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Hydrazones as substrates for cycloaddition reactions

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The [2 + 2]-, [4 + 2]- and [3 + 2]-cycloaddition reactions of hydrazones and 1,2-diazabuta-1,3-dienes, azomethine imines, nitrile imines and azomethine ylides formed upon hydrazone transformations with dienophiles, dipolarophiles and dienes are considered. The principal issues of structure and reactivity of active substrates and the influence of the reaction conditions and catalysts on the reaction regioselectivity and efficiency are discussed.
The bibliography includes 288 references.

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I. Introduction

The chemistry of hydrazones has started to vigorously develop since the middle of the 20th century.[1, 2] An important trend in the practical application of hydrazones is their use as reactants in the synthesis of various heterocyclic compounds.[1 – 20] Hydrazones may act as electrophiles and nucleophiles, and also undergo various oxidative and reductive transformations.[1 – 5, 19, 20] They are of special interest as substrates for pericyclic transformations. Depending on the substituents and functional groups present, hydrazones can be directly involved in the corresponding reactions or may be precursors for generating the active components for the hetero-Diels – Alder reaction (with 1,2-diazabuta-1,3-dienes) or [3 + 2]-cycloaddition (with azomethine imines, nitrile imines, azomethine ylides). In these processes various heterocyclic systems are formed, playing an important role in the chemistry of natural and biologically active compounds and being used as chiral ligands and catalysts for the asymmetric synthesis.[2, 5 – 20] Experimental data on the cycloaddition reactions of hydrazones accumulated over the last 15 – 20 years have not been virtually analyzed except for reactions of 1-amino-1-azabutadienes.[8] Moreover, possible prospects for application of hydrazone derivatives in cycloaddition reactions have not been considered since 1974, when a monograph of Kitaev and Buzykin was published.[2] The present review is aimed at the analysis of hydrazone structure and reactivity determining their applicability in cycloaddition reactions as well as special features of the mechanism of their reactions with dienophiles, dienes and dipolarophiles. The scope of these transformations and the influence of various factors (temperature, solvent nature, catalysts) on their efficiency are also discussed.

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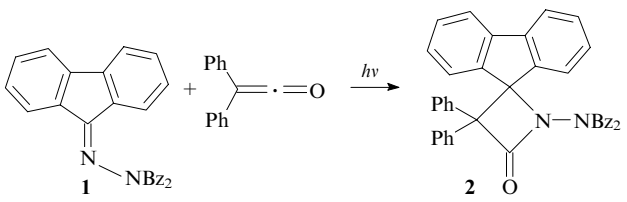
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II. The [2 + 2]-cycloaddition reactions of hydrazones

The possibility for the C=N bond to undergo [2 + 2]-cycloaddition has been originally demonstrated for the cycloaddition reaction of fluorenone dibenzoyl hydrazone (**1**) with diphenyl ketene yielding spirocyclic derivatives of 1-aminoazetidin-2-one **2** under UV irradiation (Scheme 1).[2]

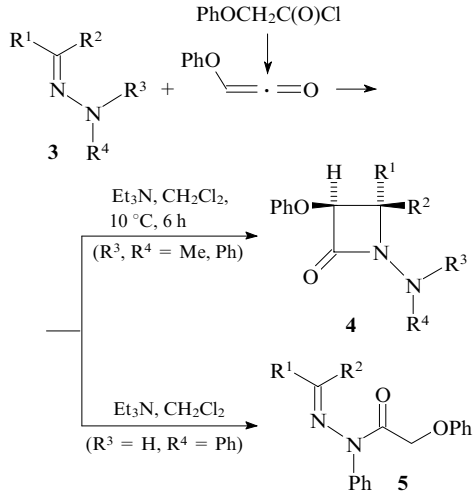
This transformation is considered to be a kind of cycloaddition of imines and ketenes (The Staudinger reaction) and presents a convenient method for the synthesis of novel biologically active racemic β-lactams. Subsequent studies have shown that it is suitable for hydrazones of both

Scheme 1



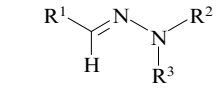
aldehydes and ketones.[21–23] The reaction efficiency depends on substituents at the carbon atom and nitrogen atom of the hydrazone group, and often the reaction proceeds without using the UV radiation.[6,21–28] The absence of hydrogen atom at the amine nitrogen of the hydrazone moiety is the basic requirement for this cycloaddition reaction. Alternatively, acylation involving NH-nucleophilic centre takes place instead of the [2 + 2]-cycloaddition.[21] Thus *N*,*N*-diphenyl- and *N*-methyl-*N*-phenylhydrazones **3** (R^3 = Ph: R^4 = Me, Ph) react with phenoxyketenes yielding monocyclic β-lactams **4**, whereas phenylhydrazones **3** (R^3 = H, R^4 = Ph) transform into *N*-acyl derivatives **5**, which do not react with the second ketene molecule even with an excess of phenoxyacetyl chloride (Scheme 2).

Scheme 2



R^1 = H, Me, Ph, Bz; R^2 = Me, Et, Pr^i, Ph, 2-ClC_6H_4, PhCH=CH; R^3 = H, Me, Ph; R^4 = Me, Ph

Dimethylhydrazones **3** (R^3 = R^4 = Me) (see Scheme 2) and aldehyde hydrazones (R^2 = H) in which the amine nitrogen atom is a part of the pyrrolidine ring (Fig. 1) are used most frequently, as the starting compounds.[6,23–28] A wide range of compounds having chiral centres can undergo the [2 + 2]-cycloaddition reaction with alkoxy- or aminoketenes; hence, this provides a new synthetic approach to enantiomerically pure 3-alkoxy- and 3-amino-β-lactams, which are the key moieties of many antibiotics.[22] The stereoselectivity of the process depends on the hydrazone structure and temperature.[24–28] Thus *N*-benzyl-*N*-(benzyloxycarbonyl)glycine (**6**), being a precursor of aminoketene **7**, reacts with *N*-(2,5-dimethylpyrrolidin-1-yl)ethane imines



R^1 = H, Pr^i, Bu^i, n-C_5H_{11}, $PhCH_2CH_2$, Ph;

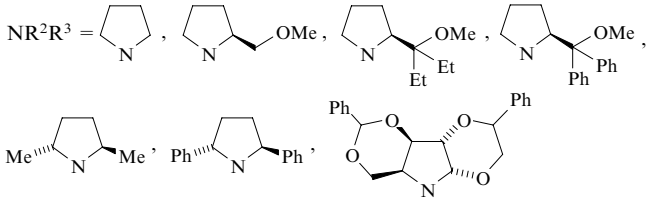
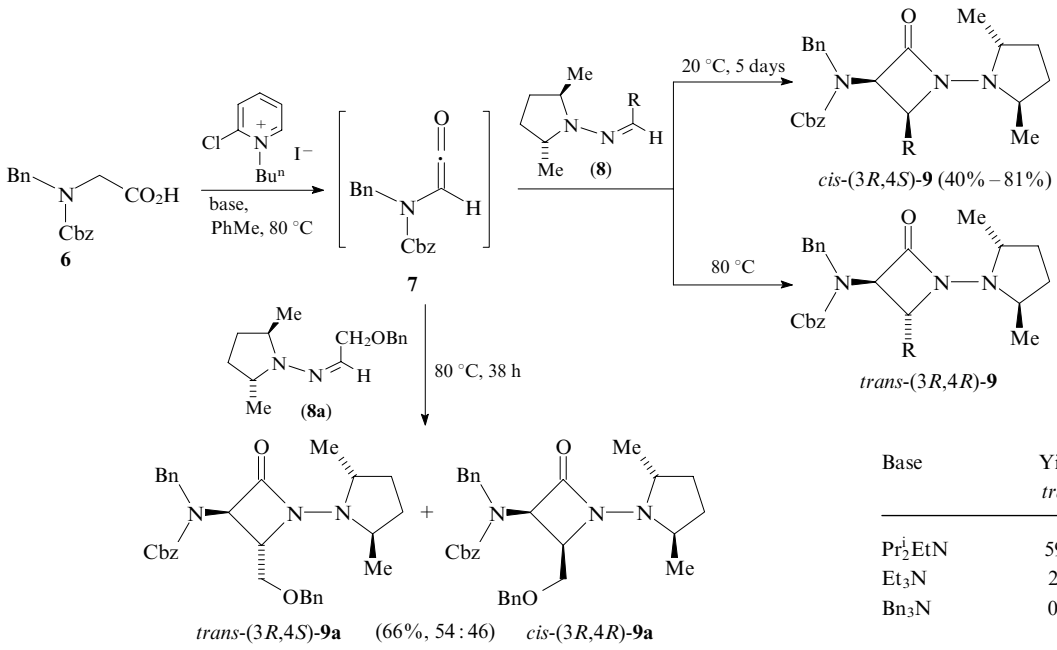


Figure 1. Aldehyde hydrazones used most often in [2 + 2]-cycloaddition.

Scheme 3



Base	Yield of *trans*-(3*R*,4*R*)-**9** (%)
Pr^i_2EtN	59 – 74
Et_3N	25 – 50
Bn_3N	0

trans-(3*R*,4*S*)-**9a** (66%, 54 : 46) *cis*-(3*R*,4*R*)-**9a**

R = Me, Pr^i, Bu^i, n-C_5H_{11}, $PhCH_2CH_2$; Cbz is benzyloxycarbonyl

8 on heating (80 °C) yielding *trans*-adducts **9** (Scheme 3), whereas at room temperature *cis*-adducts **9** are formed. The reaction between benzyloxyacetaldehyde hydrazone **8a** and aminoketene **7** is an exception; in this case, diastereomer mixture **9a** is obtained. The nature of the base used in the reaction significantly affects the yield of cycloadduct **9**. There is no reaction when tribenzylamine is used, whereas with Et_3N and Pr^i_2EtN, 1-aminoazetidin-2-ones **9** are formed in moderate and good yields, respectively (see Scheme 3).[27]

The benefits of using hydrazones in [2 + 2]-cycloaddition are caused by their stability compared with imines, good yields of the cycloadducts, mild conditions and high stereoselectivity of the process. The latter circumstance (enantioselectivity of addition at the 3-position of the azetidin-2-one ring) is of great importance for the synthesis of biologically or pharmacologically active molecules.

III. The [4 + 2]-cycloaddition reactions of hydrazones comprising 1-azabuta-1,3-diene system

The hydrazones participating in [4 + 2]-cycloaddition are, most often, derivatives of 1-azabuta-1,3-dienes, obtainable through the condensation of α,β-unsaturated aldehydes and ketones with hydrazines.[7–12] The Diels–Alder reaction involving 1-azadienes is a widely used approach to functionalized polycyclic six-membered heterocycles *via* regio- and stereocontrolled cycloaddition involving the conjugated C=N and C=C bonds in compounds of types **I** and **II** (Fig. 2).

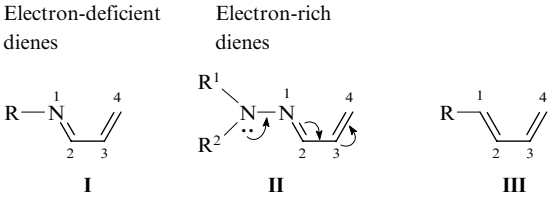


Figure 2. Butadienes and their aza analogues participating in the Diels–Alder reaction.

The presence of the nitrogen atom in the 1-position of butadiene system decreases the highest occupied molecular orbital (HOMO) energy of the system and results in the π-electron-deficiency. Therefore, compounds **I** are characterized by lower reactivity than the corresponding buta-1,3-dienes **III** in the classical Diels–Alder reactions with electron-deficient dienophiles controlled by the $HOMO_{(diene)}-LUMO_{(dienophile)}$ interaction (LUMO is the lowest unoccupied molecular orbital). The introduction of an amino group to the terminal nitrogen atom N(1) enhances nucleophilic character of azadiene and counterbalances the electron deficiency of its π-system owing to participation of the lone electron pair of nitrogen of the N-amino group in conjugation.[8,29]

III.1. The effect of substituents on the reactivity of 1-amino-1-azabuta-1,3-dienes

Despite the fact that 1-azadiene system features moderate reactivity, synthetic applications of hydrazones **IV**–**VI**

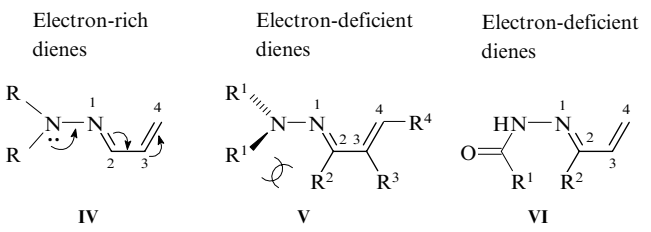
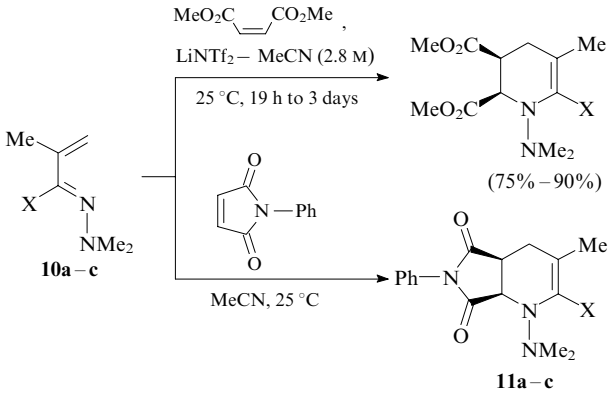


Figure 3. *N*-Aminoazadienes as participants of the Diels–Alder reaction.

(Fig. 3) comprising this system of conjugates bonds are progressively extending.[6–12] This is associated with the possibility to control the electronic structure of a diene by varying the nature of substituents and their location in the molecule. The introduction of an alkyl substituent to the C(2) carbon atom in hydrazones of type **V** (R^2 = Alk) counterbalances the effect of the lone pair of electrons of the amino group by hampering the conjugation between the p-orbital in which they are located with the π-system (see Fig. 3).[8,29–31]

To get around this problem and to enhance the amino-group conjugation with the diene system, dimethylhydrazones **V** were synthesized comprising electron-withdrawing substituents (R^2 = EWG) at the C(2) atom, and their reactions with dienophiles were studied.[8,31] Contrary to the corresponding 1-azadiene **10a**, which has no substituent at the C(2) atom (X = H) and reacts with both electron-deficient and electron-rich dienophiles, dimethylhydrazones **10b**,**c** bearing an electron-deficient group (Scheme 4) react neither with ethyl vinyl ether nor with methoxystyrene. Moreover, their reactions with phenylmaleimide (yielding bicyclic compounds **11**) and with dimethyl maleate are considerably slower than those of hydrazone **10a**.[31]

Scheme 4

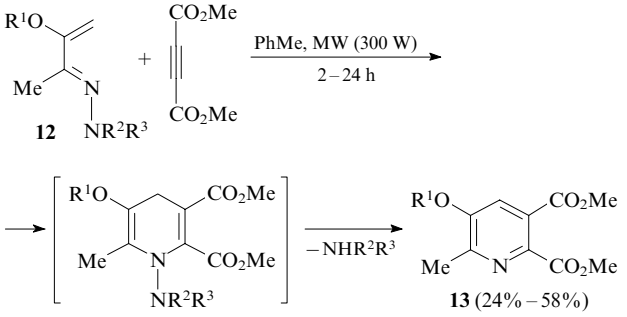


X	Yield of **11** (%)	Reaction time /day
H	95	1
CO_2Me	76	3
CN	82	14

It should be noted that the cycloaddition of dimethylhydrazones **10** may be catalyzed by bis(trifluoromethane)sulfonimide lithium salt ($LiNTf_2$) in organic solvents. This reduces the reaction time from several days down to several hours.[31]

The introduction of electron-donating groups to the C(3) atom of 2-substituted 1-azabuta-1,3-dienes **V** (see Fig. 2) facilitates their reactivity towards electron-deficient dienophiles.[8, 31, 32] Hydrazones **12** with electron-donating substituents at the C(2) and C(3) atoms react with dimethyl acetylenedicarboxylate (DMAD) to give tetrasubstituted pyridines **13** (Scheme 5). Increasing the temperature, microwave radiation (MW) or increase in the dienophile concentration favour an increase in the product yields. Further, the reaction proceeds with high yields when *tert*-butyldimethylsilyl ethers **12** (R^1 = TBDMS) are used. Trimethylsilyl ethers **12** (R^1 = TMS) form cycloaddition products **13** in lower yields, while *tert*-butyldiphenylsilyl ether (R^1 = TBDPS) does not react at all (see Scheme 5).[32]

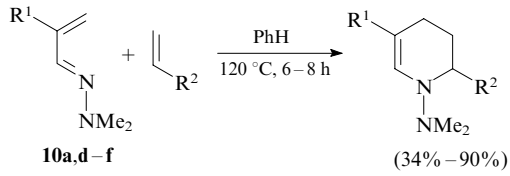
Scheme 5



R^1 = TMS, TBDMS; NR^2R^3 = NMe_2, NMeCbz, piperidino

The presence of electron-donating substituents at the C(3) atom accelerates the reaction between 1-amino-1-azadienes and nucleophiles.[8, 31–43] α-Alkylacrolein dimethylhydrazones **10a**,**d**–**f** react rather readily even with the nitrile and methyl ester of acrylic acid (Scheme 6).[31, 33–35]

Scheme 6

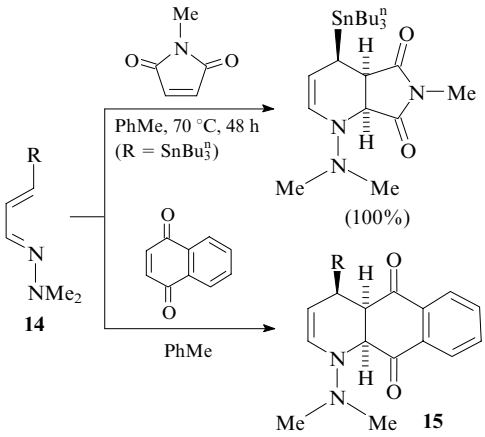


10: R^1 = Me (**a**), H (**d**), Et (**e**), OTBDMS (**f**); R^2 = CN, CO_2Me

The electron-donating substituent at the C(4) atom enhances the reactivity of compounds **14**, especially in reactions with electron-deficient dienophiles.[8–10, 41–50] To the contrary, introducing electron-withdrawing substituents into this position lowers the reactivity of the 1-amino-1-azadiene system and, correspondingly, the yield of product **15** (Scheme 7).[44]

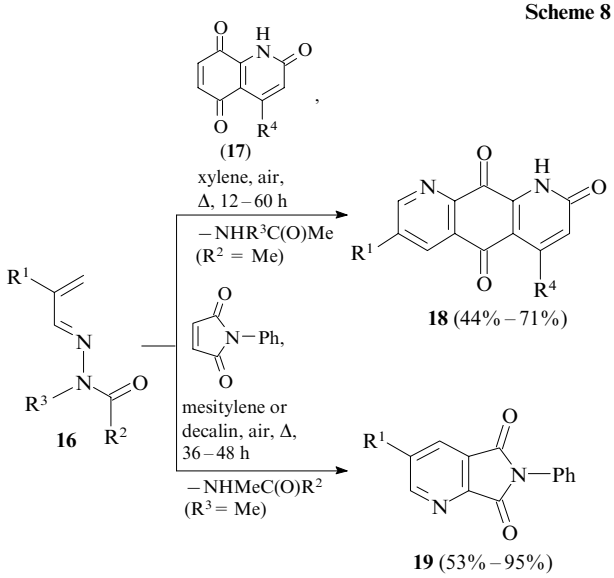
1-Acylamino-1-azadienes of type **VI** (see Fig. 3) also undergo [4 + 2]-cycloaddition, though their reactivity is lower than that of dialkylamino derivatives **V**. For example, refluxing *N*-acylhydrazones **16** with quinolinetriones **17** in xylene or with *N*-phenylmaleimide in mesitylene or decalin affords pyrido[3,2-*g*]quinolinetriones **18** and pyrrolo[3,4-*b*]-pyridinediones **19**, respectively, in moderate or good yields (Scheme 8).[46, 51]

Scheme 7



R	*T*/°C	Yield of **15** (%)
$SnBu^n_3$	70	71
CO_2Me	110	16

Scheme 8

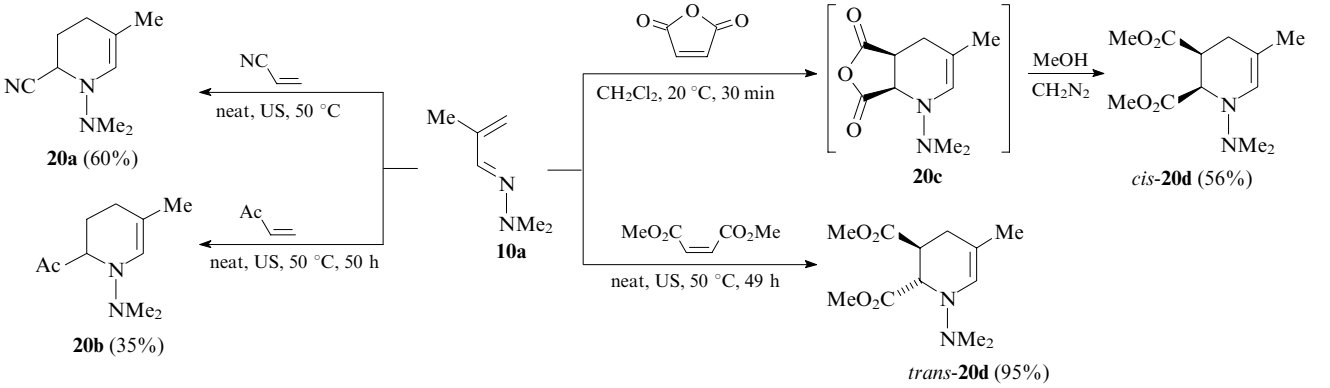


18: R^1 = H, Me, Et; R^3, R^4 = H, Me;
19: R^1 = Me, Et; R^2 = $(CH_2)_2C{\equiv}CH$, $(CH_2)_2CH{=}CH_2$

III.2. Intermolecular [4 + 2]-cycloaddition of hydrazones of α,β-unsaturated aldehydes and ketones to alkenes and alkynes

