

Review

Reaction of Nitrilimines and Nitrile Oxides with Hydrazines, Hydrazones and Oximes

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Abstract: This review article discusses the reaction of nitrilimines and nitrile oxides with hydrazines, hydrazones, and oximes. Three reaction modes were observed. The article mainly covers our work published over the last fifteen years, in which interesting heterocycles such as oxadiazoles, triazoles, and tetrazines were synthesized and fully characterized.

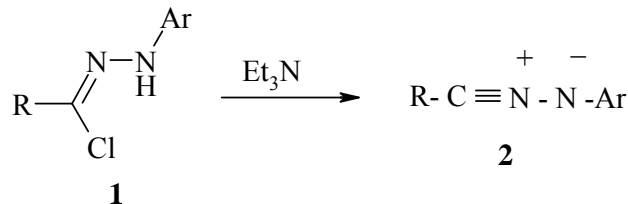
Keywords: Nitrilimines, nitrile Oxides, hydrazines, hydrazones, oximes.

Introduction

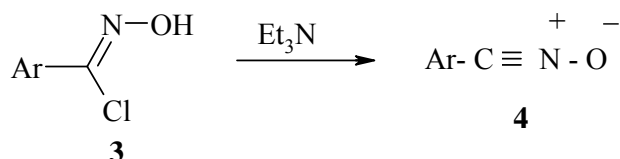
The concept of 1,3-dipoles was first introduced by Huisgen in 1963 [1]. Since that time, a lot of work has been done on their reactions and the mechanism of 1,3-dipolar cycloaddition. A comprehensive review discussing the chemistry of 1,3-dipoles appeared in 1984 [2]. Numerous significant papers have been published over the last two decades on the reaction of nitrilimines and nitrile oxides with substituted hydrazines, hydrazones and oximes. Different aspects of these reactions will be outlined in this short review.

Nitrilimines and nitrile oxides

Nitrilimines **2**, also called nitrile imides, are transient intermediates in solution. The most common method for their generation is dehydrohalogenation of hydrazoneyl halides **1** in the presence of triethylamine [2,3].

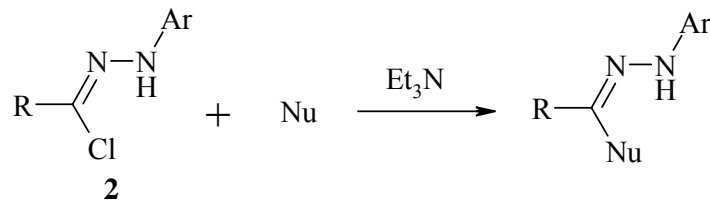


Likewise, nitrile oxides **4** are usually generated and trapped *in situ*; the most common method for their generation is dehydrohalogenation of α -chloro-oximes **3** upon reaction with a base (usually triethylamine). Nitrile oxides dimerize easily and it is usually beneficial to generate them slowly at low temperature, in presence of the trapping agent, so their concentration remains low [2].

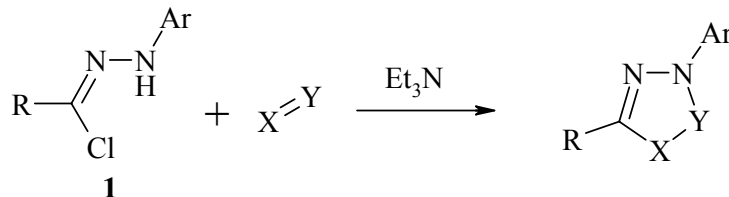


Both nitrilimines **2** and nitrile oxides **4** are widely used in the synthesis of different heterocycles. Three modes of reaction were observed for their reaction with different dipolarophiles [3]; namely:

i) Replacement reactions with nucleophiles (Nu) leading to acyclic adducts:

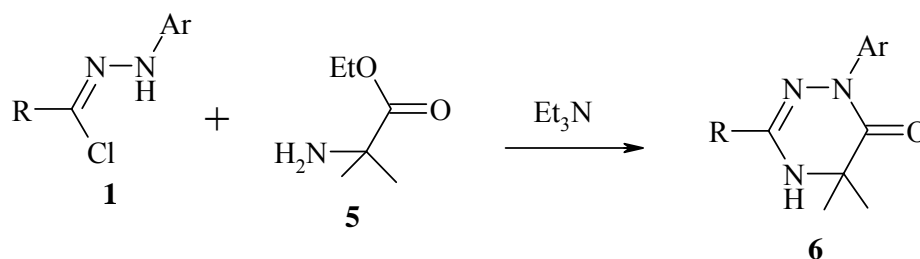


ii) Cycloaddition reactions with multiple bonds leading to five-membered heterocycles. The reactions proceed with almost complete stereochemical control and a remarkable regiochemical control in many cases.



iii) Cyclocondensation reactions with nucleophiles incorporating suitably located electrophilic centers leading to five- or six-membered heterocyclic rings. An example is the reaction of

nitrilimines generated in situ from the respective hydrazoneyl halides **1** with α -amino acid esters **5** leading to 4,5-dihydro-1,2,4-triazin-6-ones **6** [4].

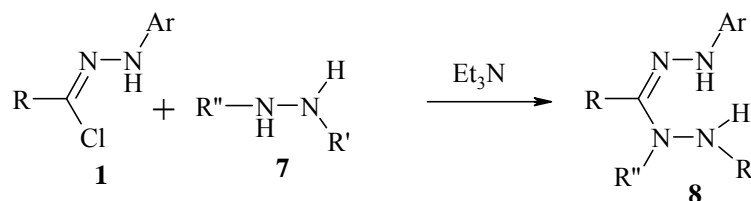


All the above modes of reaction were observed for the reaction of nitrilimines **2** and nitrile oxides **4** with differently substituted hydrazines, hydrazones and oximes.

Reactions of Nitrilimines and Nitrile Oxides with Hydrazines

Reaction with phenyl-, acetyl- and benzoylhydrazines

Nitrilimines undergo 1,3-additions with phenyl-, acetyl- and benzoylhydrazines **7** leading to the acyclic adducts **8a** or **8b** [5].



