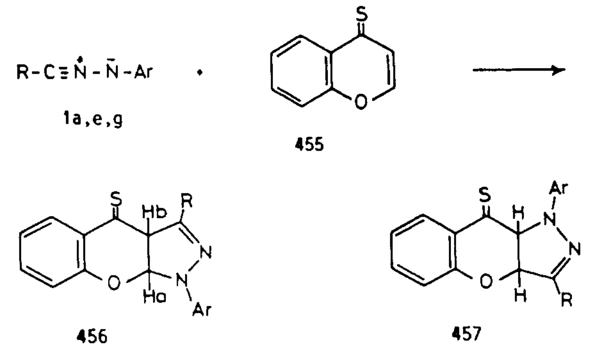


2*H*-1-Benzopyran-2-thione (**451**) reacts with the nitrilimines **1a**, **1e**, and **1g** to yield the cycloadducts **452a**, **452b**, and **452c**, respectively.[199] It was reported that there was no evidence for the formation of the other regioisomers **453** or the spirocycloadducts **454**.[199]



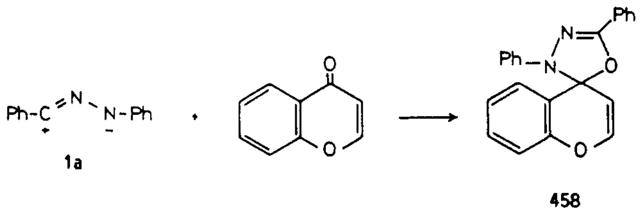
	R
a	Ph
b	CH3CO
c	EtOOC

4*H*-1-Benzopyran-4-thione (**455**) reacts smoothly with various nitrilimines (**1a,e,g**) regioselectively to yield the cycloadducts **456**.[200] None of the other regioisomers (**457**) could be detected. However, the spirooxadiazole **458** was obtained by the reaction of diphenylnitrilimine



1a,e,g 455 456 457

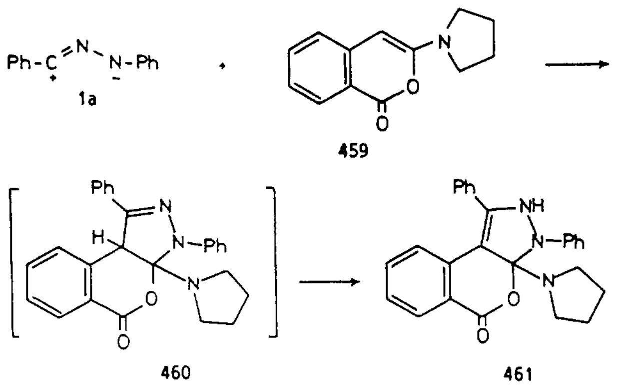
(1a) with chromone 457.[192] The formation of 458 was



1a 458

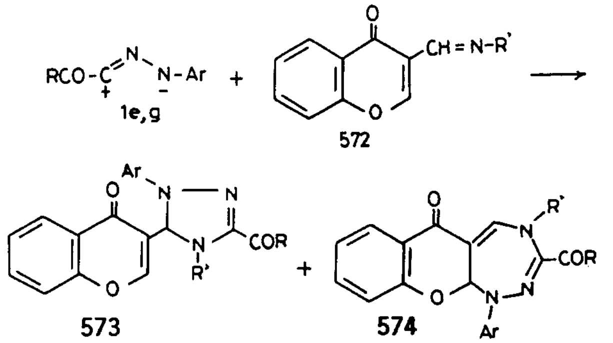
rationalized in terms of the strong resonance interaction between the etheric oxygen and the carbonyl group as evidenced by the basicity and dipole moment of chromone.[201,202]

Reaction of 3-pyrrolidino-2-benzopyran-1-one (459) with diphenylnitrilimine (1a) afforded the pyrazolobenzopyranone derivative 461, which seems to result from a prototropic rearrangement of the initially formed cycloadduct 460.[203]



1a 459 460 461

The chromone imines 572 were reported to react smoothly with the nitrilimines 1e,g to yield in each case a mixture of 1,2,4-triazolinyl- (573) and triazepinochromones (574).[231]

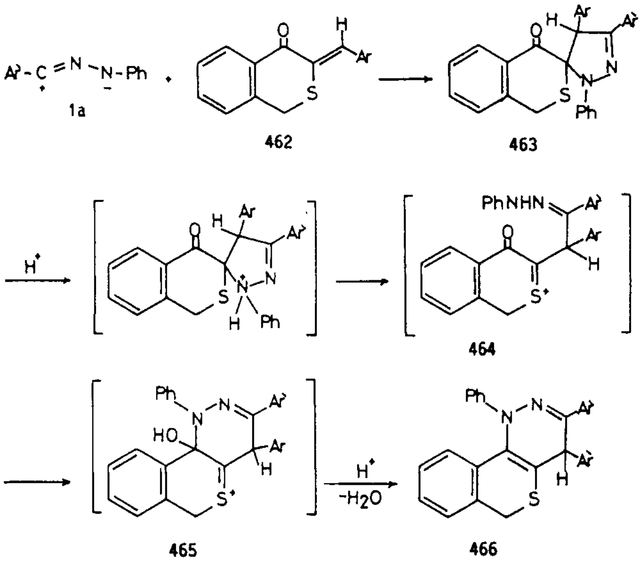


1e,g 572 573 574

R = CH_3, CH_3CH_2O

9. Isothiochromanones

The cycloaddition reaction of diarylnitrilimines (1a) with 3-arylidene-4-isothiochromanones (462) occurs very readily and yields the cycloadducts 463 in good yield.[204] The treatment of the latter products with a trace of trifluoroacetic acid in chloroform solution afforded the corresponding 4,9-dihydro-10-thia-3,4-diazaphenanthrene derivatives 466 via the reaction sequence outlined below.[204]

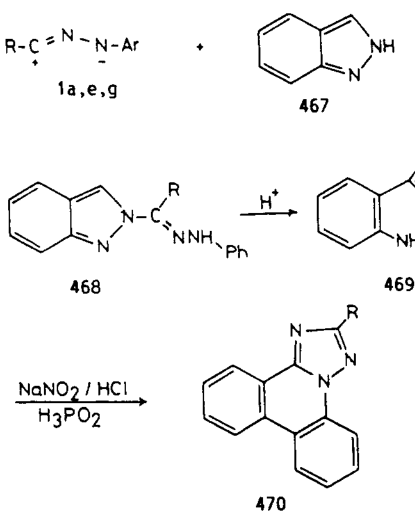


1a 462 463 464 465 466

I. Reactions of Two-Ring Heterocycles with Two Heteroatoms

1. Indazoles

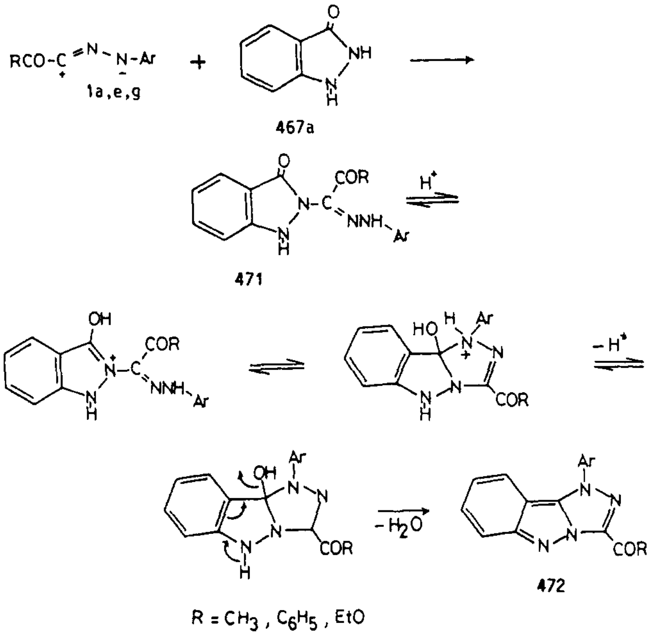
1-Unsubstituted indazole 467 reacts with nitrilimines 1a, 1e, and 1g to yield the corresponding 1,3-adducts 468a, 468b, and 468c, respectively.[205,206] The latter amidrazones underwent acid-catalyzed transformation to give the corresponding triazole derivatives 469, which afforded the triazolo[1,5-*f*]phenanthridines 470 upon diazotization.[205]