Introduction of the dialkylamino group at the N(1) nitrogen atom greatly activates 1-azadienes so they can react with a variety of electron-deficient dienophiles by a cycloaddition mechanism and form dihydro- and tetrahydropyridines. These heterocyclic products are very important as building blocks for the synthesis of polycyclic alkaloids.[7–11] Depending on the process conditions (temperature and solvent) and the reactant structure, the formation of 1-dialkylamino-1,2,3,4-tetrahydropyridine may be followed by elimination of dialkylamine and oxidation. The electronic nature of the dienophile, the process conditions and the catalyst, along with the substituent effects in the azadiene system disscussed above, are also important factors determining the rate of the Diels–Alder reaction. Among 1-amino-1-azadienes, *N*,*N*-dialkylhydrazones (**IV**,

Scheme 9

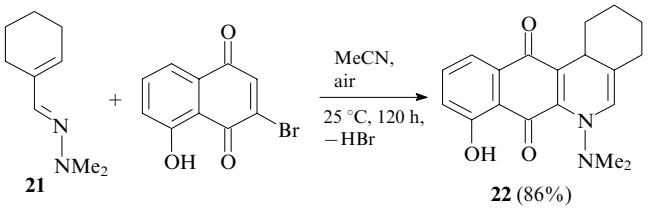


V; NR_2 = $NAlk_2$, pyrrolidino, morpholino; see Fig. 3) are most commonly used in the hetero-Diels–Alder reactions.[8–10]

The cycloaddition reactions between *N*-dialkylhydrazones and linear or cyclic activated alkenes and alkynes (propiolic acid esters, maleates, maleimides, acrylates, *etc.*) have been widely investigated.[6–11,29–37,40–43,51–60] The reactions proceed according to the normal electron demand to afford a single regioisomer. The yield of cycloadducts may be increased by adding Lewis acids (BF_3, $AlCl_3$, $InCl_3$, $LiClO_4$)[8,30] or by ultrasonication (US) (Scheme 9).[37] The reaction of equimolar amounts of hydrazone **10a** with acrylonitrile, methyl vinyl ketone, maleic anhydride, dimethyl maleate or dimethyl fumarate furnishes mono- and bicyclic tetrahydropyridines **20a–d**. Dimethyl maleate and dimethyl fumarate react to give *trans*-adduct **20d** only, being the result of the dimethyl maleate isomerization, according to the authors' opinion (Scheme 9).[8–11,31,33–37]

The C=C double bond of the 1-azadiene system of hydrazone may form a part of a carbocyclic moiety or a heterocycle.[8,33,45,61,62] Thus, reaction between cyclohex-1-enecarbaldehyde hydrazone (**21**) and 2-bromo-8-hydroxynaphthalene-1,4-dione is used to obtain angular tetracyclic quinones **22** (Scheme 10).[45]

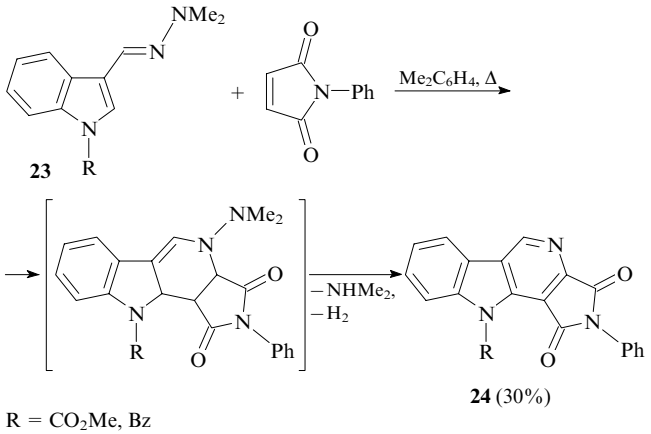
Scheme 10



Hydrazones of indole-3-carbaldehydes **23** react with *N*-phenylmaleimide to produce annulated γ-carbolines **24** *via* the cycloaddition followed by the elimination of dimethylamine and dehydrogenation (Scheme 11).[61,62] However, no cycloaddition products are observed for maleic anhydride, naphthoquinone and DMAD.

The reaction between hydrazone of 2-methylenecyclopentanone or 2-methylenecyclohexanone (**25a**,**b**) and acrylonitrile or methyl acrylate is completed within 2 h on heating in an autoclave at 110 °C to yield tetrahydropyridine annulated to five- or six-membered carbocycle.[33] Hydrazones **25a**,**b** react with *N*-methylmaleimide much faster.

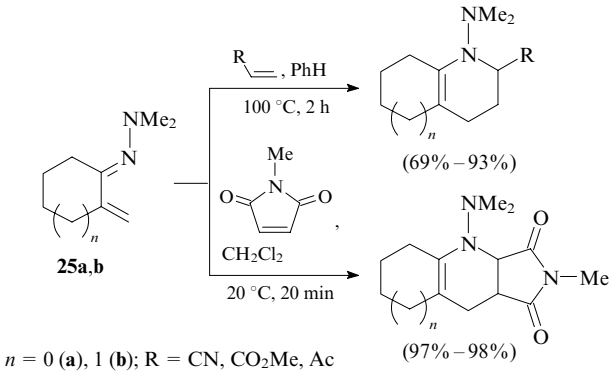
Scheme 11



R = CO_2Me, Bz

For this reaction to be completed, it is sufficient to stir the reactants for 20 min at room temperature (Scheme 12).

Scheme 12

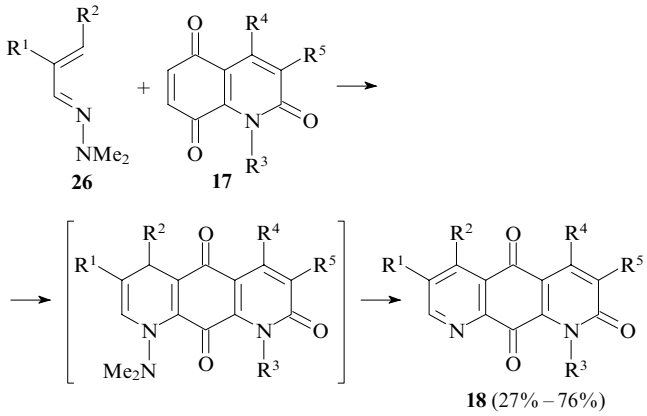


n = 0 (**a**), 1 (**b**); R = CN, CO_2Me, Ac

It should be noted that in most cases, in the [4+2]-cycloaddition reactions of dialkylhydrazones of α,β-unsaturated aldehydes and ketones, quinones are used as dienophiles.[6–11,37–46,63–78] This is mainly due to the practical application of the products for the synthesis of natural compounds and biologically active compounds.

The cycloaddition of dimethylhydrazones **26** to 1*H*-quinoline-2,5,8-triones **17** provides a synthetic approach to pyrido[2,3-*g*]quinolinetriones **18**, which are the starting compounds in the synthesis of antibiotic diazaquinomycin A (Scheme 13).[63]

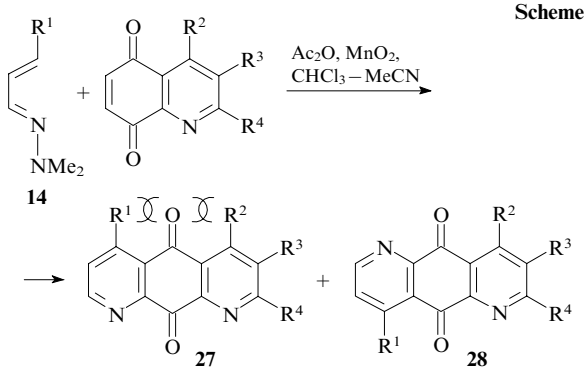
Scheme 13



R^1, R^3 = H, Me; R^2 = H, Me, Et, Pr^n, Ph; R^4 = H, Me, Et; R^5 = H, Me, Pr^n, CH_2OAc

In principle, the reaction between hydrazones comprising α,β-unsaturated bond in the molecule with unsymmetric dienophiles may result in two regioisomers. Actually, in some cases, for example, in reaction of but-2-enal hydrazone **14** with quinoline-5,8-diones, isomeric diazaanthraquiniones **27** and **28** were obtained. The second isomer formed in greater amount, which may be caused by the steric hindrance in the molecule of regioisomer **27** (Scheme 14).[41,47,48]

Scheme 14

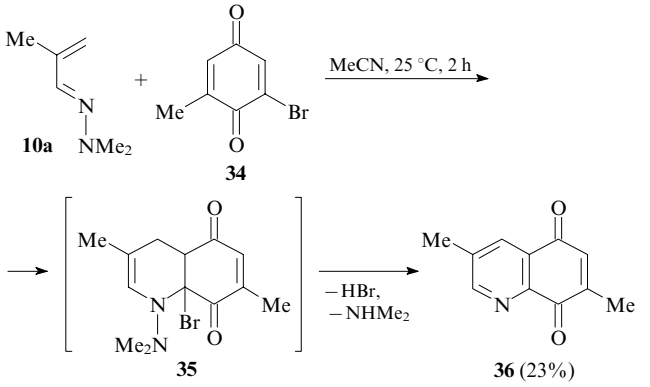


R^1 = Me, $C_6H_4NO_2$-2, $NHC(O)CF_3$; R^2 = H, Cl, NO_2, OMe, Br, NHAc; R^3 = H, CO_2Et; R^4 = H, OMe, Cl

A similar reaction of *N*,*N*-dimethylhydrazones of α-methylacrolein (**10a**), cyclohex-1-enecarbaldehyde (**21**) and crotonic aldehyde (**14a**) with isoquinoline quinone **29** affords regioselectively 1,7-diaza-1,4-dihydroanthra-5,10-quinones **30**, **31**, 1,7-diazaanthra-5,10-quinone **32** and pyrido[3,4-*b*]phenanthridine **33** in moderate yields. The formation of one regioisomer takes place according to the prediction of frontier molecular orbital theory (Scheme 15).[45]

The introduction of the bromine atom into a quinone molecule increases its reactivity and governs the regioselectivity of cycloaddition.[41,42,46,49,50,63,79–81] Hydrazone **10a** readily reacts with 2-bromoquinone **34**. The cycloaddition step is followed by aromatization of the originally formed tetrahydroquinolinedione **35** to give the corresponding quinoline quinone **36** *via* elimination of HBr and dimethylamine molecules (Scheme 16).[79–81]

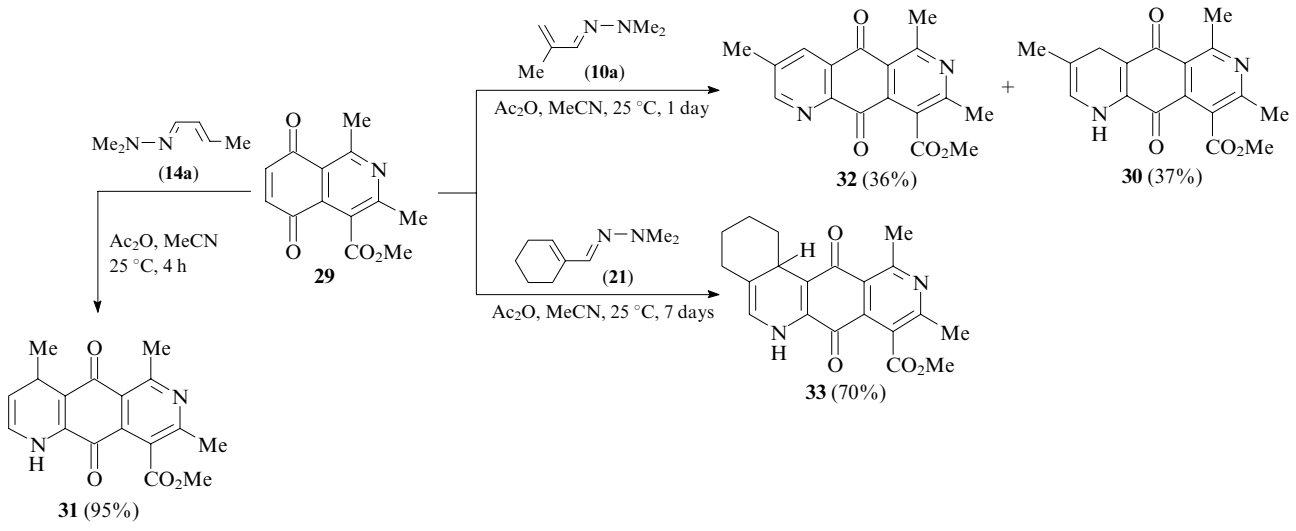
Scheme 16



It should be noted that aromatization of azanaphthoquinone **35** proceeds easily even in the course of cycloaddition whereas in other cases, intermediate tetrahydroanthraquinones were isolated in good yields and their aromatization required special conditions (pyrolysis).

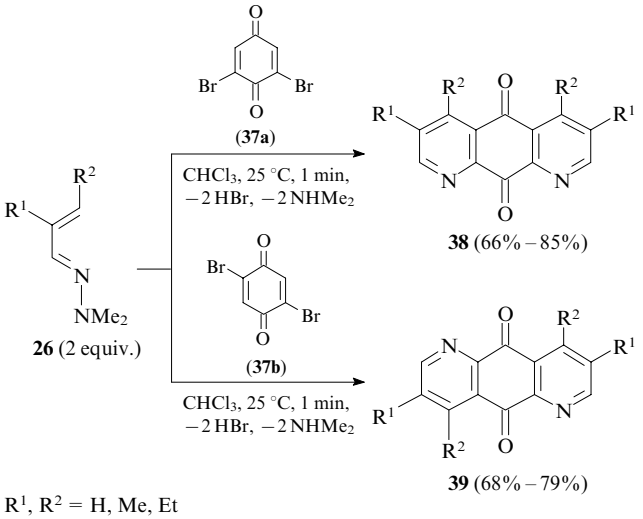
Using dihaloquinones **37a**,**b** as dienophiles in the reaction with dimethylhydrazones **26** gives bis-condensation

Scheme 15



products, namely, 1,8- and 1,5-diazaanthraquinones **38** and **39**, their structure being determined by the location of the bromine atom (Scheme 17).[42, 63, 77]

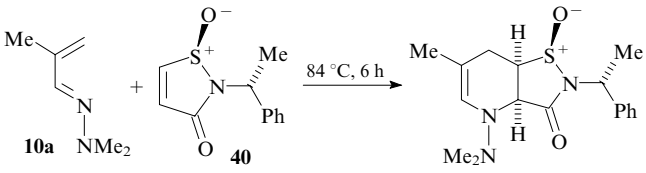
Scheme 17



R^1, R^2 = H, Me, Et

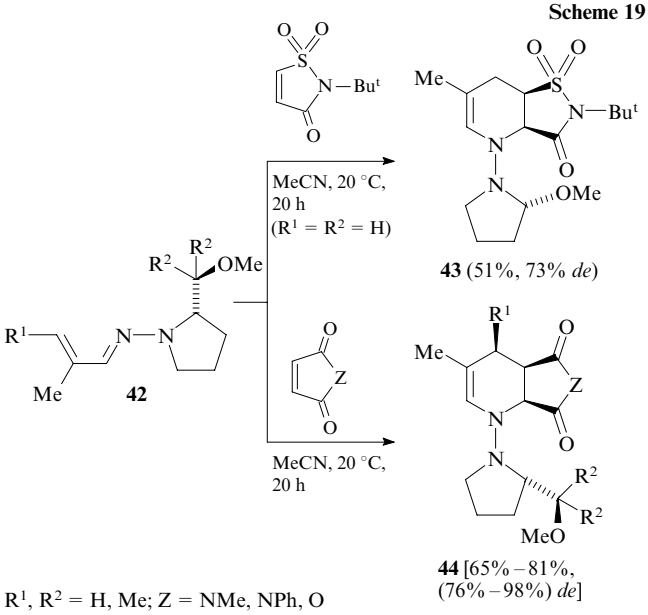
Examples of application of the chiral dienophiles or dienes in the diastereoselective synthesis of dihydro- and tetrahydropyridines are reported in literature.[29, 52–60] For instance, dimethylhydrazone **10a** reacts with chiral dienophile **40** to give cycloadduct **41** in good yield and with high stereoselectivity even at high temperature (Scheme 18).[53]

Scheme 18



Chiral 1-azadiene **42** also reacts with cyclic dienophiles stereoselectively. This gives enantiomerically pure derivatives of tetrahydropyridine **43** and **44** (Scheme 19).[54]

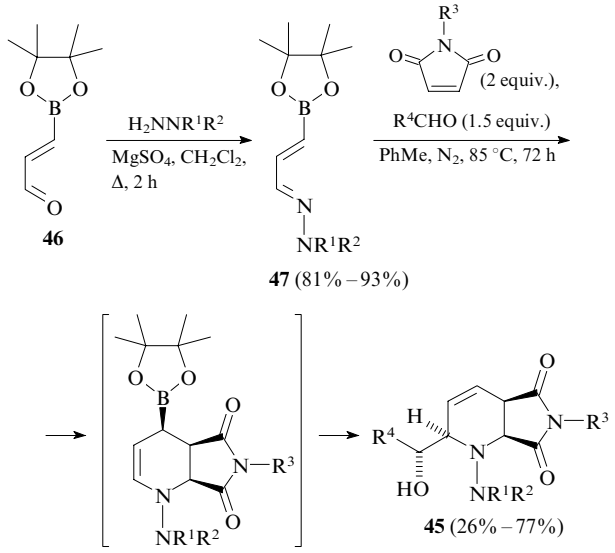
Scheme 19



R^1, R^2 = H, Me; Z = NMe, NPh, O

One of the modern trends in synthetic application of the [4 + 2]-cycloaddition of dialkylhydrazones is connected with the strategy of multicomponent synthesis.[55–60] The three-component process involving tandem aza-[4 + 2]-cycloaddition and allylboration yielded a number of polysubstituted α-hydroxyalkyldehydropiperidines **45** (Scheme 20).

Scheme 20



NR^1R^2 = NMe_2, NMePh, NPh_2, NHPh, NHAc, NHBoc;
R^3 = Me, Ph; R^4 = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 2-MeC_6H_4, 2-$MeOC_6H_4$, 2,4,6-$Cl_3C_6H_2$, cyclo-C_6H_{11}, Pr^iCH_2, 2-Py; Py is pyridyl

Despite the formation of 4 asymmetric centres, the reaction proceeds stereoselectively. The reason is that the first step, *i.e.*, [4 + 2]-cycloaddition, obeys exclusive *endo*-selectivity, and the spatial structure of the cyclic transition state of allylboration provides for a rigorously defined disposition of substituents due to coordination of the aldehyde oxygen to the boron atom. Note that the stereochemistry of the polysubstituted dehydropiperidines obtained is similar to that of certain alkaloids and azasugars, rendering the above method relevant for the synthesis of analogues of natural cyclic aminoalcohols. The reaction is general and tolerant to the use of aldehydes and hydrazones bearing substituents with different electronic and steric effects. Moreover, this process may be carried out as four-component one by simultaneous mixing of the required hydrazine, 3-(1,3,2-dioxaborolan-2-yl)acrolein (**46**), maleimide and aldehyde, thus eliminating the neccessity of isolation and purification of hydrazone **47**.[55–60]

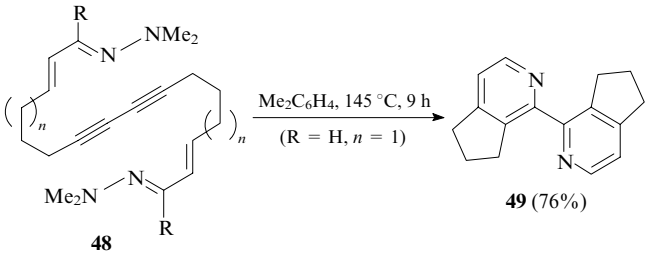
III.3. Intramolecular cycloaddition of 1-amino-1-azadienes

The intramolecular cycloaddition of 1-azadienes is a convenient route to polycyclic systems containing a fused pyridine moiety.[6, 8, 10, 51, 82–86] A limitation on using this reaction is associated with poor accessibility of the starting compounds comprising both 1-amino-1-azabuta-1,3-diene system and an additional multiple bond in a position suitable for the interaction.

Among compounds **48** in which azadiene is linked to a diyne moiety through an oligomethylene chain, only bishydrazone with $n = 1$ is readily converted to tetrahydro-2,2′-

bi(cyclopenta[*c*]pyridine) (**49**) in good yields (Scheme 21).[82, 83]

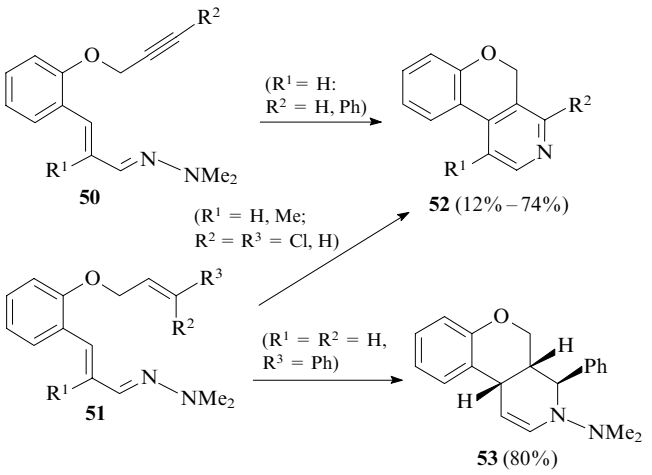
Scheme 21



R = H, Me; *n* = 1, 2

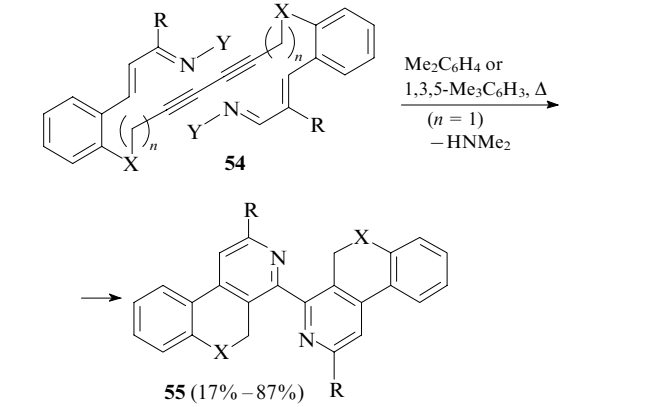
Propargyl and allyl ethers **50** and **51** cyclize to give 5*H*-chromeno[3,4-*c*]pyridines **52** and tetrahydro-3*H*-chromeno[3,4-*c*]pyridines **53**.[84] In the course of the reaction, aromatization of the pyridine moiety may proceed upon elimination of the dimethylamine molecule (Scheme 22).