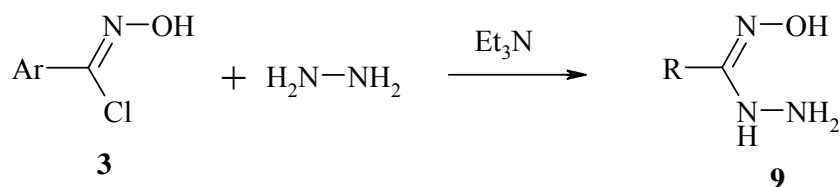
8a: R' = H, Ph, C(O)CH₃, C(O)Ph

R'' = H

8b: R' = H

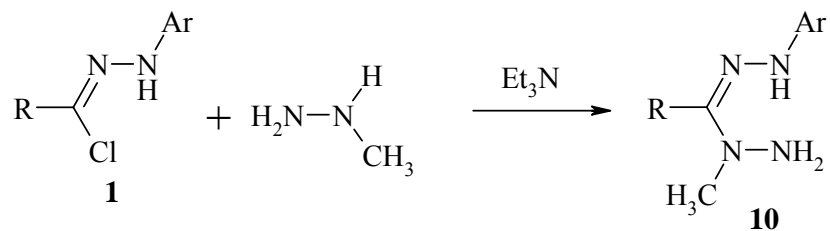
R'' = alkyl

The reaction of nitrile oxides with hydrazine hydrate was similarly reported to give hydrazidoximes [6].

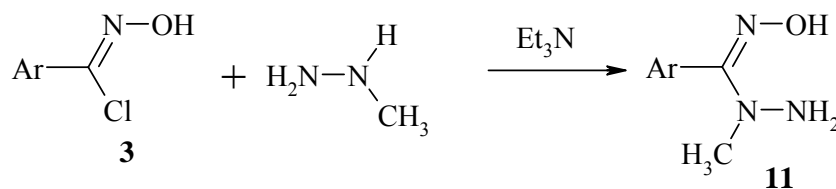


Reaction with methylhydrazine

The reaction with methylhydrazine occurs at the N-Me group, rather than the NH₂ group, leading to the acyclic adducts **10** [7].

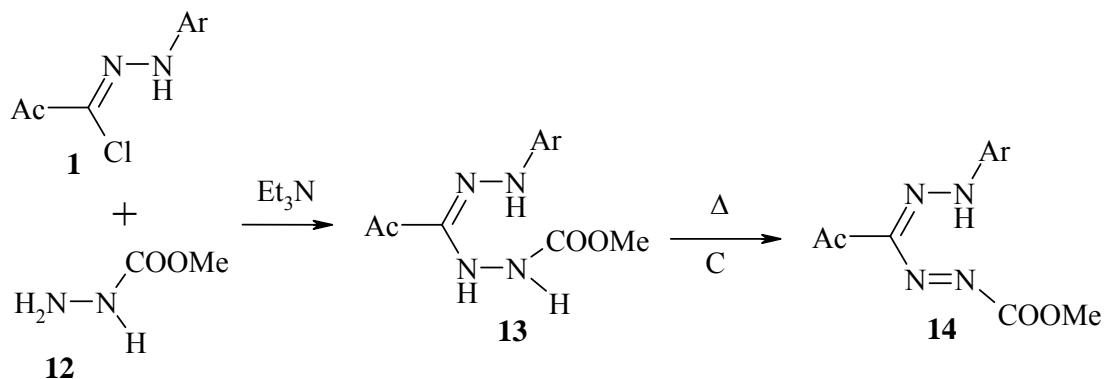


A similar reaction was reported for the reaction of nitrile oxides with methylhydrazine to yield **11** [6,8].

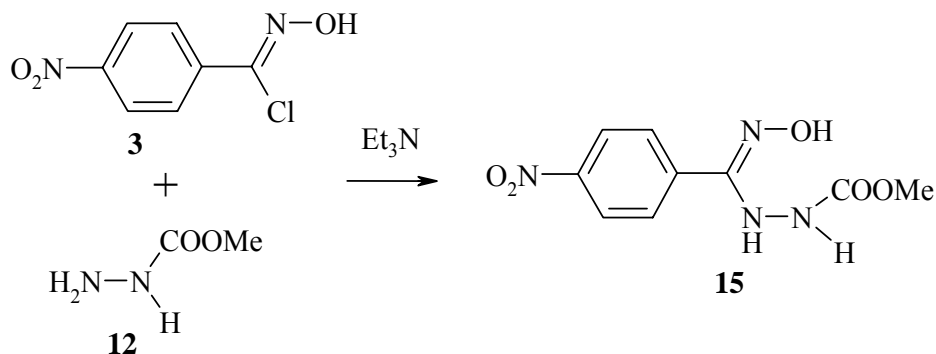


Reaction with methoxycarbonylhydrazine

The reaction of C-acetyl-N-aryl nitrilimines with methoxycarbonylhydrazine (**12**) afforded the acyclic adduct 1-methoxycarbonyl-2-[1-arylhydrazono-propane-2-one]hydrazine (**13**). Refluxing compound **13** with charcoal in toluene for six hours gave the oxidized product 3-acetyl-1-methoxycarbonyl-5-arylformazan (**14**) in high yield. No other cyclic products were observed [9].

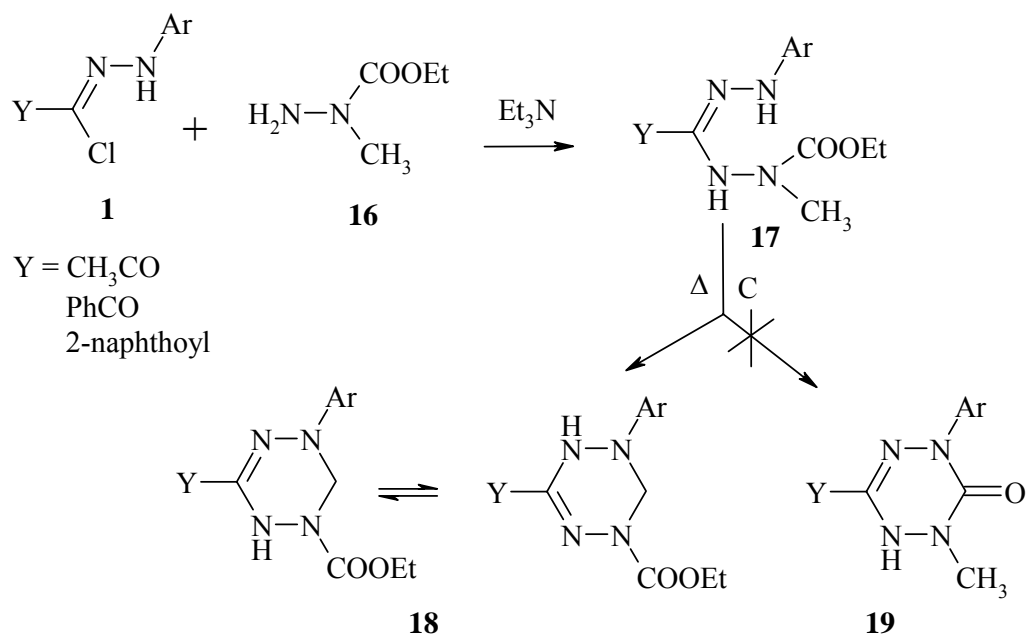


Similarly, nitrile oxides react with methoxycarbonylhydrazine (**12**) to give the acyclic adducts **15**, albeit in poor yield (about 20%).