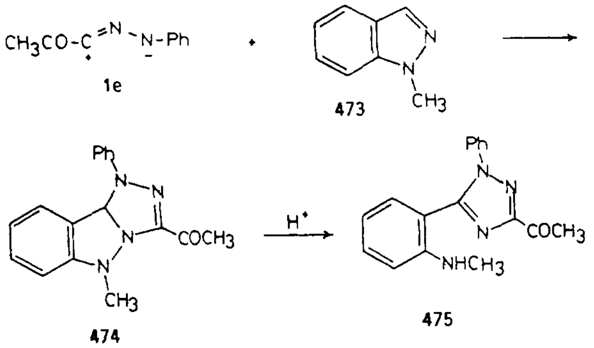
1a,e,g 467 468 469 470

	R
a	CH_3CO
b	COOEt
c	Ph

Similarly, reaction of 3-indazolinone (**467a**) with nitrilimines **1e,f,g** in tetrahydrofuran at room temperature gives the amidrazone derivatives **471**, which underwent intramolecular cyclization when refluxed in ethanol containing concentrated hydrochloric acid to give 1,2,4-triazolo[4,3-*b*]indazoles **472**.[207]

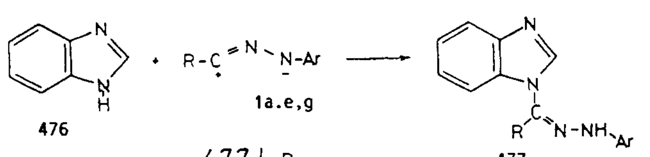


Reaction between 1-methylindazole (**473**) with a stoichiometric amount of the nitrilimine **1e** in tetrahydrofuran afforded the cycloadduct **474**.[208] Acid treatment of the latter yielded the triazole derivative **475**.[208]

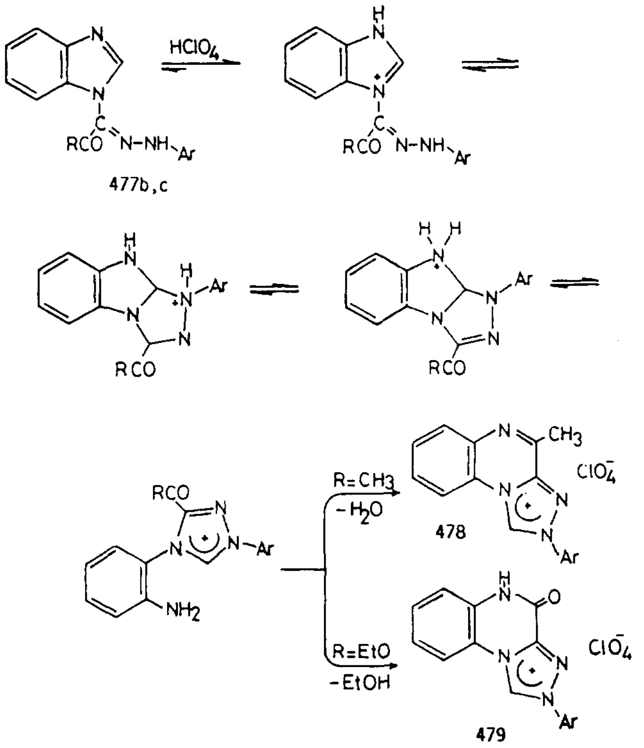


2. Benzimidazoles

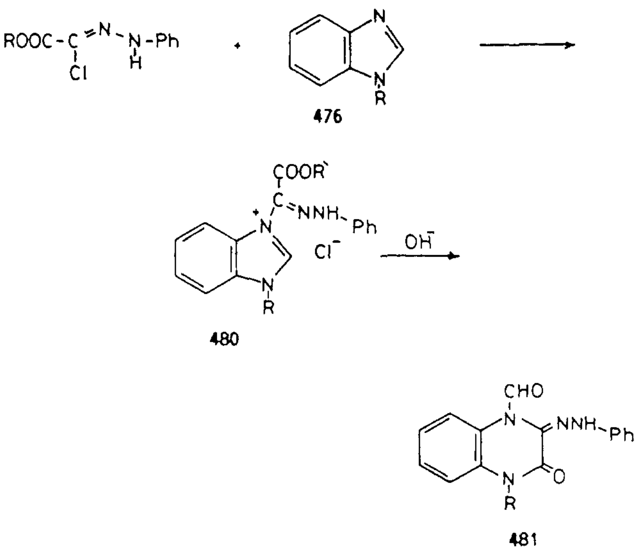
Reactions of benzimidazole **476a** with the nitrilimines **1a,e,g** were reported to give in all cases the 1,3-adducts **477a–c**.[119,209] The products **477b,c** underwent rearrangement upon treatment with perchloric acid in boiling butanol to give 2-aryl-1,2,4-triazolo[4,3-*a*]quinoxalinium perchlorate salts **478** and **479**.[209]

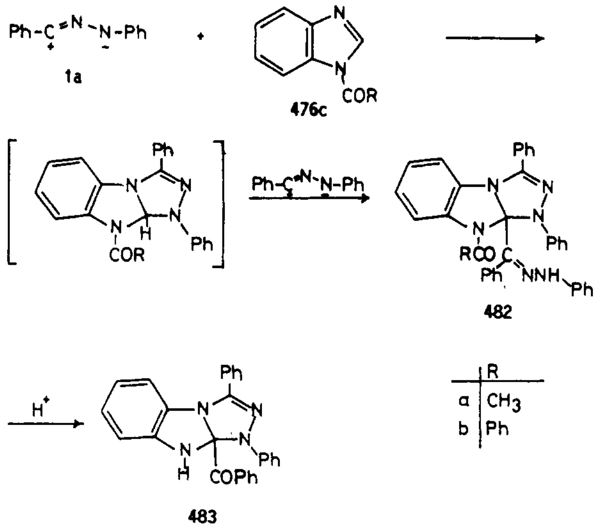


477	R
a	Ar
b	COOEt
c	CH₃CO



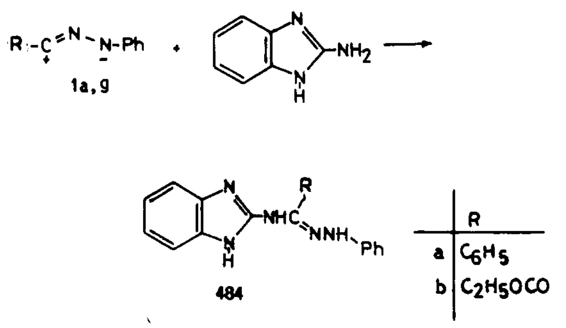
1-Alkylbenzimidazoles react with the *C*-(ethoxycarbonyl)nitrilimine precursors to give the corresponding salts **480**, which yielded the 3,4-dihydroquinoxalin-2-one derivatives **481** when treated with aqueous sodium hydroxide in ethanol.[104] Interestingly, the reaction of 1-acylbenzimidazoles (**476c**) with diphenylnitrilimine (**1a**) was reported to give the cycloadduct **482**, which hydrolyzed upon acid treatment to give **483**.[118]





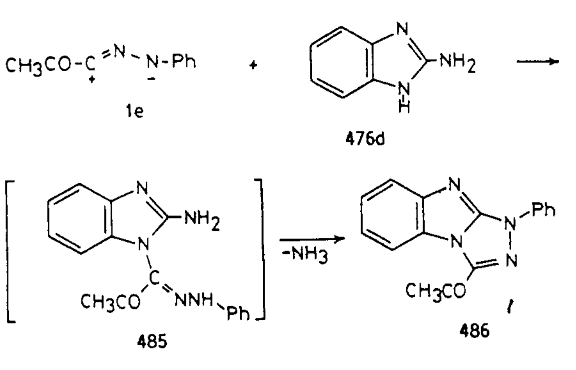
	R
a	CH_3
b	Ph

2-Aminobenzimidazole (**476d**) reacts with nitrilimines **1a** and **1g** to give the corresponding 1,3-adducts **484a** and **484b**, respectively.[99,100,105] However, reaction of

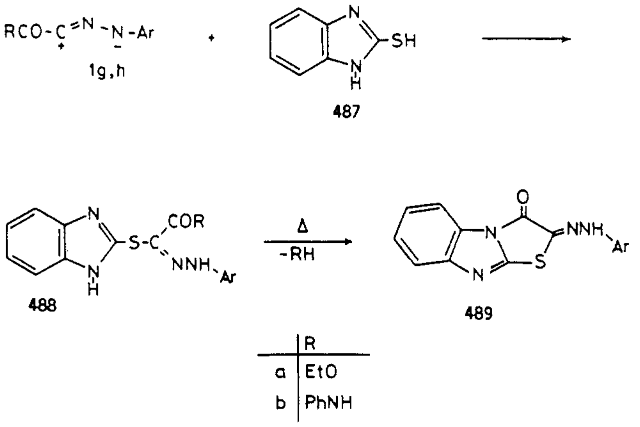


	R
a	C_6H_5
b	C_2H_5OCO

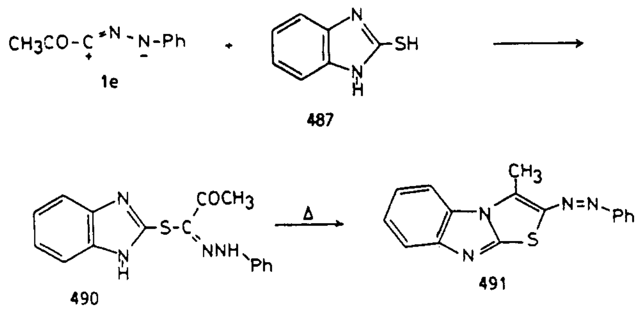
476d with *C*-acetylnitrilimine **1e** was reported to give the tricyclic product **486** via cyclization of the initially formed 1,3-adduct **485**.[99,100]