Scheme 22



The intramolecular cycloaddition of bis(*N*,*N*-dimethylhydrazones) **54** to multiple bonds is used to obtain bisheterocycles **55** (Scheme 23).[82, 83]

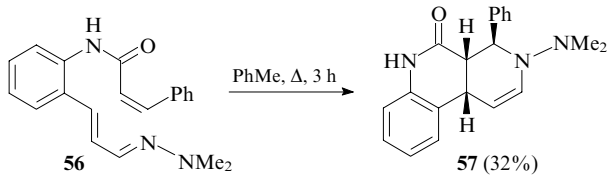
Scheme 23



R = H, Me; X = O, NBn; Y = NMe_2; *n* = 1, 2

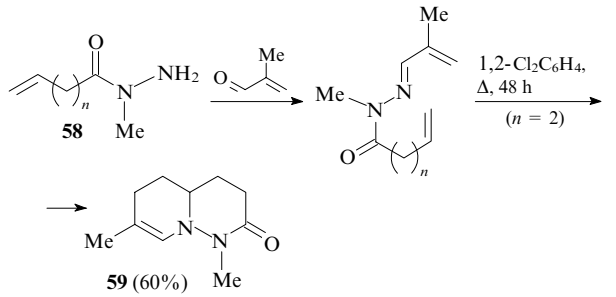
Phenylacrylamide **56** cyclizes to form tetrahydrobenzo[*c*][2,7]naphthyridin-1-one **57** in boiling toluene upon simultaneous formation of two tetrahydropyridine rings. This takes place because of the favourable spatial arrangement of substituents in the *cis*-position (Scheme 24).[84]

Scheme 24



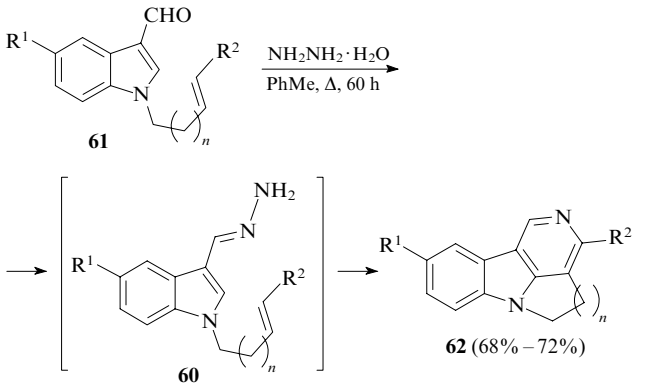
Heating hydrazides **58** with 2-methylpropenal in dichlorobenzene affords only tetrahydro-1*H*-pyrido[1,2-*b*]-pyridazin-2(3*H*)-one **59** (*n* = 2).[51] With the butenoic acid hydrazide **58** (*n* = 1), intramolecular cycloaddition does not proceed even upon heating to 200 °C (Scheme 25).

Scheme 25



Hydrazones **60** cyclize even in the course of their synthesis from 1*H*-indole-3-carbaldehydes **61** and hydrazine hydrate to give dihydrobenzopyridopyrrolizines (*n* = 1) and dihydroindolonaphthyridines (*n* = 2) **62** by the intramolecular [4 + 2]-cycloaddition mechanism. An attempt to isolate intermediate hydrazones **60** failed (Scheme 26).[86]

Scheme 26



R1 = H, OMe; R2 = CO_2Et; *n* = 1, 2

The above examples show that unlike the intermolecular [4 + 2]-cycloaddition, intramolecular cycloaddition of 1-amino-1-azadienes to multiple bonds proceeds more easily and even in the absence of the activating electron-withdrawing groups at the double or triple carbon–carbon bonds.

IV. Hydrazones as dienophiles in the aza-Diels–Alder reactions

New prospects for the application of [4 + 2]-cycloaddition of hydrazones in the chemistry of heterocyclic compounds are associated with their ability to take part in these reactions as electron-deficient dienophiles in reactions with dienes, which may include tetrazines and 1-alkoxy-3-buta-1,3-dienes (Danishefsky's dienes).[12, 13, 87–94]

Formaldehyde hydrazones **63** (R^1 = H) react with tetrazines **64**, which may be considered as cyclic 2,3-diazadienes, to evolve nitrogen and to give the products of the [4 + 2]-cycloaddition, *i.e.* 4,5-dihydro-1,2,4-triazines **65** in high yield. Dimethylhydrazones of aromatic aldehydes **63** (R^1 = Ar) are less reactive and the yields of the cycloadducts **66** are considerably lower even upon long-term heating (Scheme 27).[87]

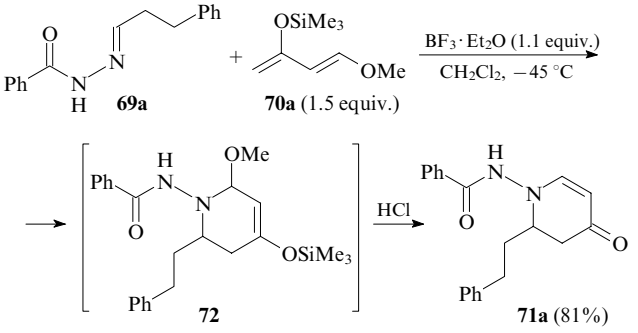
It is noteworthy that reaction of cinnamaldehyde hydrazone **63** (R^1 = PhCH=CH) with tetrazine **64** (R^3 = CO_2Me) affords a mixture of two cycloaddition products formed due to a participation of different double bonds of the dienophile molecule (C=C and C=N). Along with the 1,2,4-triazine **67**, 4-phenyl-4,5-dihydropyridazine **68** was isolated in a moderate yield. The reaction proceeds according to the inverse electron demand.[12, 87]

Hydrazones can also be dienophiles in the cycloaddition reaction with Danishefsky's dienes.[88–94] Addition of Lewis acids significantly accelerates the reaction. Thus, benzoylhydrazone of 3-phenylpropionic aldehyde (**69a**) reacts with buta-1,3-diene **70a** in the presence of $BF_3 \cdot Et_2O$ to give 3,4-dihydropyridone **71a** (Scheme 28).[88]

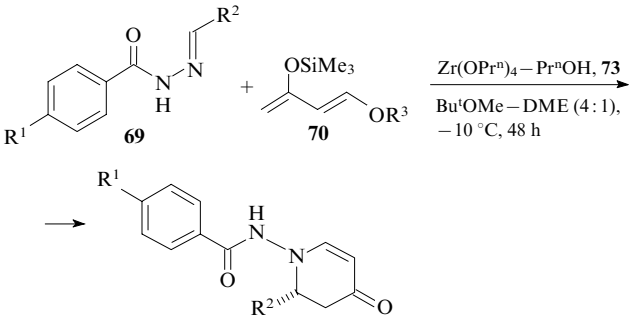
An attempt to isolate intermediate cycloadduct **72** failed as this compound is extremely unstable. The possibility of its formation was demonstrated by the reaction between imines and Danishefsky s dienes as an example.[90]

Aroylhydrazones **69** react with butadienes **70** in the presence of a chiral zirconium catalyst with a (*R*)-3,3′,6,6′-I_4-BINOL ligand (**73**), yielding optically active dihydropyridones **71** (Scheme 29).[88]

Scheme 28

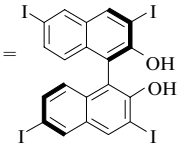


Scheme 29



R^1 = H, CF_3, Cl, OMe; R^2 = Pr^n, Bu^i, cyclo-C_6H_{11}, $(CH_2)_2Ph$;
R^3 = Me, Bu^t; DME is dimethoxyethane;

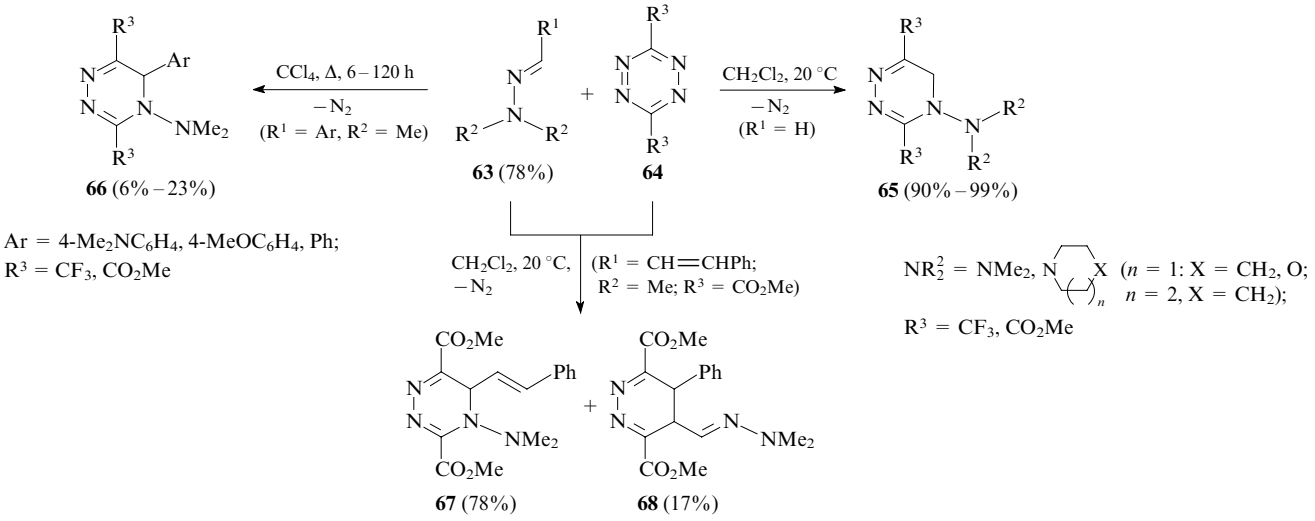
73 =



By using various solvents (MeCN, acetone, toluene, CH_2Cl_2, EtOAc, $MeNO_2$, DMF) and Lewis acids {$Sc(OTf)_3$, $Yb(OTf)_3$, $ZnCl_2$, $Mo_2(OAc)_4$, $Mo_2[OC(O)CF_3]_4$, $Mo_2(OBz)_4$, *etc.*}, the solvent effect on the process efficiency was elucidated and the optimal conditions were found. This allowed introducing a variety of starting compounds into the reaction and obtaining functionalized dihydropyridin-4(1*H*)-ones **71** in high yields and with high enantioselectivity.[89, 91, 92]

It is worth noting that the mechanism of the cycloaddition between Danishevsky's dienes and the C=N

Scheme 27

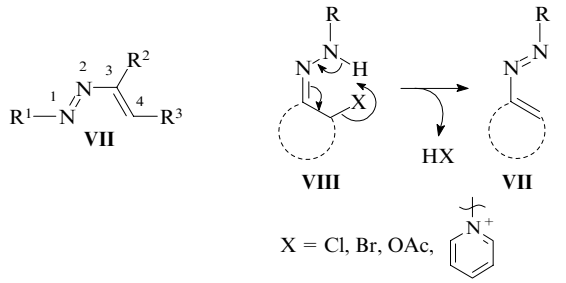


bonds of imines and hydrazones has been actively investigated and discussed in the scientific literature since the very first publications and up to now.[13] Apart from the accepted concerted (but asynchronous) mechanism formally assigned to normal electron demand [4+2]-cycloaddition, a concept of formation of an acyclic intermediate according to the Mannich reaction pattern is discussed in the literature.[90, 93, 94]

V. Synthetic methods and cycloaddition reactions of 1,2-diazabuta-1,3-dienes

Hydrazones that have a good leaving groups at the α-position to the carbon atom of the hydrazone moiety serve as the starting compounds to generate heterodienes **VII**, which may react with dienophiles by the [4+2]-cycloaddition mechanism (Scheme 30).[11, 14, 95, 96] These compounds are titled as 1,2-diazabuta-1,3-dienes, enyldiazenes, diazadienes or azolkenes. The main method for the synthesis of azoalkenes **VII** is based on the elimination of a substituent from the α-position to the hydrazone group of the corresponding functionalized type **VIII** hydrazones (see Scheme 30).[11, 14, 95–117]

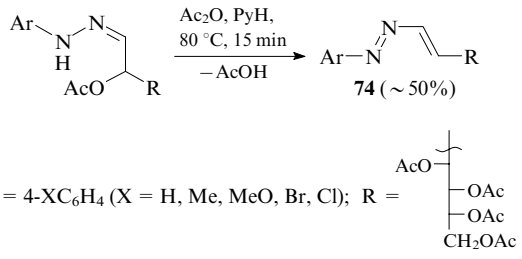
Scheme 30



Most often, halogen derivatives of arylhydrazones are used as the starting compounds for the synthesis of 1,2-diazabuta-1,3-dienes. Traditionally, this requires addition of a base (Et_3N, Na_2CO_3, K_2CO_3).[14, 95, 96, 104–117] The above method for the azoalkene generation is most convenient regarding the availability of starting hydrazones **VIII**, the ease of leaving group elimination and the possibility to introduce various structural moieties into molecules of the compounds in question.

Most of diazadienes are unstable and are often used either *in situ* or without additional purification or isolation. However, in some cases, they may be obtained as liquid or crystalline products.[103–110] Thus, 1,2-diazabuta-1,3-dienes **74** comprising D-arabinose residue in the molecule were isolated in moderate yields as crystalline products (Scheme 31).[103]

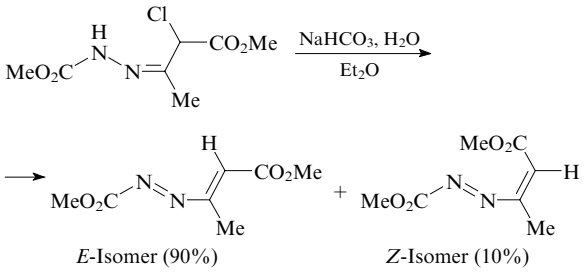
Scheme 31



Azoalkenes are also labile in solution and decompose at 0 °C within several hours. They can be stored for 2–3 days in cooled dilute solutions.[106]

Owing to the presence of two double bonds in 1,2-diazabuta-1,3-diene molecules, geometric isomers may exist (Scheme 32).[109] Preferred formation of one isomer over another depends on the nature and steric peculiarity of the substituents in the molecule.[99, 100, 107–110]

Scheme 32



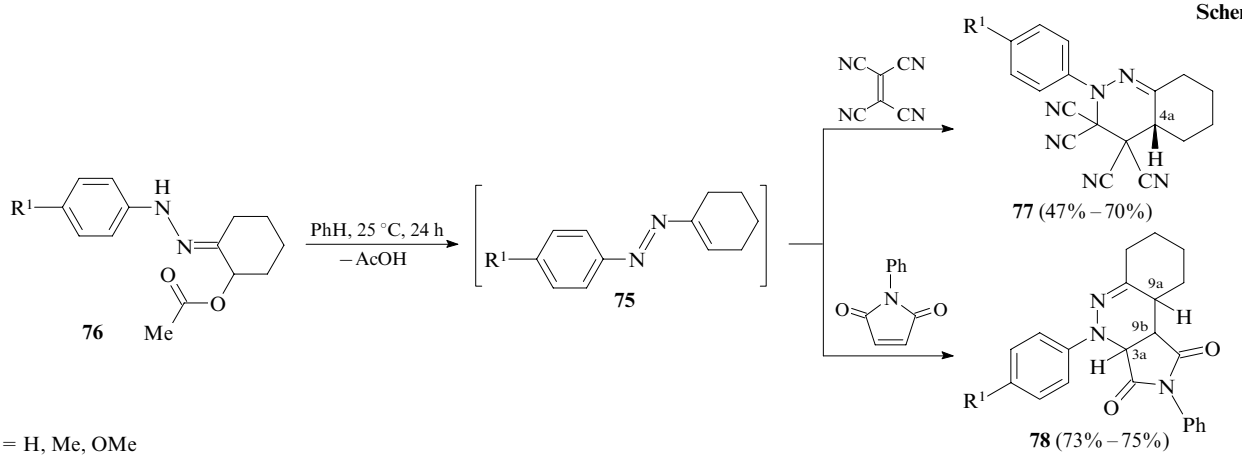
V.1. Intermolecular cycloaddition reactions of 1,2-diazabuta-1,3-dienes

Similarly to monoazadienes **IV**–**VI** (see Fig. 3), diazadienes **VII** (see Scheme 30) are used in the organic synthesis for the preparation of functionalized nitrogen-containing heterocycles.[15] Cycloaddition reactions of 1,2-diaza-1,3-dienes **VII** with alkenes and alkynes represent a convenient method for the stereo- and regioselective formation of polyfunctional pyridazines or dihydropyridazines,[14, 95, 96, 106–131] which are applied in the synthesis and also exhibit important types of pharmacological activity (cardiovascular activity, effect on the central nervous system).[14] A variety of 1,2-diazabuta-1,3-dienes obtained from aryl- or alkoxyhydrazones can be involved in the Diels–Alder cycloaddition reaction. In most cases, the reactions are regiospecific and stereoselective.

Theoretical studies of [4+2]-cycloaddition of 1,2-diazabuta-1,3-dienes both with electron-rich methyl vinyl ether and with electron-deficient methyl acrylate by the density functional theory (DFT) method [B3LYP/6–31G(d)] have shown [114, 119–123] that these heterodienes are more reactive than butadienes **III** or monoazadienes **I** (see Fig. 2). Also, 1,2-diazadienes **VII** are more reactive towards methyl methacrylate than towards methyl vinyl ether, though in the latter case, the cycloadduct is formed with high *endo*-stereoselectivity and regiospecificity. It should also be noted that in reactions with monosubstituted alkenes, the formation of new σ-bonds in the transition state is concerted but asynchronous, since, according to the the quantum chemical calculations, the C–N bond is shorter than the C–C bond in the transition state. However, it should be mentioned that the length of these bonds is not necessarily an adequate criterion for the synchronism of their formation, as the nature of the participating atoms is different.[119–122]

Both the classical cycloaddition to electron-deficient dienophiles and inverse electron demand reaction with electron-rich dienophiles are possible for these compounds. However, there are very few examples of azoalkene cycloaddition to the classical electron-deficient dienophiles.[116–118, 122] Thus, arylazocyclohexenes **75** derived from arylhydrazones of α-acetoxycyclohexanone **76** react with tetracyanoethylene and *N*-phenylmaleimide at room temperature in benzene.[116] The value of the vicinal spin–spin coupling constant (12 Hz) suggests an axial position of the proton at the bridgehead carbon atom C(4a) of tetrahy-

Scheme 33



R^1 = H, Me, OMe

drocinnolines **77**. However, the researchers were unable to establish the stereochemical details for octahydro-1*H*-pyrrolo[3,4-*c*]cinnoline-1,3(2*H*)-diones **78** from ^{1}H NMR spectral data (Scheme 33).

3-Arylazo-2-methyl-1*H*-quinolin-4-ones **79** react with phenylpropiolic acid to give pyridazinoquinolines **80**, while with β-nitrostyrene the reaction affords a mixture of three isomeric products: *trans*-**81**, *cis*-**81** and *trans*-**82**. The structure of the obtained compounds (particularly, mutual disposition of Me and Ph substituents) was established by NOE 2D NMR (Scheme 34, the position of substituents in the starting quinolinone is indicated).[118]

The largest group of [4+2]-cycloaddition reactions of 1,2-diazabuta-1,3-dienes covered in the literature are reactions with dienophiles having the C=C bond.[95, 96, 106–108, 111–117, 124, 125] 1,2-Diazabuta-1,3-dienes **VII** react with carbocyclic and heterocyclic dienophiles (cyclopentadiene, furan, N-substituted indoles, 1*H*-indene, dihydropyran) yielding bi- and tricyclic pyridazines **83**–**86** (Scheme 35).[108, 114]

It should be noted that cycloadducts **86** were obtained only for N-substituted indoles but in low yields.[114]

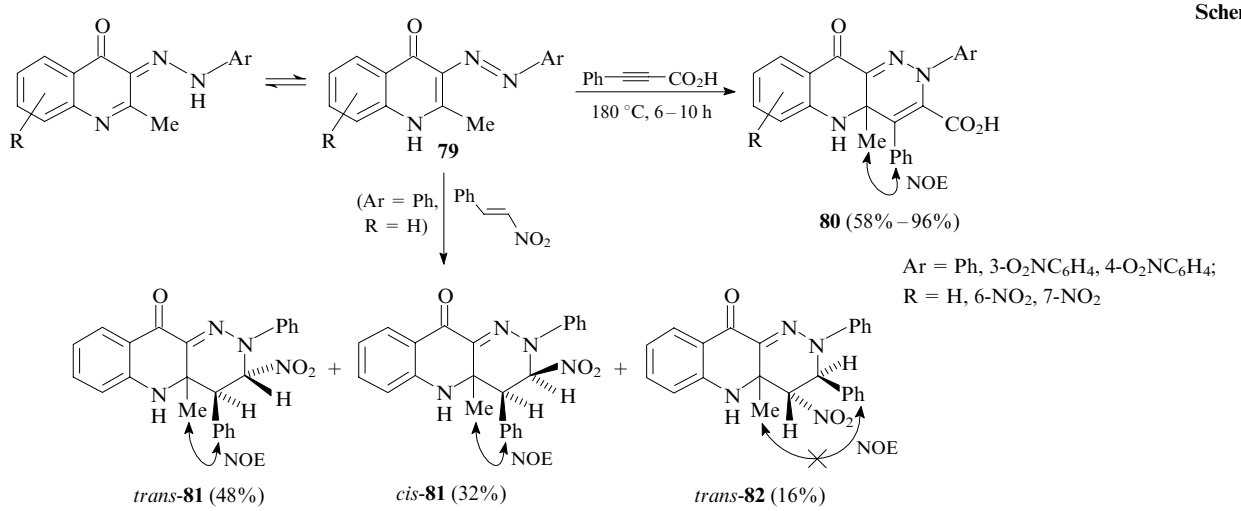
Chiral diazabutadienes **74** containing the D-arabinose residue do not react with diethyl acetylenedicarboxylate. Reactions between quinoid dipolarophiles (quinone and naphthoquinone) and acrylonitrile proceed slowly at room temperature affording diastereomeric cinnolinediones **87**, **87′** and 1-aryl-6-cyano-1,4,5,6-tetrahydropyridazines **88**, **88′**.[120–123] Raising the temperature results in the formation of side products, especially when quinones serve as dienophiles. Refluxing the reactants in toluene for 24 h gave the major isomer **87** in 20%–30% yield. Noteworthy is the high regioselectivity of the process, since according to the NMR spectroscopy data, there are even no traces of the alternative 5-cyanotetrahydropyridazines in the reaction between diazadienes **74** and acrylonitrile (Scheme 36).