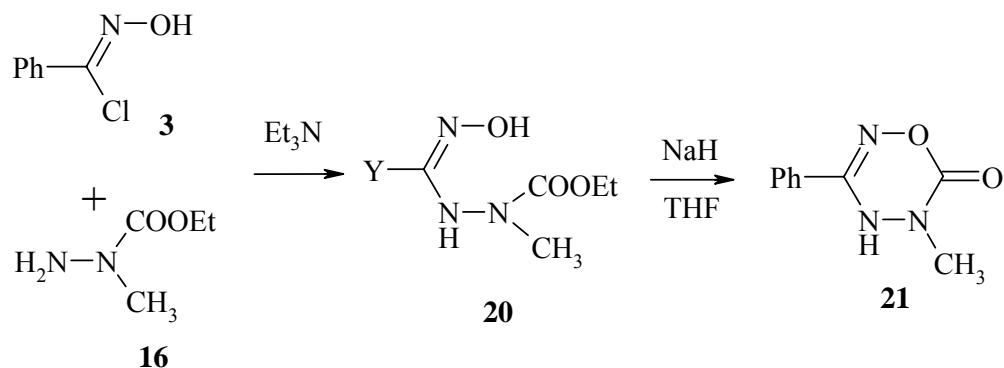


Reaction with 1-ethoxycarbonyl-1-methylhydrazine

This reaction gave the acyclic product 1-ethoxycarbonyl-1-methyl-2(1-arylhydrazonopropane-2-one)hydrazine (**17**). Thermal oxidative cyclization of compound **17** gave unexpected products, as these were found to be the s-tetrazines **18** rather than the expected tetrazinones **19**. Structural assignment of compounds **16** was based on elemental analysis, mass spectra, ^1H - ^{13}C - and 2D-NMR spectral data, including HMQC and HMBC experiments. These compounds exist as a pair of tautomers in solution. This reaction was carried out with C-acetyl [9], C-benzoyl- and C-2-naphthoyl nitrilimines [11].

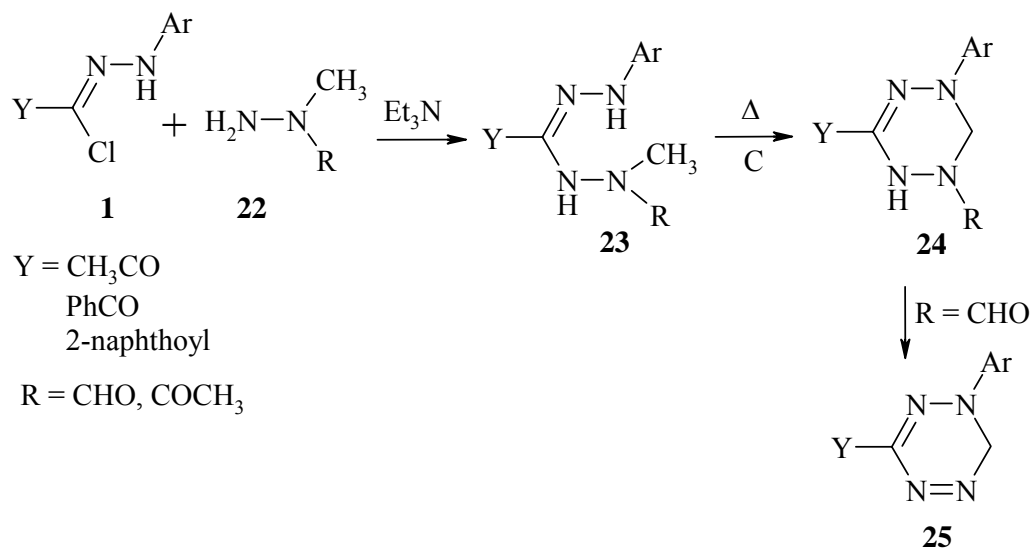


On the other hand, 1-ethoxycarbonyl-1-methylhydrazine (**16**) readily reacts with the nitrile oxide generated by the action of triethylamine on benzohydroxamoyl chloride, yielding the acyclic adduct 2-benzohydroxamoyl-1-ethoxycarbonyl-1-methylhydrazine (**20**) in moderate yield. The latter cyclizes almost quantitatively to the corresponding novel 4,5-dihydro-,1,2,4,5-oxatriazin-6-one (**21**) upon stirring with excess sodium hydride in dry tetrahydrofuran for 30 min. at room temperature [11].



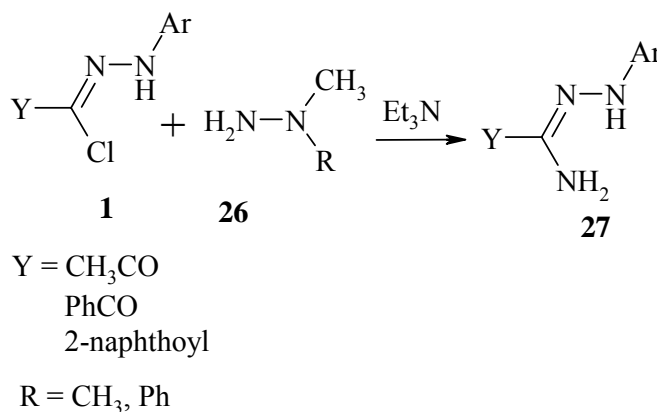
Reaction with 1-acetyl- and 1-formyl-1-methylhydrazine

C-acetyl-, C-benzoyl- and C-(2-naphthoyl)nitrilimines react also with 1-acetyl- and 1-formyl-1-methylhydrazines **22** to give the acyclic adducts **23**. Thermal cyclization of the latter adducts gave tetrahydro-1,2,4,5-tetrazines **24**. Dihydro-1,2,4,5-tetrazines **25** were also obtained upon elimination of formaldehyde from compounds **24** [12].



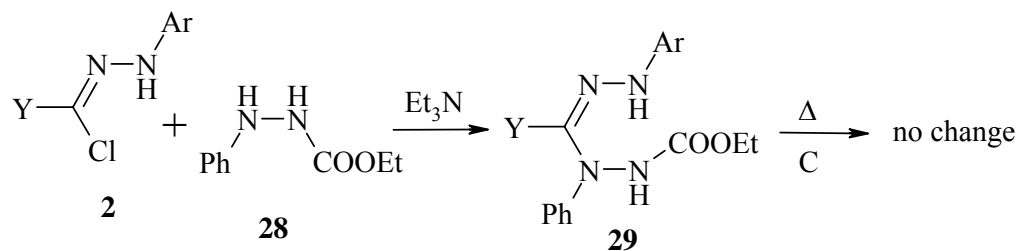
Reaction of nitrilimines with 1,1-dimethylhydrazine and 1-methyl-1-phenylhydrazine

C-acetyl-, C-benzoyl- and C-(2-naphthoyl)nitrilimines react with 1,1-dimethylhydrazine and 1-methyl-1-phenylhydrazine **26** giving the amidrazones **27** [12].