2-Mercaptobenzimidazole (**487**) reacts with *C*-(ethoxycarbonyl)- and C-(phenylcarbamoyl)nitrilimines **1g** and **1h** to yield the corresponding 1,3-adducts **488a** and **488b**, respectively.[108] Acid treatment of the latter products results in their cyclization to give the thiazolo[3,2-*a*]benzimidazol-3-one **489**. Similarly, reaction of *C*-acetylnitrilimine **1e** with **487** afforded the thiohydrazonate ester **490** that cyclizes upon heating to yield **491**.[108]

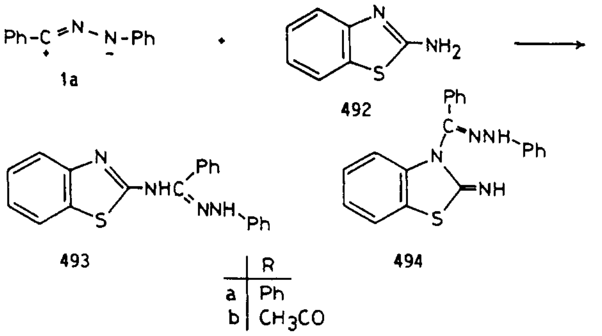


	R
a	EtO
b	PhNH

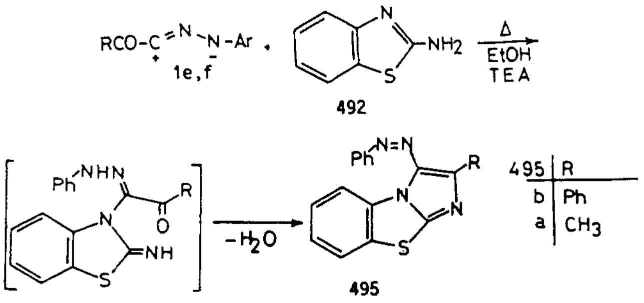


3. Benzo[d]thiazoles

The C=N double bond of 2-aminobenzothiazole **492** proved to be inert toward nitrilimines. Thus, it was reported that reaction of the nitrilimines **1a** and **1e** with **492** afforded the corresponding 1,3-adducts **493a** and **493b**, respectively.[107] The other possible 1,3-adducts (**494**) were not produced, however. In another report, it was claimed that **492** reacted with *C*-acetyl- and *C*-benzoylnitrilimines **1e** and **1f** in refluxing ethanol to give **495a** and **495b**, respectively.[210] Similarly,

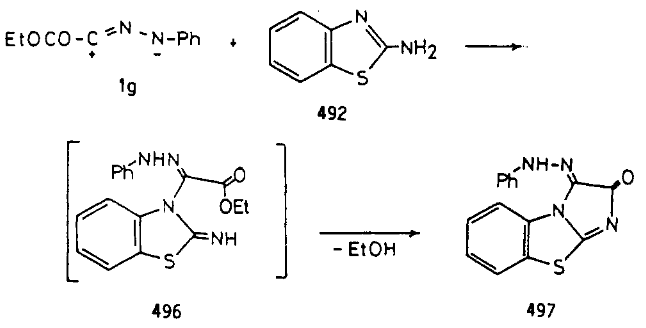


	R
a	Ph
b	CH_3CO



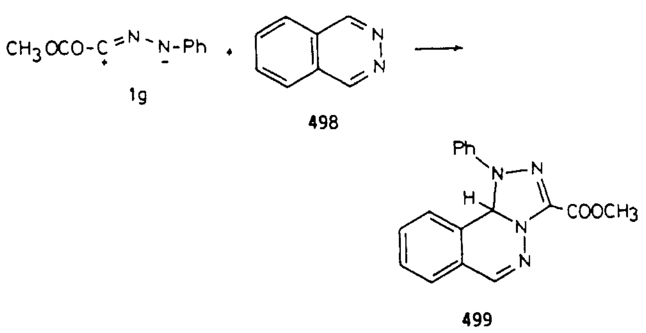
495	R
b	Ph
a	CH_3

reaction of **492** with the nitrilimine **1g** afforded **497** via the cyclization of the initially formed 1,3-adduct **496**.[210]

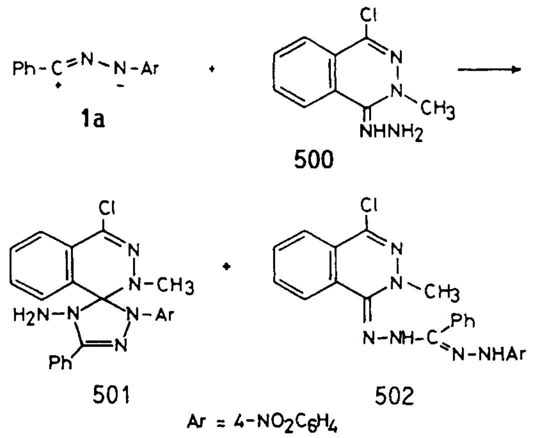


4. Phthalazines, Quinazolines, and Quinoxalines

Reaction of phthalazine (**498**) with nitrilimines of type **1g** gives the 1:1 cycloadduct **499**.[167]

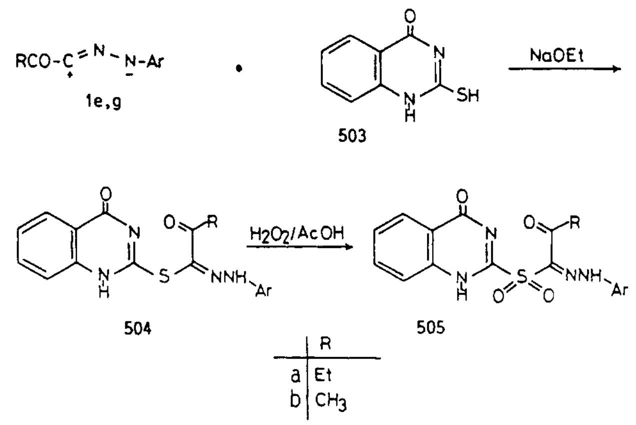


Litvinov et al.[211] reported that the reaction of nitrilimines **1a** with the phthalazine derivative **500** yielded a mixture of **501** and **502** in 60% and 14% yields, respectively.

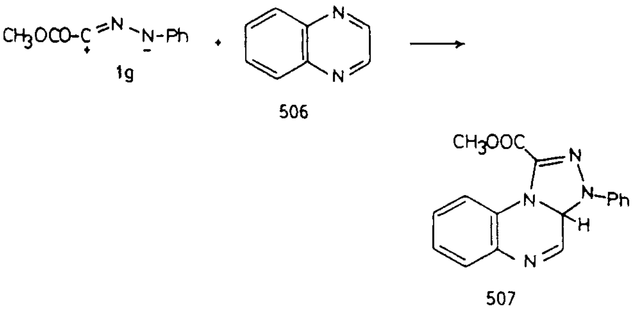


$Ar = 4\text{-}NO_2C_6H_4$

2-Mercaptoquinazolin-4(1*H*)-one (**503**) reacts with the nitrilimines **1e** and **1g** to yield the 1,3-adducts and **504a** and **504b**, respectively.[109] Oxidation of **504** afforded the corresponding sulfone derivatives **505**.