The reactions of diazadienes with enamines represent a special case where the pathway depends on the reaction conditions.[126–131] A study of the reaction of diazadienes **89**, derived from chloro derivatives of hydrazones **90**, with enamines **91** demonstrated that depending on the temperature and the solvent used, the same reactants afford pyridazines **92** or pyrroles **93** chemoselectively and in good yields (Scheme 37).[130]

Basing on the data obtained, the authors suggested two alternative mechanisms of this reaction. In hexane, azoalkene **89** reacts as a heterodiene according to inverse Diels–Alder reaction yielding regioselectively and stereoselectively the product of *endo*-cycloaddition **92**. An alternative reaction pathway is asynchronous polar stepwise process with intermediate formation of hydrazones **94**, the cyclization of which followed by elimination of a pyrrolidine molecule yields *N*-aminopyrroles **93**.

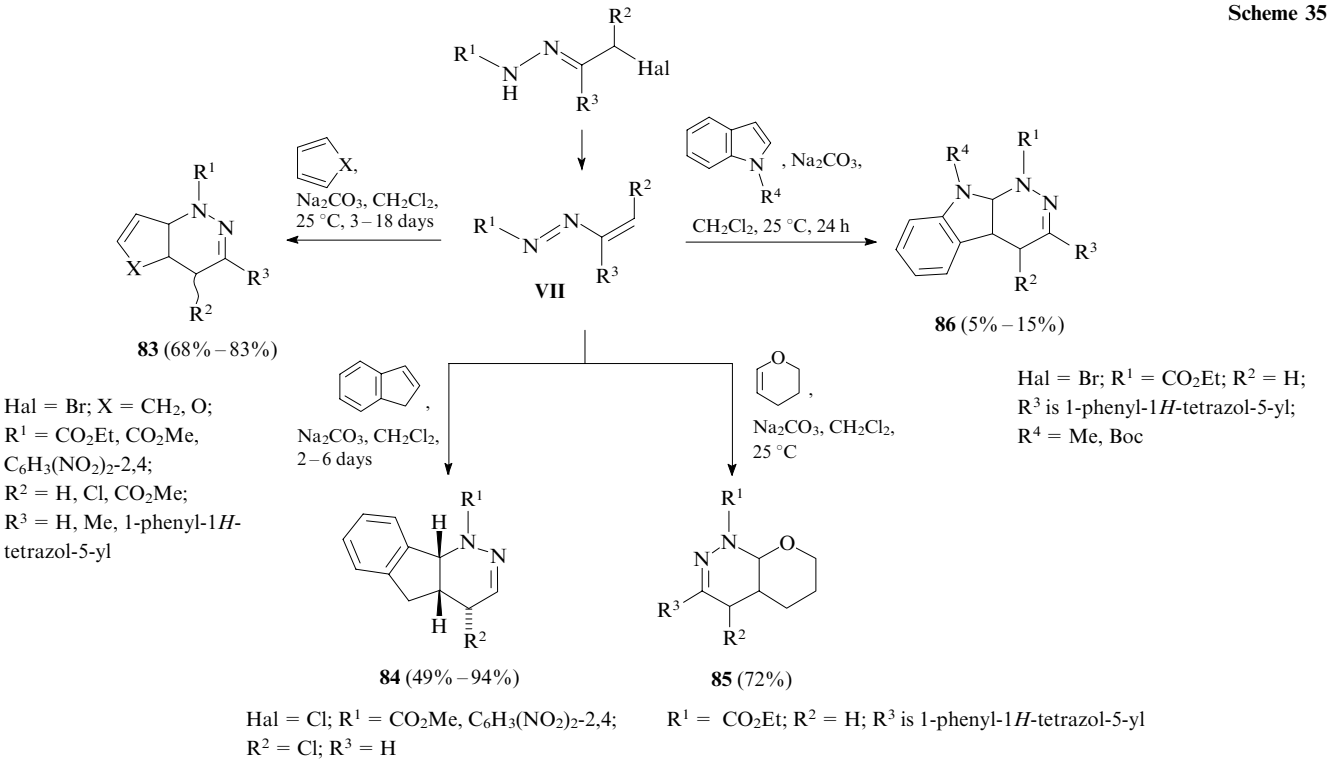
The aza-Diels–Alder reactions of 4-phosphinyl- and 4-phosphonyl-1,2-diazabuta-1,3-dienes **95** (R^2 = Ph, OEt), obtained by dehydrogalogenation of chloro hydrazones **96**,

Scheme 34

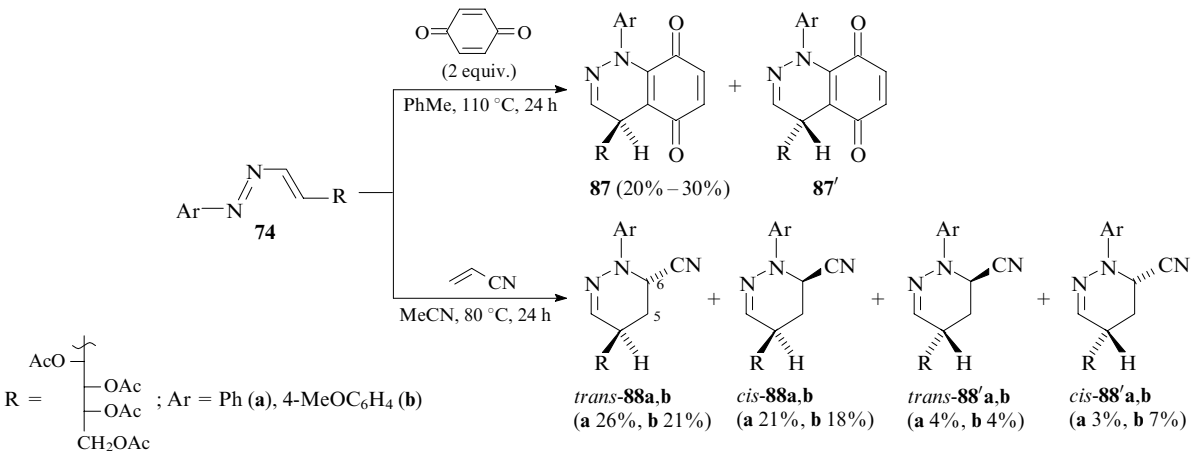


Ar = Ph, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$;
R = H, 6-NO_2, 7-NO_2

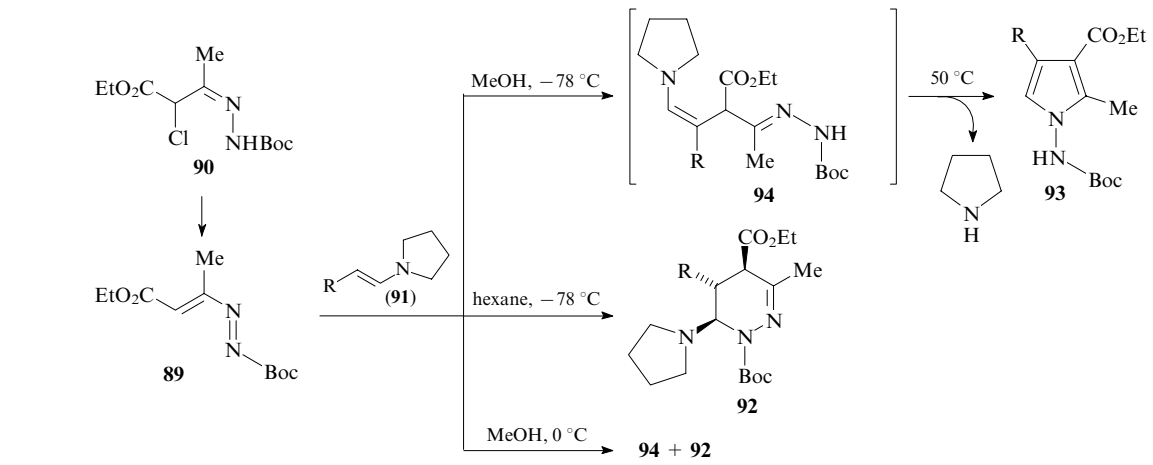
Scheme 35



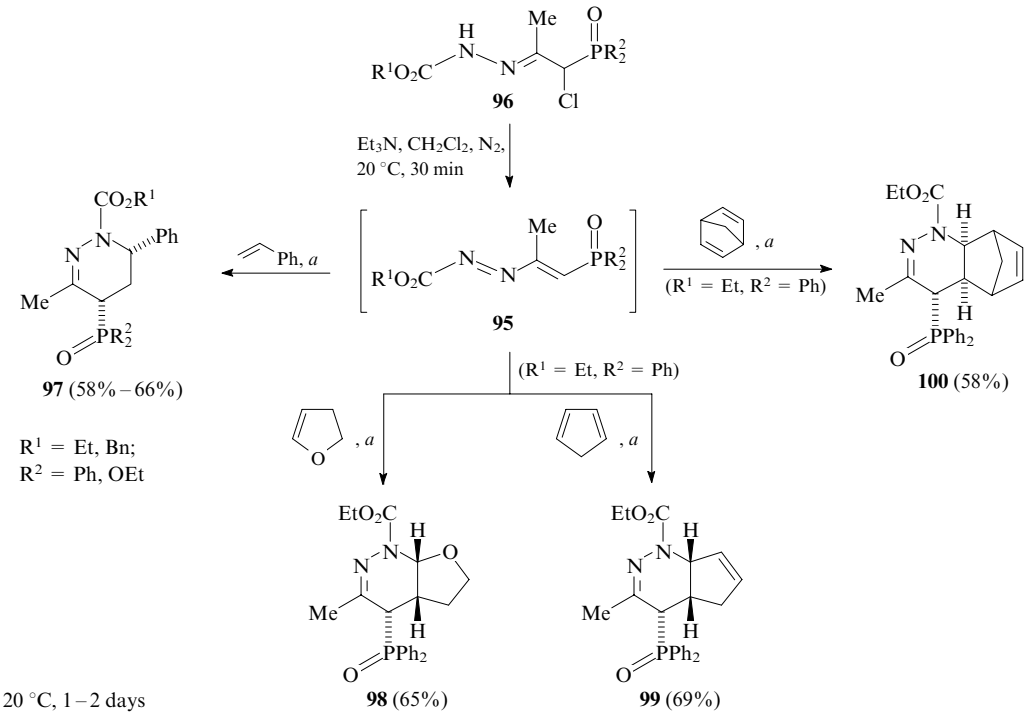
Scheme 36



Scheme 37



Scheme 38



96

95

97 (58%–66%)

100 (58%)

98 (65%)

99 (69%)

with styrene, 2,3-dihydrofuran, cyclopentadiene and norbornadiene furnish regio- and stereoselectively mono-, bi- and tricyclic tetrahydropyridazines **97**–**100**, bearing phosphine oxide or phosphonate group (Scheme 38).[110, 111]

Note that the reaction with styrene, cyclopentadiene and dihydrofuran proceeds *via endo*-transition state, whereas that with norbornadiene involves an *exo*-transition state.

Meanwhile, reactions between diazabutadienes **95** and electron-deficient dienophiles (alkyl acetylenedicarboxylates and tetracyanoethylene) furnished no cycloadducts. This result is expected, since the presence of electron-withdrawing groups at the terminal nitrogen atom and C(4) atom in 1,2-diazabuta-1,3-dienes **95** suggests that these compounds should tend to undergo inverse cycloaddition reactions with electron-rich dienophiles.

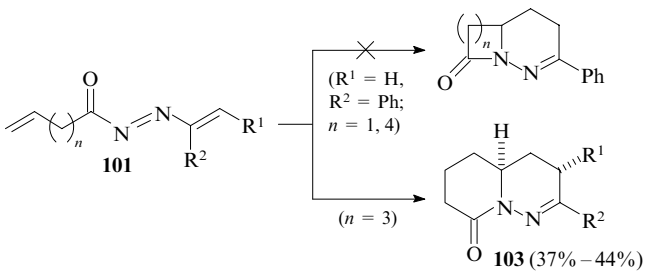
V.2. Intramolecular [4 + 2]-cycloaddition reactions of 1,2-diazabuta-1,3-dienes having multiple carbon–carbon bonds

Similarly to other intramolecular processes, the intramolecular cycloaddition reactions of 1,2-diazabuta-1,3-dienes, occur rather easily when 5/6- or 6/6-fused bicyclic systems are formed.[123, 132–134]

Diazadiene derivatives of hex-5-enoic acid **101** ($n = 3$) and pent-4-ynoic acid **102** cyclize to hexahydro-8*H*-pyrido[1,2-*b*]pyridazin-8-ones **103** and dihydropyrrolo[1,2-*b*]-pyridazines **104**. Attempts to involve in a similar transformation the derivatives of but-3-enoic acid **101** ($n = 1$) and hept-6-enoic acid ($n = 4$) under the same conditions were failed (Scheme 39).[132]

Contrary to the intermolecular cycloaddition, the intramolecular reactions generally require no activation of a diene or dienophile. High stereoselectivity is another special feature of this type of reaction. Studies of the mechanism of the intramolecular cycloaddition of cycloalkenes by the DFT (B3LYP/6-31G*) and MP2 (6-31G*) methods showed that it is a concerted process with a slight deviation from the synchronism of forming the new σ-bonds.[123]

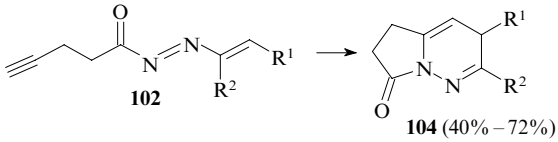
Scheme 39



101

103 (37%–44%)

R^1 = H: R^2 = Ph, CO_2Et, Me; R^1–R^2 = $(CH_2)_4$



102

104 (40%–72%)

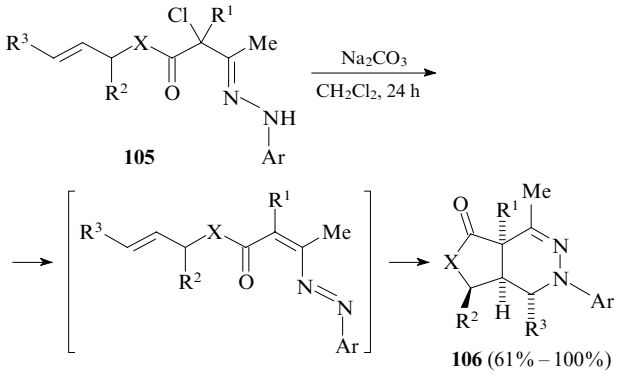
R^1 = H, CO_2Et; R^2 = Ph, CO_2Et, Me

The intramolecular cyclization of esters and amides **105** containing an azoalkene moiety proceeds stereoselectively to yield tetrahydrofuro[3,4-*d*]- and tetrahydropyrrolo[3,4-*d*]pyridazines **106** as single diastereomers (Scheme 40).[133]

Azoalkenes **107** with a terminal triple bond cyclize to form dihydropyridazino[6,1-*c*]oxazines **108** (Scheme 41).[132]

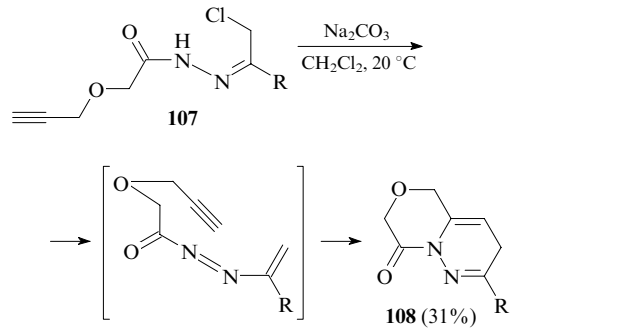
Analogously, upon intramolecular cycloaddition of azoalkenes to the double bond of the cyclopentene moiety, compounds **109** cyclize at room temperature yielding fused tricyclic compounds, namely, hexahydrodiazacyclopenta[*cd*]indenones **110** with the *cis*-disposition of the hydrogen atoms (Scheme 42).[134]

Scheme 40



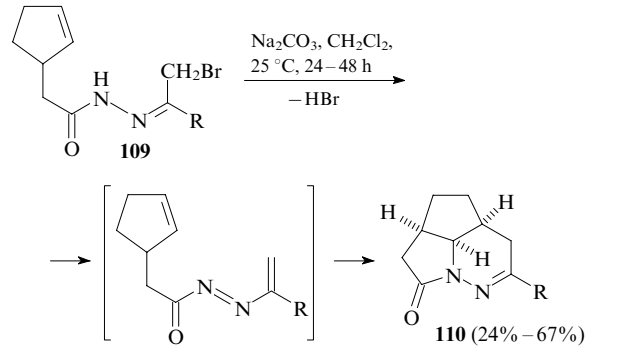
R^1 = H, Me, Cl; R^2 = H, Me; R^3 = H, Ph; X = O, NH

Scheme 41



R = Ph, CO_2Et

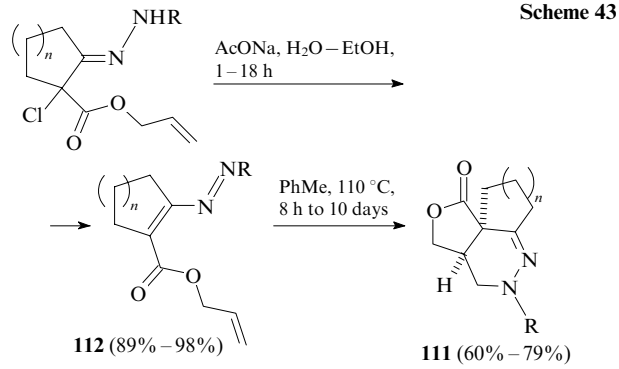
Scheme 42



R = Ph, CO_2Et

When the C=C bond of a diazadiene forms a part of a carbocyclic system, the formation of tricyclic adducts **111**

Scheme 43



R = 2,4-$(O_2N)_2C_6H_3$, Boc, Ph; *n* = 1, 2

occurs; however, the reaction proceeds under drastic conditions (long-term heating in toluene).[134] Intermediate diazadienes **112** are red liquid substances, more stable than the corresponding acyclic derivatives (Scheme 43).

Thus, similarly to 1-amino-1-azadienes, 1,2-diazabuta-1,3-dienes are widely used in organic synthesis to prepare functionalized nitrogen-containing heterocycles as well as fused heterocyclic systems.

VI. Methods for generation of azomethine imines and their 1,3-dipolar cycloaddition reactions

Azomethine imines relate to 1,3-dipoles of the allyl anion type and have four π-electrons in three p_z-orbitals of the π-system perpendicular to the plane of the dipole.[15 – 17, 135 – 142]

In 1970, Hesse [143] pioneered in using azomethine imines as substrates for the 1,3-dipolar cycloaddition reactions and since then these compounds have been widely used for the synthesis of complex heterocyclic structures having a pyrazoline or pyrazolidine ring.

According to the modern classification, azomethine imines are subdivided into three types: acyclic (**IX**), N,N′-cyclic (**X**) and C,N-cyclic ones (**XI**) (Fig. 4).[144]

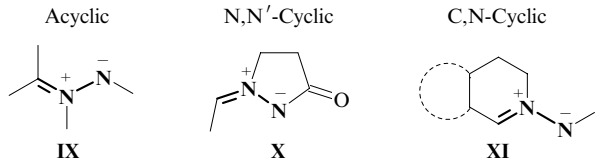
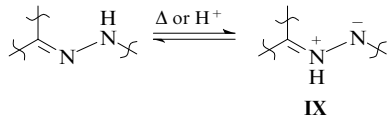


Figure 4. Three types of azomethine imines (see text).

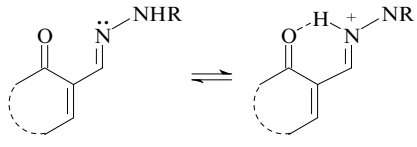
Most common are linear (acyclic) azomethine imines **IX**, which are generated by two known methods (Scheme 44).[135 – 148] An idea of thermal isomerization of hydrazones to form NH-azomethine imines **IX** was first suggested by Grigg.[136] Since that time, the typical procedure for the 1,3-dipolar cycloaddition has included heating a hydrazone and dipolarophile at reflux in an organic solvent (benzene, xylene, EtOH, dichloroethane, acetonitrile, *etc.*).[135 – 147]

Scheme 44



Izomerization of hydrazones containing groups capable of stabilizing the azomethine imine intermediates through intramolecular hydrogen bonding proceeds under milder conditions, sometimes even at room temperature (Scheme 45).[145]

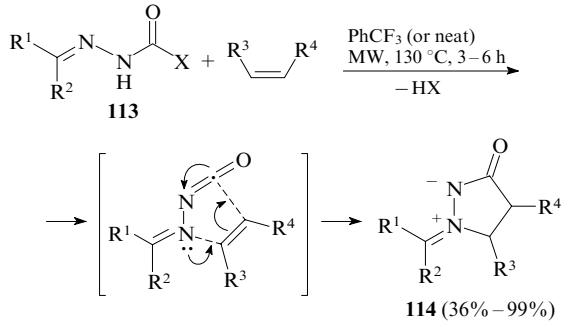
Scheme 45



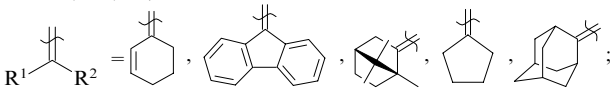
Another method for azomethine imine generation involves acid-catalyzed (CF_3CO_2H, conc. H_2SO_4, a mixture of H_2SO_4 and AcOH) 1,2-proton shift from the terminal to central nitrogen atom of the hydrazone (see Scheme 44).[147, 148] Generation of dipolar species in the presence of an acid is more convenient as in this case, the cycloaddition proceeds faster and more effectively than under heating. Moreover, it occurs even at room temperature, and contrary to the thermal variant, it is not restricted to aldehyde hydrazones but ketone hydrazones are also eligible.