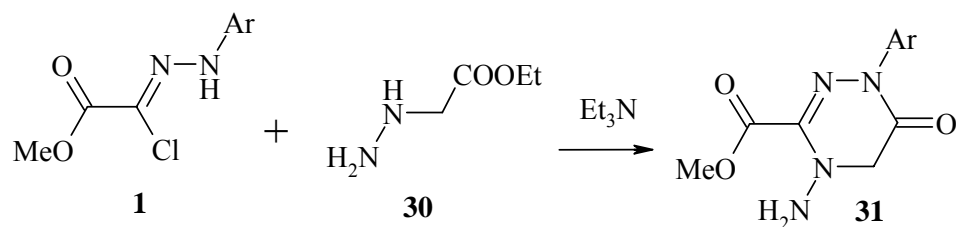
Reaction of nitrilimines with 1-ethoxycarbonyl-2-phenylhydrazine

This reaction gave the acyclic adducts **28**. Refluxing **28** with charcoal in either toluene or xylene for several hours gave no reaction and the starting material was recovered unchanged [9].

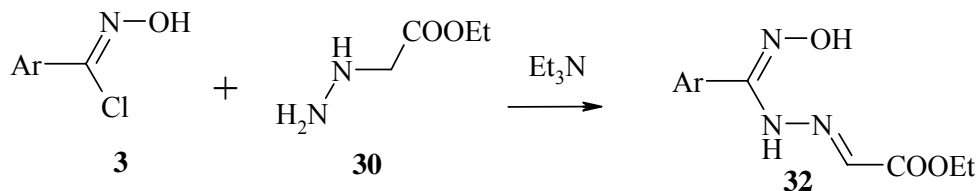


Reaction with ethyl hydrazinoacetate

Reaction of C-methoxycarbonyl nitrilimines with ethylhydrazino acetate (**30**) under mild conditions gave 4-amino-1-aryl-3-methoxycarbonyl-6-oxo-1,4,5,6-tetrahydro-1,2,4-triazines **31** [13].



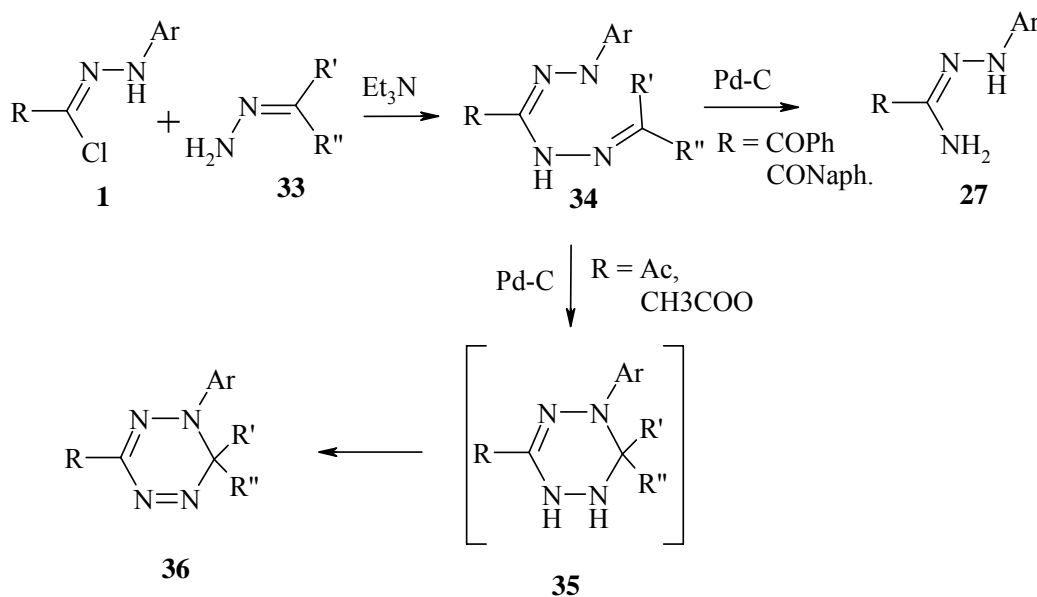
On the other hand, the reaction of nitrile oxides with ethyl hydrazine acetate gave the acyclic adducts **32**, which resulted from nucleophilic addition through the terminal NH_2 followed by oxidation [14].



Reaction with hydrazones

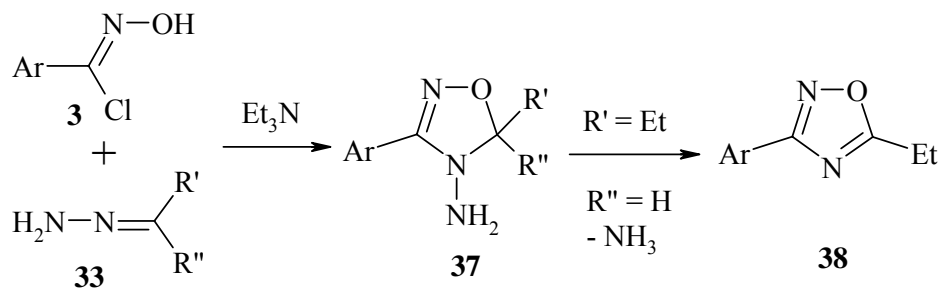
Reaction with substituted simple hydrazones

Simple hydrazones derived from aliphatic aldehydes and ketones **33** reacted with C-acetyl- and C-methoxycarbonyl nitrilimines at ambient temperature to furnish the acyclic products **34**. Attempts to cyclize the latter by heating in tetrahydrofuran or ethanol were unsuccessful. However, treatment of solutions of these acyclic adducts with Pd-C at room temperature brought about oxidative cyclization to the orange-red coloured 1,6-dihydro-s-tetrazines **36** [15].

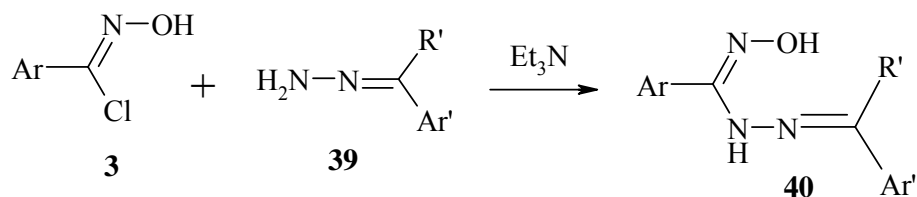


Attempts to isolate the tetrahydrotetrazine intermediate **35** were generally unsuccessful. C-benzoyl and C-2-naphthoyl nitrilimines were also found to give acyclic adducts **34**. However, these adducts gave a mixture of complicated products upon heating with Pd-C from which amidrazones **27** were separated as the major products.

