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Synthesis and properties of nitrogenous heterocycles containing a spiro-fused cyclopropane fragment

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Abstract. The published data on the methods of synthesis and chemical transformations of nitrogenous heterocyclic compounds spiro-fused with a cyclopropane fragment are described systematically and generalised. The bibliography includes 146 references.

I. Introduction

Synthesis and studies of the properties of highly strained carbocyclic compounds, including those incorporating a cyclopropane ring, is a field of organic chemistry which is developing most intensely. Today, many methods for the synthesis of cyclopropanes are known; their chemical transformations have been studied, and diverse spheres of practical use of these compounds have been found by now. The introduction of a spiro-fused cyclopropane fragment in a heterocyclic molecule changes the reactivity of the heterocycle. The high strain of the three-carbon ring predetermines is ability to undergo facile opening with a change in the spiro-carbon atom hybridisation from sp^3 to sp^2. Since heterocyclic compounds (including mono- and polynitrogen-containing ones) find use as medicines and as chemical means for plant and animal protection, synthesis of their analogues with a spirocyclopropane fragment is interesting both from the theoretical viewpoint and for the preparation of new biologically active compounds, in particular, potential pharmaceuticals.

Synthesis of heterocycles containing a spiro cyclopropane fragment involves either the formation of a heterocyclic structure from compounds that already possess a three-carbon ring or the formation of a cyclopropane ring in structures incorporating the required heterocycle. The first approach is primarily based on various [3 + 2]- and [4 + 2]-cycloaddition reactions that can be carried out using either cyclopropane-containing dipolarophiles (dienophiles), *e.g.*, methylidenecyclopropanes, or nitrogen-containing 1,3-dipoles or dienes in which one atom of the cyclopropane ring is involved in the reactive fragment. Diazocyclopropane generated *in situ*, which readily reacts with certain unsaturated compounds to give spiro[cyclopropanedihydropyrazoles], is a promising building block of the latter type.

The second approach is based on the addition of aliphatic diazo compounds to the activated exocyclic double bond in a heterocycle followed by dedinitrogenation of the resulting dihydropyrazoles, as well as on the addition of carbenes or ylides to methylidene-substituted heterocycles.

This review is a first attempt at generalisation of the published data on the synthesis and some chemical transformations of heterocyclic compounds incorporating a spirocyclopropane fragment and at least one nitrogen atom in the ring. The presented material is mostly arranged according to the class of the key compounds used for the construction of the spirocyclopropane-containing azaheterocycles. The structures in which the cyclopropane fragment is not spiro-fused directly with the azaheterocycle are not considered.

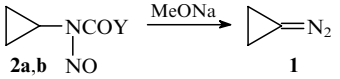
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II. The formation of nitrogen-containing heterocyclic systems from compounds with a cyclopropane fragment

1. Cycloaddition involving diazocyclopropane

Diazocyclopropane (**1**) is a promising compound for the synthesis of compounds incorporating a spiro-fused cyclopropane fragment which are difficult to access.[1–4] Generally, diazocyclopropane (**1**) is generated by decomposition of *N*-cyclopropyl-*N*-nitrosourea (**2a**)[1,4] or *N*-cyclopropyl-*N*-nitrosocarbamate (**2b**)[2,3] on treatment with strong bases, by analogy with the synthesis of aliphatic diazo compounds.[5] Unlike the majority of the known aliphatic and cyclic diazo compounds, both diazocyclopropane (**1**) and all of its derivatives mentioned in the literature[6–9] are quite unstable compounds which have not been detected in individual form. Nevertheless, the formation of diazocyclopropanes *in situ* follows from the methods used for their generation and chemical trapping. For example, its reactions with unsaturated compounds result in 1,3-dipolar cycloaddition products, *viz.*, the corresponding spiro[cyclopropane-4,5-dihydro-3*H*-pyrazoles].

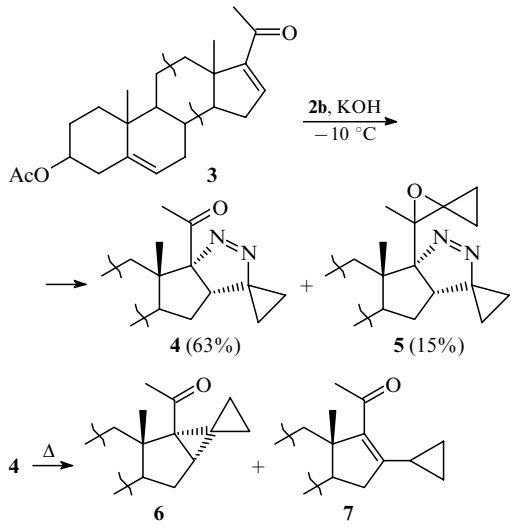


2a,**b** **1**

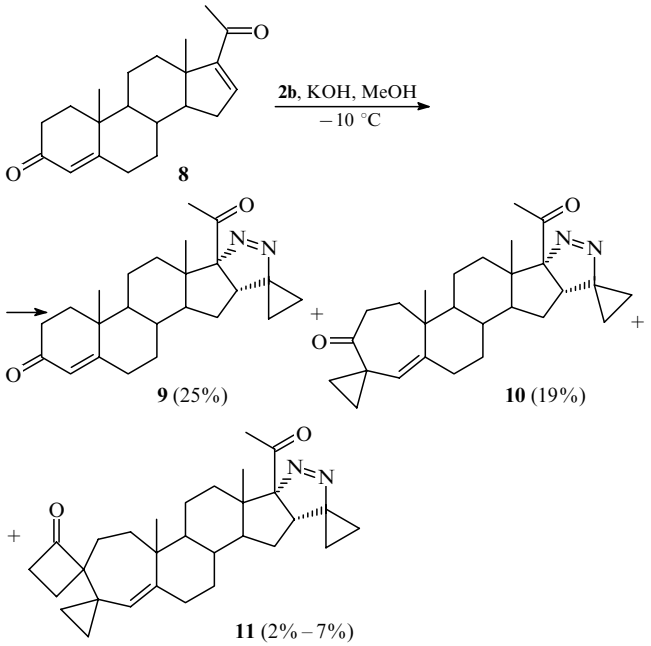
Y = NH_2 (**a**), OEt (**b**).

The reaction of diazocyclopropane (**1**) with oxosteroids[2,3] should be noted as one of the first examples of the trapping of compound **1** with unsaturated compounds. For example, diazo-

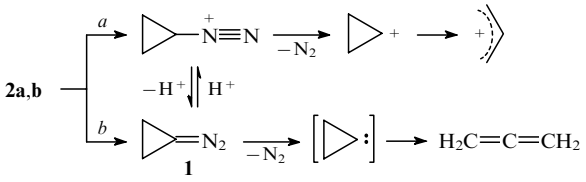
cyclopropane (**1**) generated *in situ* undergoes selective addition to the Δ^{16} bond of the diene **3** to give dihydropyrazole **4**. The reaction of an excess of the diazo compound **1** with the carbonyl group of the adduct **4** results in oxaspiropentane **5**. Thermolysis[2] of the dihydropyrazole **4** isolated in individual form, as in the case of similar dihydropyrazoles obtained by the addition of other diazoalkanes,[10] occurs non-selectively: in addition to the usual reaction product, *viz*., the spiropentane derivative **6**, the β-substituted α,β-enone **7** is formed (the ratio **6** : **7** is 3.5 : 1).



It should be noted that the reaction of diazocyclopropane (**1**) with the cyclohexenone fragment of steroids under the same conditions occurs in a different way.[3] For example, the reaction of compound **8** gives not only the expected addition product to the Δ^{16} bond, *i.e*., the adduct **9**, but also compound **10** due to the six-membered ring expansion, which is similar to homologisation of cyclic ketones on treatment with diazomethane.[11] Cyclobutanone **11** formed upon formal addition of cyclopropylidene to the carbonyl group of the cycloheptane fragment of compound **10**[3] was identified as a minor product.

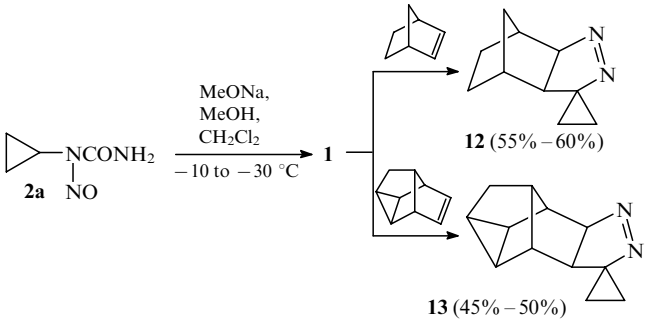


Although diazocyclopropane (**1**) can in principle be trapped by alkenes to give spiro[cyclopropanedihydropyrazoles], this reaction did not find synthetic application for a long time, primarily because the nature of unsaturated substrates which can enter into 1,3-dipolar cycloaddition with compound **1** was not determined with certainty. In fact, there are several examples where generation of diazocyclopropane (**1**) in the presence of unsaturated compounds, such as cyclohexa-1,4-diene,[12] bicyclopropylidene,[13] or cycloalkyl-substituted bicyclopropylidenes,[14–16] resulted in spirane hydrocarbons rather than dihydropyrazoles which were formed due to [1 + 2]-cycloaddition of cyclopropylidene to these compounds. Generation of diazocyclopropane from compounds **2a,b** can produce, in addition to cyclopropylidene, other unstable species. The pathways of transformation of cyclopropylnitrosourea **2a** and cyclopropylnitrosoureas substituted at the cyclopropane ring on treatment with reagents of different basicity and nucleophilicity were studied in a series of works by Kirmse *et al*.[1,17–27] It was assumed that their reactions give rise to cyclopropyldiazonium salts, as well as cyclopropyl and allyl cations due to the dedinitrogenation of these salts.

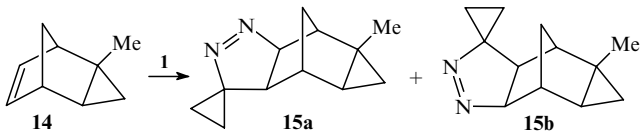


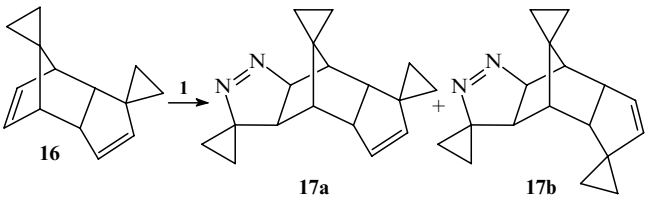
(*a*) weak base; (*b*) strong base.

Systematic studies of 1,3-dipolar cycloaddition of diazocyclopropane (**1**) to alkenes, first of all a systematic search for efficient traps for compound **1** to give spiro[cyclopropanedihydropyrazoles], date back to the beginning of the 1990s. It was found that reactions of diazocyclopropane (**1**), generated *in situ* on treatment of cyclopropylnitrosourea (**2a**) with sodium methoxide, with norbornene[4] and other compounds containing the bicyclo[2.2.1]heptene fragment[28] mostly result in spiro[cyclopropanedihydropyrazoles] of the types **12** and **13**, exclusively as *exo*-isomers. Good yields (50%–70%) are achieved if a molar excess as low as 1.5-fold of the unsaturated substrate with respect to cyclopropylnitrosourea (**2a**) is used.

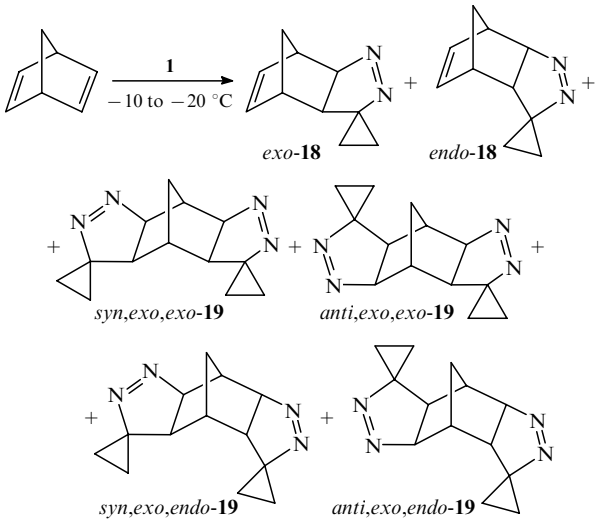


The asymmetrically substituted hydrocarbon **14** gives a mixture of isomeric spiro[cyclopropanedihydropyrazoles] **15a** and **15b** due to the different approach of diazocyclopropane to the double bond; their ratio was ~ 1 : 1 and the overall yield was 55%–58%. The polycyclic diene **16** reacts with diazocyclopropane (**1**) in a similar way.[28] Despite the steric hindrance created by the spirocyclopropane fragment in the norbornene moiety, dihydropyrazoles **17a** and **17b** (in a ratio ~ 1.4 : 1) are also formed exclusively as *exo*-isomers, although their overall yield (23%) is markedly lower than that of norbornene unsaturated at position 7. It should be noted that this reaction did not give any addition products of diazocyclopropane (**1**) (or cyclopropylidene) to the cyclopentene double bond.



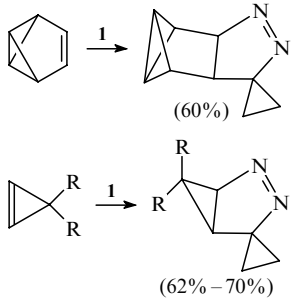


The reaction of norbornadiene with diazocyclopropane (**1**) generated *in situ* also occurs as 1,3-dipolar cycloaddition, although less selectively, and results in a mixture of isomeric mono- (**18**) and bisadducts (**19**) in 32%–35% and 35%–38% yields, respectively.[4]



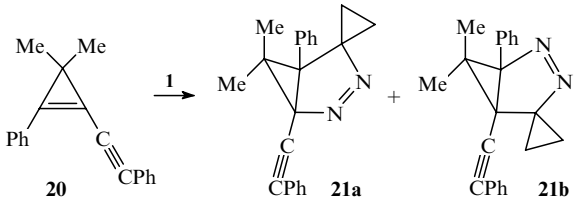
Unlike the adducts **12**, **13**, **15** and **17**, monospiro[cyclopropanedihydropyrazoles] **18** are a mixture of *exo*- and *endo*-isomers in the ratio ~ 4 : 1, while the bisadducts **19** formed from them are a mixture of four isomers in the ratio ~ 10 : 7 : 1.3 : 1. Although a two-fold excess of norbornadiene is used, bisadducts **19** are formed in an even greater quantity than monoadducts **18**; the addition of the second diazocyclopropane molecule to monoadducts **18** occurs exclusively at the *exo* position.

Benzvalene and 3,3-disubstituted cyclopropenes are also efficient trapping agents for diazocyclopropane (**1**).[4, 28, 29]

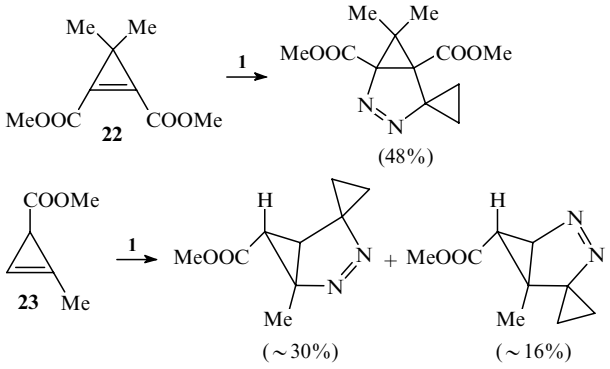


R = Me; R–R = $(CH_2)_3$.