Apart from diaziridine ring opening in the presence of aldehydes, the reaction between pyrazolidin-3-ones and aldehydes and the reaction between 1,2-disubstituted hydrazines and alkenes, it is possible to obtain N,N′-cyclic azomethine imines (3-oxopyrazolidin-1-azomethine imines) **X** (see Fig. 4) by the reaction of hydrazone derivatives **113** bearing ester or amide moieties at the N-atom with alkenes (aminocarbonylation) in the absence of a solvent or in α,α,α-trifluorotoluene (Scheme 46).[144, 149, 150] The generation of N,N′-cyclic azomethine imines from hydrazones and alkenes is a thermal concerted reaction proceeding *via* the formation of an imino isocyanate intermediate the existence of which was confirmed by quantum chemical calculations.[150]

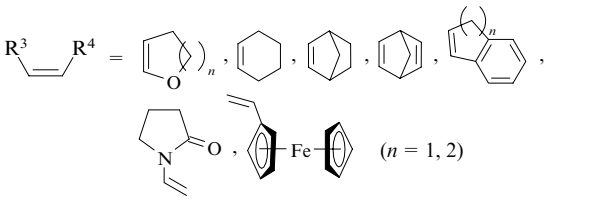
Scheme 46



R^1 = Pr^i, 2-Fu, 2-Th, Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-ClC_6H_4, 2-BrC_6H_4, 1-Naph (Fu is furyl, Th is thienyl, Naph is naphtyl);
R^2 = H, Me, Pr^i;



X = OBu^t, OEt, OCH_2CF_3, OPh, SEt, SPh, NPr^i_2;
R^3 = H, Me, Et, Ph; R^4 = Me, Et, Bu^n, Ph, OBu^n, OC_6H_{11}-cyclo;

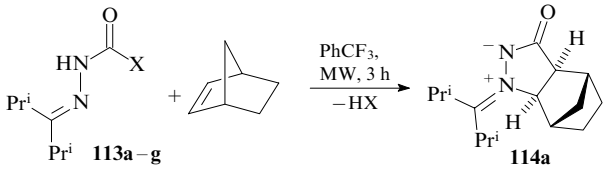


A variety of heterocyclic dipoles **114** were synthesized by using this procedure. In all cases, a single isomer was formed. The compounds obtained were white or yellow crystalline solids isolated by column liquid chromatography and characterized by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy and high-resolution mass spectrometry data. It should be noted that stability of the starting hydrazone **113**, being determined by the nature of the substituent X, has a significant impact on the conditions of dipole generation. Thus, most unstable is benzoylhydrazone **113d**, which reacts with norbornene to give a considerable amount of azomethine imine **114a** even at 100 °C (Scheme 47, Table 1).[150]

Table 1. Effect of the nature of the leaving group on the aminocarbonylation of hydrazones **113a–g** at different temperatures.[150]

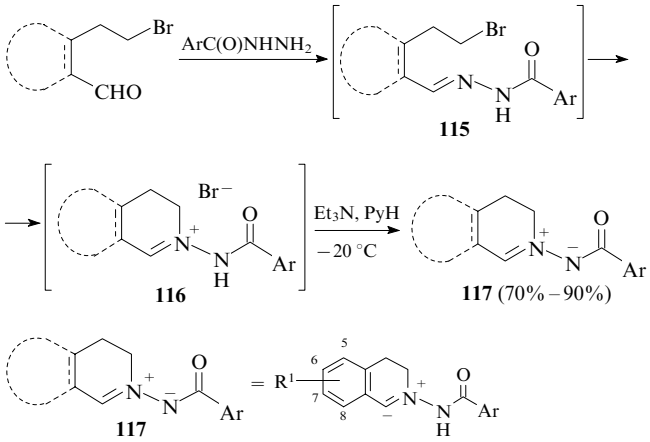
Compound **113**	X	Yield of **114a** (%)			
		150 °C	120 °C	100 °C	80 °C
a	OBu^t	99	69	23	7
b	OEt	99	8	0	0
c	OCH_2CF_3	82	55	30	9
d	OPh	92	85	84	38
e	SEt	98	64	46	11
f	SPh	90	69	60	31
g	NPr^i_2	90	69	46	13

Scheme 47

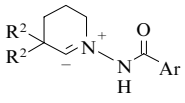


C,N-Cyclic azomethine imines **XI** (see Fig. 4) have been known for a rather long time;[2] however, they are less accessible and, therefore, are used more rarely than acyclic azomethine imines. The method for their synthesis is based on the intramolecular alkylation of aroylhydrazones **115** affording salts **116** (Scheme 48).[151–155] Being neutralized with a base, the latter form azomethine imines **117** and may be us–d in the 1,3-dipolar cycloaddition reactions. Azomethine imines **117** are unstable compounds but certain salts of cyclic C,N-azomethine imines (quinoline betaines) **116** were isolated in a crystalline state and characterized by spectral data.[151–155]

Scheme 48



(R^1 = H, 5-Me, 6-Me, 7-Me, 8-Me, 6-MeO, 6-Br, 7-Br, 7-F),



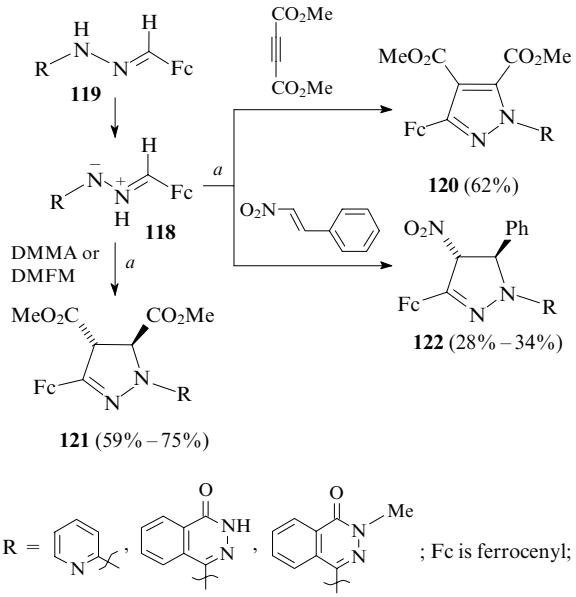
[R^2 = Me; $R^2–R^2$ = $(CH_2)_4$, $(CH_2)_5$];

Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$

VI.1. Intermolecular 1,3-dipolar cycloaddition reactions of azomethine imines

The reaction of azomethine imines with dipolarophiles has a wide scope of applicability and produces cycloadducts in high yields.[15–17,135–148,156–159] Azomethine imines react with activated alkenes and alkynes to form pyrazoles and pyrazolines, which are the key heterocyclic moieties of some natural and biologically active compounds. Drastic conditions are needed for the first step (1,2-shift) to occur in the hydrazone molecule.[157,158] As noted above, to generate acyclic azomethine imines **IX** (see Fig. 4) and to carry out the cycloaddition reaction, heating (up to 150 °C) of hydrazones and dipolarophiles in solvents or adding an acid is generally required (sometimes a stoichiometric amount of sulfuric acid is necessary). For example, the 1,3-dipolar cycloaddition of the azomethine imine **118**, obtained by heating ferrocenylhydrazone **119**, to DMAD, dimethyl maleate (or dimethyl fumarate) or β-nitrostyrene afforded pyrazoles **120** and pyrazolines **121** or **122** (Scheme 49).[146]

Scheme 49

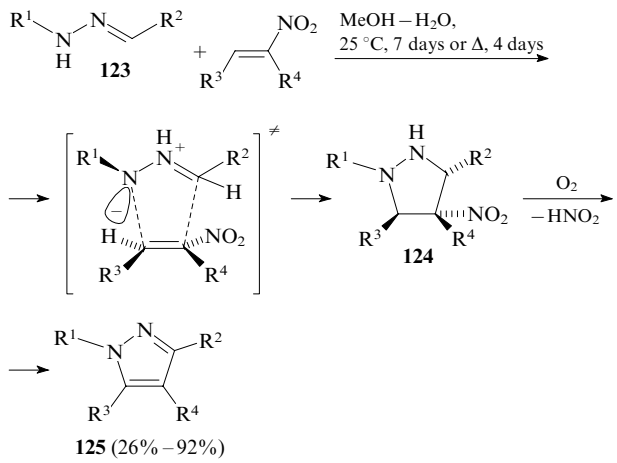


(*a*) MeCN, MS 3 Å, Δ, 15 h; MS are molecular sieves;
DMMA is dimethyl maleate, DMFM is dimethyl fumarate

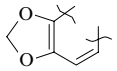
The reaction between aldehyde N-monoalkylhydrazones **123** and nitroalkenes proceeds as the [3 + 2]-cycloaddition and represents a regioselective method for the synthesis of pyrazolidines **124** substituted at four ring atoms, which transform readily into the corresponding pyrazoles **125** (Scheme 50).[148,158] The addition of water was found to accelerate the reaction and to increase the yields of the cycloadducts **125**.

Other factors affecting the efficiency of the reaction between hydrazones and alkenes are microwave irradiation[159] and catalysts.[160–167] The [3 + 2]-cycloaddition of azomethine imine **126a**, formed *in situ* from hydrazone **127a**, to the cyclopentadiene proceeds under mild conditions and at a higher rate when Lewis acids [$BF_3 \cdot Et_2O$, $Zr(OTf)_4$, $Hf(OTf)_4$ and $Sc(OTf)_3$] are used in either stoichiometric or catalytic amounts (Scheme 51).[160] In this case, the yields of adducts **128** and reaction stereoselectivity depend on the type of acid (see Scheme 51, Table 2).

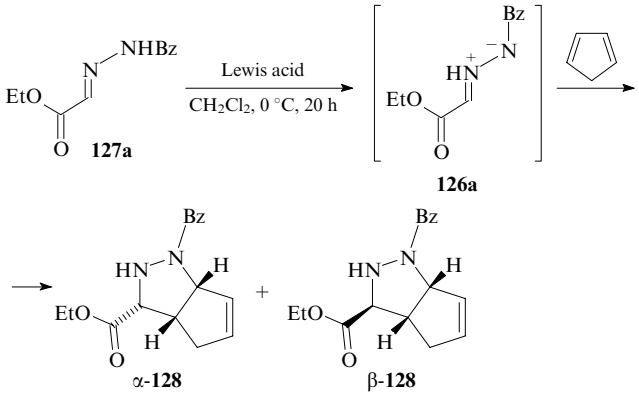
Scheme 50



R^1 = Me, Pr^i, Bu^t, Bn; R^2 = Et, Bu^t, Bn, Ph, 4-MeC_6H_4, 4-ClC_6H_4;
R^3 = Ph, R^4 = Me; R^4 = H: R^3 = Ph, 4-MeC_6H_4; $R^3 - R^4$ = $(CH_2)_4$,



Scheme 51



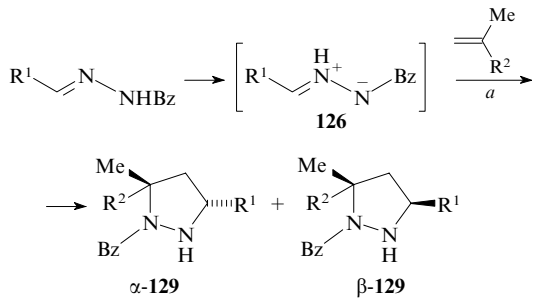
The cycloaddition of azomethine imines **126** to alkenes in the presence of $BF_3 \cdot Et_2O$ or $Zr(OTf)_3$ afforded pyrazolidines **129** as two diastereomers (α and β) in satisfactory yields (Scheme 52).[160]

Asymmetric synthesis using chiral catalysts opens up new prospects for using the 1,3-dipolar cycloaddition of azomethine imines to dipolarophiles containing multiple carbon–carbon bonds.[157,162–167]

Table 2. Effect of the Lewis acid nature and amount on the product yields and stereoselectivity of the reaction between azomethine imine **126a** and cyclopentadiene.[160]

Lewis acid (equiv.)	Yield of α-**128** + β-**128** (%)	Ratio α-**128** : β-**128**
$Sc(OTf)_3$ (0.20)	46	89 : 11
$Zr(OTf)_4$ (0.20)	46	99 : 1
$Zr(OTf)_4$ (0.10)	73	94 : 6
$Zr(OTf)_4$ (0.05)	62	95 : 5
$Hf(OTf)_4$ (0.20)	57	98 : 2
$Hf(OTf)_4$ (0.10)	69	94 : 6
$Hf(OTf)_4$ (0.05)	57	96 : 4
$BF_3 \cdot Et_2O$ (1.10)	93	86 : 14

Scheme 52



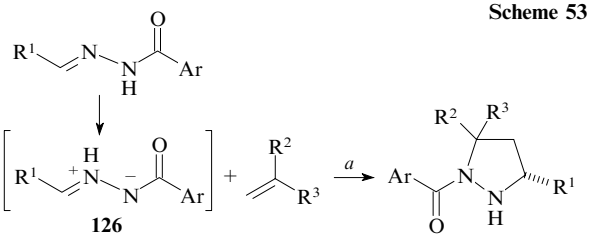
(37%–77%, α-**129** : β-**129** form 56 : 44 to 85 : 15)

R^1 = $Ph(CH_2)_2$, Ph, EtO_2C; R^2 = $CH{=}CH_2$, $C{\equiv}CPh$, $C{\equiv}CC_5H_{11}$, $C{\equiv}CSiMe_3$; (*a*) $BF_3 \cdot OEt_2$ (1.2 equiv.) or $Zr(OTf)_4$ (0.1 equiv.), CH_2Cl_2, 0 °C, 24 h

The method is suitable for the synthesis of biologically active pyrazolines and pyrazolidines.

The[3 + 2]-cycloaddition of azomethine imines **126** to alkenes proceeds in high yield and with a high degree of selectivity when a chiral zirconium catalyst is used (Scheme 53).[162, 163] The process is a concerted type of [3 + 2]-cycloaddition with the simultaneous formation of two bonds in the **TS-1** transition state and shift of the hydrogen atom to one of the ligands of the catalyst. This results in two diastereomers **129** having the same absolute configuration of the carbon atom bearing the R^1 substituent (Scheme 54, R^3 = H).

Scheme 53



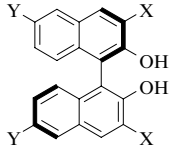
129 [60%–90%, (95%–98%) *ee*]

Ar = Ph, 4-$O_2NC_6H_4$;

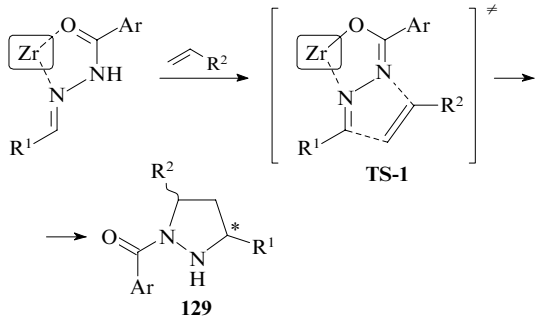
R^1 = Pr^n, Bu^s, n-C_5H_{11}, cyclo-C_6H_{11}, Bn, $Ph(CH_2)_2$, $Bu^tMe_2SiO(CH_2)_2$;

R^2 = H: R^3 = OEt, OPr^n, OBu^t, SEt; R^2 = R^3 = SMe;

(*a*) $Zr(OPr^n)_4$–Pr^nOH, (*R*)-BINOL-deriv, PhMe

(*R*)-BINOL-deriv =  (X = Y = I; X = I, Y = H; X = Br, Y = H)

Scheme 54

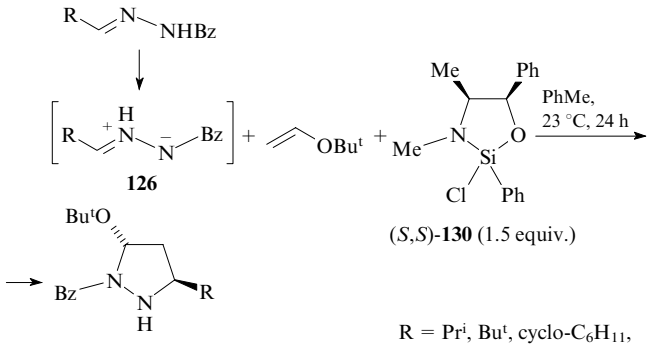


TS-1

129

In a continuation of these studies, reactions between various aliphatic, aromatic and heteroaromatic azomethine imines **126** and *tert*-butyl vinyl ether in the presence of chiral phenylsilane (*S*,*S*)-**130** were investigated (Scheme 55).[167] The silane (*S*,*S*)-**130** proved to be an effective chiral catalyst (Lewis acid) for the cycloaddition of acylhydrazones to alkenes and this allowed for a successful high diastereo- and enantioselective synthesis of pyrazolidine derivatives **129**, which is of special importance for medicine.

Scheme 55

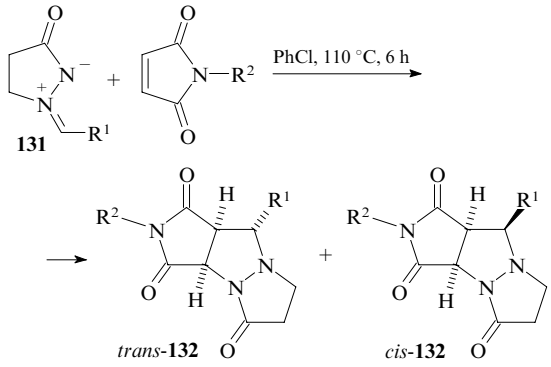


129 [76%–85%, (90%–98%) *ee*, *dr* from 95 : 5 to 97 : 3]

R = Pr^i, Bu^t, cyclo-C_6H_{11}, $(CH_2)_2Ph$, CH_2OBn, Ph, C_6H_4F-4, 2-Fu

Cyclic *N*,*N*′-azomethine imines of type **X** (see Fig. 4) may be used in the synthesis of bicyclic pyrazolidines *via* reactions with acrylates, α,β-unsaturated aldehydes, vinyl sulfones or 3-acryloyloxazolidin-2-ones.[149, 150, 168–182] For example, azomethine imines **131** react with *N*-arylmaleimides to give tricyclic system **132** as a mixture of *cis*- and *trans*-isomers in good yield (Scheme 56).[168]

Scheme 56

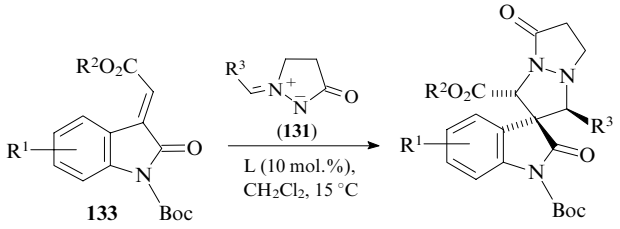


(65%–73%, *dr* form 1.4 : 1 to 3.1 : 1)

R^1 = Ph, 4-$MeOC_6H_4$; R^2 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4

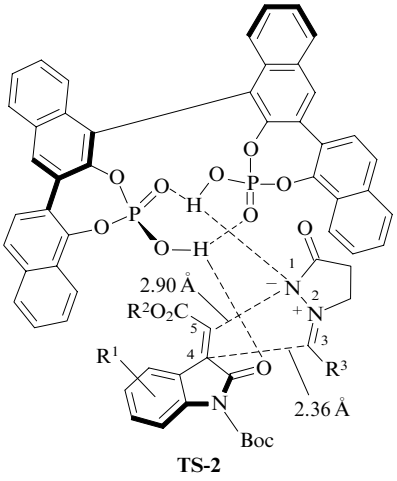
The [3 + 2]-cycloaddition reactions of *N*,*N*′-azomethine imines catalyzed by metals or organic catalysts, particularly, the catalytic asymmetric cycloaddition, have found the most extensive use.[170–181] For instance, the reaction of methylideneindolinones **133** with azomethine imines **131** in the presence of chiral bisphosphoric acids (L) furnished enantiomerically pure spiro(pyrazolidine-3,3′-oxindoles) **134** in good yields and with high regioselectivity (Scheme 57).[175] It was shown by quantum chemical calculations (the DFT method) that most probable is the transition state **TS-2**, where both reactants are activated simultaneously through hydrogen bonding with the OH groups of the phosphoric acid residues (see Scheme 57).

Scheme 57



134 [68 – 94%, (93% – 99%) *ee*, *dr* = (6 – 20) : 1]

R^1 = H, 5-Cl, 5-Br, 5-Me, 5-MeO; R^2 = Me, Et, Bu^t;
R^3 = Ph, 2-ClC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 3-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$



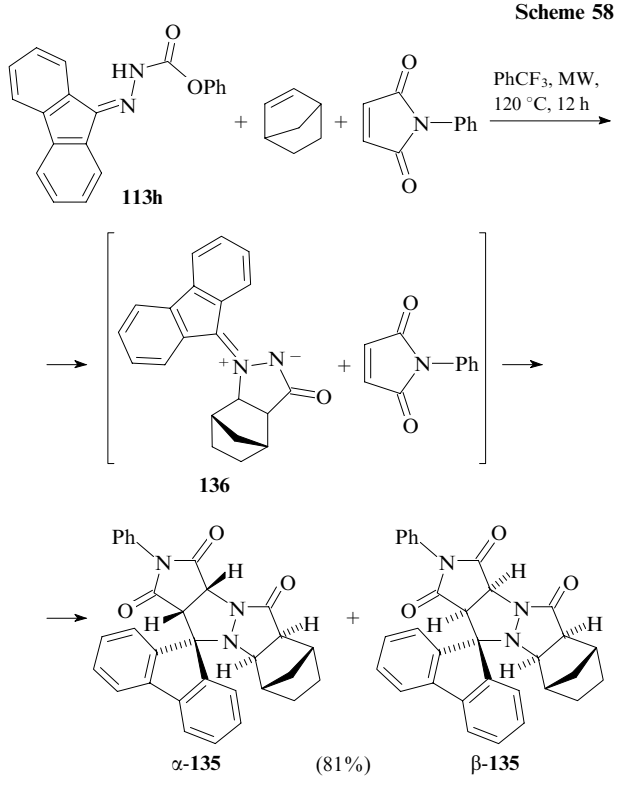
TS-2

An interesting feature of the reactivity of N,N′-azomethine imines should be mentioned: even in the course of their formation from hydrazones and alkenes (see Scheme 51), the 1,3-dipoles formed may react with alkene and afford 2 : 1 adducts. This is promoted by performing the reaction with an alkene under more drastic conditions or by using more stable hydrazone (see Scheme 51 and Table 2).[150] This feature of the reactivity of N,N′-azomethine imines may be best illustrated by the reaction between acylhydrazone **113h** and two alkenes differing in the reactivity (*N*-phenylmaleimide and norbornene), furnishing polycyclic adduct **135** as a mixture of two diastereomers (α-**135** : β-**135** = 3 : 2) in high yield (Scheme 58).[150]

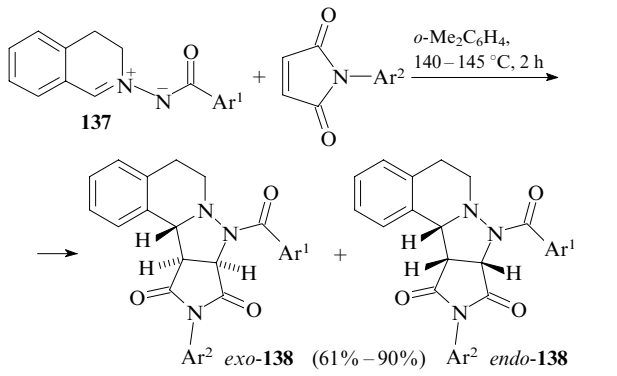
Being a more reactive alkene, norbornene reacts to form, in the first step, 1,3-dipolar intermediate **136**, which subsequently undergoes the [3 + 2]-cycloaddition yielding the final adduct **135**.