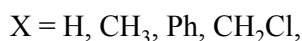
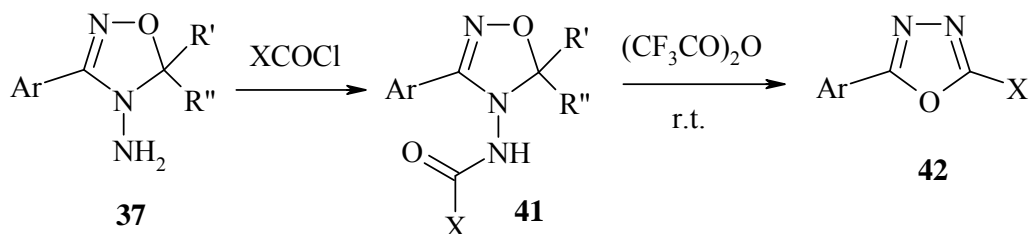
On the other hand, aryl nitrile oxides undergo 1,3-dipolar cycloaddition with alkanone hydrazones **33** to give the cycloaddition product 4-amino-3-aryl-5,5-dialkyl-4,5-dihydro-1,2,4-oxadiazole (**37**). The reaction with alkanal hydrazones gave, however, a complex mixture of intractable products, from which the oxadiazole **38** was the major product [17].



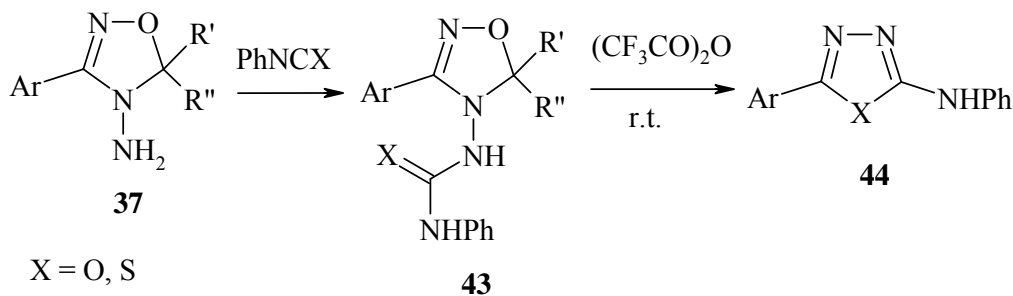
Reaction of hydrazones of aryl aldehydes and ketones **39** with nitrile oxides gave, however, the corresponding acyclic adducts **40**, formed through nucleophilic addition of the hydrazones to nitrile oxides. 1,3-Dipolar cycloaddition across azomethine π -bond of the hydrazones was not observed here [18].



It is worth mentioning that acylation of the 4-amino-4,5-oxadiazoles **37** in refluxing toluene or treatment of the acyl derivatives of these compounds **41** with trifluoroacetic anhydride brings up ring transformation to the aromatic 1,3,4-oxadiazoles **42** [18].

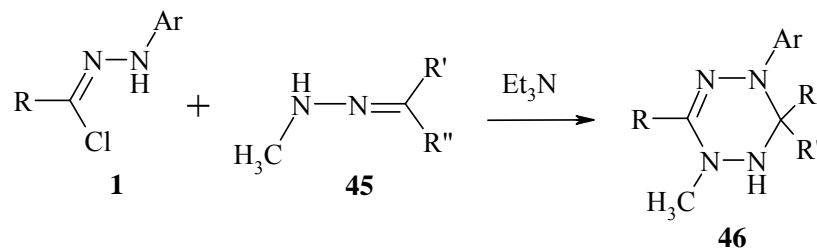


Similarly, 4-amino-4,5-dihydro-1,2,4-oxadiazole **37** are transformed into the corresponding 2-arylamino-1,3,4-oxadiazoles (**44**, X = O) or thiadiazoles (**44**, X = S) *via* reaction with phenylisocyanate or phenylisothiocyanate, followed by brief treatment of the resulting adducts **43** with trifluoroacetic anhydride at ambient temperature [19].

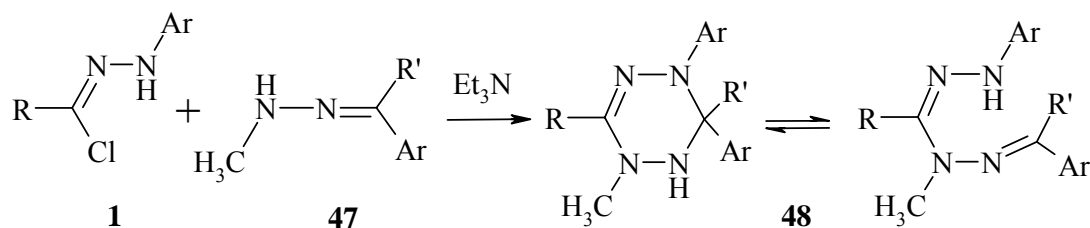


Reaction of nitrilimines and nitrile oxides with substituted methylhydrazones

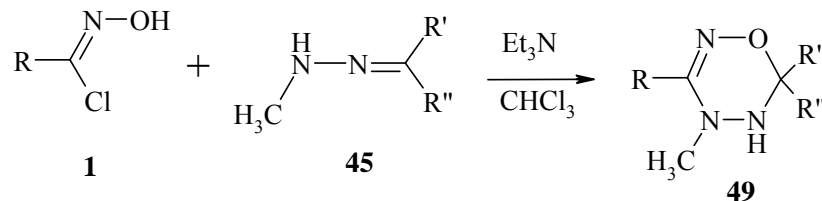
The interaction between methylhydrazones of aliphatic alkanones and alkanals **45** provided a direct synthetic route to 1,2,3,4-tetrahydro-1,2,4,5-tetrazines **46** [20].



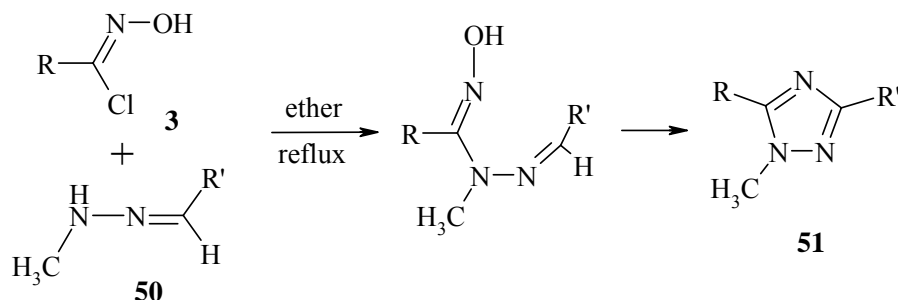
The reaction with methylhydrazones of aromatic aldehydes and ketones **47** gave “ring-chain” tautomerism, where the tautomeric ratio was found to be dependent on the steric and electronic effects of the substituent at C-3, C-6 and N-4 [21].