The reaction of diazocyclopropane (**1**) with alkynylcyclopropene **20** results in regioisomeric dihydropyrazoles **21a** and **21b** in the ratio ~ 3 : 1; this reaction does not involve the triple bond.[29]

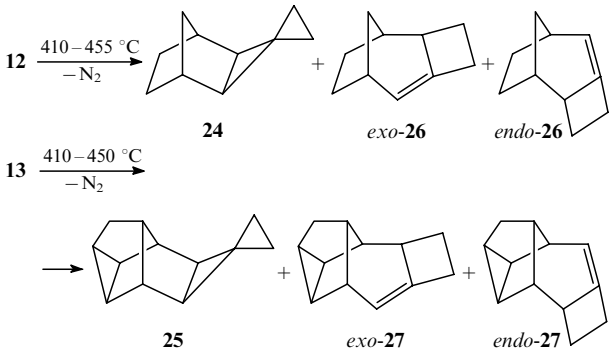


1,3-Dipolar cycloaddition products are formed in reactions of diazocyclopropane (**1**) with methyl cyclopropenecarboxylates **22** and **23**.[28, 29] The regioselectivity is low in the case of the cyclopropene **23**.

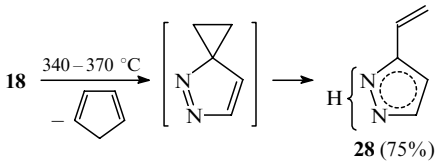


In the synthesis of dihydropyrazoles from cyclopropenes **20** and **22**, alternate addition of cyclopropylnitrosourea (**2a**) and the corresponding cyclopropene to a suspension of MeONa in a MeOH–ether mixture at −20 to −30 °C was found to be the method of choice.[29]

It should be noted that the majority of the resulting polycyclic spiro[cyclopropanedihydropyrazoles] possess rather high thermal stability.[30] For example, dihydropyrazoles **12** and **13** are stable when heated to 200 °C. In the gas phase at 410–450 °C, they undergo dedinitrogenation to give a mixture of strained hydrocarbons, *viz*., spiro[tricyclo[3.2.1.$0^{2,4}$]octane-1,3′-cyclopropane] (**24**) or spiro[pentacyclo[4.4.0.$0^{2,8}$.$0^{3,5}$.$0^{7,9}$]decane-4,1′-cyclopropane] (**25**), as well as isomeric compounds **26** or **27** containing a fused cyclobutane fragment (overall yield 30%–70%). An increase in temperature favours the isomerisation of the spirane hydrocarbons **24** and **25** to the corresponding unsaturated compounds **26** and **27**.

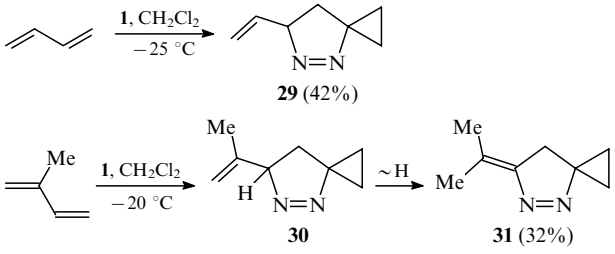


The unsaturated 4,5-dihydro-3*H*-pyrazole **18** obtained by the addition of diazocyclopropane (**1**) to norbornadiene eliminates cyclopentadiene instead of N_2 on thermolysis to give 3(5)-vinylpyrazole (**28**).[30]

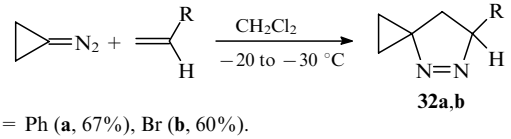


In addition to strained cyclic unsaturated compounds, conjugated aliphatic dienes such as buta-1,3-diene can also play the role of trapping agents for diazocyclopropane (**1**).[28] At −25 °C, 6-vinyl-4,5-diazaspiro[2.4]hept-4-ene (**29**) is formed as the major product; unlike polycyclic dihydropyrazoles, it readily undergoes polymerisation to give a rubber-like substance. The reaction of diazocyclopropane (**1**) with 2-methylbuta-1,3-diene also occurs as 1,3-dipolar addition, but 6-isopropylidene-4,5-diazaspiro[2.4]-hept-4-ene (**31**) rather than 5-isopropenyldihydropyrazole **30** is formed in this case as the main reaction product. Apparently, the addition of diazocyclopropane occurs mostly to the unsubstituted

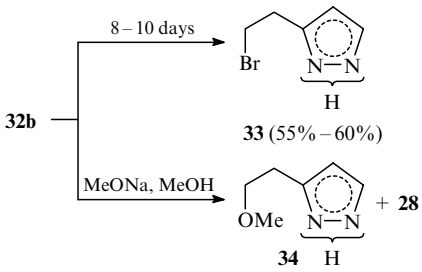
double bond, while the resulting dihydropyrazole **30** undergoes isomerisation under the reaction conditions.[28]



It is well known that the reactivity of alkenes with respect to diazomethane and other aliphatic diazo compounds in 1,3-dipolar cycloaddition reactions is largely determined by the nature of the double bonds and that the reaction accelerates upon introduction of electron-withdrawing substituents.[31] Successful 1,3-dipolar cycloaddition in the case of low-activity alkenes is usually provided by keeping the reaction mixture for a long time. This technique cannot be employed in reactions with diazocyclopropane because of its instability, which undoubtedly decreases the number of potential unsaturated partners of this reaction. It has recently been established that styrene[32] and vinyl bromide[33] are rather good trapping agents for diazocyclopropane (**1**) generated *in situ*.[33] 1,3-Dipolar cycloadditions involving these alkenes occur regioselectively to give 5-phenyl- (**32a**) and 5-bromospiro[cyclopropane-1,3′-dihydropyrazoles] (**32b**), respectively. However, unlike the majority of spiro[cyclopropanedihydropyrazoles] considered above, including compound **32a**, bromodihydropyrazole **32b** is unstable and undergoes partial resinification and partial transformation to 3(5)-(2-bromoethyl)pyrazole (**33**) upon storage in an inert atmosphere at 15 °C for 8–10 days.[33] The reaction of the compound **32b** with MeONa in MeOH at 25 °C for 2 h results in a mixture of 3(5)-(2-methoxyethyl)- (**34**) and 3(5)-vinylpyrazoles (**28**) [overall yield ~ 80%, ratio (3–4) : 1].[33]

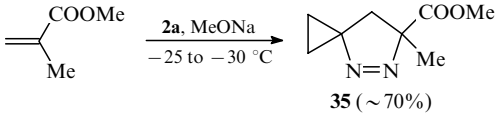


R = Ph (**a**, 67%), Br (**b**, 60%).

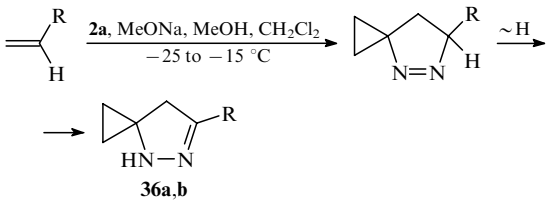


It should be noted that the reaction of diazomethane with vinyl bromide in ether readily results in pyrazole hydrobromide due to the facile dehydrobromination of the bromodihydropyrazole formed initially.[34] Thus, the spirocyclopropane moiety in the compound **32b** reduces the ability of the heterocyclic fragment to undergo deprotonation.

Acrylic acid derivatives are good substrates for reactions involving diazocyclopropane (**1**); for example, the addition of cyclopropylnitrosourea (**2a**) to a mixture of methyl methacrylate and sodium methoxide (ratio 1 : 1.5 : 1.5) affords dihydropyrazole **35** in a yield up to 70%.[35]



Diazocyclopropane (**1**) reacts with acrylonitrile and methyl acrylate with equal efficiency. However, in this case the composition of the reaction products depends on the conditions and the reagent ratio.[36] In particular, generation of diazocyclopropane (**1**) by the addition of cyclopropylnitrosourea (**2a**) to a mixture of an unsaturated compound and MeONa in a solvent was found to be unacceptable due to a side reaction of methanol addition to the electron-deficient double bond of acrylonitrile or methyl acrylate. The side reaction can be inhibited almost completely by changing the order of addition of the reagents.[36] At the ratio **2a** : acrylate ~ 1 : 1, the expected spiro[cyclopropane-1,5′-4,5-dihydro-1*H*-pyrazoles] **36a,b** are formed as the main reaction products (yields ~ 70%).[36]

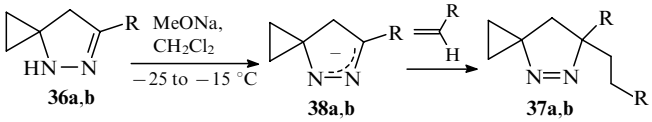


R = CN (**a**, 70%), COOMe (**b**, 69%).

It was shown later[37] that the synthesis of dihydropyrazole **36a** can be carried out with equal success with the use of K_2CO_3 instead of MeONa, but in this case complete decomposition of cyclopropylnitrosourea (**2a**) at 0–5 °C takes as long as 1–2 h.

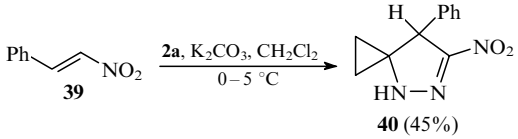
Dihydropyrazoles **36a,b** (especially **36b**) are rather labile compounds which undergo partial decomposition even under the conditions of preparative TLC.

An increase in the amount of acrylonitrile or methyl acrylate to 2–2.5 equiv. with respect to cyclopropylnitrosourea decreases the fraction of dihydropyrazoles **36a,b** to ~ 15% and results in new reaction products, *viz*., functionally substituted dihydropyrazoles **37a,b**, which, as shown in special experiments,[36–38] are formed upon reaction of dihydropyrazoles **36a,b** with the excess of unsaturated substrates. The generation of the anions **38a,b** is probably the driving force of the observed transformations. This procedure makes it possible to obtain spiro[cyclopropanedihydropyrazoles] containing functional substituents in the side chain and in the dihydropyrazole ring (see Section III).

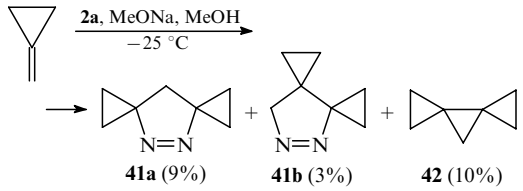


R = CN (**a**, 84%), COOMe (**b**, 80%).

Diazocyclopropane (**1**) undergoes regioselective addition to *trans*-β-nitrostyrene (**39**) to give 3- nitro-4-phenylspiro[cyclopropane-1,5′-4,5-dihydro-1*H*-pyrazole] (**40**).[37]

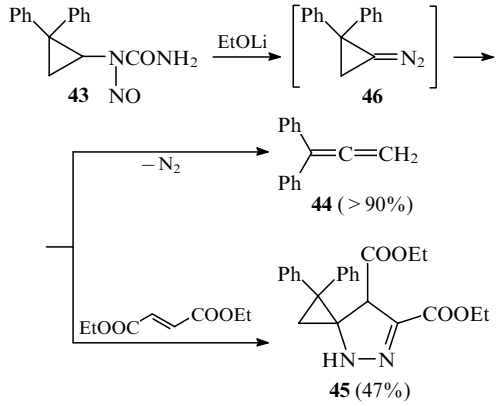


1,3-Dipolar cycloaddition of diazocyclopropane (**1**) to phenyl vinyl sulfide,[38] divinyl ether[37] and methylidenecyclopropane[4] occurs with low efficiency (the yields of dihydropyrazoles are 5%, 13% and 12%, respectively). The reaction with methylidenecyclopropane gave a mixture of two regioisomers **41a,b** in the ratio ~ 3 : 1; in addition to dihydropyrazoles, the reaction of cyclopropylidene with methylidenecyclopropane also gave dispiro[2.0.2.1]heptane (**42**). As it could be expected, cyclopropyl methyl ether and allene were the main side products of decomposition of cyclopropylnitrosourea (**2a**).[4]



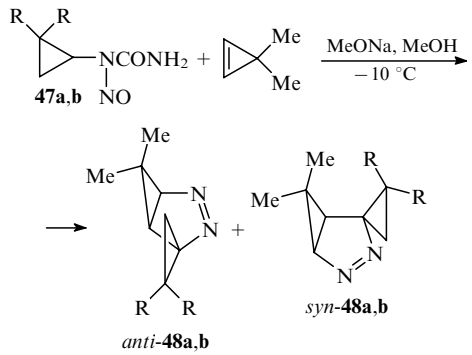
2. Cycloaddition involving substituted diazocyclopropanes

Along with the cycloaddition of diazocyclopropane (**1**) generated *in situ* to the unsaturated compounds considered above, there are examples of [3 + 2]-cycloaddition of substituted diazocyclopropanes to activated C=C bonds. For example, in the beginning of the 1960s, American authors obtained *N*-(2,2-diphenylcyclopropyl)-*N*-nitrosourea (**43**) and studied its decomposition in the presence of bases or on heating.[7,39,40] On treatment with lithium ethoxide in saturated hydrocarbons, nitrosourea **43** is decomposed with evolution of N_2 but without the yellow coloration typical of diazo compounds; this reaction gives 1,1-diphenylallene (**44**) in high yield. In the presence of diethyl fumarate, the corresponding dihydropyrazole **45** is formed upon 1,3-dipolar cycloaddition of 2,2-diphenyldiazocyclopropane (**46**) to the double bond.[7]



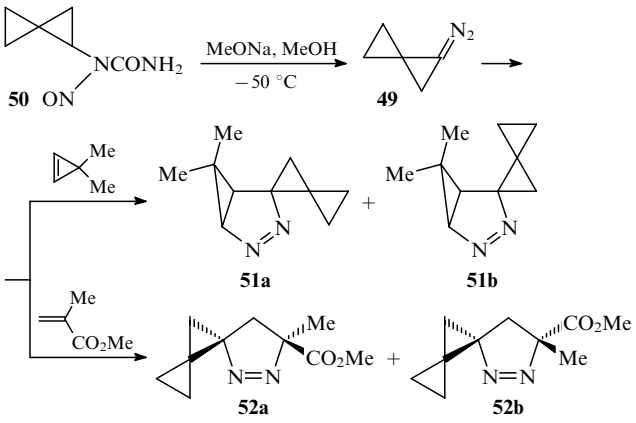
Thermal decomposition (60–82 °C) of nitrosourea **43** in heptane or in an excess of diethyl fumarate results in the same compounds **44** and **45** (yields 95% and 44%, respectively);[40] this is untypical of other *N*-alkyl-*N*-nitrosamides.

The reaction of 2,2-dimethyl- and 2,2-dichlorodiazocyclopropanes, generated *in situ* from the corresponding *N*-nitroso-*N*-cyclopropylureas **47a**,**b**, with a reactive dipolarophile, *viz*., 3,3-dimethylcyclopropene, was studied.[8] In both cases, a mixture of two isomeric dihydropyrazoles was formed in ~ 70% yield; the ratio of the *anti* and *syn* isomers was 2.2 : 1 for compound **48a** and 1 : 1.3 for compound **48b**.