The 1,3-dipolar cycloaddition of the cyclic C,N-azomethine imines of type **XI** (see Fig. 4) has attracted particular interest of scientists during the last years. Such azomethine imines are highly reactive and add both to electron-deficient and to electron-rich dipolarophiles. The [3 + 2]-cycloaddition reactions of C,N-cyclic azomethine imines with alkynes,[183 – 185] alkenes,[151, 152, 186 – 188] allenoates,[153, 189, 190] carbon disulfide and isothiocyanates,[155, 191] thioesters and thioketones[192] and isocyanides[193] affording fused pyrazolidines, thiadiazolidines, triazolidines, hexahydropyridazines and 1,3,4-oxadiazines have been studied. For example, betaines **137** react with maleimides to give pyrrolo[3′,4′:3,4]pyrazolo[5,1-*a*]isoquinolines **138** as a mixture of *exo*- and *endo*-isomers (Scheme 59).[155, 186]

Scheme 58



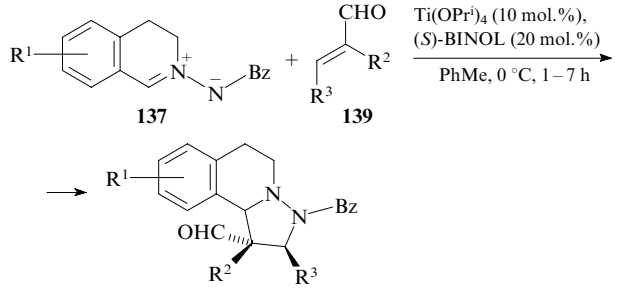
Scheme 59



Ar^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$;
Ar^2 = Ph, 2,4,6-$Me_3C_6H_2$, 4-BrC_6H_4

The catalytic versions of the dihydroisoquinoline betaine cycloaddition give cycloadducts with high regio-,

Scheme 60



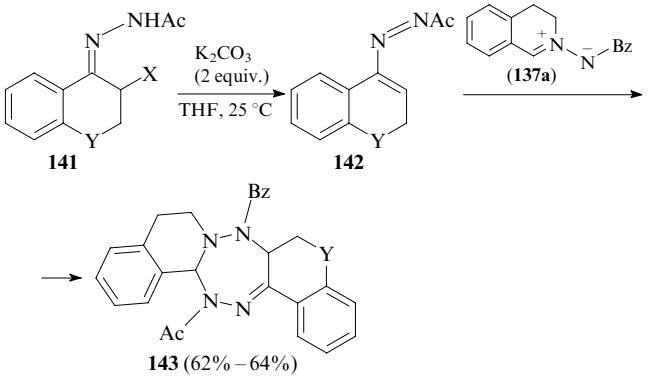
140 [85% – 99%, (85% – 99%) *ee*, *exo* : *endo* = 95 : 5]

R^1 = H, 5-Me, 6-Me, 7-Me, 8-Me, 6-MeO, 6-Br, 7-Br;
R^2 = H, Me; R^3 = Me, Pr^n, Ph

stereo- and enantioselectivity.[151–154, 187] The stereoselective [3 + 2]-cycloaddition of C,N-cyclic azomethine imines **137** is exemplified by their reaction with α,β-unsaturated aldehydes **139**, providing an effective method for the synthesis of optically active tetrahydropyrazolidino[5,1-*a*]isoquinolines **140** (Scheme 60).[154]

A specific feature of cyclic C,N-azomethine imines **XI** (see Fig. 4) is that they may participate not only in [3 + 2]-cycloaddition but also in the formal [4 + 3]-cycloaddition. The reaction between *N*-acetylhydrazones **141**, which are the precursors of 1,2-diazabuta-1,3-dienes **142**, and the azomethine imine **137a** is an example of such transformation.[151] As a consequence, annulated 1,2,4,5-tetrazepines **143** are produced (Scheme 61).

Scheme 61

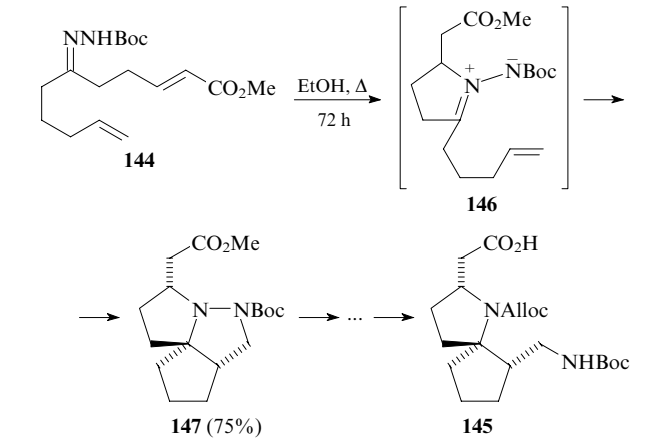


X = Cl, Br; Y = CH_2, O

VI.2. Intramolecular cycloaddition of azomethine imines to miltiple bonds

The intramolecular 1,3-cycloaddition of azomethine imines represents a synthetic approach to complex heterocyclic structures with a pyrazolidine ring.[136, 137, 141, 142, 163, 194, 195] Azomethine imines **144** containing a terminal C=C bond are starting compounds for the synthesis of spirodiamino acid **145**, which serves a unique trifunctional scaffold for the combinatorial chemistry (Scheme 62).[137, 142, 194]

Scheme 62

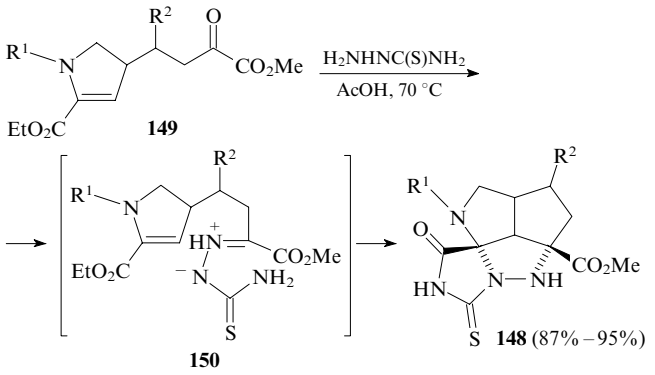


Alloc = C(O)OAll

The sequence of transformations in this case comprises the intramolecular Michael addition resulting in the intermediate **146**, the azomethine imine moiety of which then adds to the terminal double bond to form tricyclic pyrazolidine **147**.

The synthesis of triazacyclopenta[*cd*]pentalenes **148** includes the formation of thiosemicarbazones from α-ketoesters **149** and the intramolecular 1,3-dipolar cycloaddition of the generated azomethine imine moiety of intermediate **150** to the double bond of dihydropyrrole to give triazacyclopenta[*cd*]pentalene system **148**. These compounds serve as the reactants for the synthesis of complex guanidine alkaloids (Scheme 63).[195]

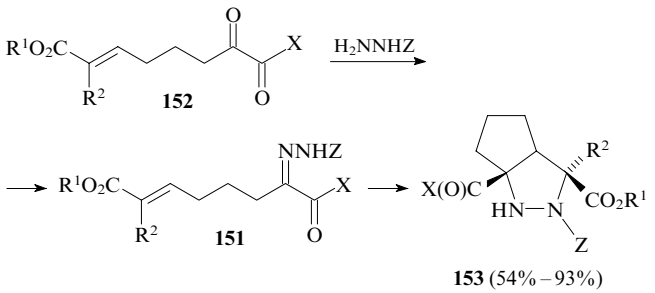
Scheme 63



R^1 = Cbz, $SO_2(CH_2)_2SiMe_3$; R^2 = H, $OSiBu^tMe_2$

Hydrazones **151** obtained *via* the condensation of α-ketoesters **152** with hydrazines are converted on heating to *cis*-cyclopentapyrazolidines **153** (Scheme 64). The reaction proceeds successfully not only on heating but also when catalyzed by protic acids or Lewis acids.[141]

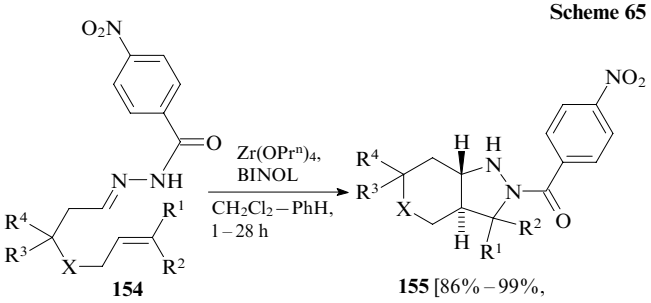
Scheme 64



R^1 = Et, Me; R^2 = H, OMe; X = OPr^i, OMe; Z = $C(S)NH_2$, Bz, $C(O)C_6H_4Ph$-4, Ac, $C(O)(CH_2)_2CH{=}CH_2$

The intramolecular [3 + 2]-cycloaddition of aldehyde hydrazones containing moieties present in natural compounds is used to obtain biologically active pyrazolidine derivatives.[163, 196] For example, transformation of methylcitronellal 4-nitrobenzoylhydrazone **154** ($R^1 = R^4$ = Me, $R^2 = R^3$ = H, X = CH_2) in the presence of a chiral catalyst (a zirconium complex with BINOL ligand, catalyzing effectively a variety of processes including the hetero-Diels–Alder reactions) produces pyrazolidine **155** as a single *trans*-isomer (Scheme 65). The use of other substrates **154** gave *trans*-pyrazolidines with high enantioselectivity and in high yields.[163] This is the first example of the catalytic asymmetric intramolecular cycloaddition of azomethine imines. Chiral pyrazolidines **155** are of interest as potential biologically active compounds.

Scheme 65

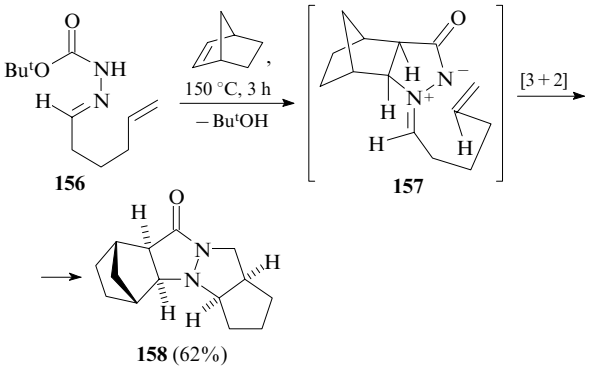


154 **155** [86%–99%, (75%–96%) *ee*]

R^1, R^2 = H, Me; R^1-R^2 = $S(CH_2)_2S$; R^3, R^4 = H, Me; R^3-R^4 = $S(CH_2)_2S$; X = CH_2, O

An interesting intramolecular cycloaddition reaction takes place during the aminocarbonylation–dipolar intramolecular cycloaddition cascade transformations carried out between norbornene and hydrazone **156** (Scheme 66).[142, 149] Apparently, this reaction initially occurs to form the azomethine imine **157**, the *Z*-isomer of which is further transformed into the cyclopenta[4,5]pyrazolo[1,2-*a*]indazole **158**.

Scheme 66

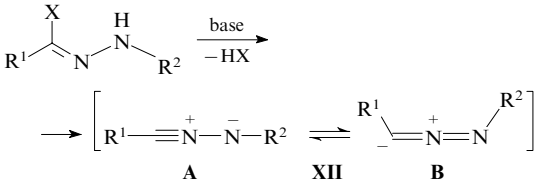


156 **157** **158** (62%)

VII. Methods for synthesis and1,3-dipolar addition reactions of nitrile imines

In the presence of a base, halogenated hydrazones readily undergo dehydrohalogenation and transform into highly reactive dipolar compounds — nitrile imines **XII** (Scheme 67).[1–3, 17–20, 197–201]

Scheme 67

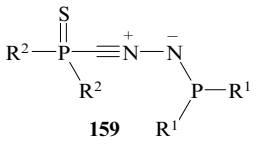


A **XII** **B**

X = Cl, Br

This method for generation of nitrile imines has received wide acceptance compared with other methods such as thermolysis of 2,5-disubstituted tetrazoles or oxadiazolin-5-ones, oxidation of aldehyde hydrazones and photochemical decomposition of sydnones.[17–20] The chemistry of nitrile imines attracts attention due to a great potential of these compounds as important building blocks in the organic synthesis and, particularly, in the heterocyclic chemistry.[17–20, 137–139, 199–203] Stable nitrile imines may be obtained by introducing electron-withdrawing or bulky substituents into the molecule.[204–207] For example, nitrile imines **159** are stable in solution at room temperature for several weeks, which allowed for the study of their structure by spectroscopy and by X-ray diffraction analysis.[206]

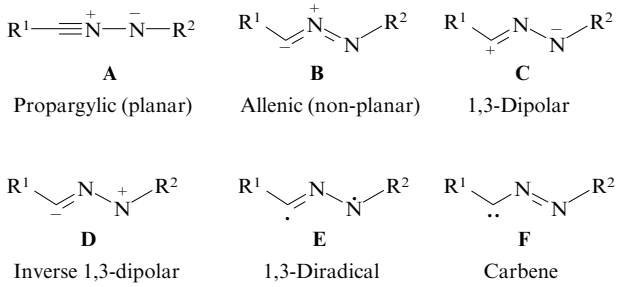
Structures 159



159 R^1, R^2 = Bu^t, NPr^i_2

VII.1. Specific features of nitrile imine structure

The structure and reactivity of nitrile imines are still debated. The literature suggests six possible alternative structures for the stabilized nitrile imines (**A**–**F**) (Fig. 5).[208–212] Theoretical studies provided contradictory results. According to early quantum chemical calculations, nitrile imines are low-reactive molecules able to exists in propargylic (**A**) or allenic form (**B**) with a low activation barrier to interconversion.[208] The results of quantum chemical calculations for formylnitrile imine, which may be considered to be the parent compound for 1,3-dipolar species of this type, performed at a higher level in extended basis set with account for the configuration interaction [QCISD/6-311 + G(2df,2f)] suggest that a non-planar allenic geometry is preferred.[209] Moreover, it turned out that the propargylic structure has no stable minimum in the potential energy surface. Hereinafter, all correlation methods used for the calculations demonstrated lower energy of allenic configuration compared with the propargylic one.[210–212]



A Propargylic (planar) **B** Allenic (non-planar) **C** 1,3-Dipolar

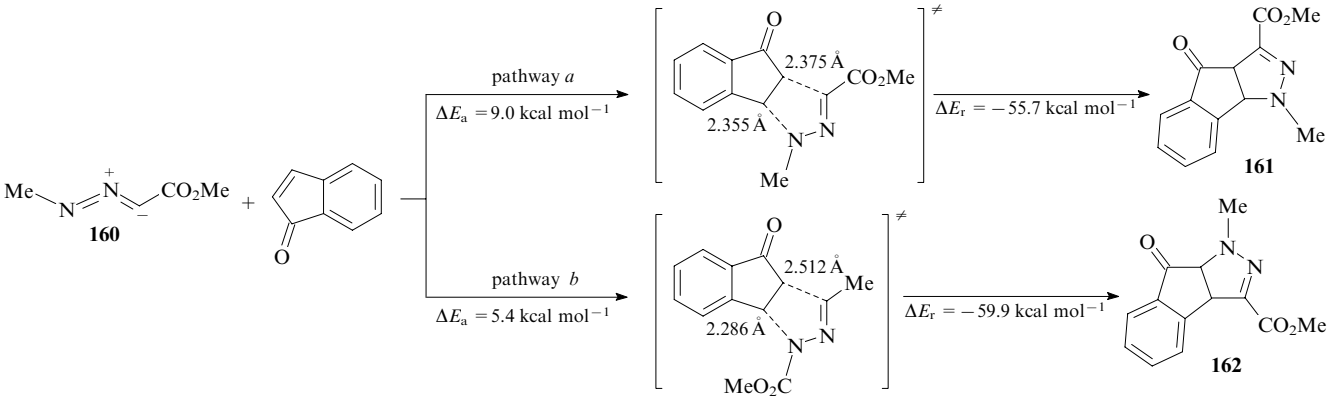
D Inverse 1,3-dipolar **E** 1,3-Diradical **F** Carbene

Figure 5. Possible structures of stabilized nitrile imines.

VII.2. Intermolecular cycloaddition of nitrile imines

Nitriles are dipoles for which both the $HOMO_{(dipole)}-LUMO_{(dipolarophile)}$, and $HOMO_{(dipolarophile)}-LUMO_{(dipole)}$ relationships are significant for cycloaddition.[137, 138] The dipolarophiles used in the cycloaddition reactions with nitrile imines include both electron-rich and electron-deficient compounds having C=C and C=N cyclic bonds, as well as C=C, C=N and C=S linear and exocyclic structural moieties. The reactions gave monocyclic, fused or spiro heterocyclic systems comprising pyrazole, pyrazoline, thiadiazole and triazole rings.[213–261]

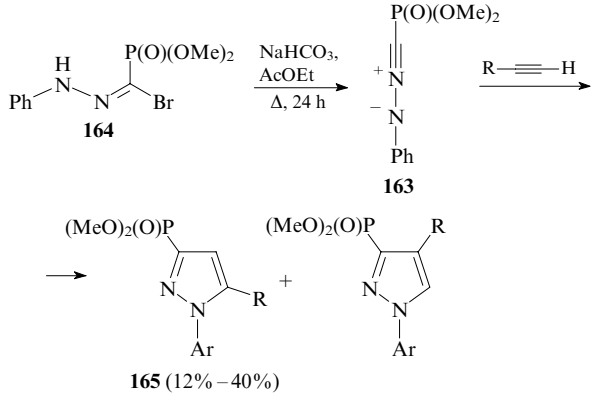
Scheme 68



Apart from the synthetic application, this reaction has always attracted attention in view of theoretical aspects concerning both the chemistry of nitrile imines and the 1,3-dipolar cycloaddition as a whole, particularly regarding its regio- and stereoselectivity. This type of cycloaddition is the most obvious example of violation of regioselectivity, often used in the debate about the reaction mechanism as a significant argument in favour of the formation of radical intermediates.[213, 214] Synthetic chemists still keep returning to study this phenomenon using various approaches and varying different parameters. A substantial argument in the discussion was the result of DFT (B3LYP/6-311G*) quantum chemical calculations of the geometry and energy parameters for transition states and cycloadducts of various reactions between nitrile imines and dipolarophiles. According to the theoretical studies, the proccess is concerted but the bonds are formed asynchronously, the degree of asynchronism depending on the electronic and steric effects of substituents [215–220] adjacent to the reacting centres and the way the reactants approach each other (Scheme 68).[215] Thus, for the reaction of nitrile imine **160** with indenone, the quantum chemical calculations indicate that the synchronism in the formation of new σ-bonds is more pronounced in the case of compound **161** than for its isomer **162**. The reaction along pathway *b* is more preferable as having a lower activation barrier (ΔE_a) and a somewhat higher enthalpy (ΔE_r) (see Scheme 68).

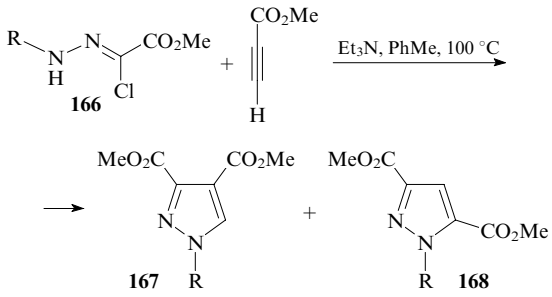
The reaction between nitrile imines and alkynes is a convenient route to formation of pyrazole ring.[202, 204, 207, 216, 218–224] The [3 + 2]-cycloaddition of nitrile imines **163** derived from halohydrazones **164** to the terminal alkynes proceeds regioselectively yielding mainly (in a total yield of 78% to 95%) 5-substituted pyrazoles **165** (Scheme 69).[218, 219] Quantum chemical calculations using the B3LYP/6-311 + G(d + p) method have demonstrated that the regioselectivity of the process corresponds to the overlap of orbitals at the reaction centres with maximum orbital coefficients.[218]

Scheme 69



The effect of the electronic properties of substituents in the aromatic ring of arylhydrazonoyl chlorides **166** on the yield and ratio of pyrazoles **167** and **168** have been studied for the reaction with methyl propiolate (Scheme 70, Table 3).[219] The introduction of electron-donating substituents is seen to improve the reactivity of hydrazones **166**, but has a little effect on the regioselectivity.