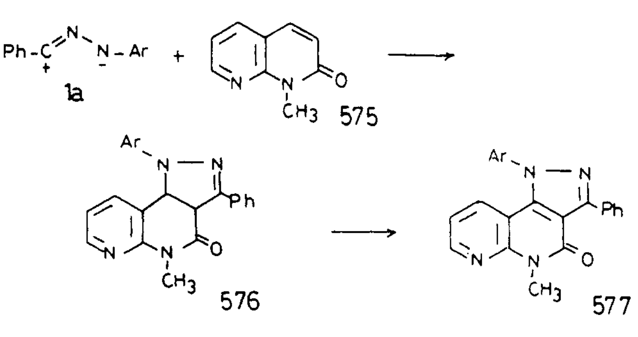


As seen in the reaction with phthalazine, the nitrilimine **1g** was reported to react with quinoxaline **506** in chloroform at room temperature to yield the 1:1 cycloadduct **507**.[167]



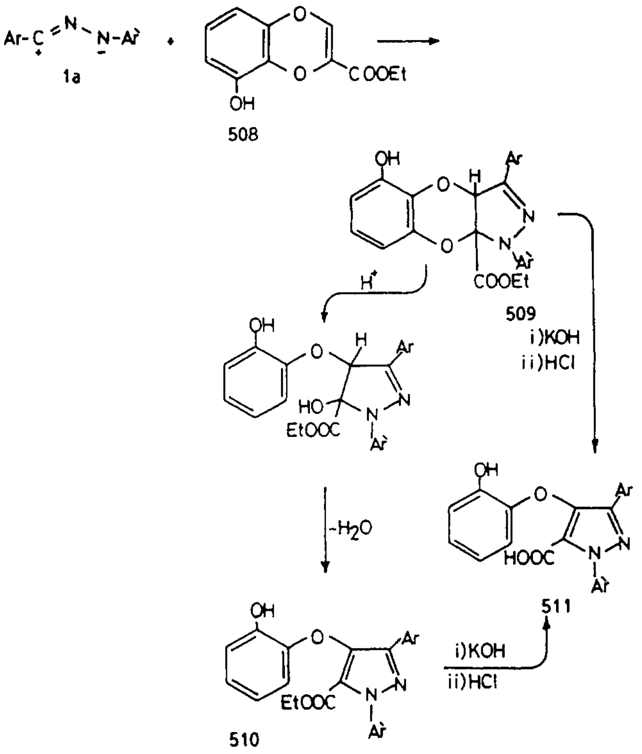
5. Naphthyridines

Naphthyridinone derivatives **575** underwent a cycloaddition reaction with diarylnitrilimines **1a** to give the pyrazolo[4,5-*c*][1,8]naphthyridines **576**.[232] The latter cycloadducts were dehydrogenated by chloranil to give **577**.[232]



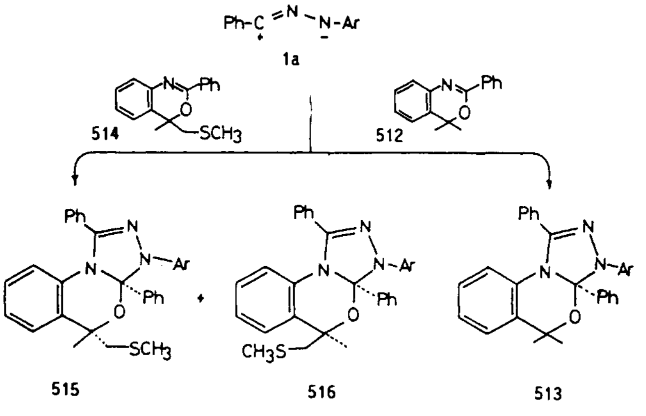
6. 1,4-Benzodioxines

Reaction of diarylnitrilimines (**1a**) with ethyl 1,4-benzodioxine-2-carboxylate (**408**) in benzene yields a single cycloadduct, namely **409**.[212] Acid treatment of the latter afforded the ester **510**, which afforded the acid **511** upon saponification followed by acidification. The latter acid can also be obtained by direct saponification of the cycloadduct **509**.[212]



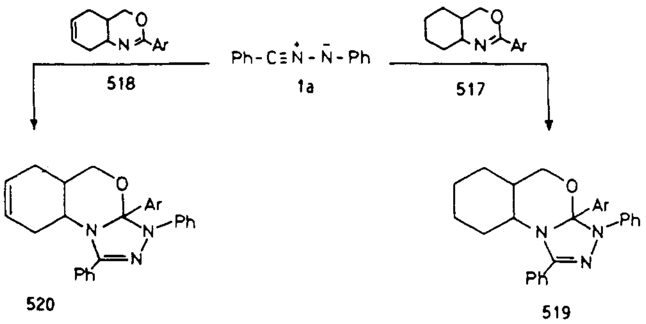
7. Benzoxazines and Benzothiazines

A single cycloadduct (**513**) was obtained from the reaction of diarylnitrilimines (**1a**) with 4,4-dimethyl-2-phenyl-4*H*-benzoxazine (**512**) whereas a pair of diastereoisomers, namely **515** and **516**, were obtained from the reaction of **1a** with 4-methyl-4-(methylthio)-2-phenyl-4*H*-benzoxazine **514**.[213]

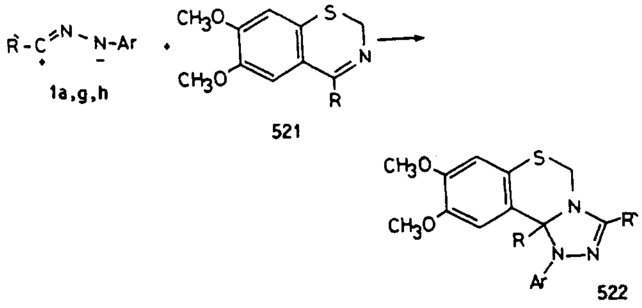


Ar = 4-$NO_2C_6H_4$

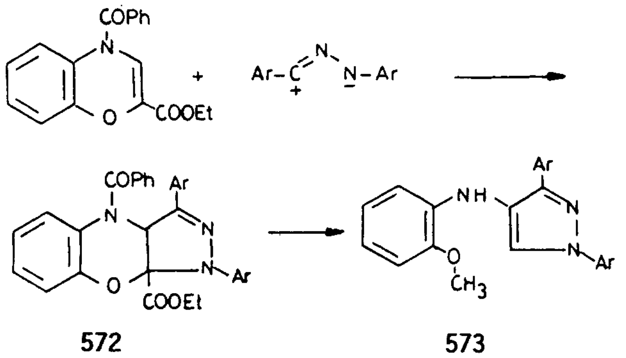
Reactions of *cis*-4,5-tetramethylene-2-aryl-4*H*-5,6-dihydroxazine (**517**) and its unsaturated analogue **518** with diphenylnitrilimine (**1a**) give the corresponding cycloadducts **519** and **520**, respectively.[214,215]



Similarly, reaction of 2*H*-1,3-benzothiazine derivatives **521** with nitrilimines **1a**, **1g**, and **1h** afforded the angularly condensed triazolobenzothiazines **522a**, **522b**, and **522c**, respectively.[216]

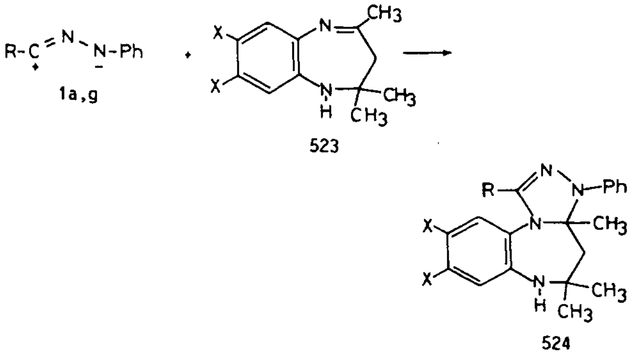


In 1988, Hlimi et al.[217] reported that the cycloaddition of nitrilimine **1a** to ethyl *N*-benzoyl-1,4-benzoxazine-2-carboxylate yielded the cycloadduct **572**. The structure of the reaction product was confirmed by its conversion into 1,3-diarylpyrazole derivative **573**.[217]

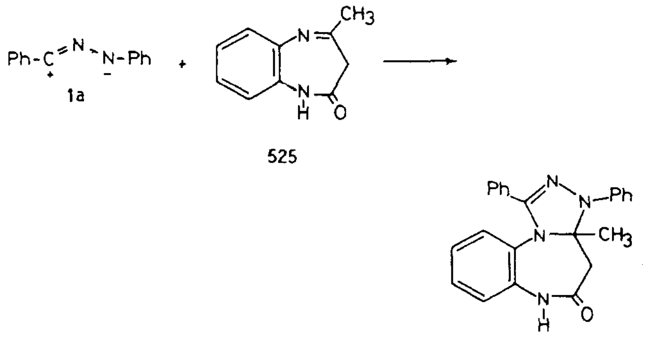


8. Benzodiazepines, Benzoxazepines, and Benzothiazepines

1*H*-1,5-Benzodiazepine derivatives **523** react with nitrilimines **1a,g** in boiling tetrahydrofuran and yield the corresponding 3a,4,5,6-tetrahydro-3*H*-[1,2,4]triazolo[4,3-*a*]-1,5-benzodiazepines **524**.[218] Under similar