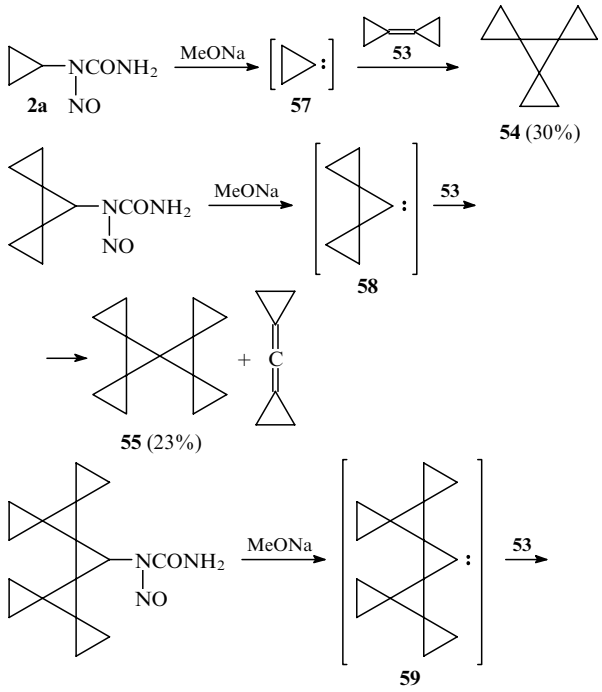
R = Me (**a**), Cl (**b**).

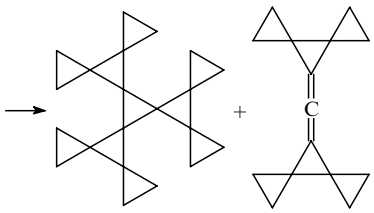
Generation of substituted diazocyclopropanes from substituted *N*-nitroso-*N*-cyclopropylureas is a promising method for the synthesis of nitrogenous heterocycles containing a polyspiran fragment. It has been shown recently[9,41,42] that diazospiropentane (**49**) generated *in situ* from *N*-nitroso-*N*-spiropentylurea (**50**) reacts with 3,3-dimethylcyclopropene or methyl methacrylate to give 4,5-dihydro-3*H*-pyrazoles **51a**,**b** or **52a**,**b** fused with the spiropentane fragment (as mixtures of isomers in the ratio ~ 1 : 1).



The yields of the 1,3-dipolar cycloaddition products **51** and **52** increase considerably with a decrease in the temperature of the reaction. For example, the yield of dihydropyrazoles **52** is ~ 20% at −20 °C and increases to 72% at −50 °C.[9] Evidently, diazospiropentane (**49**) is even less stable than diazocyclopropane (**1**).

Unlike strained cycloalkenes or alkenes with electron-withdrawing substituents, bicyclopropylidene (**53**) reacts with diazocyclopropanes generated *in situ* to give polyspirocyclopropane-containing hydrocarbons, in particular, triangulans **54**–**56**, instead of dihydropyrazoles ([3 + 2]-cycloaddition products).[13–16,43] Evidently, diazocyclopropanes cannot react with bicyclopropylidene (**53**) according to 1,3-dipolar cycloaddition due to a specific nature of the double bond in this compound, which manifests itself, in particular, in a noticeable shortening of this bond;[44] these compounds undergo dedinitrogenation to give the corresponding cyclopropylidenes **57**–**59**, which are mostly isomerised into allenes. The reaction of cyclopropylidenes **57**–**59** with the original bicyclopropylidene (**53**) occurs as [1 + 2]-cycloaddition to give triangulans **54**–**56**.





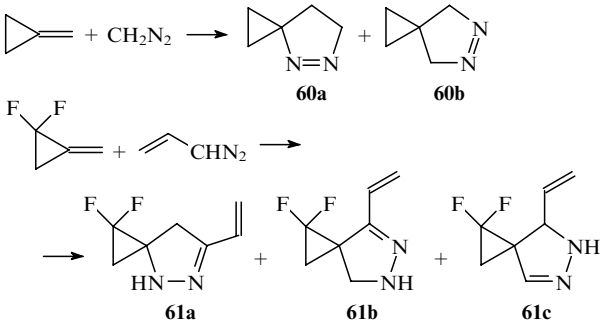
56 (14%) (27%)

Diazocyclopropane and cyclopropylidene do not react with alkynes, such as PhC≡CH, $MeO_2CC{\equiv}CCO_2Me$ and $HC{\equiv}CC(Me){=}CH_2$.[29,37]

3. Cycloaddition to methylidenecyclopropane and its derivatives

Syntheses of spirocyclopropane-containing azaheterocycles make use of cycloaddition of nitrogen-containing 1,3-dipoles to methylidenecyclopropane and its derivatives with substituents both in the cyclopropane ring and at the double bond.

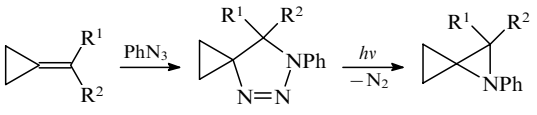
For example, the reaction of diazomethane with methylidenecyclopropane at 3 °C for two weeks results in a mixture of two regioisomeric dihydropyrazoles **60a**,**b** (overall yield 90%, ratio 55 : 45).[45] The addition of diazomethane and 3-diazoprop-1-ene to 2,2-difluoromethylidenecyclopropane also occurs non-selectively; a mixture of three regioisomeric 4,5-dihydro-1*H*-pyrazoles **61a**–**c** (~ 3.7 : 1 : 1) is formed in the latter case.[46]



60a **60b**

61a **61b** **61c**

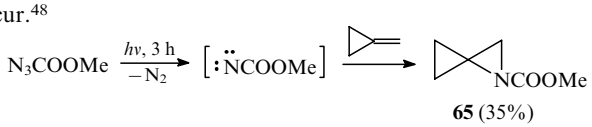
Phenyl azide slowly adds to methylidene- (**62a**), benzylidene- (**62b**) or (diphenylmethylidene)cyclopropane (**62c**) to give the thermally stable spiro[dihydrotriazolecyclopropanes] **63a**–**c**. It is assumed[47,48] that the reaction occurs through a concerted mechanism with the addition of the terminal nitrogen atom of phenyl azide to the tetrasubstituted carbon atom of the cyclopropane ring. Photolytic dedinitrogenation of 4,5-dihydro-1*H*-1,2,3-triazoles **63a**–**c** (Pyrex, high-pressure mercury lamp) affords new azaheterocycles **64a**–**c**, which are derivatives of 1-phenylazaspiropentane (yields 90%, 99% and 90%, respectively).[47,48]



62a–**c** **63a**–**c** **64a**–**c**

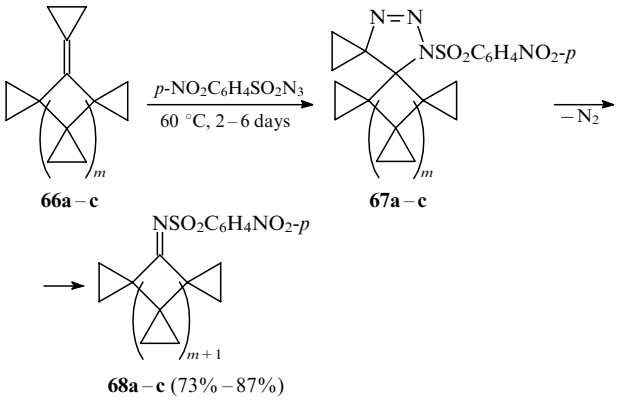
Compound	R^1	R^2	T /°C	t /days	Yield of **63** (%)
a	H	H	20	60	70–80
			50	1	70–80
b	H	Ph	100	1–2	38
c	Ph	Ph	100	1–2	51

Apparently, the azaspiropentane fragment can also be formed upon direct addition of nitrenes to the double bond of methylidenecyclopropanes. At least, this is how the photochemical reaction of methyl azidoformate with methylidenecyclopropane to give 1-(methoxycarbonyl)azaspiropentane (**65**) is believed to occur.[48]



65 (35%)

Unlike phenyl azide, cyanogen azide and *p*-nitrobenzenesulfonyl azide do not give any stable dihydrotriazoles in reactions with cyclopropylidenecycloalkanes: they readily undergo dedinitrogenation. The addition of cyanogen azide to cyclopropylidenecyclohexane (~20 °C, 7 days) probably occurs non-regioselectively, since hydrolysis of the reaction mixture gives spiro[2.6]nonan-4-one and spiro[3.5]-nonan-1-one (yields 46% and 30%, respectively).[49] The reactions of *p*-nitrobenzenesulfonyl azide with cyclopropylidenepolyspiroalkanes **66** occur regioselectively *via* dihydrotriazoles **67** which readily undergo dedinitrogenation with simultaneous ring expansion to give imides **68**.[50–52]



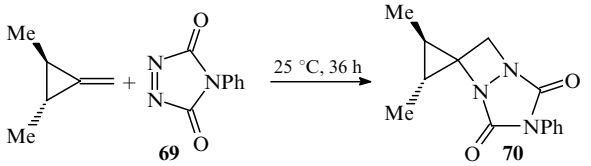
66a–**c** **67a**–**c**

68a–**c** (73%–87%)

m = 0 (**a**), 1 (**b**), 2 (**c**).

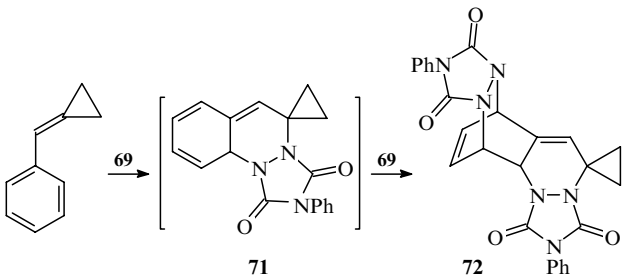
Similarly, diazocyclopropane (**1**) probably adds to the imide **68a** *via* an unstable dihydrotriazole, which is transformed into the imide **68b**.[52]

Diverse heterocyclic compounds containing a spirocyclopropane fragment are obtained by treatment of methylidenecyclopropanes with dihydrotriazoledione **69**; the reaction pathway depends considerably on the nature of the substituents at the cyclopropane ring. In particular, [2 + 2]-cycloaddition of *trans*-2,3-dimethyl-1-methylidenecyclopropane to dihydrotriazoledione **69** at room temperature to give the adduct **70** occurs slowly.[53]



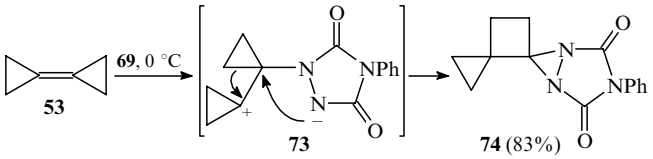
69 **70**

With benzylidenecyclopropane, dihydrotriazoledione **69** reacts much faster. However, in this case compound **71** formed in the first step, *i.e.*, a product of formal [4 + 2]-cycloaddition involving the benzene ring of the substituent, contains a cyclohexadiene fragment and readily adds the second molecule of dihydrotriazoledione **69** to give the bisadduct **72**.[53]

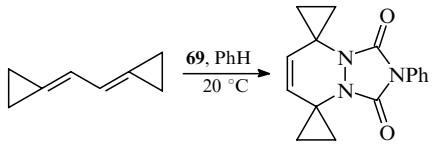


71 **72**

The cycloaddition of dihydrotriazoledione **69** to bicyclopropylidene (**53**) occurs in an unexpected way; simple closure of the four-membered heterocycle in the resulting zwitter-ion **73** does not occur in this case. After an alkyl shift, the carbon atom in the cyclopropane fragment that was involved in the formation of the first C—N bond is attacked by the nucleophilic nitrogen atom. Diaziridine **74** is the only reaction product that was isolated.[54]

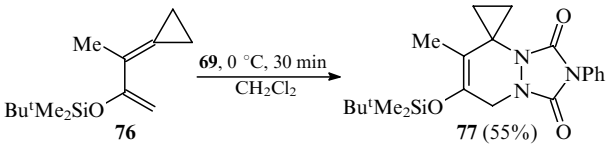


Unlike the methylidenecyclopropanes considered above, conjugated alkenylidenecyclopropanes react with dihydrotriazoledione **69** as true dienes to give [4 + 2]-cycloadducts. For example, the reaction with bis(cyclopropylidene)ethane occurs almost instantaneously and gives high yield of the cycloadduct **75** where both cyclopropane fragments are retained in the molecule.[55]



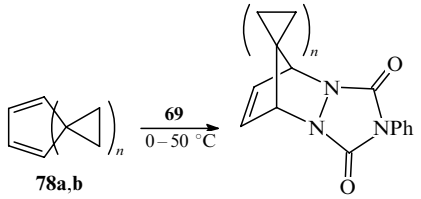
75 (90%)

1-Methyl-2-silyloxyprop-2-enylidenecyclopropane (**76**) can act as a 1,3-diene in the reaction with the dihydrotriazoledione **69**, giving a heterocyclic compound **77** in 55% yield.[56]



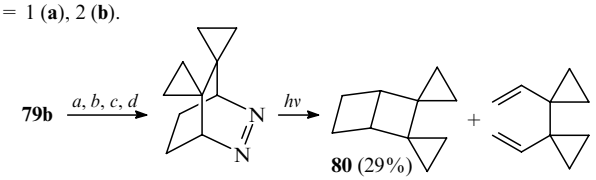
76 **77** (55%)

Synthesis of polycyclic heterocycles with a spirocyclopropane fragment in the molecule is carried out using the reaction of the dihydrotriazoledione **69** with cyclic dienes **78a**,**b** or with their derivatives. The [4 + 2]-cycloadducts **79a**,**b** are formed in high yields under mild conditions.[57–61] Subsequent transformations of the heterocyclic adduct **79b** afforded highly strained dispiro[2.0.2.4]decane **80**.[59, 60]



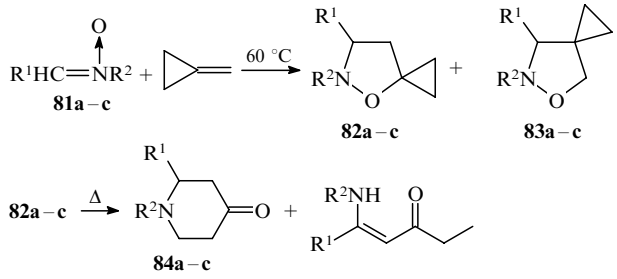
78a,**b** **79a**,**b** (50%–60%)

n = 1 (**a**), 2 (**b**).



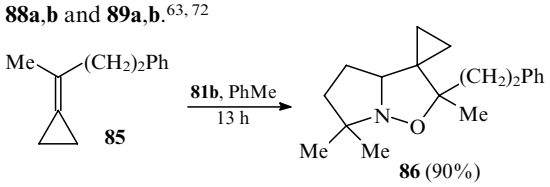
(*a*) H_2, Pd/C, MeOH; (*b*) Bu^{t}OK, DMSO, H_2O; (*c*) $CuCl_2$, H_2O, EtOH; (*d*) KOH.

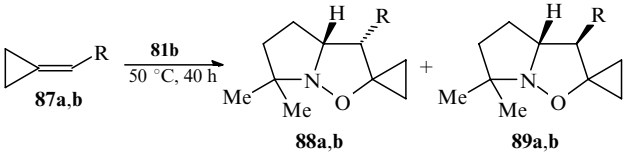
Both linear and cyclic nitrones can act as 1,3-dipolar compounds in reactions with methylidenecyclopropanes.[62–66] The reaction of methylidenecyclopropane with nitrones **81a**–**c** occurs as [3 + 2]-cycloaddition with retention of the cyclopropane fragment; in this case, mixtures of regioisomers **82a**–**c** and **83a**–**c** are formed in the ratio (2–9) : 1 in 69%–86% yield,[62] which are difficult to separate. Spiro[cyclopropane-1,4′-isoxazolidines] **83a**–**c** are more thermally stable than their regioisomers **82a**–**c**. The latter undergo rearrangement (400 °C, 0.2 mm Hg) to derivatives of 4-piperidones **84a**–**c** and enaminones, which allows one to isolate the isoxazolidines **83a**–**c** from the reaction mixture.



R^1 = Ph, R^2 = Me (**a**); R^1–R^2 = $CH_2CH_2C(Me)_2$ (**b**), $(CH_2)_4$ (**c**).