Scheme 70



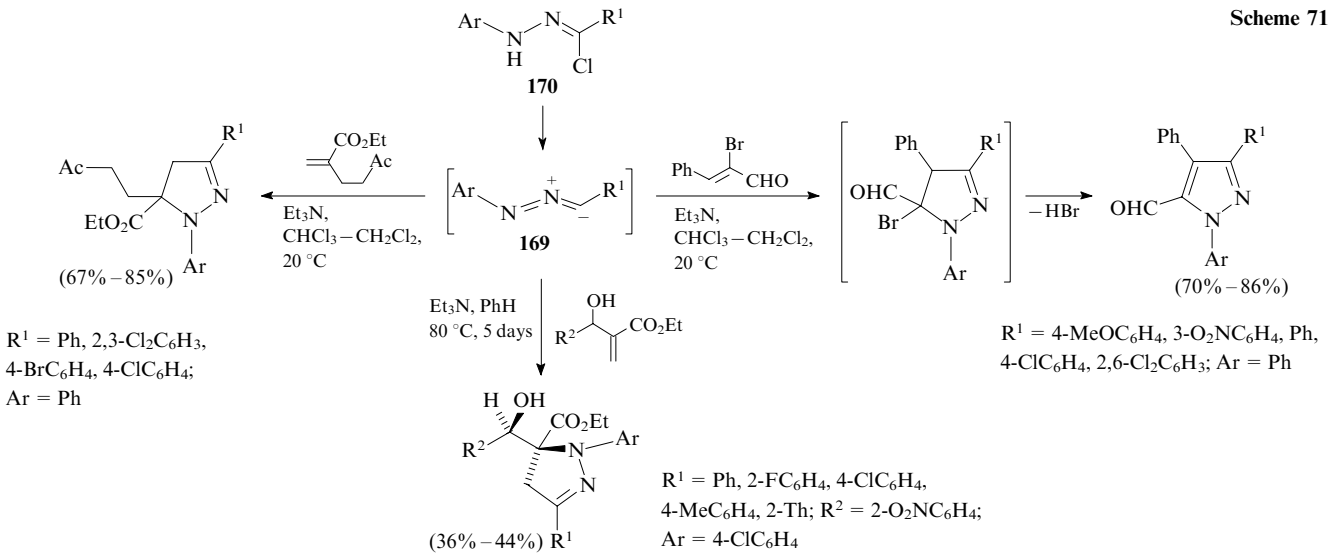
Nitrile imines **169**, derived *in situ* from arylhydrazonoyl chlorides **170**, react readily with various mono- and disubstitued alkenes. The formation of the corresponding pyrazoline upon cycloaddition in these reactions is often followed by its aromatization *via* elimination of good leaving groups (Scheme 71) or oxidation.[202–207, 216–218, 225–234]

The reaction of nitrile imines **169** with maleimides or 1,4-dihydro-1,4-epoxyanthracene proceeds easily and gives high yields of cycloadducts **171** and **172** (Scheme 72).

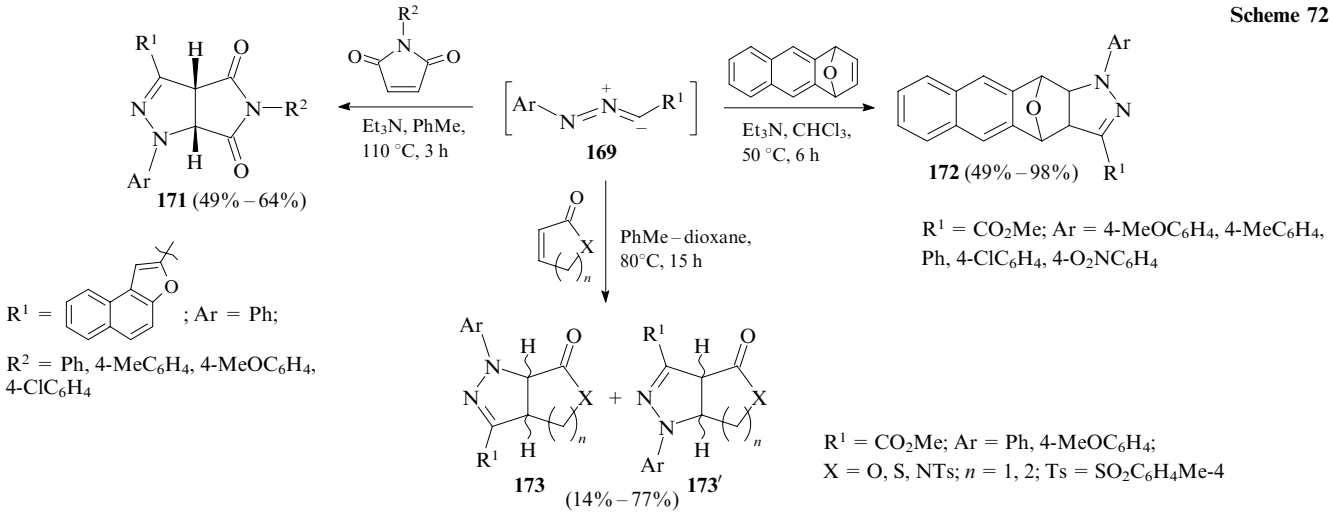
Table 3. Effect of substituents in hydrazones **166** on the yield and ratio of pyrazoles **167** and **168**.[219]

R	Time /min	Total yield (%)	Ratio **167** : **168**
4-MeOC$_6$H$_4$	20	63	56 : 44
4-MeC$_6$H$_4$	30	95	66 : 34
Ph	45	69	56 : 44
4-FC$_6$H$_4$	60	48	53 : 47
4-ClC$_6$H$_4$	20	63	56 : 44
4-O$_2$NC$_6$H$_4$	240	6	51 : 49

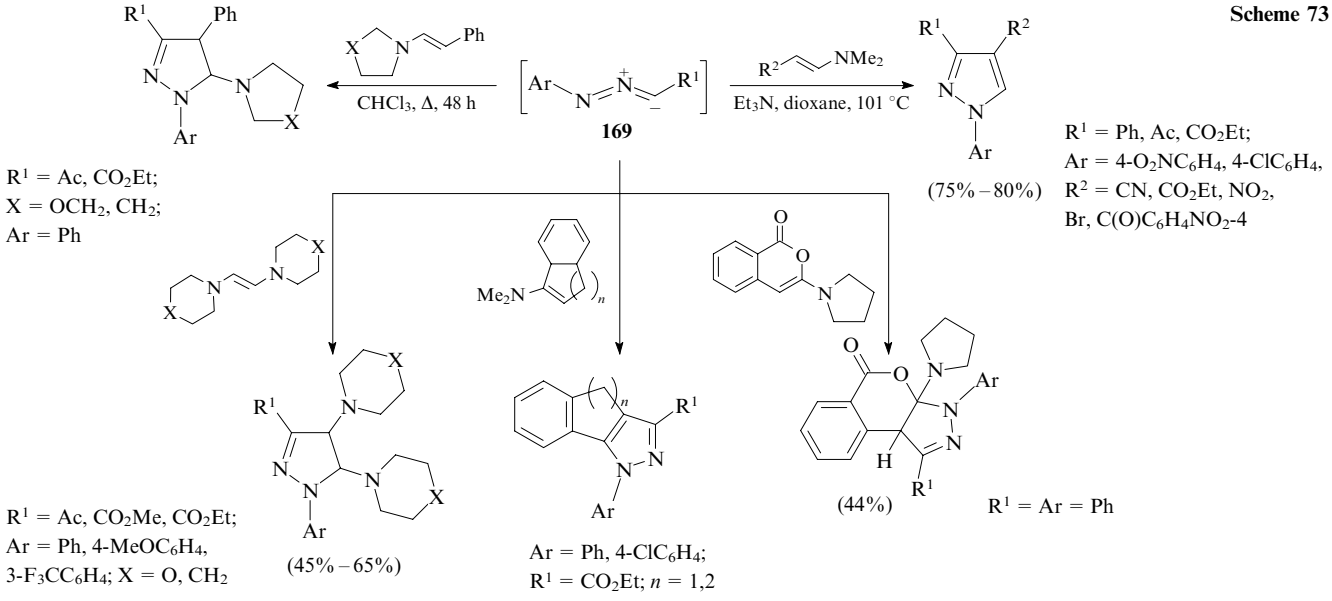
Scheme 71



Scheme 72



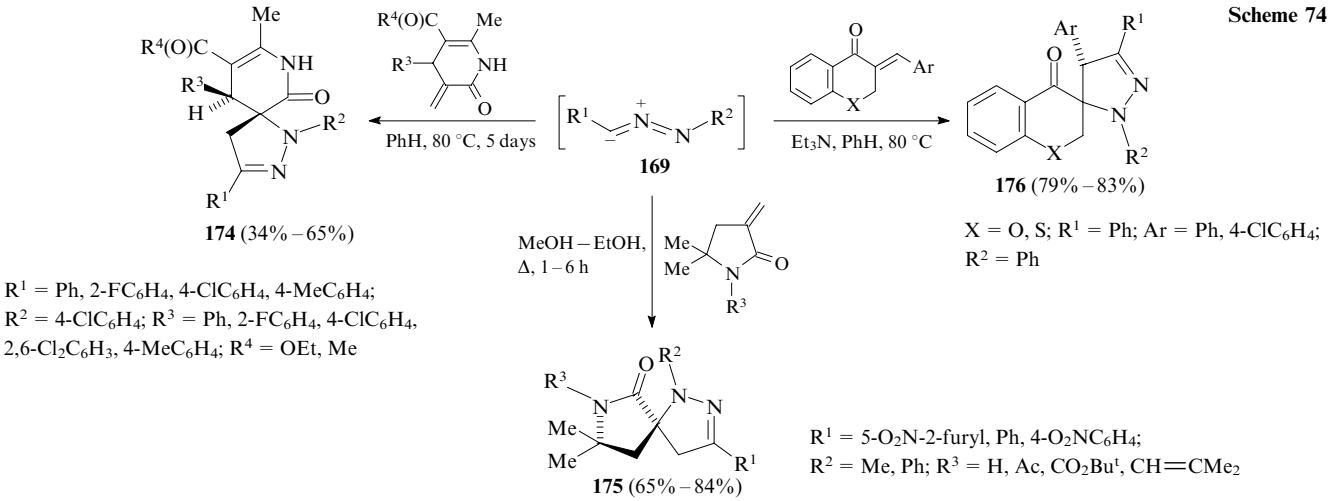
Scheme 73



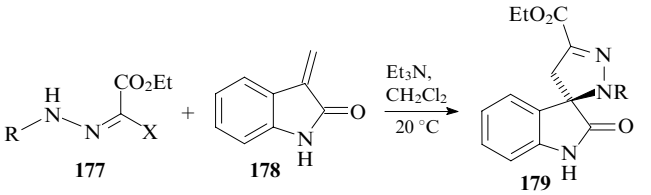
However the yield of bicyclic pyrazolines **173** and **173′**, formed in the reaction with α,β-unsaturated five- and six-memebered lactones, thiolactones or lactams, depends significantly on the ring size. The slowest reaction (15 h) is observed between nitrileimine **169** and five-membered lactones.[215, 216, 235 – 240]

Moderate or good yields and regioselectivity are observed in the reaction between nitrile imines **169** and

Scheme 74



Scheme 75



R	X	Base	Yield of **179** (%)
Ph	Cl	Et_3N	58
Ph	Cl	$NaHCO_3$	0
Ph	Br	Et_3N	93
Ph	Br	$NaHCO_3$	93
Bn	Cl	Et_3N	23
Bn	Br	Et_3N	85

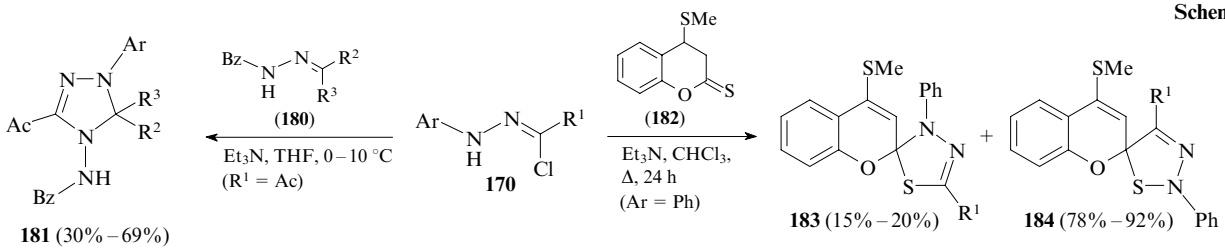
enaminonitriles, enaminones, enaminoesters or other enamines having a C=C bond in an acyclic, carbocyclic or heterocyclic moiety (Scheme 73).[20, 202, 203, 239, 241]

There are a lot of examples of cycloaddition of nitrile imines to exocyclic C=C bonds in various carbo- and heterocyclic derivatives. Most often, the synthesis of such compounds is related to the search for novel biologically active substances comprising a spirocyclic moiety, *e.g.*, pyrazolines **174**–**176** (Scheme 74).[20, 203, 230, 233, 243–248]

In an investigation of the 1,3-dipolar cycloaddition of nitrile imines derived from halohydrazones **177** to 3-methylidene oxindole (**178**), the process efficiency was found to depend on the halogen nature and the type of the base in use (Scheme 75).[247] Indeed, chloro derivatives **177** (X = Cl) react only in the presence of Et_3N as a base. If aqueous solutions of inorganic bases ($NaHCO_3$ or K_2CO_3) are added, the cycloaddition product cannot be detected even by ^1H NMR spectroscopy. Meanwhile, for bromohydrazones **177** (X = Br), dehydrohalogenation affording nitrile imines proceeds effectively in the presence of either Et_3N or aqueous solution of $NaHCO_3$ giving rise to spiro(pyrazoline-3,3′-oxindoles) **179** in high yields (see Scheme 75).

Nitrile imines may add to the C=N bonds incorporated in hydrazones, azomethines, oximes or heterocyclic nitrogen-containing compounds, to produce triazolines,[137, 250–255] and when adding to the C=S bond of isothiocyanates, thioamides or thioketones, they give thiadiazolines.[256–261] Cycloaddition of nitrile imines derived from hydrazonoyl chlorides **170** (R1 = Ac) to aldehyde or ketone hydrazones **180** proceeds regioselectively yielding substituted 1,2,4-triazoles **181**.[254] Meanwhile, similar chloro hydrazones **170** (R1 = Ar) react with chromene-2-thione **182** to give a mixture of spiro(chromene-2,2′-[1,3,4]thiadiazoles) **183** and spiro(chromene-2,5′-[1,2,3]thiadiazoles) **184** (Scheme 76).[256]

Scheme 76

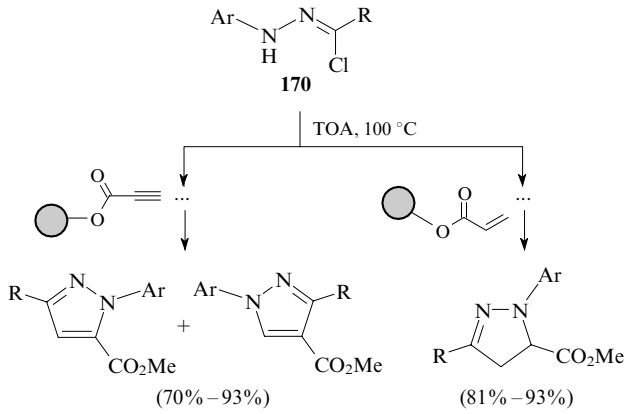


Ar = Ph, 4-ClC6H4, 4-BrC6H4, 4-O2NC6H4; R2 = Me, Et; R3 = H, Me, Et; R2–R3 = (CH2)n (n = 4–7), (CH2)3CH(Me)CH2, (CH2)3CH(But)CH2, (CH2)2N(Me)(CH2)2, (CH2)2N(CO2Et)(CH2)2

R1 = Ph, 4-ClC6H4, 4-O2NC6H4, 4-MeC6H4

The reactions of arylhydrazonoyl chlorides **170** with propiolic and acrylic acids immobilized on a solid support (polyethylene glycol, PEG) demonstrate that the 1,3-dipolar cycloaddition in these cases proceeds in high yields, while in the case of alkenes, the reaction involves the C=C bond and is regioselective (Scheme 77).[262, 263]

Scheme 77



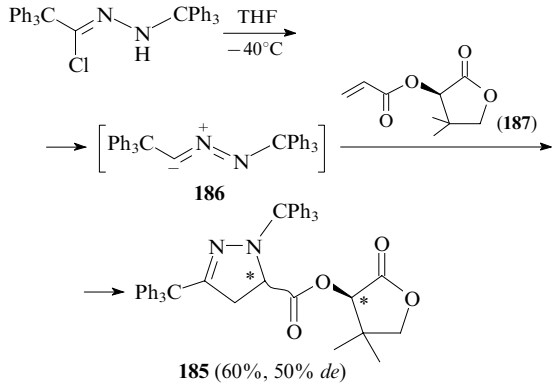
R = Ph, 4-MeC$_6$H$_4$, 2-Fu, Pr^n; Ar = 4-FC$_6$H$_4$; TOA is tri-n-octylamine

= PEG 4000

R = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$; Ar = 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$

Diastereoselective 1,3-dipolar cycloaddition reactions are of particular interest for the synthesis of heterocyclic compounds.[210, 264–268] Diastereoselective synthesis of pyrazolines **185** is exemplified by the reaction between bis(trityl)nitrile imine (**186**) and (*R*)-α-(acryloxy)-β,β-dimethyl-γ-butyrolactone **187** (Scheme 78).[210]

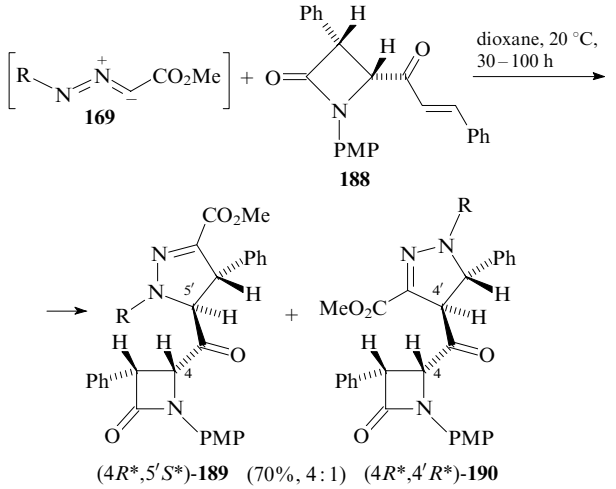
Scheme 78



The cycloaddition of nitrile imines **169** to (3*R**)-phenyl-(4*R**)-cinnamoylazetidin-2-one **188** proceeds with high diastereoselectivity and affords pyrazolines **189**, **190**.[265–266] These compounds arouse interest due to the fact that certain derivatives of pyrazole and 4,5-dihydropyrazole exhibit anticoagulant and anti-inflammatory activities (Scheme 79).

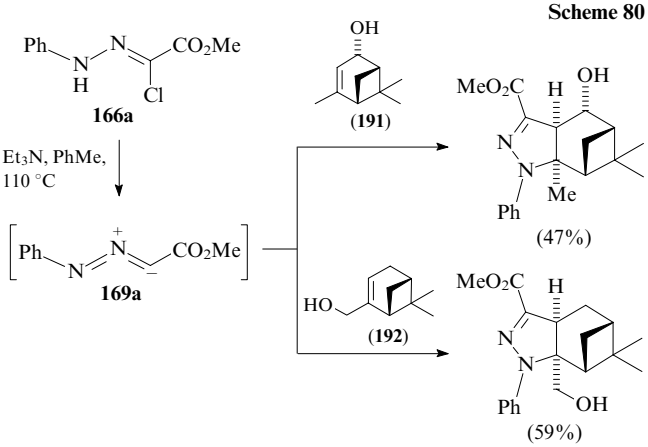
The 1,3-dipolar cycloaddition of nitrile imine **169a** to chiral dipolarophiles, (*S*)-*cis*-verbenol (**191**) and (1*R*)-(−)-myrtenol (**192**), proceeds regio- and stereoselectively (Scheme 80).[267]

Scheme 79



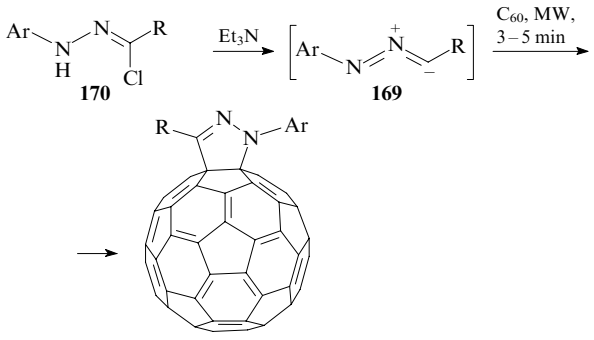
R = 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$; PMP = 4-MeOC$_6$H$_4$

Scheme 80



Another interesting application of 1,3-dipolar cycloaddition of nitrile imines is functionalization of carbon nanotubes or fullerenes (*e.g.*, the synthesis of derivatives **193**) through the introduction of a pyrazolinone chromophore in order to improve their photochemical properties (Scheme 81).[242, 269–272] Compared with other methods of fullerene functionalization, the [3 + 2]-cycloaddition using

Scheme 81

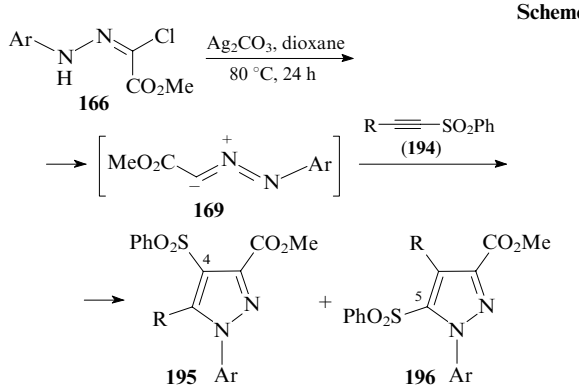


R = Me, Ph, 4-O$_2$NC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, 3,5-(F$_3$C)$_2$C$_6$H$_3$; Ar = Ph, 4-O$_2$NC$_6$H$_4$, 2,4-(O$_2$N)$_2$C$_6$H$_3$

nitrile imines is distinguished by high stereoselectivity and good yield of cycloadduct.

The addition of catalysts is important for the cycloaddition of nitrile imines to dipolarophiles to proceed successfully under mild conditions. Thus, soft Lewis acids are known to promote the 1,3-dipolar cycloaddition of hydrazonoyl chlorides to alkynes and alkenes and also to enhance the reaction regioselectivity.[221,248,265–267,273–278] In the reaction between nitrile imines **169** and ethynylsulfonylbenzene **194** (R = H), catalytic amounts of $Sc(OTf)_3$ increase the yield of the 4-regioisomer **195**.[221] The mechanism of its action is related to the formation of a transition state complex incorporating the methoxycarbonyl group of 1,3-dipole, the sulfonyl substituent of the dipolarophile and the catalyst. In the reaction of nitrile imines **169** with ethyl 3-(phenylsulfonyl)propiolate **194** (R = CO_2Et), the addition of Lewis acids induces no change in the ratio of pyrazole regioisomers **195** and **196**. Apparently, in this case $Sc(OTf)_3$ is not involved in the transformation and regioselectivity of the process is substrate-dependent (Scheme 82, Table 4).