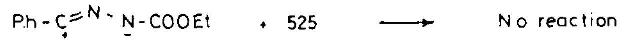


conditions the triazolobenzodiazepine derivative **526** was obtained from the reaction of diphenylnitrilimine **1a** with 4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepin-2-one (**525**).[218] However, the reaction of **525** with the *C*-(ethoxycarbonyl)nitrilimine **1g** under the same reaction conditions failed to give the expected cycloadduct.[218] On the other hand, reaction of 2,4-disubstituted-3*H*-1,5-benzodiazepines **527** with diphenylnitrilimine (**1a**) afforded the bis-cycloadducts **528**.[218]

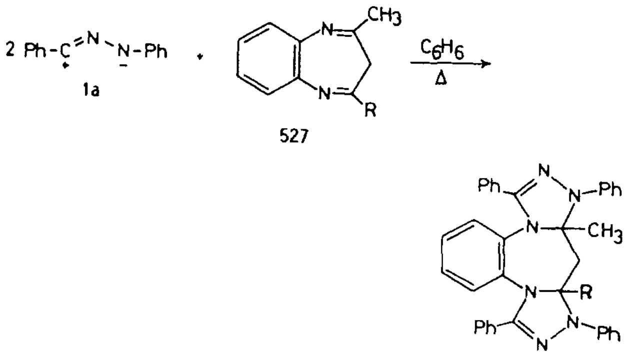

1a

525

526


$\overset{+}{\mathrm{Ph}\text{-}\mathrm{C}}{\equiv}\mathrm{N}\text{-}\overset{-}{\mathrm{N}}\text{-}\mathrm{COOEt} + 525 \longrightarrow$ No reaction

1n

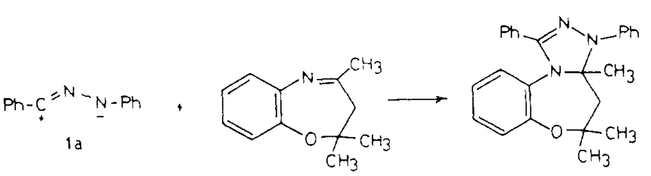


1a

527

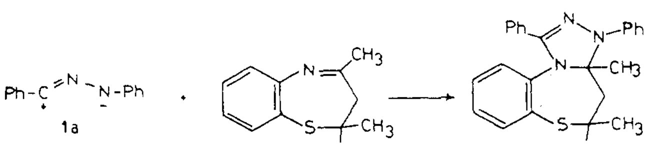
528

Diphenylnitrilimine (**1a**) reacts with the 2,3-dihydro-1,5-benzoxazepine derivative **529** and its thia analogue **531** in tetrahydrofuran to give the corresponding cycloadducts **530** and **532**, respectively.[219,220]


1a

529

530


1a

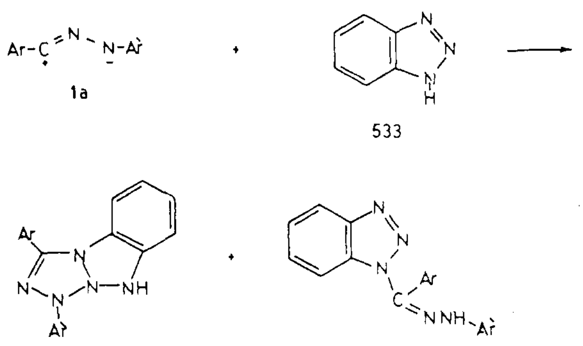
531

532

J. Reactions of Two-Ring Heterocycles with Three or More Heteroatoms

1. Benzo[*d*]triazoles

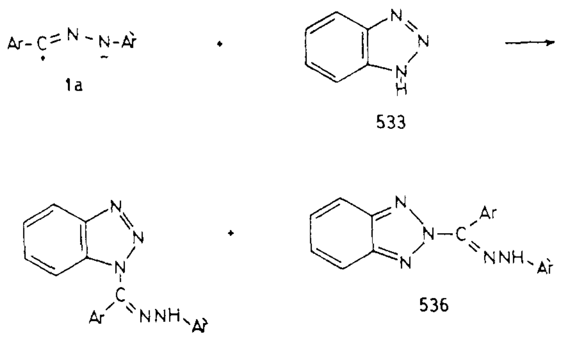
Benzotriazole **533** was reported to react with diarylnitrilimines (**1a**) to give in each case a mixture of 1,3-diaryl-1*H*,9*H*-tetrazolo[1,2-*a*]benzotriazole derivative **534** in 15–25% yield and the isomeric 1,3-adduct **535**.[221] However, it was reported that the products of this reaction are the 1- and 2-substituted benzotriazoles **535** and **536** and that no 1,3-dipolar cycloadducts were produced.[96,222]


1a

533

534

535


1a

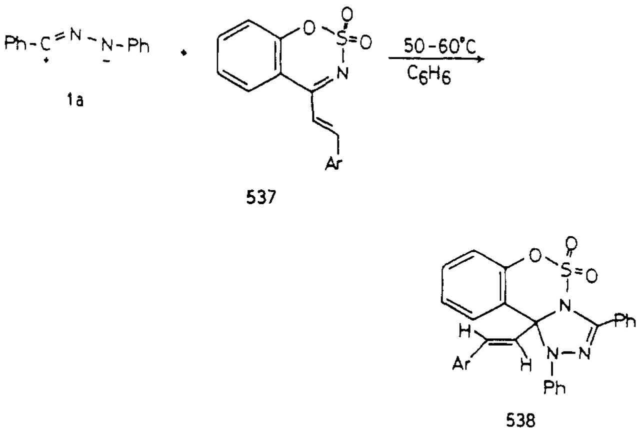
533

535

536

2. Benzoxathiazines

Reaction of diphenylnitrilimine (**1a**) with 4-styryl-1,2,3-benzoxathiazine 2,2-dioxide (**537**) was reported to give the cycloadduct **538**.[223]



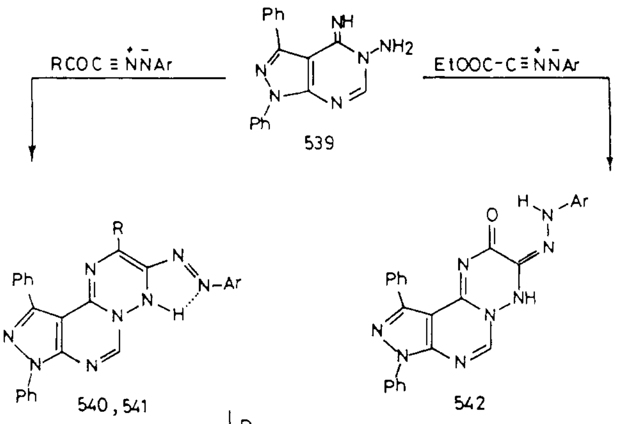
1a

537

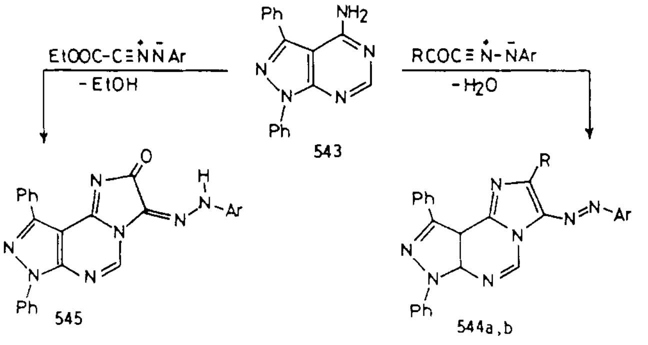
538

3. Pyrazolo[3,4-*d*]pyrimidines

Recently it was shown that the pyrazolo[3,4-*d*]pyrimidine derivative **539** reacts with *C*-acyl- and *C*-(ethoxycarbonyl)nitrilimines **1e**, **1f**, and **1g** in ethanol to yield the fused heterocyclic compounds **540**, **541**, and **542**, respectively.[224] Similarly, the 4-aminopyrazolo[3,4-*d*]pyrimidine derivative **543** reacts with the nitrilimines **1e**, **1f**, and **1g** and yields the tricyclic products **544a**, **544b**, and **545**, respectively.[224] Such reactions were assumed to proceed via the same reaction sequence followed by reactions of 2-aminopyridine with the same nitrilimines.[77,98,101,102,162]