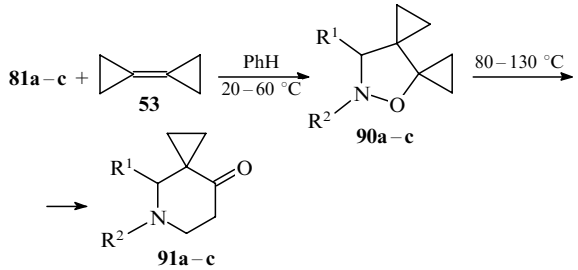
The use of alkyl- and aryl-substituted methylidenecyclopropanes and derivatives of cyclopropylideneacetic acid in these transformations makes it possible to obtain various fused spiro[cyclopropaneisoxazolidines] which are of interest as starting compounds in the syntheses of isoquinoline, quinolizidine, indolizidine and some other heterocyclic structures.[63–72] Electron-donating substituents at the double bond favour the formation of spiro[cyclopropane-1,4′-isoxazolidines], whereas the 1,5′-regioisomers are formed in the presence of electron-withdrawing substituents. For example, the addition of cyclic nitrone **81b** to substituted methylidenecyclopropane **85** results exclusively in isoxazolidine **86**, whereas the reaction of the same nitrone **81b** with the methyl ester **87a** or cyclopropylideneacetonitrile (**87b**) affords stereoisomeric spiro[cyclopropane-1,5′-isoxazolidines] **88a**,**b** and **89a**,**b**.[63, 72]





Compound	R	Yield of **88** (%)	Yield of **89** (%)
a	CO_2Me	21	42
b	CN	70	17

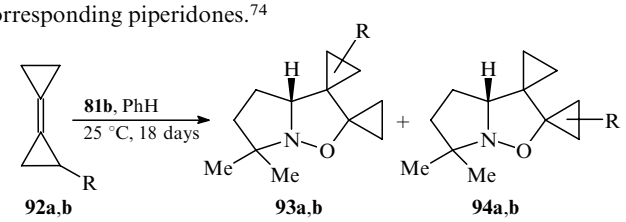
The nitrones **81a**–**c** react with bicyclopropylidene (**53**) at 20–60 °C to give high yields of isoxazolidines **90a**–**c**, in which both spirocyclopropane fragments are retained. However, heating of the reaction mixture in aromatic hydrocarbons as solvents at 80–130 °C results in isomerisation of the isoxazolidines obtained to the corresponding spiro[cyclopropane-1,3′-piperidin]-4-ones **91a**–**c**; only the cyclopropane ring adjacent to the labile N—O bond is involved in the rearrangement.[73, 74]



Compound	R^1	R^2	Yield of **90** (%)	Yield of **91** (%)
a	Ph	Me	93	63
b	$(CH_2)_2CMe_2$		80	80
c	$(CH_2)_4$		60	65

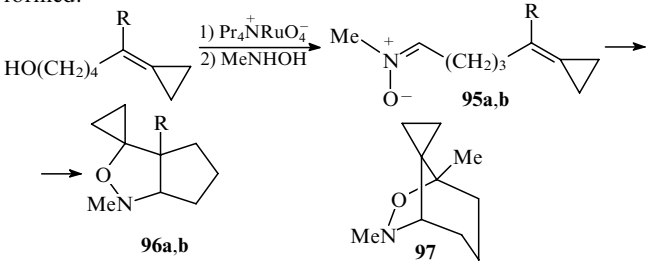
Isomerisation of isoxazolidines **90a–c** to piperidones **91a–c** probably occurs by homolytic cleavage of the N–O bond in the heterocycle followed by fast rearrangement of the radicals and ring closure.

Only reactions with nitrones with symmetrically substituted bicyclopropylidenes, where isoxazolidines incorporating a spirocyclopropane fragment are formed selectively, are of preparative value. Otherwise, a complex mixture of isomeric compounds is formed, as is the case, *e.g.*, of the cycloaddition of the nitrone **81b** to monosubstituted bicyclopropylidenes **92a,b**. Mixtures of isomers **93** and **94** (overall yield 65%–85%) could not be separated chromatographically or after their thermal rearrangement to the corresponding piperidones.[74]



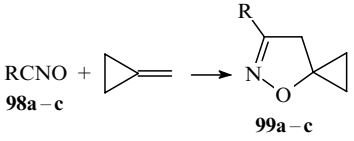
R = CO_2Me (**a**), SPh (**b**).

The cycloaddition of nitrones to the double bond of the methylidenecyclopropane fragment can occur in an intramolecular manner as well. The reaction with nitrone **95a** containing a trisubstituted double bond (25 °C, 24 h, yield 87%) occurs regioselectively to give the cycloadduct **96a**. The presence of an additional methyl group in the nitrone **95b** decreases the polarity of the double bond and the reactivity of the nitrone. At 80 °C (2 h), a mixture of two isomers **96b** and **97** in the ratio ~ 2 : 1 is formed.[75]

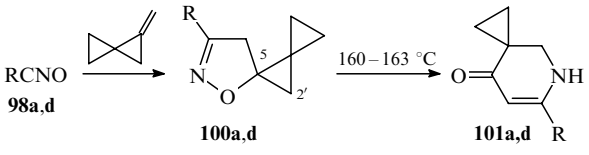


R = H (**a**), Me (**b**).

Unsaturated analogues of isoxazolidines, *viz.*, spiro[cyclopropanedihydroisoxazoles], can be obtained by 1,3-dipolar cycloaddition of nitrile oxides to methylidenecyclopropanes. The reaction of nitrile oxides **98a–c** with non-substituted methylidenecyclopropane occurs regioselectively to give spiro[cyclopropane-1,5′-dihydroisoxazoles] **99a–c**.[76] Only in the case of acetonitrile oxide (**98c**) was the formation of a different regioisomer (~ 3%) observed.



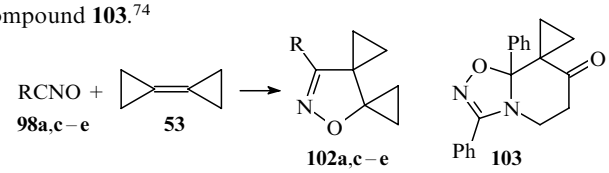
R = Ph (**a**, 65%), Bn (**b**, 35%), Me (**c**, 60%).



R = Ph (**100a**, 64%), 2,4,6-$Me_3C_6H_2$ (**100d**, 100%).

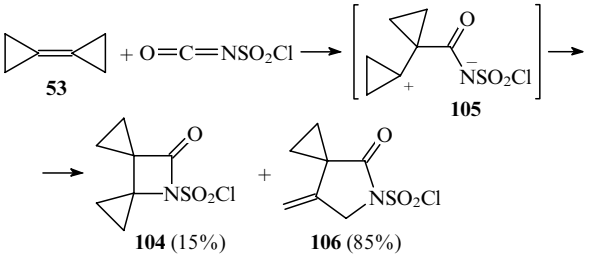
Spiro[cyclopropane-1,5′-dihydroisoxazoles] substituted in the cyclopropane ring are obtained in a similar way from nitrile oxides **98a–d** and substituted methylidenecyclopropanes.[77] Reactions of methylidenespiropentane with nitrile oxides **98a** (20 °C, 16 h) and **98d** (60 °C, 4 h) in benzene results in dihydroisoxazoles **100a,d**, thermal rearrangement of which to ketones **101a,d** occurs regioselectively, exclusively with opening of the inner cyclopropane ring at the C(5)–C(2′) bond.[78]

The cycloaddition of nitrile oxides **98a–c** to bicyclopropylidene (**53**) occurs less efficiently than to methylidenecyclopropane.[73,74] Because of this, partial dimerisation of nitrile oxides to furoxans occurs. The yields of dispirano dihydroisoxazoles **102** can be increased by performing slow generation of nitrile oxide *in situ* (*e.g.*, in the synthesis of nitrile oxide **98a** by treatment of benzohydroxymoyl chloride with $NaHCO_3$) or by using spatially hindered nitrile oxides, *e.g.*, **98d**. However, the presence of extremely bulky substituents in the nitrile oxide molecule, *e.g.*, in compound **98e**, again decreases the yield of the target product. It should be noted that in the case of the nitrile oxide **98a** the resulting dihydroisoxazole **102a** partially reacts with it to give compound **103**.[74]

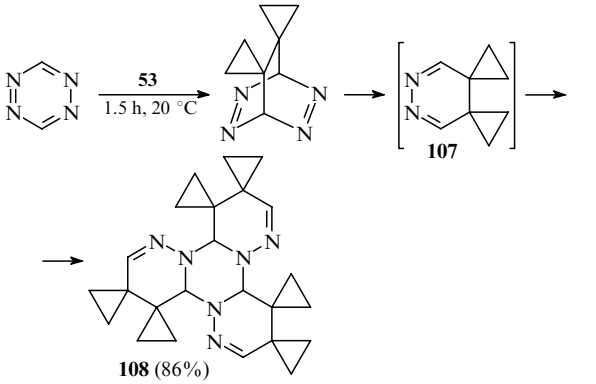


Compound	R	*T* /°C	*t* /days	Yield of **102** (%)
a	Ph	66	7	40
c	Me	20	7	10
d	2,4,6-$Me_3C_6H_2$	110	2	67
e	Ph_3C	110	7	17

Bicyclopropylidene (**53**) undergoes [2 + 2]-cycloaddition to chlorosulfonyl isocyanate to give the β-lactam **104**, but this is not the main product. Evidently, the reaction can occur as a two-step process to give the 1,4-zwitter ion **105**. The main reaction product is methylidene-γ-lactam **106** formed by opening of one cyclopropane ring in the intermediate **105**.[54]

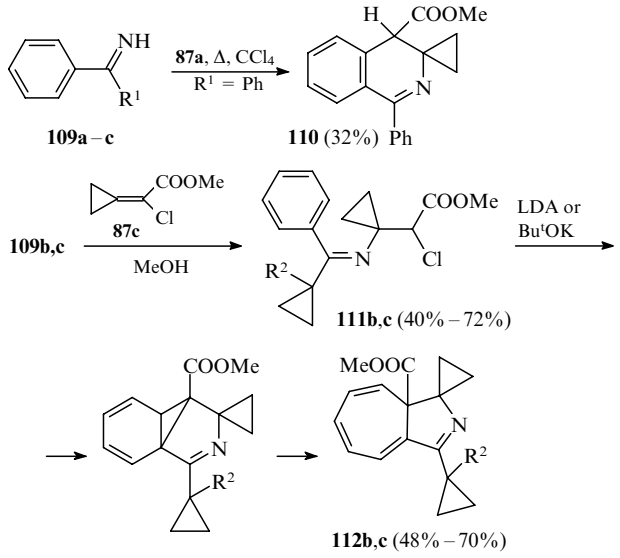


Bicyclopropylidene (**53**) readily undergoes [4 + 2]-cycloaddition to heterodienes such as 1,2,4,5-tetrazine and its derivatives. The primary cycloaddition product readily undergoes dedinitrogenation, while the resulting 8,9-diazadispiro[2.0.2.4]deca-7,9-diene (**107**) undergoes trimerisation to the fused heterocyclic



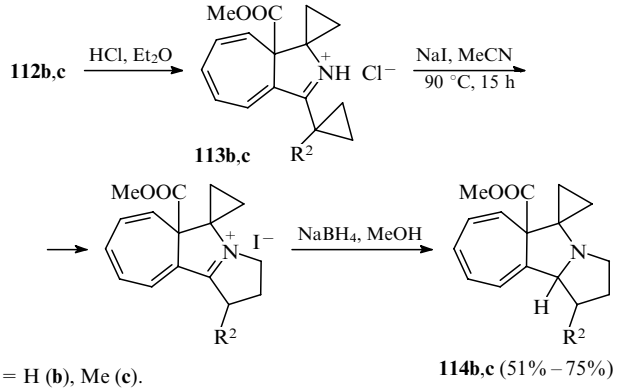
compound **108** with six spiro-fused cyclopropane fragments in the molecule (a mixture of two stereoisomers).[79] Attempts to trap the heterodiene **107** failed.

Synthesis of fused azaheterocycles with a spirocyclopropane fragment can be carried out by the reactions of cyclopropylideneacetates with imines. For example, the ester **87a** undergoes formal [4 + 2]-cycloaddition to imine **109a** to give spiro[cyclopropane-1,3′-dihydroisoquinoline] **110**. The reaction of chloro-substituted methylidenecyclopropane **87c** with imines **109b,c** in methanol gives the Michael adducts **111b,c** in almost quantitative yields. These adducts are thermally stable, but in the presence of lithium diisopropylamide or potassium *tert*-butoxide, carbenes are generated; the latter are transformed to compounds **112b,c** with a dihydro-2-azaazulene skeleton due to intramolecular cycloaddition to the benzene ring followed by isomerisation.[80,81] This bicyclic system has been studied much less than the 1-azaazulene derivatives.



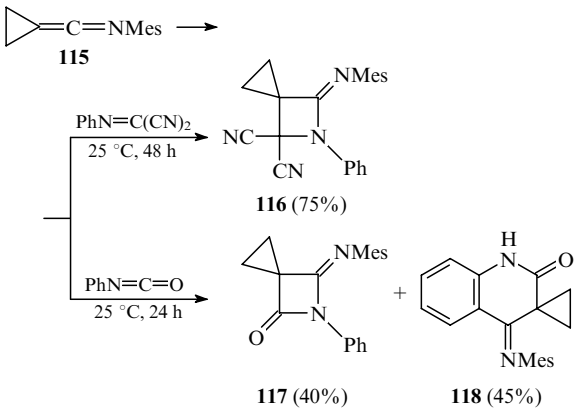
R^1 = Ph (**a**),  [R^2 = H (**b**), Me (**c**)].

The cyclopropyl substituent at position 1 of azaazulenes **112b,c** can be opened on treatment with electrophilic reagents, which enables intramolecular cyclisation of the salts **113b,c** to give derivatives **114b,c**.[81]



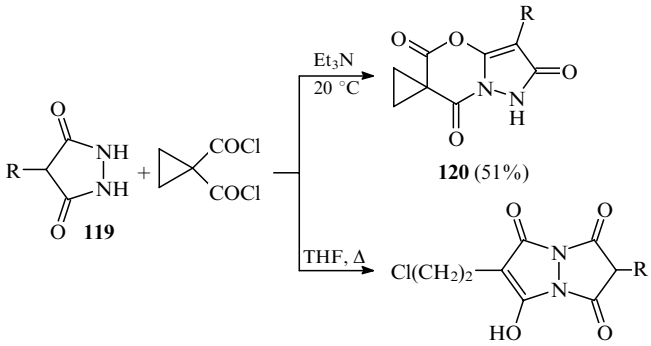
R^2 = H (**b**), Me (**c**).