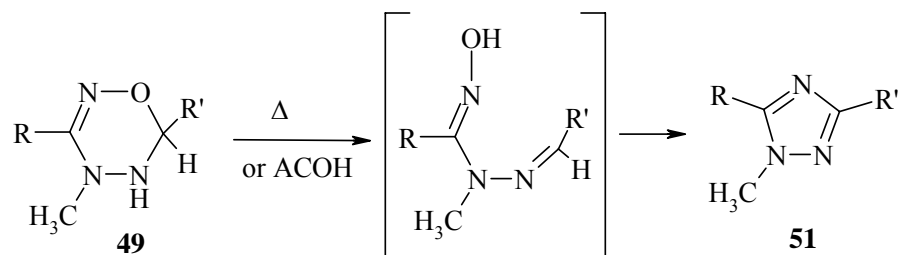
The reaction of nitrile oxides with methylhydrazones **45** in chloroform was found to constitute a convenient synthetic route to the novel 4,5-dihydro-6H-1,2,4,5-oxatriazines **49** [6].



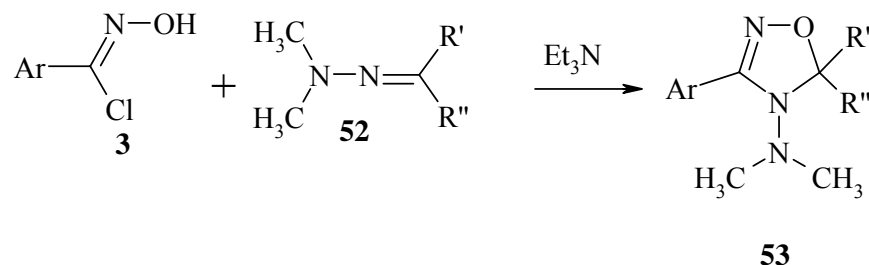
Risitano and coworkers obtained the triazoles directly from the appropriate monomethylhydrazones of aryl aldehydes in refluxing ether for 2 hours [22].



1,2,3,4-tetrahydro-1,2,4,5-tetrazines **49**, derived from methylhydrazones of aryl aldehydes, underwent ring contraction, *via* elimination of H₂O, to yield the respective 1H-1,2,4-triazoles **51**. This transformation was envisaged to proceed *via* the ring-opened (*E*)-hydrazone oximes which then suffered dehydrative cyclization. The process is acid-catalyzed and was thermally induced. Apparently, the driving force for this transformation is linked to the aromaticity of the triazole product [8].

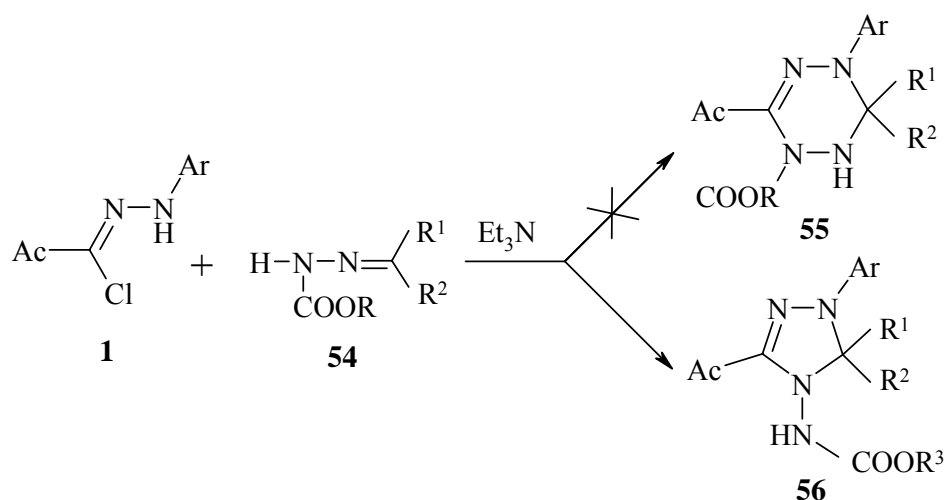


The reaction of nitrile oxides with 1,1-dimethylhydrazones **52** yields the cycloaddition products, the N,N-dimethylamino-oxadiazolines **53**.



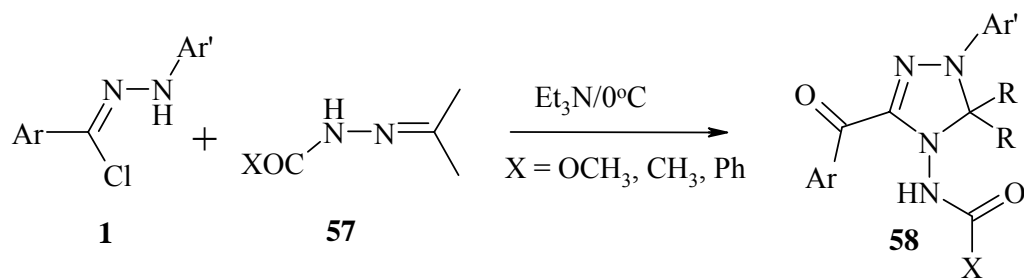
Reaction of nitrilimines with hydrazones carrying electron withdrawing groups

Hydrazonoyl halides reacted with alkanone and cycloalkanone alkoxy carbonylhydrazones **54** to give the cycloaddition products 4,5-dihydro-1,2,4-triazoles **55**, rather than the tetrazine cyclocondensation products **56** [23].



	a	b	c	d	e	f	g	h
R ¹ , R ²	Me, Me	Et, Et						
R ³	Me	Me	Et	Et	Et	Et	Et	Et
X	Cl	Cl	Cl	Br	Cl	Cl	Cl	Cl