Scheme 82



R = H, CO_2Et; Ar = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$

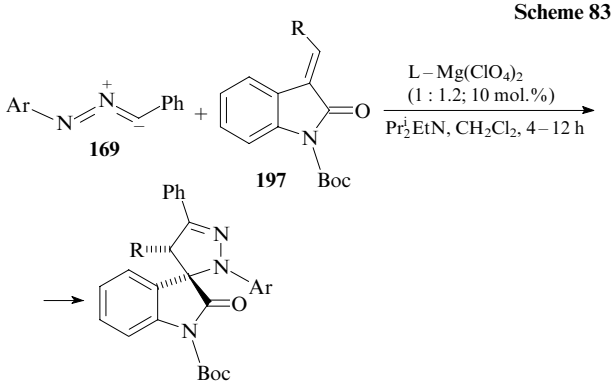
Combining chiral ligands with Lewis acids not only reduces the reaction time and increases the yields of the cyclic products, but also results in the formation of pyrazolines with high regio- and stereoselectivity.[248,266–267,277,278] The cycloaddition of nitrile imines **169** to 3-alkylydenoxindoles **197** catalyzed by a chiral complex of $Mg(ClO_4)_2$ with *N*,*N*′-dioxide ligand L makes it possible to synthesize spiro(pyrazoline-3,3′-oxindoles) **198** in 65%–98% yields and with enantioselectivity of up to 98% (Scheme 83).[277,278]

Table 4. 1,3-Dipolar cycloaddition of nitrile imines **169** to alkyne **194** without a catalyst or with the $Sc(OTf)_3$ catalyst.[221]

Ar	R	Reaction without $Sc(OTf)_3$		Reaction with $Sc(OTf)_3$ (10 mol.%)	
		yield of **195**+**196** (%)	ratio **195**:**196**	yield of **195**+**196** (%)	ratio **195**:**196**
Ph	H	49	65:35	38	88:12
4-$O_2NC_6H_4$	H	35	60:40	34	86:14
4-$MeOC_6H_4$	H	58	46:54	39	86:14
Ph	CO_2Et	63	89:11	72	92:8
4-$O_2NC_6H_4$	CO_2Et	65	80:20	67	85:15
4-$MeOC_6H_4$	CO_2Et	60	90:10	64	91:9

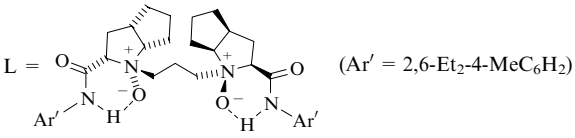
Mild conditions and a convenient procedure attest to the high activity of the catalytic system.

Scheme 83



198 [65%–98%, (63%–98%) *ee*]

Ar = 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 4-FC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3-BrC_6H_4, 3-MeC_6H_4, 3-$F_3CC_6H_4$, 3-BzC_6H_4, 1-Naph, 2-Naph; R = Pr^i, 2-ClC_6H_4, 4-ClC_6H_4, 2,6-$Cl_2C_6H_3$, 2,3-$(MeO)_2C_6H_3$, 2-BrC_6H_4, 2-$O_2NC_6H_4$, 1-Naph



VII.3. Intramolecular cyclization of nitrile imines

Intramolecular cyclization of nitrile imines occurs when the molecule has multiple bonds and may afford a variety of fused heterocyclic products.[279–285] For instance, intramolecular transformations of azomethine imines **199**, resulted in the synthesis of 1,2,4-triazolo[1,5-*a*]quinolines **200**, cyclopropa[*c*]cinnolines **201** and benzodiazepines **202** (Scheme 84).[279]

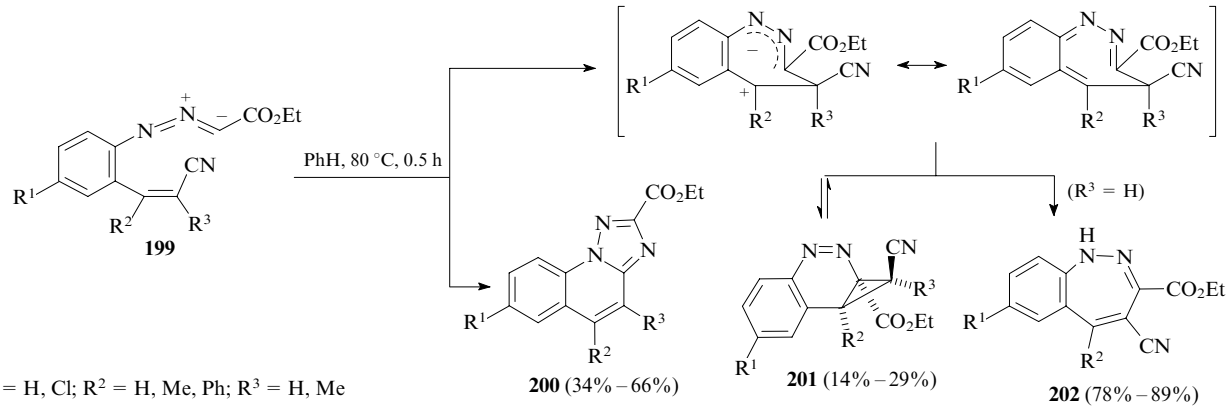
For nitrile imines having a terminal C=C double bond, both intramolecular cyclization and intermolecular reaction are possible. For example, upon cyclization of nitrile imines **203**, both tricyclic pyrazolines **204**, resulting from intramolecular cyclization, and macrocyclic bis(heterophanes) **205**, resulting from tandem intermolecular and intramolecular cycloadditions, were isolated. The ratio of the intra- and intermolecular cyclization products depends on the chain length between the two reacting moieties (Scheme 85).[280]

However, such reaction are often characterized by simultaneous formation of two five-membered rings[282–284] or combinations of six- and five-membered rings.[281,285] For example, heating *cis*-alkene **206** at reflux in toluene affords dihydropyrazolobenzoxazines **208** *via* intermediate nitrile imine **207** in a good yield (Scheme 86).[281]

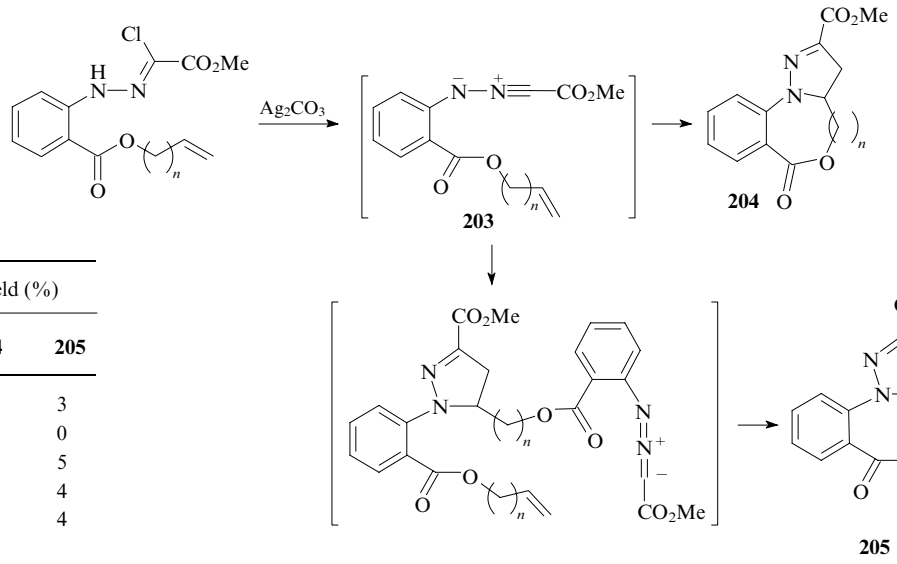
Conversely, heating *trans*-alkene **206** under the same conditions yields benzoxadiazine **209** as the major product (Scheme 87). This compound is formed upon intramolecular cyclization of nitrile imine **210** generated *via* the Claisen rearrangement.[281]

A substituent with a multiple bond may be bound to a carbon atom of the hydrazone group. An interesting example of such reaction is intramolecular cyclization of homochiral hydrazonoyl chlorides **211a–c** furnishing enantiomerically pure furo[3,4-*c*]pyrazoles α-**212** and β-**212**

Scheme 84

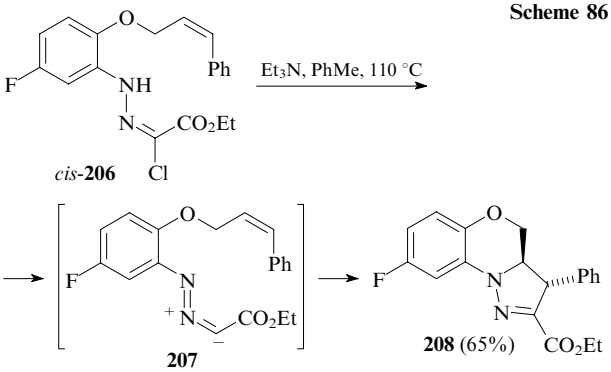


Scheme 85

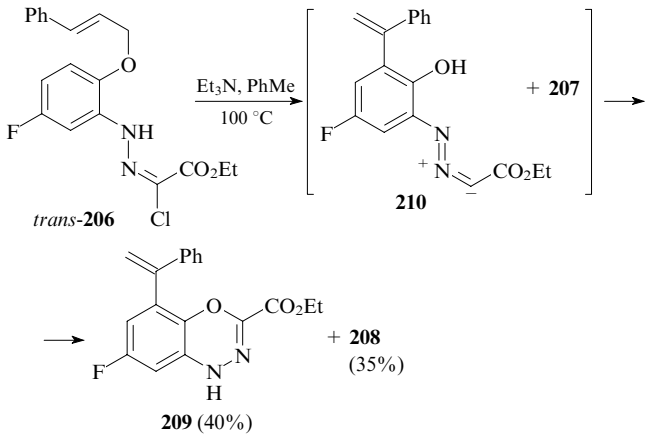


n	Yield (%)	
	204	**205**
3	18	3
4	37	0
5	21	5
8	9	4
9	9	4

Scheme 86



Scheme 87

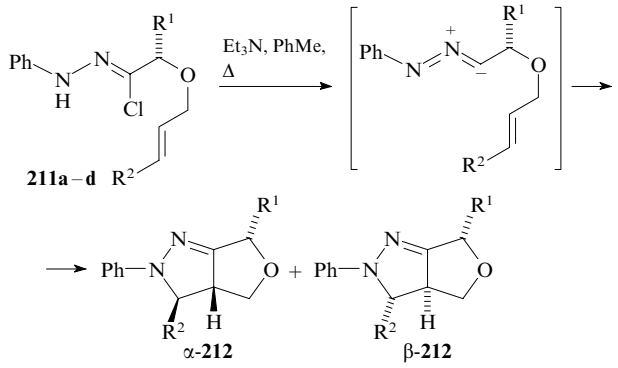


in good yield and with high diastereoselectivity (Scheme 88).[282] The isomer ratio depends on the steric characteristics of the R^1 substituent. Hydrazone **211d** bearing a less bulky substituent (R^1 = H) produces a racemic mixture, whereas in the case of R^1 = Ph, single isomer α-**212** is formed.

The intramolecular cycloaddition of nitrile imines **213** across the thiophene ring is an attractive example of synthesis of strained tricyclic derivatives **214**, which may further react with the starting 1,3-dipole by intermolecular cycloaddition pathway involving the thiophene or pyrazoline ring (Scheme 89).[283]

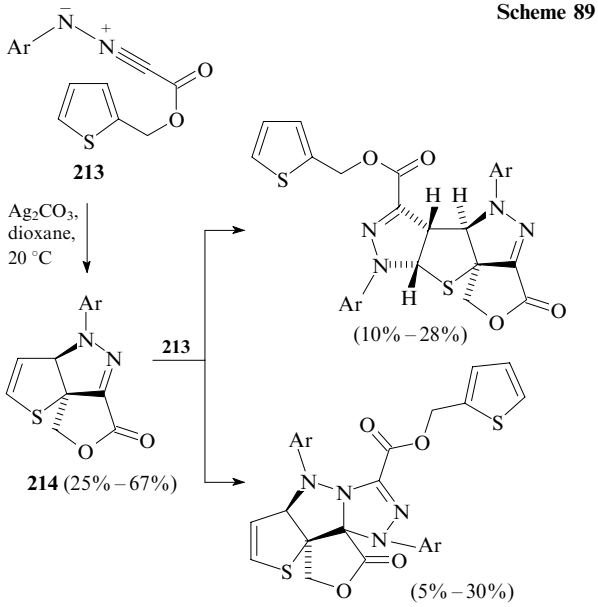
Hydrazonoyl chlorides **215** comprising an azetidine ring transform into enantiomerically pure tricyclic β-lactames **216** with an annulated pyrazoline ring in the presence of the silver salt used as a base (Scheme 90).[284]

Scheme 88



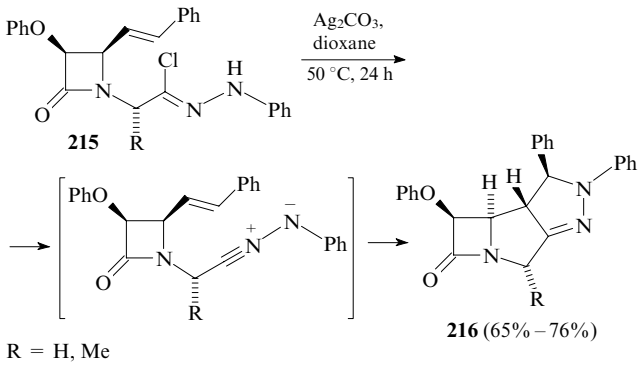
Compound **211**	R^1	R^2	Time /h	Yield of α-**212** + β-**212** (%)	Ratio α-**212** : β-**212**
a	Me	H	4	74	86 : 14
b	Me	Me	8	65	70 : 30
c	Ph	H	5	39	100 : 0
d	H	H	3	96	50 : 50

Scheme 89



Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-$O_2NC_6H_4$

Scheme 90



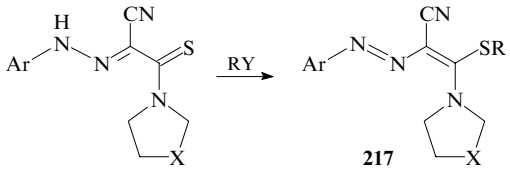
R = H, Me

The given examples of 1,3-dipolar cycloaddition reactions demonstrate their important role in synthetic organic chemistry as well as in the development of theoretical aspects of pericyclic transformations. The pyrazole and pyrazoline derivatives thus obtained are key components of some dyes, polymers and also exhibit certain interesting biological properties.[202, 203]

VIII. Hydrazonothioacetamides as precursors of 1,3-dipoles of the azomethine ylide type

Evidently, the scope of reactions which may involve hydrazones is considerably extended upon introducing various functionalities and substituents. In some cases, functionalization favours the generation of novel active intermediates (nitrile imines or 1,2-diazabutadienes), while in other cases, it promotes new heterocyclization reactions by intermolecular or intramolecular cycloaddition mechanisms. It should be noted that a number of substituents or functionalities in use is rather limited. In most cases, hydrazones bearing an active halogen atom in α- or β-position are used. Our recent investigations demonstrated that a suitable functionality to form a diazadiene system is the thiocarbamoyl group, which can be easily modified to a substituted sulfanyl group at the C=C double bond (Scheme 91).[286–288]

Scheme 91



X = CH_2, $(CH_2)_2$, OCH_2; Ar = 4-$EtO_2CC_6H_4$, 4-$F_3CC_6H_4$, 4-ClC_6H_4, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 2,3-$Me_2C_6H_3$; Y = Br, I; R = Me, All, $HC{\equiv}CCH_2$

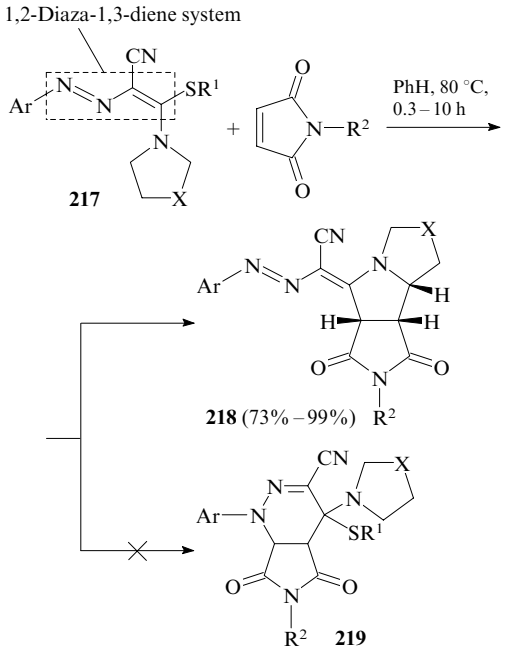
However, the reactions between 1,2-diazabutadienes **217** and phenyl- and methylmaleimides under different conditions (temperature, solvent) afforded hexahydropyrrolopyrrolizines **218**. 1*H*-Pyrrolo[3,4-*c*]pyridazines **219**, which might have been expected upon [4 + 2]-cycloaddition, were not detected (Scheme 92).

The mechanism of such transformation of diazadienes **217** with a terminal S,N-acetal group may be explained by the generation of 1,3-dipolar azomethine ylide intermediates **A** upon 1,6-shift of the hydrogen atom from the α-position of the tertiary amino group to the nitrogen atom of the hydrazone moiety (Scheme 93).[287]

Studies of this process by experimental and theoretical (B3LYP/6-31G*) methods have shown that the activation barrier for the formation of dipole **A** is as low as 14.9 kcal mol^{-1}. Substituents in the aromatic ring and at the sulfur atom considerably influence the reactivity of the forming azomethine ylides in the cycloaddition reactions with electron-deficient dipolarophiles. Introducing electron-deficient substituents into the aromatic ring enhances the conjugation of the electron pair of nitrogen of the tertiary amino group and increases the lability of the hydrogen atom in the α-position.

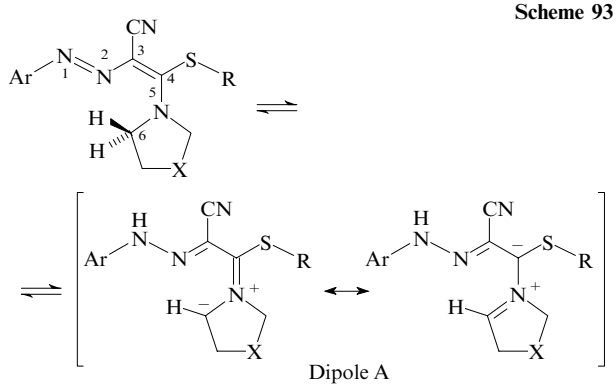
In the reaction of 3-alkylsulfanyl-2-arylazo-3-pyrrolidinoacrylonitriles **217** (X = CH_2) with DMAD and dimethyl maleate, dihydropyrrolizines **220** and hexahydropyrrolizines **221** were isolated in good or moderate yields (Scheme 94).[287]

Scheme 92

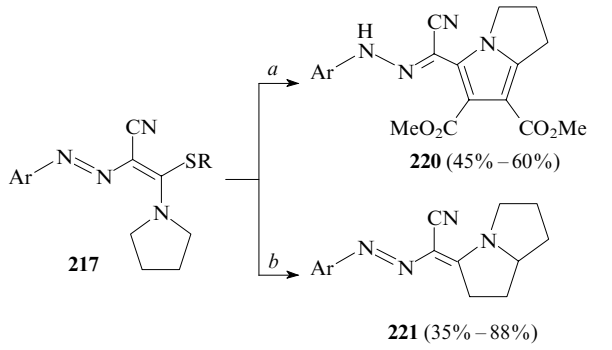


R^1 = Me, All, HC≡CCH$_2$; X = CH$_2$, (CH$_2$)$_2$, OCH$_2$;
Ar = 4-EtO$_2$CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-ClC$_6$H$_4$, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-EtOC$_6$H$_4$, 2,4-Me$_2$C$_6$H$_3$; R^2 = H, Me, Ph

Scheme 93



Scheme 94



Ar = Ph, 4-O$_2$NC$_6$H$_4$, 4-EtO$_2$CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$;
(*a*) DMAD, PhH, 80 °C (R = All);
(*b*) MeO$_2$C(H)C=C(H)CO$_2$Me, PhH, 60 °C (R = Me)

This study showed new prospects in using hydrazones as substrates for the formation of active intermediates in cycloaddition reactions.

IX. Conclusion

The analysis of the literature data concerning the reactions between hydrazones and dipolarophiles demonstrated that depending on the structure and conditions, these compounds may effectively react with various acetylenes and alkenes and, in some cases, with linear and cyclic compounds containing the C=N and C=S bonds by the hetero-Diels – Alder reaction or 1,3-dipolar cycloaddition mechanism. These transformations afford various nitrogen-containing heterocyclic, spirocyclic and polycyclic compounds, which have promising applications in medicinal chemistry, since they serve the key building blocks in the synthesis of alkaloids, peptides, azasugars,[8, 38, 120 – 122, 138, 139] as well as are used to obtain a series of antibiotics and antitumour, antiviral and anti-inflammatory agents.[8, 14, 22 – 28, 53, 63, 202, 223, 254]

It is noteworthy that the history of using hydrazones in cycloaddition reactions started as soon as these transformations were distinguished as a separate group because of their specific mechanism. Moreover, hydrazone derivatives played an important role in the development of both the theoretical ideas of pericyclic reactions and their practical application in the synthesis of various nitrogen-containing heterocycles and heterocyclic systems. Nevertheless, each successive decade opens new surprising aspects of the hydrazone reactivity and demonstrates new prospects for their application in different kinds of [4 + 2]- and [3 + 2]-cycloaddition reactions.

An important factor is availability of hydrazones as well as the possibility of introduction of various substituents, functionalities, carbo- and heterocyclic moieties into their molecules, which makes it possible not only to study the structure – reactivity relationship but also to obtain novel compounds of high practical importance.

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