Unlike 1-alkenylidenecyclopropanes which react with dihydrotriazoledione **69** or with chlorosulfonyl isocyanate with opening of the cyclopropane ring,[82] *N*-mesitylcyclopropylideneazomethine (**115**) reacts with *N*-(dicyanomethylidene)aniline or phenyl isocyanate to give spiro[azetidinecyclopropanes] **116** and **117**. In the latter case, a considerable amount of the cycloadduct **118** is formed.[83]



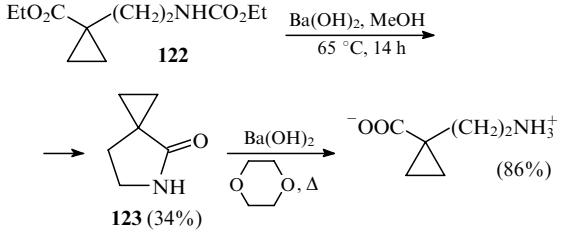
4. Other methods for the synthesis of azaheterocycles incorporating a spirocyclopropane fragment

Heterocyclic compounds incorporating a spirocyclopropane fragment in the molecule can be obtained by typical cyclocondensations involving cyclopropane derivatives. However, certain conditions have to be observed in order to keep the cyclopropane fragment unchanged in the course of the reaction. For example, the reaction of pyrazolidine-3,5-dione **119** with 1,1-cyclopropanedicarbonyl dichloride in the presence of an equimolar amount of triethylamine results in compound **120** containing a three-carbon ring. On the other hand, this reaction carried out with heating in THF in the absence of a base is accompanied by the three-carbon ring opening and results in the chloroethyl derivative **121**.[84]

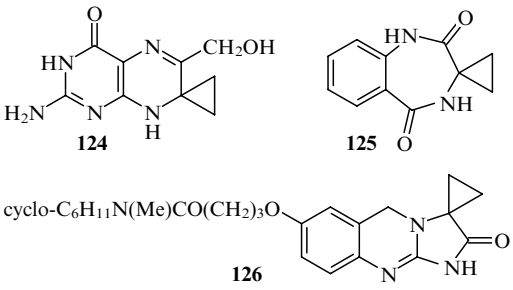


R = cyclo-C_6H_{11}.

Intramolecular cyclisation of 1,1-disubstituted cyclopropane **122** on treatment with $Ba(OH)_2$ results in lactam **123** containing a spirocyclopropane fragment. The latter undergoes heterocycle opening to give 1-(2-aminoethyl)cyclopropanecarboxylic acid on refluxing in aqueous dioxane in the presence of $Ba(OH)_2$.[85]



The cyclocondensation method with the use of 1-aminocyclopropanecarboxylic acid or its derivatives as structural blocks was used for a directed synthesis of a series of spiro compounds, *e.g.* **124**–**126**, which may be interesting as potential medicines.[86–88] For example, benzodiazepine **125** was obtained in 48% yield by cyclocondensation of methyl 1-aminocyclopropanecarboxylate with *o*-nitrobenzaldehyde.[88]

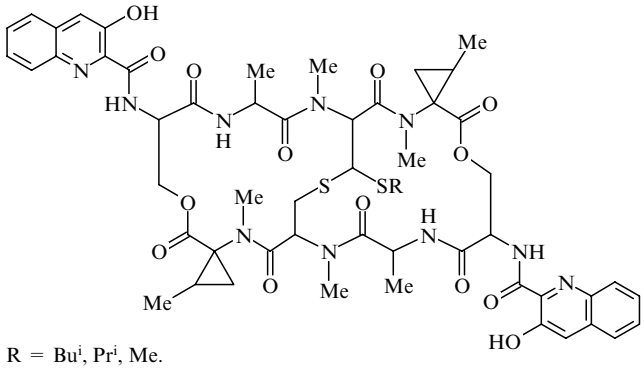


124 **125**

cyclo-$C_6H_{11}N(Me)CO(CH_2)_3O$

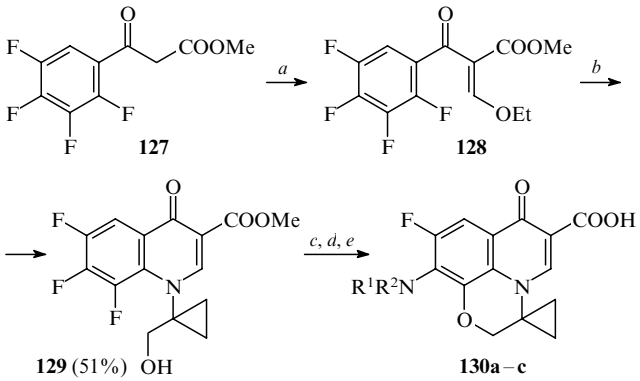
126

The 1-methylamino-2-methylcyclopropanecarboxylic acid moiety spiro-fused with the macrocycle is a constituent of cyclic octadepsipeptides, which are bifunctional antibiotics of the quinomycin series that can be intercalated into DNA.[89,90]

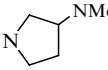


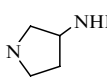
R = Bu^i, Pr^i, Me.

The incorporation of the spirocyclopropane fragment in the benzoxazine heterocycle of ofloxacin (a well-known antibacterial compound belonging to the fluoroquinolone series) was carried out according to the following scheme: condensation of β-oxoester **127** with triethyl orthoformate to give unsaturated ester **128**; formation of the 1,4-oxazine ring containing a spirocyclopropane fragment by treating compound **128** with 1-(hydroxymethyl)cyclopropylamine hydrochloride followed by heating of the reaction product **129** with anhydrous potassium fluoride in DMSO. Acid hydrolysis of the ester group followed by selective replacement of a fluorine atom by cyclic amines afforded the target compounds **130**.[91]



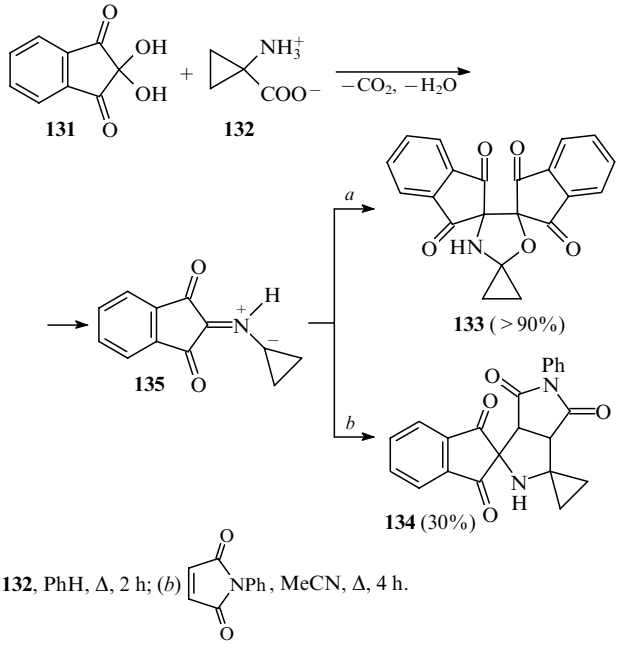
127 **128** **129** (51%) **130a–c**

NR^1R^2 =  (**130a**, 81%),  (**130b**, 56%),

 (**130c**, 86%); (*a*) $HC(OEt)_3$, $(AcO)_2O$, Δ, 2.5 h;

(*b*) , Bu^tOK, 45 °C; (*c*) KF, DMSO; (*d*) HCl; (*e*) HNR^1R^2.

In the reaction of ninhydrin (indan-1,2,3-trione hydrate) (**131**) with 1-aminocyclopropanecarboxylic acid (**132**) (molar ratio 1 : 2) in boiling benzene, decarboxylation of the acid **132** occurs to give spiro[cyclopropane-1,2′-oxazolidine] **133**. The reaction of equimolar amounts of the acid **132**, ninhydrin (**131**) and *N*-phenylmaleimide in acetonitrile under reflux results in spiro[cyclopropane-1,5′-pyrrolidine] **134**.[92] It is assumed[92] that these reactions involve the intermediate 1,3-dipole **135**.

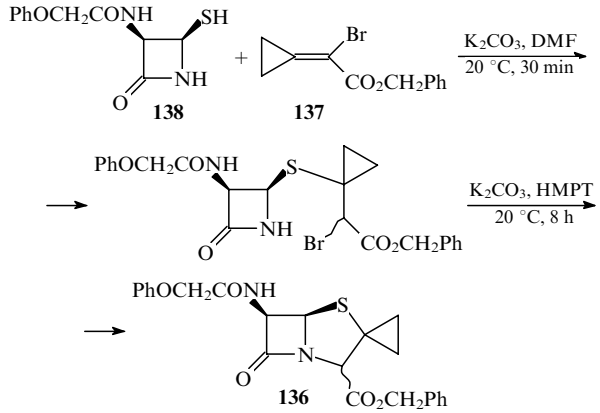


131 **132** **135** **133** (>90%) **134** (30%)

(*a*) **132**, PhH, Δ, 2 h; (*b*) , MeCN, Δ, 4 h.

In certain cases, the corresponding cyclopropane derivatives were deliberately obtained for the directed syntheses of biologically active compounds containing a spirocyclopropane fragment. For example, (1-benzyloxycarbonyl-1-bromomethylidene)cyclopropane (**137**) was obtained for the synthesis of the cyclopropane analogue of norpenicillin **136**.[93] The reaction of compound **137** with 4-mercaptoazetidin-2-one **138** in the presence of K_2CO_3 results in epimeric 2-bisnorpenicillanates **136** (ratio ~ 4 : 1, yield ~ 25%).[94]

Although the yields of the adducts are low, this method is considered to be convenient[94] because it does not give rise to side transformations of the cyclopropane ring.

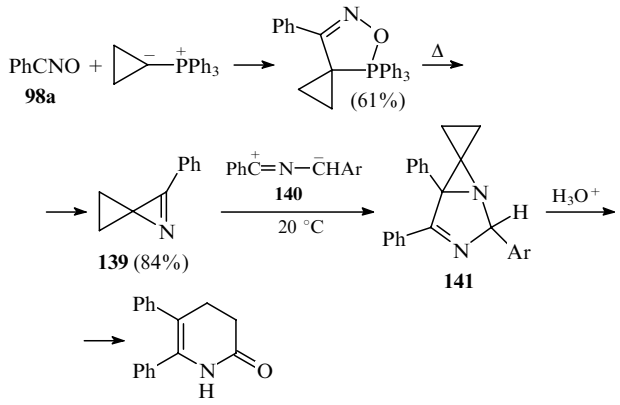


138 **137** **136**

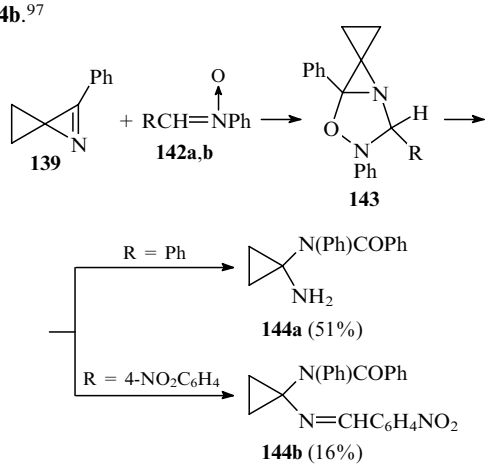
HMPT is hexamethylphosphorous triamide.

It is well known[95] that 1-azirines are widely used in the synthesis of heterocyclic systems containing a nitrogen atom in the ring. Highly strained 2-phenyl-1-azaspiropent-1-ene (**139**) is a useful starting compound for the synthesis of azaheterocycles containing a spirocyclopropane fragment. This compound is obtained by pyrolysis of the addition product of benzonitrile oxide **98a** to cyclopropylidenephosphorane.[96] The reaction of the spirane **139** with benzonitrile-4-nitrobenzylide (**140**) generated *in situ* from *N*-(4-nitrobenzyl)benzimidoyl chloride occurs regioselectively to give the spiro{cyclopropane-1,6′-1,3-diazabicyclo[3.1.0]hex-3-ene} derivative **141**, the structure of which was

established from spectroscopic data and by its hydrolysis into 3,4-dihydro-5,6-diphenyl-2-pyridone.[97]



It is well known[98] that nitrones undergo 1,3-dipolar cycloaddition to compounds containing C=N bonds. Aziridine **139** also reacts with nitrones **142a**,**b**; however, the resulting cycloadducts **143a**,**b** are unstable under the reaction conditions (benzene, Δ) and are transformed into cyclopropylamides **144a** or **144b**.[97]

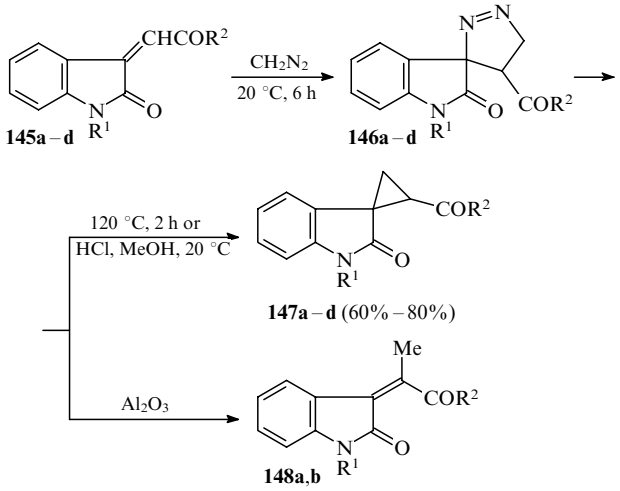


III. Formation of a cyclopropane ring spiro-fused with a heterocycle

Cycloaddition of various reagents to methylidene derivatives of the corresponding heterocycles is one of the general ways to form a spiro-fused cyclopropane ring in heterocyclic compounds. Cyclopropanation of the double bond, which is usually activated by electron-withdrawing substituents, is mostly carried out by reactions with diazo compounds and ylides. In some cases, an opposite approach is used, where the required azaheterocycle contains a diazo group capable of reacting with an unsaturated substrate. In any case, the originally formed dihydropyrazoles, *i.e.*, 1,3-dipolar cycloadducts, are then transformed into cyclopropane derivatives upon elimination of a nitrogen molecule; depending on the nature of the substituents, this either occurs spontaneously at room temperature or requires elevated temperatures. In a number of cases, the choice of the target heterocyclic compounds, *e.g.*, indolinones or cephalosporins, is dictated by the search for new biologically active compounds.[99–104]

1. Construction of a cyclopropane ring based on the formation and dedinitrogenation of dihydropyrazoles

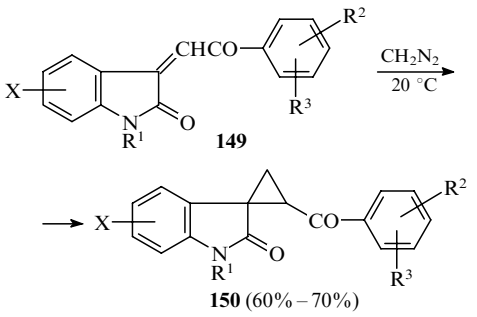
The addition of diazomethane to methylideneindolin-2-one derivatives **145a–d** results in spiro[indoline-3,3′-dihydropyrazoles] **146a–d** with high regioselectivity.[102,103] Their thermolysis in boiling dioxane or treatment with HCl in MeOH at room temperature involves elimination of nitrogen to give spiro[cyclopropane-1,3′-indolin]-2-ones **147a–d**. Chromatography of dihydropyrazoles **146a,b** on Al_2O_3 is accompanied by their transformation to conjugated enones **148a**,**b** (yields 57% and 74%, respectively) rather than to compounds **147a**,**b**.[103]



R¹ = H, R² = Ph (**146a**, 92%), Me (**146b**, 90%), OEt (**146c**, 62%);

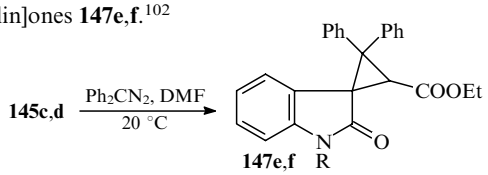
R¹ = CH_2N⟨O⟩, R² = OEt (**146d**, 74%).

Unlike methylideneindolin-2-ones **145a–d**, fluoro-substituted 3-(aroylmethylidene)indolin-2-ones **149** react with an ethereal solution of CH_2N_2 at 20 °C to give directly spiro[cyclopropaneindolin]ones **150**.[104]



X = H, 5-F, 6-F; R¹ = H, COMe, CH_2N⟨O⟩; R² = 2-F, 4-F;
R³ = H, 2-Me, 3-Me, 5-Me, 3-Cl, 3-F.