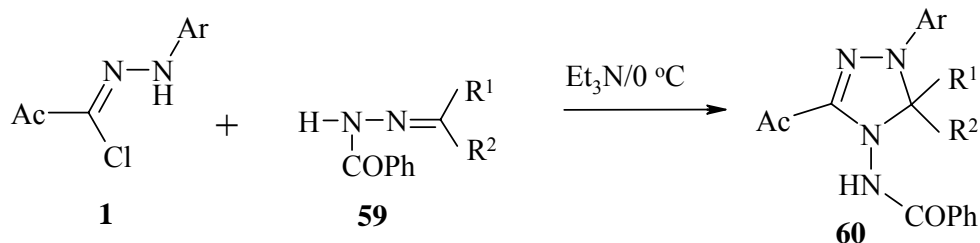
The ¹H-NMR spectra showed a signal at 6.5 – 7.0 ppm characteristic for the N-H of the five membered ring compounds **55**. The N-H of the six membered ring structure **56** is expected to appear at 4-5 ppm [1]. Signal doubling is observed both in the ¹H- and ¹³C-NMR spectra of compound **55f** containing the 4-methylcyclohexane moiety due to tautomeric isomerism. The ¹³C-NMR spectra display the characteristic signals of the suggested structures. The signal for C5 (quaternary or spiro carbon) appears in the range of 80 – 90 ppm. This was similar to reported values of quaternary and spiro carbons flanked by two nitrogens in five-membered heterocycles. This provided strong evidence in support of structures **55**, rather than the six-membered heterocyclic structure **56**, which was expected to have a C6 signal at about 70 ppm.



Ar' = 4-Cl-C₆H₄
 Ar = C₆H₅, 2-naphthoyl

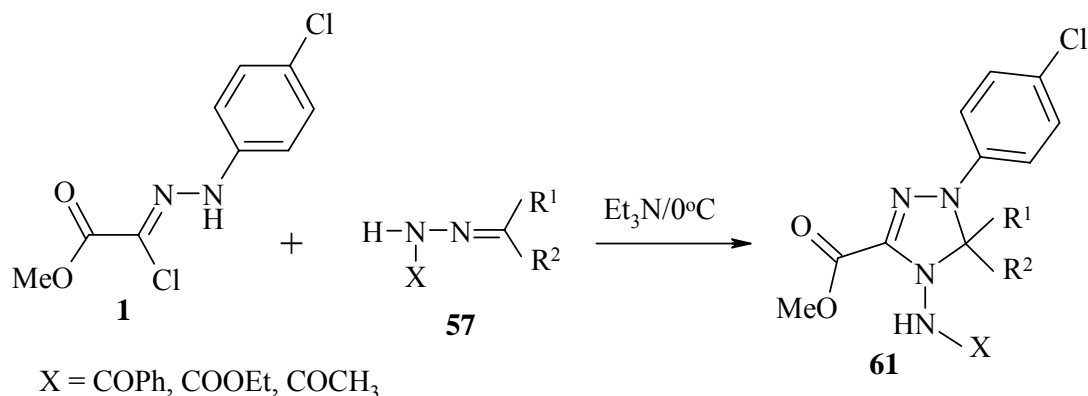
	a	b	c	d	e
R, R	Me, Me				

Similarly, alkanone and cycloalkanone hydrazones **57** carrying electron withdrawing groups (OCOCH₃, COCH₃, C₆H₅) react with C-benzoyl- and C-2-naphthoyl nitrilimines to give the cycloaddition triazole products **58**. IR, ¹H-NMR, ¹³C-NMR and mass spectral data are consistent with the assigned triazole ring system. Compounds **58** having an acetyl group, showed signal doubling in their ¹³C-NMR spectra, apparently, owing to their presence as two different mesomeric structures [24]. Ferwanah *et al.* also reported the synthesis of another series of these triazoles **60** from the reaction C-acetyl-N-arylnitrilimines (**2**) with acetaldehyde, alkanone and cycloalkanone benzoylhydrazones **59**. Interesting spiro compounds containing heteroatoms were prepared from this reaction [25].



R ¹	H	Me	Me					
R ²	Me	Me	Me					

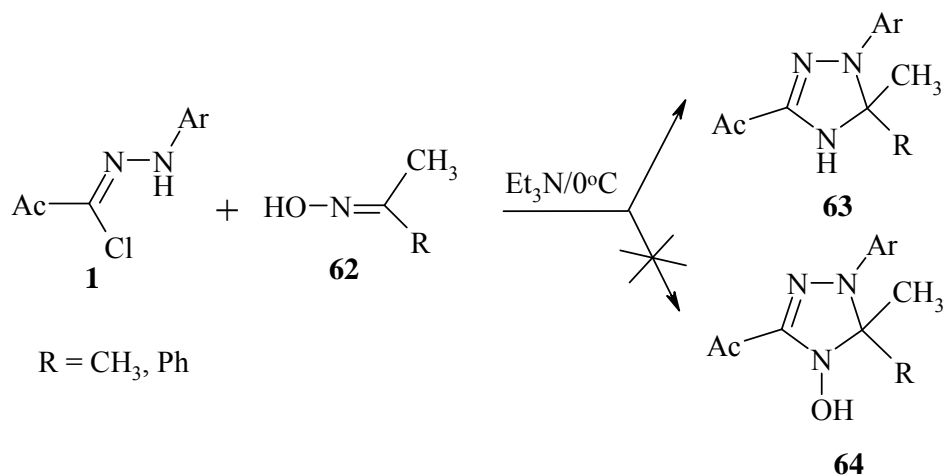
C-methoxycarbonyl hydrazonoyl halides **2** were also found to react with substituted hydrazones of alkanone, cycloalkanone and heterocyclic ketones **57** to give the cycloaddition products 3-methoxycarbonyl-4,5-dihydro-1,2,4-triazoles **61** [26].



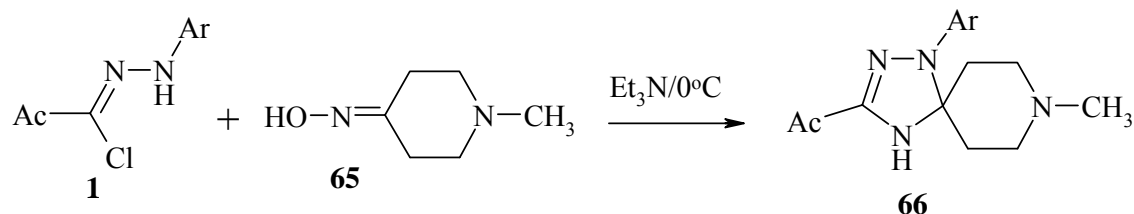
	a	b	c	d	e	f	g	h	i
R ¹	Me								
R ²	Me								