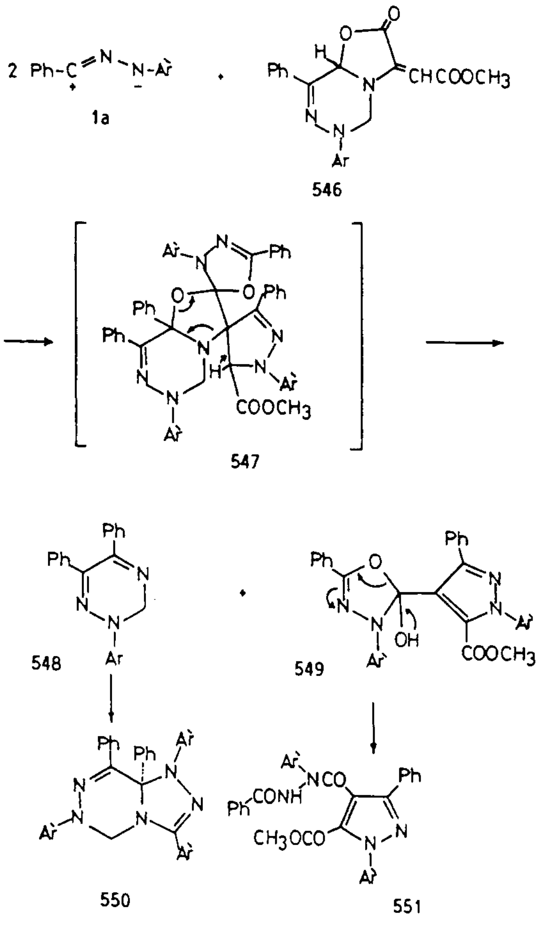
	R
540	CH_3
541	2-Thienyl



a, R = CH_3 ; b , R = 2-Thienyl

4. *Oxazolo[3,2-d]triazines*

3-[(Methoxycarbonyl)methylene]-6,8-diaryloxazolo[3,2-*d*]-1,2,4-triazine derivatives **546** were reported to react with diarylnitrilimines to give the 1,2,4-triazolo[4,3-*d*]-1,2,4-triazines **550**, along with the substituted pyrazoles **551**.[171] The reaction consumed 3 mole equiv of **1a**. In this case it was assumed that the cycloaddition occurs on both the ylidene moiety and the lactone carbonyl group to give the unstable spirocycloadduct **547**. The latter ejects a molecule of 1,2,4-triazine **548**, from which compound **550** is subsequently formed in a separate reaction. Rearrangement and ring opening of **549** gives the more stable pyrazole derivative **551**.[171]

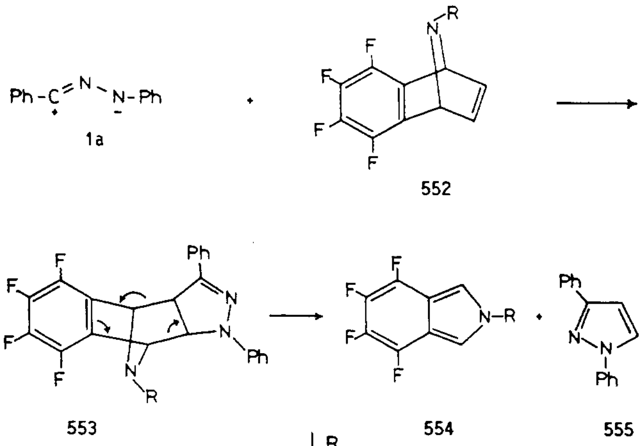


Ar = $4\text{-}NO_2C_6H_4$

K. Reactions of Three-Ring Heterocycles with One or More Heteroatoms

1. *Benzo-7-azabicyclo[2.2.1]hepta-2,5-dienes*

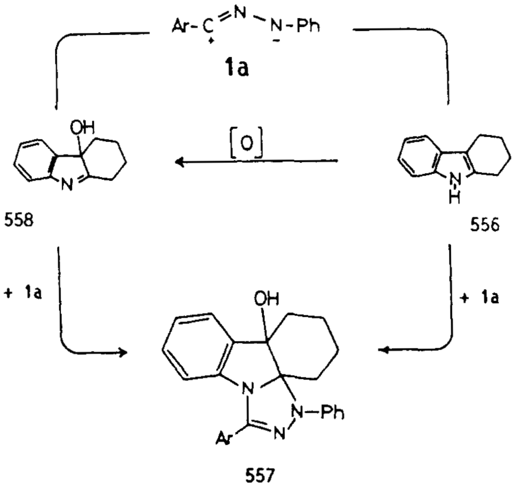
Reaction of diphenylnitrilimine (**1a**) with naphthalinimine derivative **552** and its *N*-methyl analogue gives the isoindole derivatives **554a** and **554b**, respectively, along with 1,3-diphenylpyrazole (**555**).[225]



	R
a	CH_3
b	H

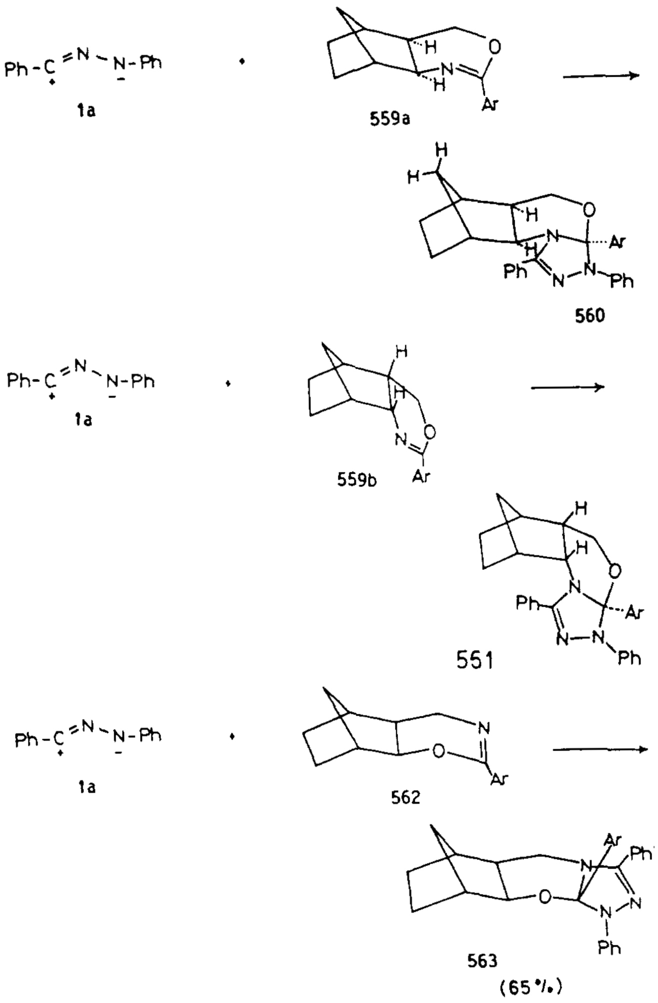
2. *Carbazoles*

Diphenylnitrilimine (**1a**) reacts with the tetrahydrocarbazole to yield the cycloadduct **557**.[181] The latter cycloadducts seem to result through the cycloaddition of **1a** to the C=N double bond of the 3-hydroxyindole **558**, a possible autoxidation of **556**. It is known that **556**, like many other indole derivatives, are susceptible to autoxidation.[226]



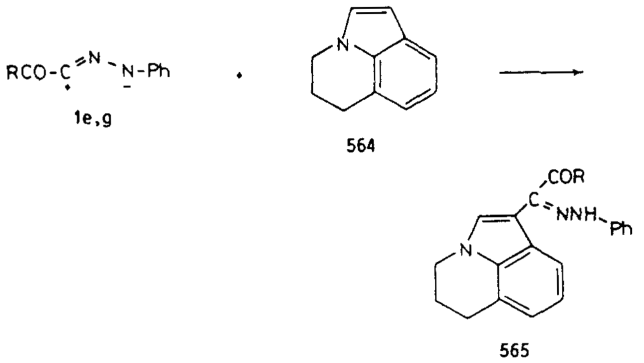
3. Norbornan-1,3-oxazines

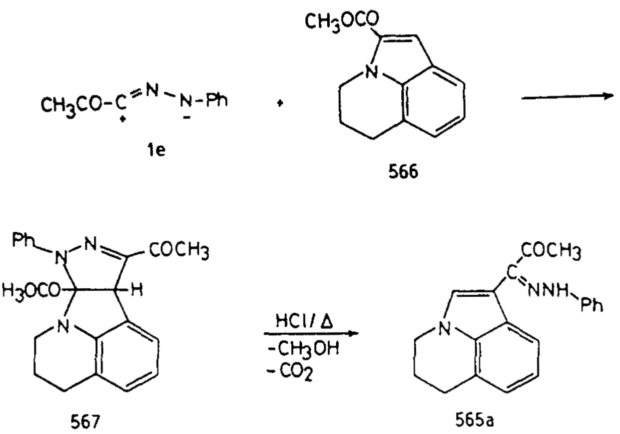
The angularly fused *diexo-* and *diendo-*norbornan-1,3-oxazinotriazolines **560** and **561** and the linearly fused analogue **563** as well were obtained from the reactions of diphenylnitrilimine (**1a**) with the norbornan-1,3-oxazines **559a**, **559b**, and **562**, respectively.[227,228]