As in the example considered above, 1,3-dipolar cycloaddition of diphenyldiazomethane to methylideneindolin-2-ones **145c**,**d** in DMF at 20 °C involves nitrogen elimination from the dihydropyrazoles formed originally to give spiro[cyclopropaneindolin]ones **147e**,**f**.[102]

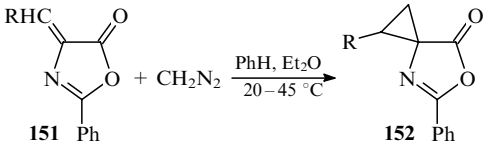


R = H (**147e**, 53%), CH_2N⟨O⟩ (**147f**, 76%).

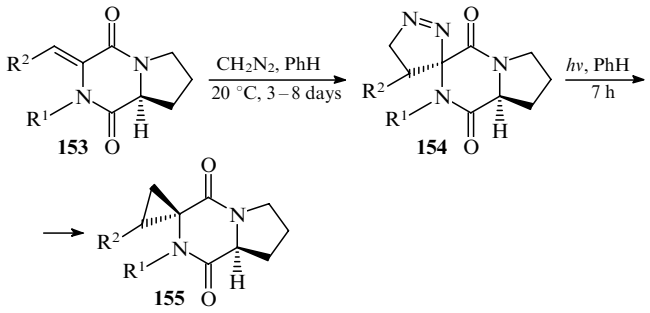
A similar approach to the construction of a spiro-fused cyclopropane fragment is also applicable to other heterocyclic systems; depending on the nature of the azaheterocycle and the substituents in the ring, the reaction of diazo compounds with the exocyclic double bond can involve both the formation of the intermediate dihydropyrazoles and their spontaneous dedinitrogenation.

The methods (including enantioselective ones) for the synthesis of 1-aminocyclopropanecarboxylic acid derivatives were

developed using 1,3-dipolar cycloaddition of diazomethane to 4-alkylidene(arylidene)-5(4*H*)oxazolones,[105–108] thiazolones[109] and piperazinediones.[110–112] The reaction with oxazolones **151** occurs at 20–45 °C with nitrogen elimination and formation of spiro[cyclopropaneoxazolines] **152**. On the other hand, the reaction of CH_2N_2 with piperazinediones **153a**,**b** gives spiro-fused azaheterocycles **154** in high yields and with high diastereoselectivity (> 95%). Photolysis of the latter results in azaheterocycles **155** in > 90% yields. Acid splitting of the six-membered heterocycle in the resulting compounds on treatment with 6M HCl in AcOH at 100 °C results in 1-aminocyclopropanecarboxylic acid derivatives.[110,111]

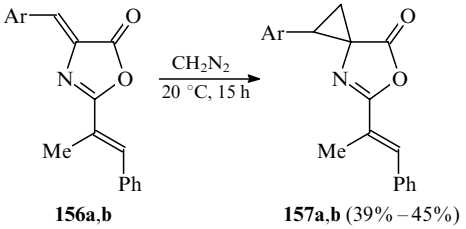


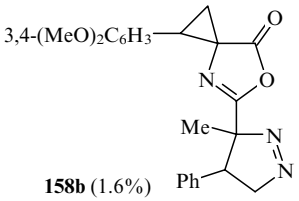
R = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$ (45%–60%), Me (25%), Cl (75%), Br.



R^1 = Ac, R^2 = Ph (**a**); R^1 = Bu^tOCO (Boc), R^2 = Et (**b**).

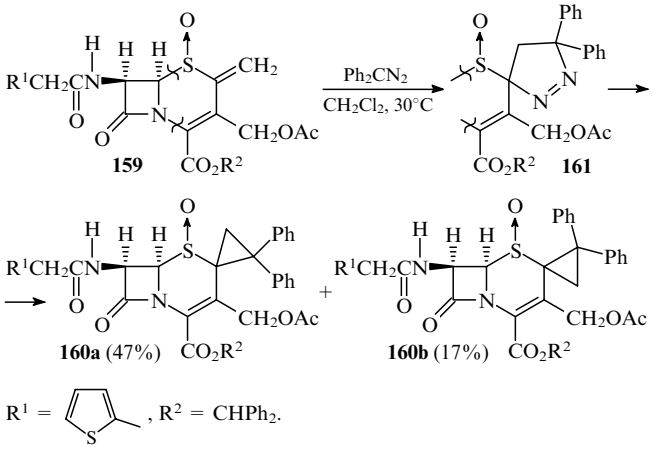
If the oxazolone ring contains both substituted methylidene and vinyl fragments (*cf.* compounds **156a**,**b**), the addition of diazomethane occurs mainly to the methylidene fragment and the corresponding cyclopropane derivatives **157a**,**b** are formed as the reaction products even at room temperature.[113] The addition of diazomethane to the vinyl group occurs only in compound **156b** and only to a minor extent to give the dihydropyrazole **158b**, which is stable under these conditions.





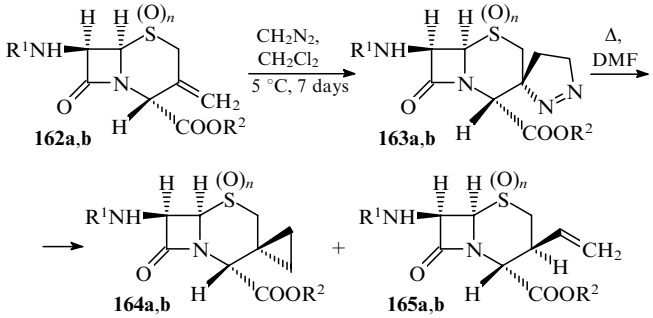
Ar = Ph (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**).

The formation of a cyclopropane fragment spiro-fused with the heterocyclic system of cephalosporins is documented.[114] For example, diphenyldiazomethane adds to the exocyclic double bond of 2-methylidenecephemes **159** (30 °C, 30 min) to give two isomeric spiro derivatives **160a** and **160b** in the ratio ~ 3 : 1. It is believed[114] that the reaction occurs through regioselective formation of the dihydropyrazole **161**.



R^1 = , R^2 = $CHPh_2$.

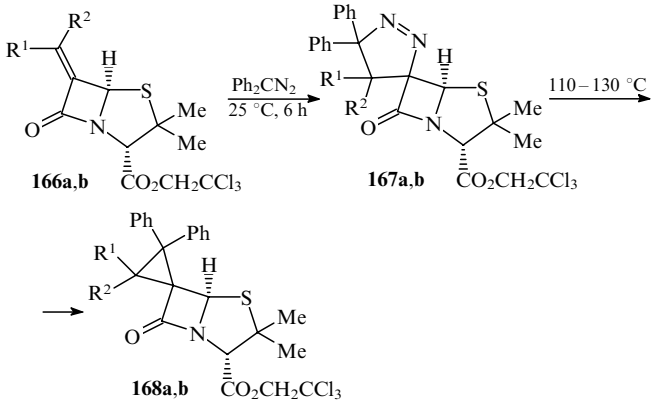
1,3-Dipolar cycloaddition of diazomethane to 3-methylidenecephames **162** occurs at 5 °C in 1 week and only with a great excess of diazomethane.[115] 1,3-Dipolar cycloaddition products **163** containing a spiro-fused dihydropyrazole fragment is formed in the first stage.



n = 0 (**a**), 1 (**b**); R^1 = $PhOCH_2CO$; R^2 = 4-$NO_2C_6H_4CH_2$.

Subsequent thermolysis of the resulting 1-dihydropyrazoles **163a**,**b** occurs non-selectively and results in both products with a cyclopropane fragment, *i.e.*, spiro[cephame-1,3′-cyclopropanes] **164a**,**b** (yields 60% and 64%, respectively), and their isomers, *i.e.*, 3-vinylcephames **165a**,**b** (20% and 15% yields, respectively).[115]

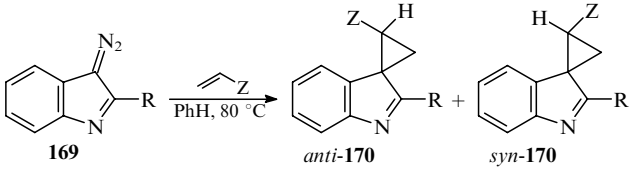
Pure *E*- and *Z*-isomers of 2,2,2-trichloroethyl penicillanates **166** containing an exocyclic double bond react with diphenyldiazomethane to give stable 4,5-dihydro-3*H*-pyrazoles **167a** or **167b**, pyrolysis of which occurs stereospecifically and results in penicillanates **168** with a spirocyclopropane fragment.[116]



Compound	R^1	R^2	Yield of **167** (%)	Yield of **168** (%)
a	CO_2Bn	H	72	89
b	H	CO_2Bn	87	15

The cyclopropane fragment spiro-fused with a heterocycle also results from the addition of the corresponding diazo hetero-

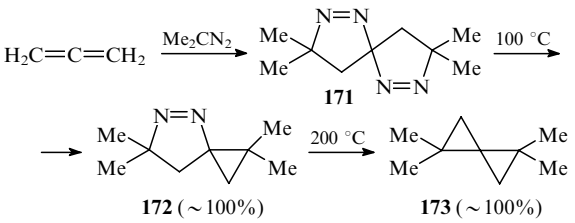
cycles to activated alkenes followed by dedinitrogenation of the resulting dihydropyrazole. For example, the reaction of 3-diazoindoles **169** with methyl acrylate or acrylonitrile in boiling benzene results in nitrogen elimination to give substituted spiro[cyclopropane-1,3′-indoles] **170** with the preferential formation of *anti*-isomers.[117] It should be noted that diazo compounds **169** are rather stable under the same conditions in the absence of unsaturated substrates. It is therefore assumed that their reactions with methyl acrylate and acrylonitrile occur as 1,3-dipolar cycloaddition; the intermediate dihydropyrazoles undergo spontaneous dedinitrogenation.



169 *anti*-**170** *syn*-**170**

R	Z	Yield of *anti*-**170** (%)	Yield of *syn*-**170** (%)
Ph	COOMe	21	11
Ph	CN	36	17
2-Pyridyl	COOMe	43	5
2-Pyridyl	CN	26	3

Exhaustive 1,3-dipolar cycloaddition of aliphatic diazo compound to allenes followed by partial dedinitrogenation of the resulting spiro-fused bis(dihydropyrazoles) makes it possible to form fragments of an azaheterocycle and a spirocyclopropane simultaneously.[118,119] For example, bis(dihydropyrazole) **171** synthesised by the addition of 2-diazopropane to allene is transformed into spiro[cyclopropanedihydropyrazole] **172** on heating to 100 °C. The loss of the second nitrogen molecule to give tetramethylspiropentane (**173**) occurs only at 200 °C.[118]

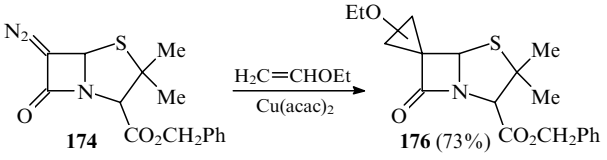


172 (~100%) **173** (~100%)

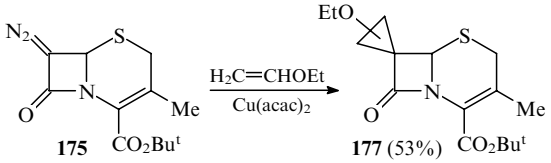
2. Cyclopropanation of unsaturated compounds with sulfur carbenes and sulfur ylides

Although the cyclopropanation of unsaturated compounds with carbenes and their synthetic equivalents is a popular modern method for the construction of three-carbon rings, there are but a few examples of such reactions resulting in azaheterocycles fused with a spirocyclopropane fragment.

Cyclopropanation of alkenes with heterocyclic diazo compounds in the presence of catalysts is an example. Diazopenicillanates and diazocephemes have been reported as cyclopropanating reagents.[116] This method is an alternative to the reaction of aliphatic diazo compounds with methylidenepenicillanates or methylidenecephemes in the construction of the same structural fragments. Cyclopropanation of unsaturated compounds activated by electron-donating substituents occurs successfully. For example, the reaction of benzyl 6-diazopenicillanate (**174**) or 7-diazoceph-3-eme (**175**) with ethyl vinyl ether in the presence of copper acetylacetonate results in ethoxycyclopropanes **176** or **177** (each as a mixture of four isomers).[120]



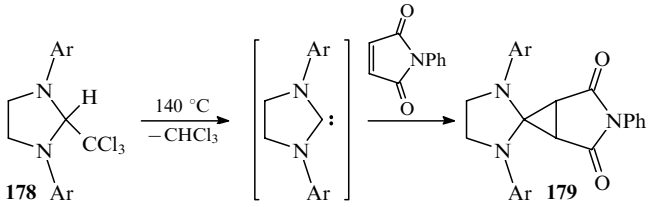
174 **176** (73%)



175 **177** (53%)

The reaction of diazo compounds **174** and **175** with vinyl acetate in the presence of $Cu(acac)_2$ occurs similarly, but the yields of the products do not exceed 10% due to the low stability of the resulting spiro-fused acetoxycyclopropanes.[120] The reaction of diazo compounds **174** and **175** with alkenes containing electron-withdrawing groups, both in the presence and in the absence of $Cu(acac)_2$, occurs as 1,3-dipolar cycloaddition and results only in the corresponding spiro-fused 4,5-dihydro-1*H*-pyrazoles.[120]

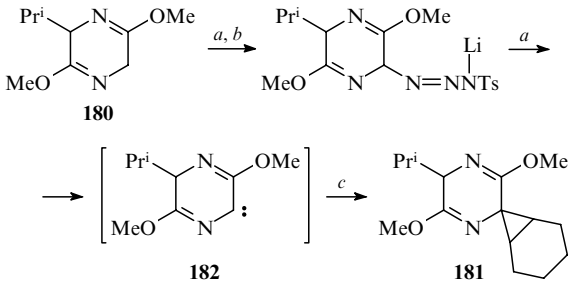
Refluxing of trichloromethyl derivatives of imidazolidines **178** in xylene is presumably accompanied by the abstraction of $CHCl_3$ and generation of a nucleophilic heterocyclic carbene which can add to activated double bonds. For example, the reaction with *N*-phenylmaleimide affords spirocyclopropane-containing adducts **179**.[121]



178 **179**

Ar = Ph (85%), 4-MeC_6H_4 (57%), 4-$MeOC_6H_4$ (77%).

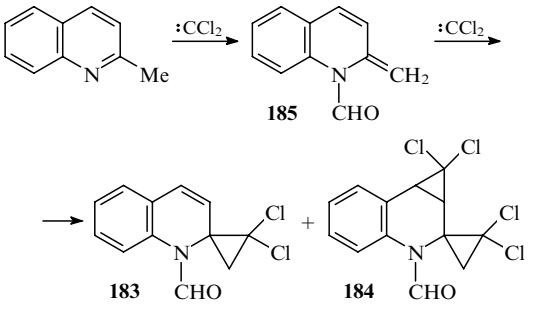
The reaction of dihydropyrazine **180** with butyllithium and tosyl azide at −70 °C in the presence of cyclohexene results in the spirane adduct **181** (overall yield > 70% with respect to the starting dihydropyrazine **180**) due to generation and [1 + 2]-cycloaddition of the heterocyclic carbene **182**.[122]



180 **182** **181**

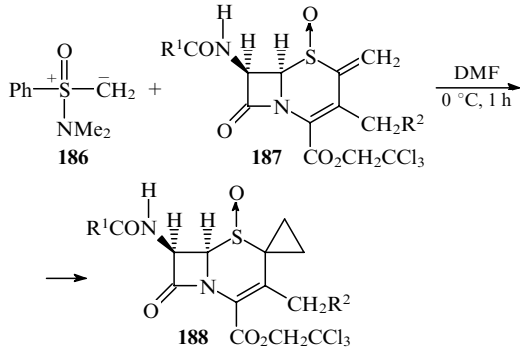
(*a*) BuLi; (*b*) TsN_3, −70 °C; (*c*) .