Reaction with Oximes

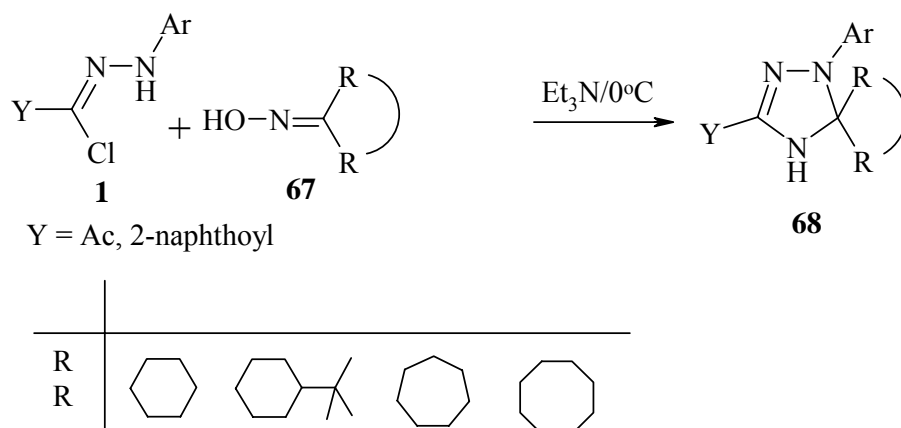
Acetone oxime **62** readily reacted with nitrilimines yielding the unexpected 3-acetyl-4,5-dihydro-5,5-dimethyl-1H-triazoles **63** in moderate yields. The 4-hydroxytriazoles **64** were not observed. Structural assignment of the resulting triazoles was based on elemental analysis, and spectral data including MS, IR, ¹H- and ¹³C-NMR spectral data. Further evidence was obtained from ¹⁵N-NMR spectra, which displays a doublet for the NH at 284.26 ppm relative to nitromethane (¹J_{N-H} = 85Hz; ³J_{N-CH₃} = 2.5Hz) [27].



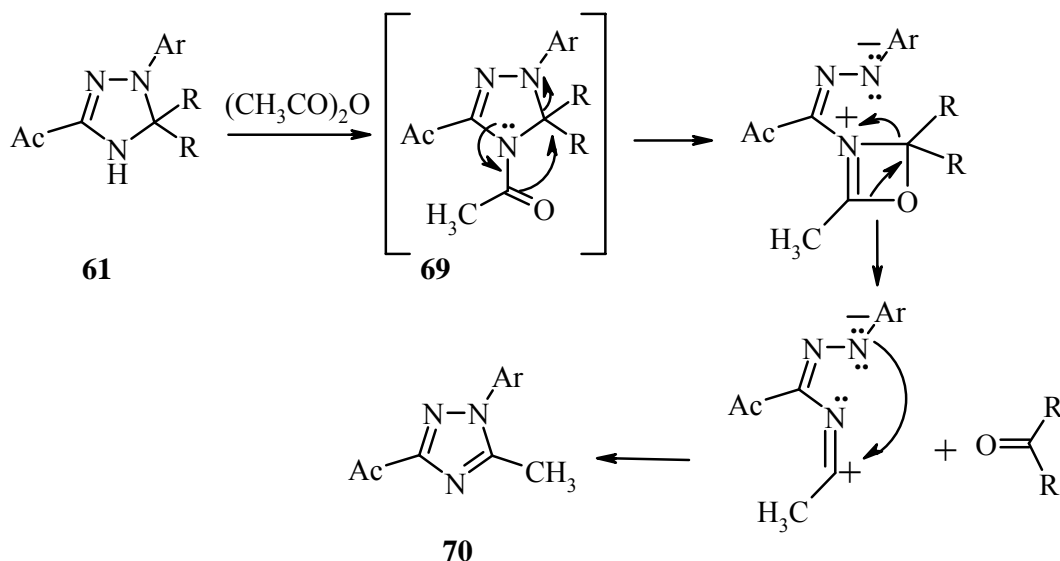
Nitrilimines reacted similarly with acetophenone oxime to afford the corresponding triazoles **63**. Similarly, the reaction with 1-methyl-4-piperidone oxime **65** yields the respective spiro triazoles **66** [28].



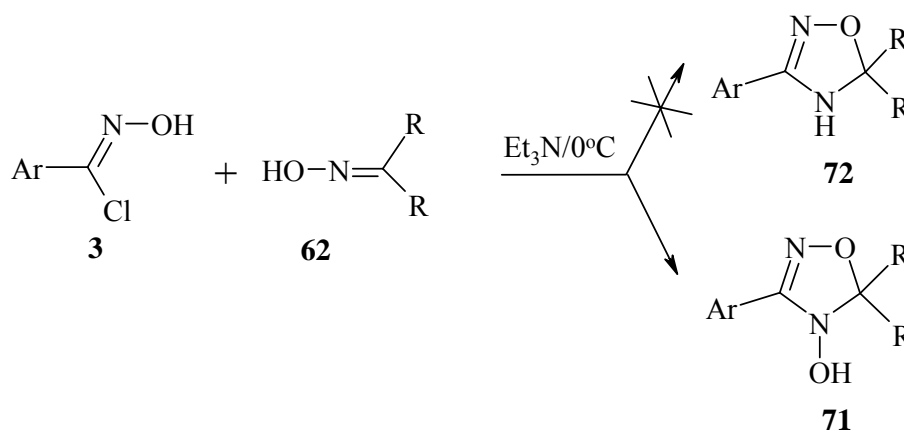
The reaction with cycloalkanone oximes **67** gave the heterocyclic spiro triazoles **68** in moderate yields [29].



Reaction of triazoles **61** with acetyl chloride or acetic anhydride gave the ring transformation product 1-Aryl-3-acetyl-5-methyl-1H-1,2,4-triazole **70** instead of the expected N-acetyl derivative **69**. This ring transformation was believed to start with N-acylation of the dihydrotriazole to form the corresponding N-acetyl derivative, which extruded the acetone *via* a four-membered ring intermediate and recycles to the aromatic triazole suggesting the conversion sequence (**61**) → (**69**) → (**70**) [29].



On the other hand, the reaction of nitrile oxides with oximes **62** was reported to give the 4-hydroxy-4,5-dihydro-1,2,4-oxadiazolines **71** [30].



Conclusions

Nitrilimines and nitrile oxides react with hydrazines giving acyclic adducts. The acyclic adducts resulting from the reaction of 1-substituted-1-methylhydrazines with nitrilimines cyclize to give s-tetrazines, and those resulting from the reaction of nitrile oxides with 1-ethoxycarbonyl-1-methylhydrazine cyclize to oxatriazinones upon stirring with sodium hydride. The reaction of nitrilimines with hydrazones give the acyclic adducts which also cyclize to s-tetrazines. The reaction with nitrile oxides gives, however, the 1,3-dipolar cycloaddition oxadiazole derivatives. s-Tetrazines and oxatriazines were obtained from the reaction of methylhydrazones with nitrilimines and nitrile oxides, respectively. Hydrazones carrying electron withdrawing groups react with nitrilimines affording the respective cycloaddition triazole products. Ketooximes react with nitrilimines yielding the respective triazoles.

References

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