4. 1,7-Trimethyleneindoles

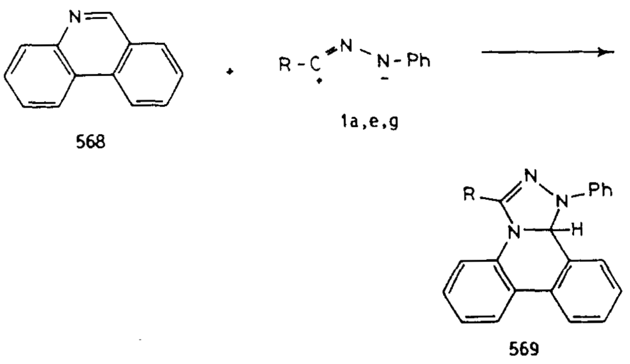
1,7-trimethyleneindole reacts with the *C*-acetyl- and *C*-(ethoxycarbonyl)nitrilimines **1e** and **1g** and yields the electrophilic substitution products **565a** and **565b**, respectively.[175] However, reaction of 1,7-trimethylene-2-(methoxycarbonyl)indole (**566**) with the nitrilimine **1e** afforded the cycloadduct **567**.[175] Treatment of the latter cycloadduct with hydrochloric acid in ethanol resulted in the hydrolytic cleavage to give **565a**.[175]





5. Phenanthridines

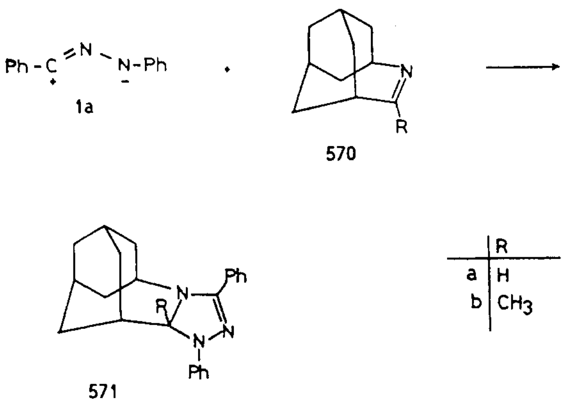
Phenanthridene (**568**) reacts with nitrilimines of types **1a**, **1e**, and **1g** to yield the cycloadducts **569a**, **569b**, and **569c**, respectively.[229]



L. Reactions of Four-Ring Heterocycles with One Heteroatom

1. 4-Azahomoadamant-4-enes

Diphenylnitrilimine (**1a**) was reported to react with 4-azahomoadamant-4-enes **570a** and **570b** at room temperature and gives after 6 days the 2-triazolines **571a** and **571b** in 37% and 50% yields, respectively.[230]

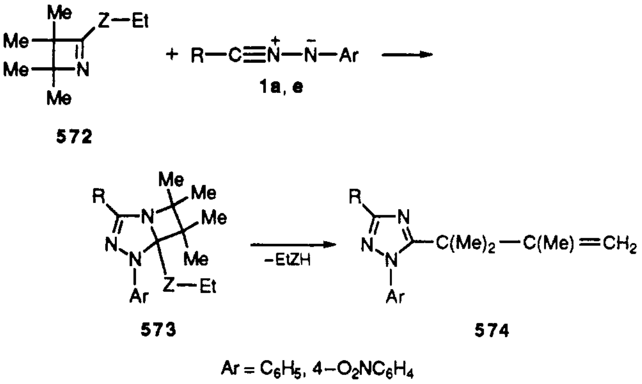


IV. Conclusions and Prospects

The research outlined in this review demonstrates useful methodology for synthesis of a wide range of polyheterocycles. The ready availability of reactants and their chemical versatility together with the generally good yields make the reactions outlined especially attractive to synthetic chemists. There are reasons to believe that the chemoselectivity and regioselectivity of some of the reactions reported need further refinement. An evident area requiring further exploration is that of the systematic study of the FMO properties of various heterocycles, which bears directly on the regiochemistry of their reactions with nitrilimines.

Note Added in Proof

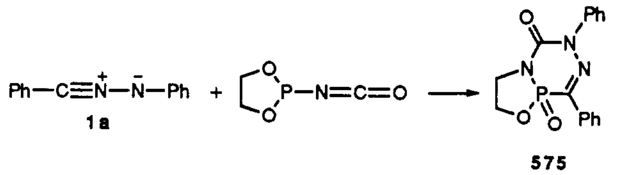
1,3-Dipolar cycloaddition of diphenylnitrilimine (**1a**) with tetramethyl-1-azetines **572** (Z = O, S) was reported to be accompanied by ring opening and loss of EtZH to give the 1,2,4-triazole derivative **574**.[233] On the other hand, reactions of **572** with *N*-(*p*-nitrophenyl)benzonitrilimines **1a** and *N*-(*p*-nitrophenyl)-*C*-(methoxycarbonyl)formonitrilimine (**1e**) afforded the expected cycloadducts **573** and/or ring-opened products **574**.[233]



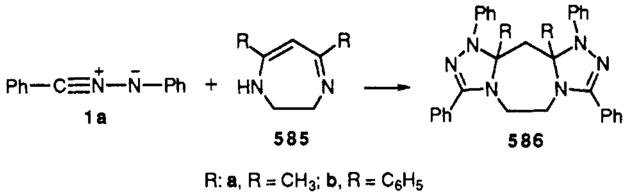
$Ar = C_6H_5, 4\text{-}O_2NC_6H_4$

Reaction of 2-isocyanato-1,3,2-dioxaphospholane with diphenylnitrilimine (**1a**) gives *N,P*-(2-ethanediyloxy)-triazaphosphorine **575** in 85% yield via intramolecular N-alkylation of the initially formed phosphorane.[234]

Very recently the reactions of diarylnitrilimines **1a** with 5-hydroxy, 5-mercapto, and 5-amino derivatives of 1-substituted tetrazoles **576a**, **576b**, and **576c**, respectively were reported[235] (Scheme IA). For **576a** and **576b** the reactions yielded the stable amidrazones **577** and the thiohydrazonates **578**, respectively. For **576c** the reactions yielded a mixture of the triazoles **579** and the azido hydrazones **580**. In this case, it was suggested that the reaction yielded the unstable amidrazone **581**, which ring opened in situ to **582**, which in turn underwent intramolecular cyclization to **579** and displacement of HN_3 which was trapped with **1a** to give **580**.[235] Treatment of **577** with NaOH in ethanol yielded the triazoles **583**. On the other hand, when the thiohydrazonates **578** were heated in toluene, benzene, or dimethyl sulfoxide, they gave the thiadiazoles **584**.[235]

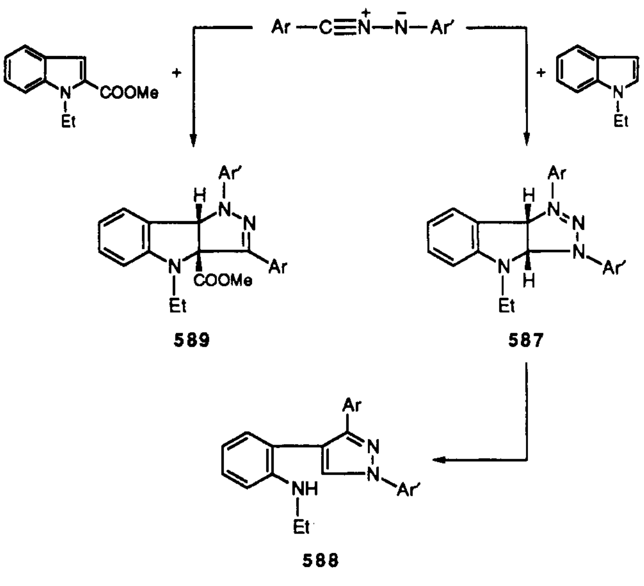


Reactions of diphenylnitrilimine (**1a**) with 2,3-dihydro-1*H*-1,4-diazepines **585a** and **585b** in benzene at reflux yielded the 2:1 adducts **586a** and **586b**, respectively.[236] Both cycloadducts showed trans stereochemistry of 10a- and 11a-substituents. Evidently, severe nonbonding interactions, owing to the presence of 1- and 10-phenyl substituents, preclude the formation of the corresponding cis-isomers. No monocyclic adducts were formed even when equimolecular amounts of **1a** and **585** were used.[235]