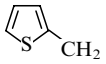
Dichlorocyclopropanation of 2-methylquinoline at 25 °C ($CHCl_3$, 50% NaOH, $Et_3N^+BnCl^-$) occurs in rather high yields to give compounds **183** and **184** with a spiro[cyclopropane-1,2′-quinoline] structure. Probably, dichlorocarbene first adds to the nitrogen atom to give an ylide, which generates 1-formyl-2-methylidenedihydroquinoline (**185**) in alkaline medium; the latter undergoes the usual dichlorocyclopropanation.[123]



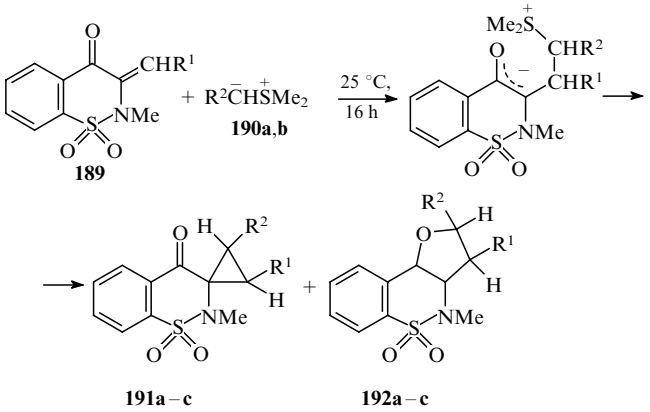
The method for building the cyclopropane ring by addition of reactive sulfur ylides to double bonds is commonly used in synthetic organic chemistry.[124] Unlike the reactions with electrophilic carbenes, alkenes activated with electron-withdrawing groups (Michael acceptors) are used in these processes.

Back in 1973, Spry [125] demonstrated the possibility of using sulfur ylides for the cyclopropanation of 2-methylidenecephalosporins. For example, the reaction of sulfonylmethylide **186** with functionally substituted methylidenecephemes **187** occurs exclusively at the exocyclic double bond to give spiro[cephalosporin-cyclopropanes] **188** in high yields.[125]



R^1	R^2	Yield (%)
$PhOCH_2$	H	80
$PhOCH_2$	OAc	85
Me	OAc	64
	OAc	72–88

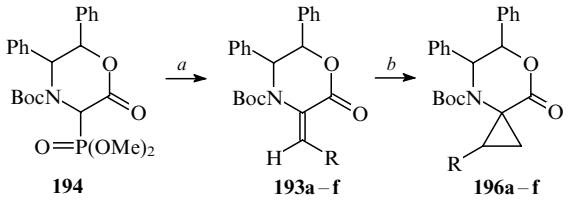
The reaction of 3-methylidene-2,3-dihydrothiazin-4-one derivatives **189** containing an enone system with ylides **190** results in spiro[cyclopropanedihydrothiazines] **191**.[126] If ylide **190** contains a benzoyl substituent, a mixture ($\sim 1:2$) of spirocyclopropane and dihydrofuran derivatives **191b**,**c** and **192b**,**c** is formed. Unsaturated ylide **190** ($R^2 = H$) reacts with the enone **189** ($R^1 = Ph$) to give only spiro[cyclopropanedihydro-1,2-benzothiazine] **191a**. It is believed [126] that the process starts with nucleophilic attack of ylides **190** on the β-carbon atom of the C=C bond in the enones **189**; this results in resonance-stabilised betaines, which then undergo cyclisation at the carbon or oxygen atoms to give three- or five-membered rings. The direction of betaine cyclisation is determined by both electronic and steric factors.[126]



R^1 = Ph, Me; R^2 = H, COPh.

Compound	R^1	R^2	Yield of **191** (%)	Yield of **192** (%)
a	Ph	H	80	–
b	Me	COPh	22	52
c	Ph	COPh	24	55

A common method for the introduction of the spirocyclopropane fragment in a morpholinone structure is the reaction of their methylidene derivatives **193**, which are obtained from the phosphonate **194** using the Wittig reaction, with sulfur ylides.[127] It should be noted that the diastereoselectivity of methylenation of the double bond by the ylide **195** is higher than that by the ylide **190a**; diastereomers of spirane derivatives **196a–f** are formed preferentially (or exclusively) in yields higher than 82% (with the exception for compound **196e**). It should be noted that the addition of diazomethane to ethylidenemorpholinone **193b** followed by photolysis of the resulting dihydropyrazole affords a diastereomeric mixture of spirane **196b** (ratio 1 : 1.6, overall yield 91%).[127]



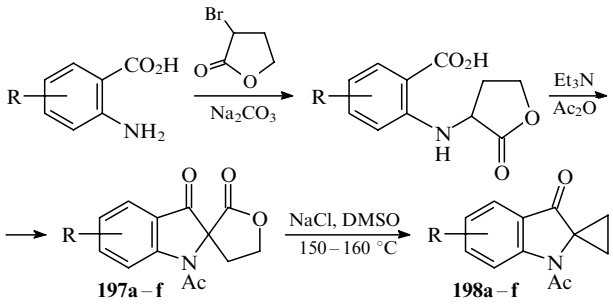
R = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**), Pr^i (**e**), Ph (**f**);

(*a*) RCHO, NaH, THF; (*b*) $PhS^{+}(O)(NEt_2)CH_2^-$ (**195**).

3. Decarboxylation and γ-elimination leading to cyclopropane ring formation

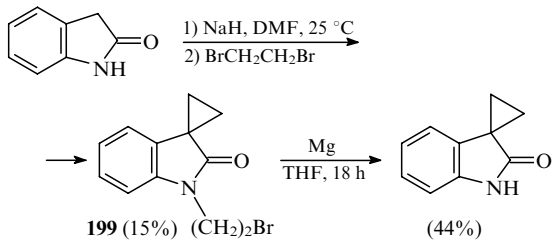
The formation of a spiro-fused cyclopropane fragment is carried out by decarboxylation of γ-lactones **197** spiro-fused with a heterocyclic system, besides elimination of an N_2 molecule from dihydropyrazoles. This method was used for the synthesis of spiro[cyclopropane-1,2′-indolin]-3-ones **198** with substituents both in the benzene ring and at the nitrogen atom aimed at the search for novel compounds with antiinflammatory and analgesic effects.[99, 100, 128]

Spiro-fused γ-lactones **197a–f** are obtained in two steps by condensation of the corresponding anthranilic acids with α-bromo-γ-butyrolactone. Decarboxylation of the lactones **197a–f** is carried out by heating (150–160 °C) in the presence of an alkali metal chloride to give the heterocycles **198** in 75%–94% yields.[100, 128] Functionalisation of the benzene ring in the spirolactone **197a** is carried out before the decarboxylation step.

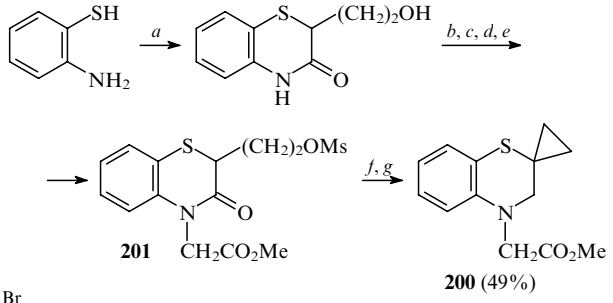


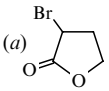
R = H (**a**), Me (**b**), OMe (**c**), Cl (**d**), Br (**e**), I (**f**).

1,3-Elimination from the corresponding functional derivatives is a useful method for the formation of a spiro-fused cyclopropane fragment applicable to various azaheterocyclic structures. In particular, this type of reaction includes cycloalkylation of compounds containing reactive hydrogen atoms with 1,2-dibromoethane. For example, the reaction of indolin-2-one with 2 equiv. of dibromoethane in the presence of sodium hydride results in compound **199**, subsequent reduction of which with magnesium in boiling THF gives unsaturated spiro[cyclopropane-1,3′-indolin]-2-one, which was later used for the synthesis of compounds with potential pharmacological activity.[129, 130]

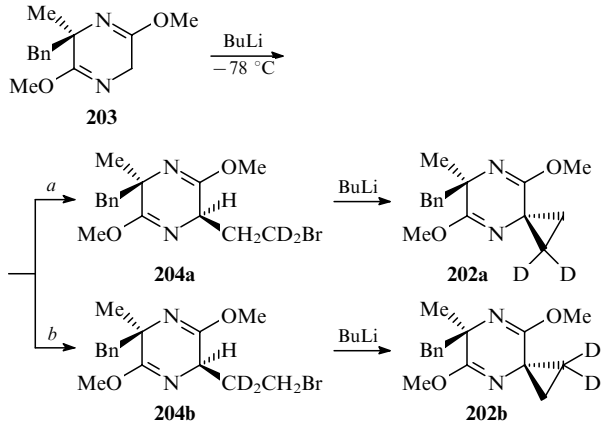


A scheme for the synthesis of spiro[1,4-benzothiazinecyclopropan]-3-one **200** with the use of 2-aminobenzenethiol as the starting compound is presented below. The required functionalised ethyl group is introduced in the initial condensation step, while the spirocyclopropane fragment is formed in the last step, *i.e.*, cyclisation of mesylate **201**.[131]



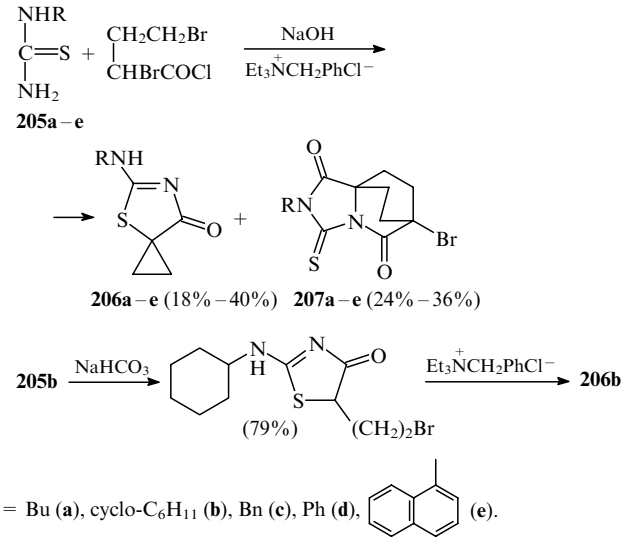
(*a*) , K_2CO_3, EtOH; (*b*) , H^+; (*c*) $BrCH_2CO_2Me$; (*d*) MeOH, TsOH; (*e*) MsCl, Et_3N, CH_2Cl_2; (*f*) NaH, 20 °C, 30 min; (*g*) 70 °C, 15 min.

Alkylation followed by 1,3-elimination was successfully used for a stereoselective synthesis of (*R*)- and (*S*)-isomers of 1-amino-2,2-dideuteriocyclopropanecarboxylic acid. Spiranes **202** were used as the starting compounds which were then hydrolysed with HCl. These transformations could also be performed starting from chiral dihydropyrazine **203** and selectively deuterated 2-bromoethyl triflates.[132, 133] Metallation of compounds **203** followed by alkylation with deuterated 2-bromoethyl triflate first gives (2-bromoethyl)dihydropyrazine **204a**,**b** (yield 86% – 88%); in this case, an isomer with a *cis* arrangement of the benzyl and bromoethyl substituents is formed as the main product. Subsequent cyclisation of compounds **204a**,**b** on treatment with BuLi in THF affords spiro[cyclopropanedihydropyrazines] **202a**,**b** (yield 46% – 55%).[132, 133]



(*a*) $BrCD_2CH_2OTf$; (*b*) $BrCH_2CD_2OTf$.

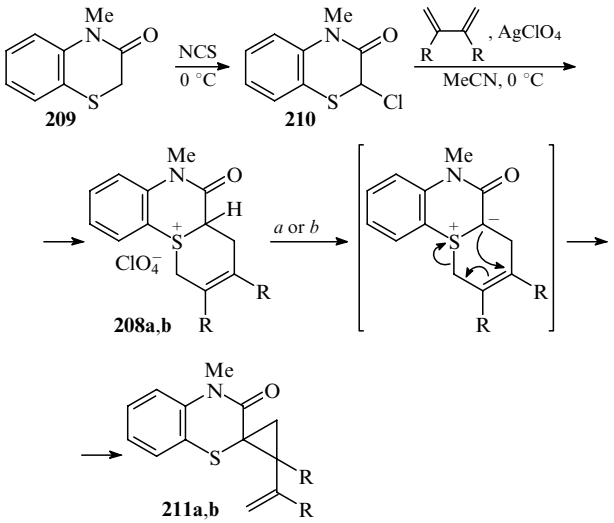
In some cases, consecutive chemical transformations result in the formation of heterocyclic and then cyclopropane fragments. For example, the reaction of substituted thioureas **205a** – **e** with 2,4-dibromobutanoyl chloride occurs on treatment with 5% NaOH in the presence of benzyltriethylammonium chloride and results in a mixture of spiro[cyclopropane-1,5′-dihydrothiazol]-4-one derivatives **206a** – **e** (yields 18% – 40%) and tricyclic compounds **207a** – **e**.[134] The reaction occurs in two steps, as shown for cyclohexylthiourea **205b**.



R = Bu (**a**), cyclo-C_6H_{11} (**b**), Bn (**c**), Ph (**d**), (**e**).

4. Miscellaneous methods for the formation of a spiro-fused cyclopropane fragment

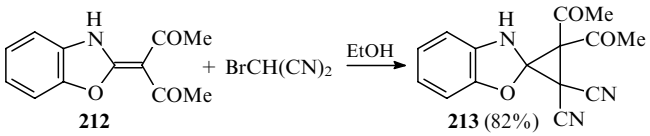
A particular case of the formation of a cyclopropane ring spiro-fused with a thiazine fragment is represented by the transformation of tricyclic benzothiazine salts **208a**,**b**, which are obtained by chlorination of benzothiazinone **209** followed by treatment of the resulting α-chloro derivative **210** with 1,3-dienes in the presence of $AgClO_4$.[135] Treatment of the benzothiazinium salts **208a**,**b** with reducing agents or bases results in 2′-vinylspiro[cyclopropane-1,2′-thiazines] **211a**,**b** in 56% – 90% yields. Electrolysis of the salt **208a** in acetonitrile (1 h) also results in spiro[cyclopropane-1,2′-thiazine] **211a** in ~ 60% yield. It was found by X-ray diffraction analysis that the vinyl group and the sulfur atom in compound **211a** are *syn*-arranged. It was assumed [135] that the formation of spiro[cyclopropane-1,2′-thiazines] **211a**,**b** can follow both an ionic and a radical mechanism, although it was not specified which particular intermediates of radical nature can be generated in this system.[135]



R = Me (**a**), H (**b**); (*a*) 20 °C: Mg, THF, or $NaBH_4$, EtOH, or Zn, AcOH; (*b*) B^-.

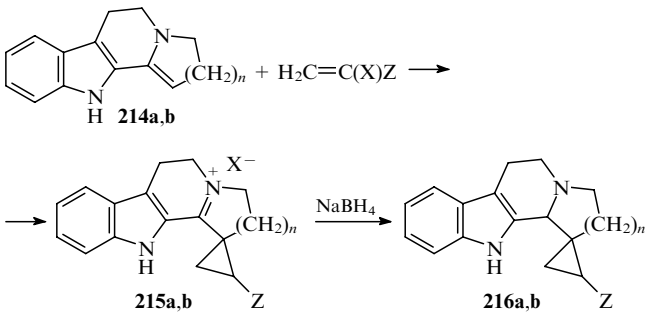
A spirocyclopropane fragment is formed in the reaction of bromomalonodinitrile with the electron-deficient exocyclic double bond of 2-methylidene-substituted dihydrobenzoxazole **212**.