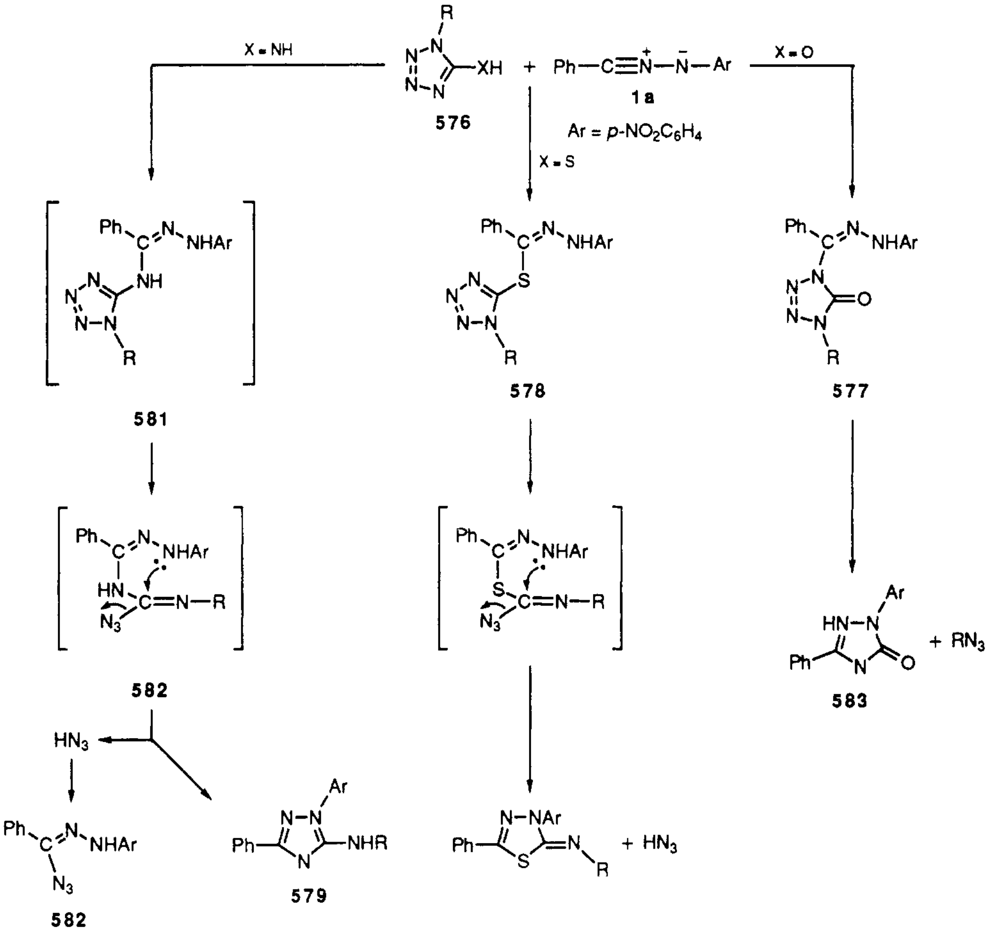
R: a, $R = CH_3$; b, $R = C_6H_5$

Reaction of *N*-ethylindole with diarylnitrilimine **1a** was reported to give mainly the pyrazolo[3,4-*b*]indoles **587**, regioselectively, which yielded upon acid hydrolysis, 1,4-diaryl-3-[2-(*N*-ethylamino)phenyl]pyrazoles **588**.[237] On the other hand, reaction of 2-(methoxycarbonyl)-*N*-ethylindole with diphenylnitrilimine (**1a**) gave the isomeric pyrazoloindole **589**.[237]

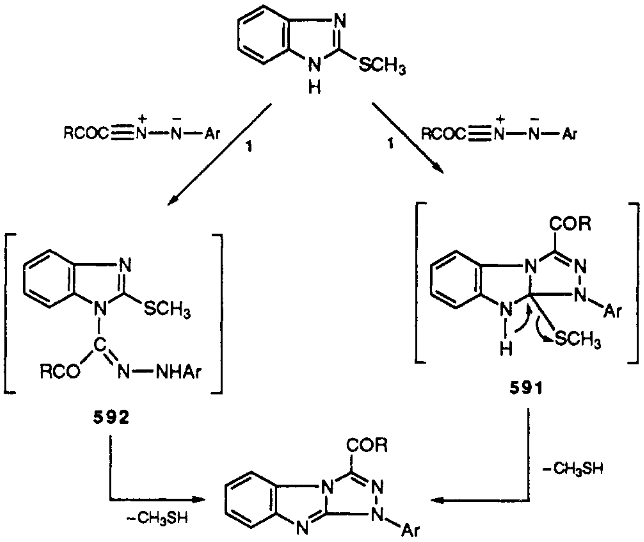


Reactions of 2-(methylthio)benzimidazole with various *C*-acylnitrilimines **1** were reported to give the

Scheme IA

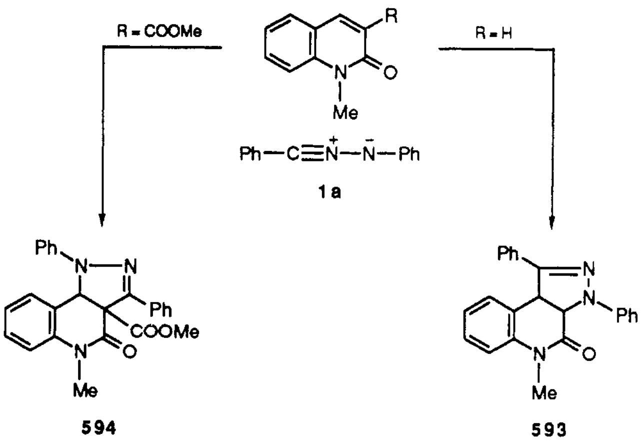


corresponding benzimidazo[2,1-*c*][1,2,4]triazoles **590**.[238] The latter products seem to result via thermal elimination of methanethiol from either the cycloadducts **591** or the 1,3-adducts **592**.[238]



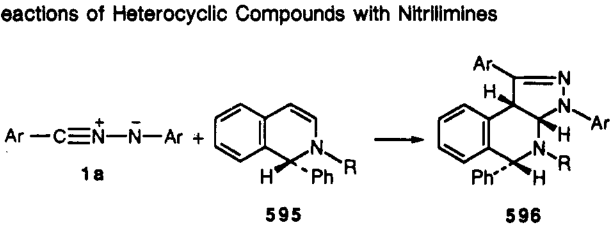
R/Ar: a, OC_2H_5/C_6H_5; b, $OC_2H_5/C_6H_4CH_3$-*p*; c, CH_3/C_6H_5; d, $CH_3/C_6H_4CH_3$-*p*; e, C_6H_5/C_6H_5; f, $C_6H_5/C_6H_4CH_3$-*p*; g, 2-thienyl/C_6H_5; h, 2-thienyl/$C_6H_4CH_3$-*p*; i, C_6H_5NH/C_6H_5; j, $C_6H_5NH/C_6H_4CH_3$-*p*; k, 2-naphthyl/C_6H_5; l, 2-naphthyl/$C_6H_4CH_3$-*p*

The cycloaddition reaction of **1a** with *N*-methyl-2-quinolinone was reported to be highly regioselective yielding the cycloadduct **593**.[239] With 3-(methoxycarbonyl)-*N*-methyl-2-quinolinone, the regiochemistry is reversed and **594** was produced.[239] These results invalidate the previously reported regiochemistry of the cycloadduct of **1a** with 2-(ethoxycarbonyl)-*N*-methylindole.[178]



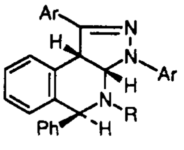
Reaction of diarylnitrilimines **1a** with 1-phenyl-1,2-dihydroisoquinoline **595a** gave mainly the cycloadduct **596**.[240] In the case of **595b** and **595c**, the isomeric products **597a** and **597b** were also formed, respectively.[240] It seems that the size of the substituent R determines the stereochemistry of the reaction.[240]

Recent X-ray investigation of the product **456**, which was isolated from the reaction of 4*H*-1-benzopyran-4-



1a **595** **596**

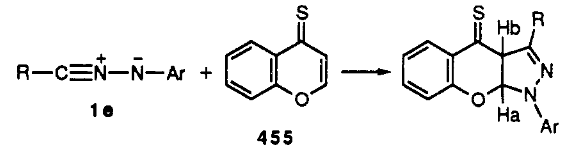
R = Me$_2$CH



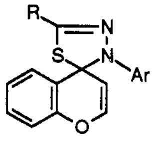
597

a, R = Me; **b**, R = Et

thione (**455**) with *C*-(acetyl)-*N*-(*p*-bromophenyl)formonitrilimine 1,[200] showed that it has the spiro structure **599**.[241]



1e **455** **456**



599

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