Spiro[cyclopropane-1,2′-dihydrobenzoxazole] **213** is formed when an equimolar mixture of the reactants is kept for 2 h at 25 °C in 95% ethanol in the absence of bases.[136]



212 **213** (82%)

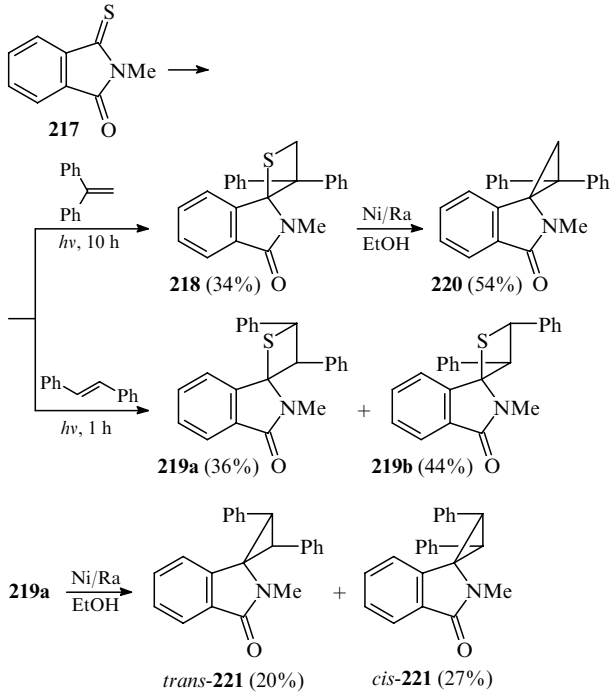
The reaction of polycyclic enamines **214** with methyl 1-bromoacrylate or 1-chloroacrylonitrile results in spirocyclopropane-containing hexahydroindoloindolizine (**215a**) or hexahydroindoloquinolizine (**215b**) salts. Treatment of these salts with $NaBH_4$ or other reducing agents results either in compounds **216** containing a spirocyclopropane fragment (in moderate yields) or in deeper reduction with the cyclopropane ring opening.[137,138]

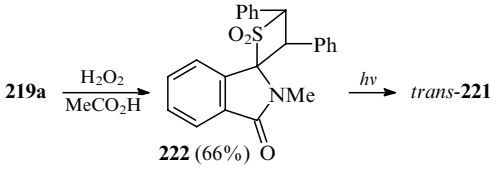


214a,**b** **215a**,**b** **216a**,**b**

n = 1 (**a**), 2 (**b**); X = Cl, Br; Z = COOMe, CN.

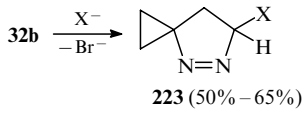
Desulfurisation of thietane derivatives can serve as yet another method for the formation of a cyclopropane fragment spiro-fused with an azaheterocycle. In particular, photolysis of a mixture of *N*-methylmonothiophthalimide (**217**) with 1,1-diphenylethylene or *trans*-stilbene results in spiro-fused thietanes **218** or **219a,b**,[139] desulfurisation of which with Raney nickel (Ni/Ra) in ethanol affords spiro[cyclopropane-1,3′-isoindolin]-1-ones **220** and **221**; a mixture of two isomeric compounds, *viz*., *trans*- and *cis*-**221**, is formed from the isomer **219a** under these conditions. However, only one derivative, *viz*., *trans*-**221**, is obtained in almost quantitative yield if thietane **219a** is first oxidised with hydrogen peroxide in acetic acid to give sulfone **222**, which is then subject to photolysis.[139]





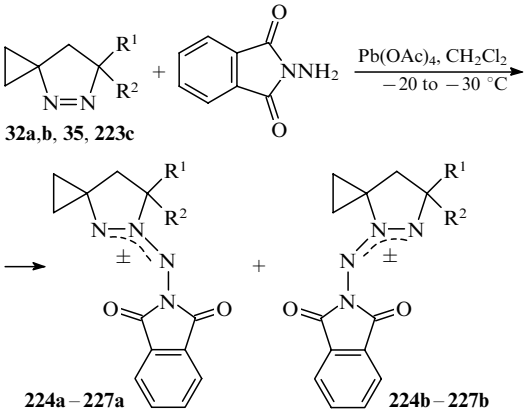
IV. Functionalisation of heterocyclic compounds containing a spirocyclopropane fragment

In this Section, we consider chemical transformations of azaheterocycles containing a spirocyclopropane fragment, which is preserved in these reactions. In particular, chemical modifications of 5-bromospiro[cyclopropane-1,3′-4,5-dihydro-3*H*-pyrazole] (**32b**) and 3-R-spiro[cyclopropane-1,5′-4,5-dihydro-1*H*-pyrazoles] **36a**,**b**, which have recently become accessible (see Section II), were studied.[33,36] It was found [33,140] that the bromine atom in compound **32b** can be replaced by nucleophiles such as PhO, PhS or N_3 to give compounds **223**, in which the spiro[cyclopropane-1,5′-dihydropyrazole] structure remains intact.



X = OPh (**a**), SPh (**b**), N_3 (**c**).

It was shown recently [32,140] that 4,5-dihydro-3*H*-pyrazoles **32a,b**, **35** and **223c** add phthalimidonitrene, which is obtained *in situ* upon oxidation of *N*-aminophthalimide with $Pb(OAc)_4$, to give pyrazolinio-*N*-phthaloimidoamides (azimines) **224a**,**b**–**227a**,**b** with retention of the cyclopropane ring. In this case, the regioisomers **a** are formed preferentially from all 4,5-dihydro-3*H*-pyrazoles (or exclusively from ester **35**).

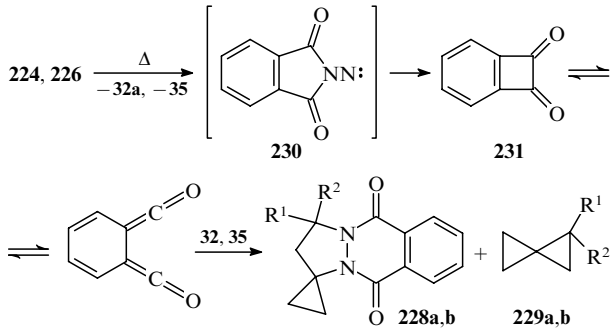


Compound	R^1	R^2	Yield (%)	Ratio **a** : **b**
224	H	Ph	70–75	5.5 : 1
225	H	Br	30–35	see [a]
226	Me	COOMe	50–55	1 : 0
227	H	N_3	60–65	3.3 : 1

[a] The isomer **225b** is unstable under the reaction conditions.

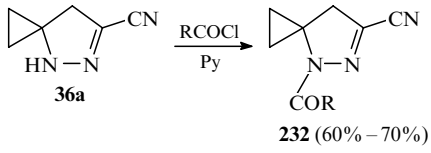
Thermolysis of the azimines **224** and **226** (*o*-dichlorobenzene, 170 °C) results in the elimination of one nitrogen molecule to give fused heterocyclic systems (compounds **228a**,**b**) with retention of the cyclopropane fragment; in addition, deeper partial dedinitrogenation of the azimines to give spiropentane derivatives **229a**,**b** is observed.[32] It is assumed [141] that spiro{cyclopropanetetrahydropyrazolo[1,2-*b*]phthalazine}diones **228** are formed due to the preliminary dissociation of azimines **224**, **226** to the starting dihydropyrazoles **32a**, **35** and phthalimidonitrene **230**. The nitrene **230** eliminates a nitrogen molecule to give benzocyclobutenedione

231, which is in equilibrium with its open diketene form. The latter reacts with dihydropyrazoles **32**, **35** to give compounds **228a**,**b** in 25% – 28% yields. The 4,5-dihydro-3*H*-pyrazoles formed upon the destruction of azimines undergo dedinitrogenation to give the corresponding spiropentanes **229a**,**b**.

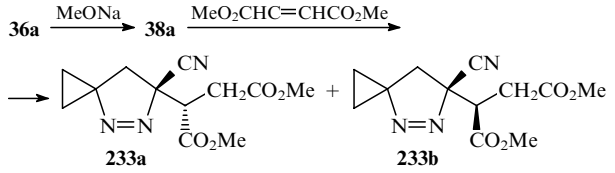


R^1 = H, R^2 = Ph (**a**); R^1 = Me, R^2 = COOMe (**b**).

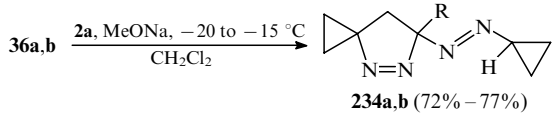
3-Cyanospiro[cyclopropane-4,5-dihydro-1*H*-pyrazole] **36a**, like other 4,5-dihydro-1*H*-pyrazoles, can be acylated with benzoyl or cyclopropanoyl chloride in the presence of pyridine to give 1-acyl-4,5-dihydro-1*H*-pyrazoles **232**.[142] On the other hand, the anions **38a**,**b** generated from 4,5-dihydro-1*H*-pyrazoles **36a**,**b** add to alkenes containing electron-withdrawing substituents exclusively as C(3)-nucleophiles [compounds **37a**,**b** are formed similarly (see Section II)].[36] For example, dihydropyrazole **36a** reacts with dimethyl maleate or dimethyl fumarate in the presence of MeONa to give a mixture of diastereomeric cyanodiesters **233a**,**b** (ratio ~ 1.5 : 1, overall yield ~ 70%).[37, 38]



R = Ph, cyclo-C_3H_5.



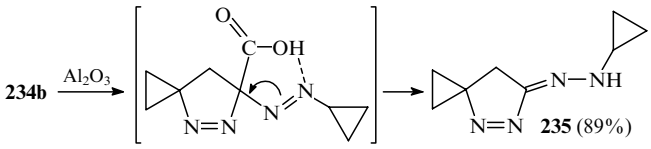
Unexpectedly, spiro[cyclopropane-1,5′-4,5-dihydro-1*H*-pyrazoles] **36a**,**b** readily react with diazocyclopropane (**1**) generated *in situ*. For example, decomposition of cyclopropylnitrosourea (**2a**) on treatment with MeONa or K_2CO_3 in the presence of dihydropyrazoles **36a**,**b** results in hitherto unknown (*E*)-cyclopropylazodihydropyrazoles **234a**,**b** as the main reaction products.[36, 42] A reaction scheme was suggested which is similar to that of the formation of azo compounds through azo-coupling of aromatic diazonium salts with various substrates, including 4,5-dihydro-1*H*-pyrazoles.[143] The reaction of the **38a**,**b** anions can probably involve diazocyclopropane precursors such as cyclopropyldiazohydroxide or the cyclopropyldiazonium cation formed upon alkaline decomposition of nitrosourea **2a**, rather than compound **1** itself.[1] This scheme is supported by the fact that aliphatic diazo compounds, *e.g.* diazomethane or methyl diazoacetate, do not enter into similar reactions with 4,5-dihydro-1*H*-pyrazoles **36a**,**b**.



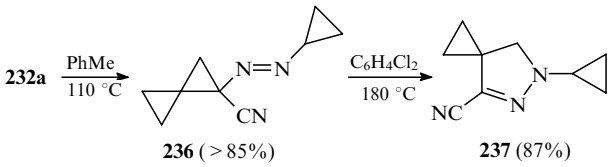
R = CN (**a**), COOMe (**b**).

It should be noted that azodihydropyrazoles **234a**,**b** can be obtained in one step by treating acrylonitrile or methyl acrylate with a two- to three-fold excess of cyclopropylnitrosourea (**2a**).[36]

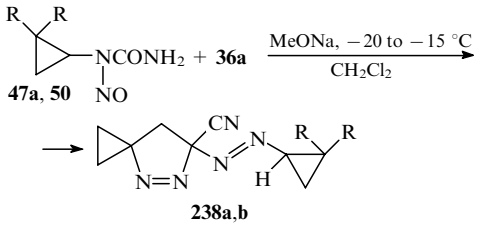
An attempt at isolation of azodihydropyrazole **234b** by TLC on Al_2O_3 resulted in its transformation to cyclopropylhydrazone **235** (probably due to hydrolysis of the ester groups followed by decarboxylation); the spiro[cyclopropane-1,5′-4,5-dihydro-3*H*-pyrazole] structure is retained under these conditions.



Thermolysis of azodihydropyrazole **234a** (110 °C, 2 h) is accompanied by elimination of the ring nitrogen atoms to give 1-cyano-1-(cyclopropylazo)spiropentane (**236**), which undergoes azocyclopropane – dihydropyrazole rearrangement at higher temperature (180 °C, 40 min)[144, 145] to give dihydropyrazole **237** with a spirocyclopropane fragment at position 4 of the heterocycle.[36]

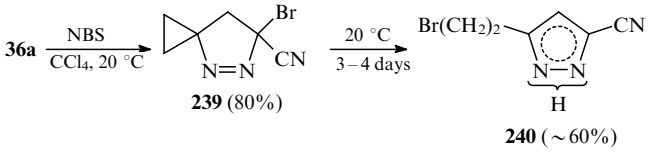


Substituted diazocyclopropanes generated by decomposition of *N*-nitrosoureas **47a** or **50** on treatment with sodium methoxide react with dihydropyrazole **36a** similarly to the unsubstituted compound **1** to give (*E*)-azodihydropyrazoles **238a** or **238b** (each as a mixture of two diastereomers in the ratio ~ 1 : 1).[42]

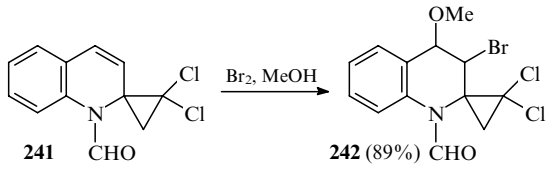


R = Me (**238a**, 70%); R – R = CH_2CH_2 (**238b**, 65%).

Bromination of cyanodihydropyrazole **36a** with *N*-bromosuccinimide (NBS) at 20 °C in the absence of radical initiators occurs at position C(3) of the heterocycle to give 3-bromo-3-cyanospiro-[cyclopropane-1,5′-4,5-dihydro-3*H*-pyrazole] (**239**) in high yield. However, the resulting bromodihydropyrazole **239** has low stability and is transformed to the isomeric (2-bromoethyl)cyanopyrazole (**240**) in 3 – 4 days at room temperature.[142]

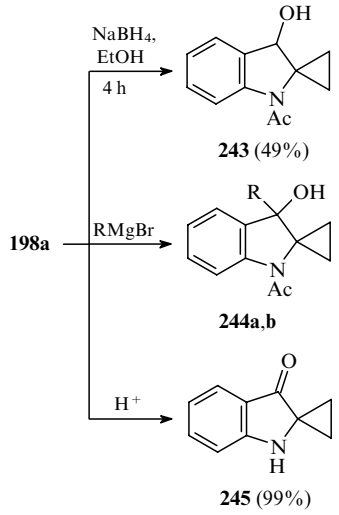


The introduction of chlorine atoms in the cyclopropane ring makes it more stable with respect to electrophilic reagents, in particular Br_2 in methanol; this enables functionalisation of the heterocyclic part of the molecule. For example, bromomethoxylation of a quinoline derivative **241** at room temperature affords a high yield of compound **242** which retains the spiro-fused cyclopropane fragment.[146]



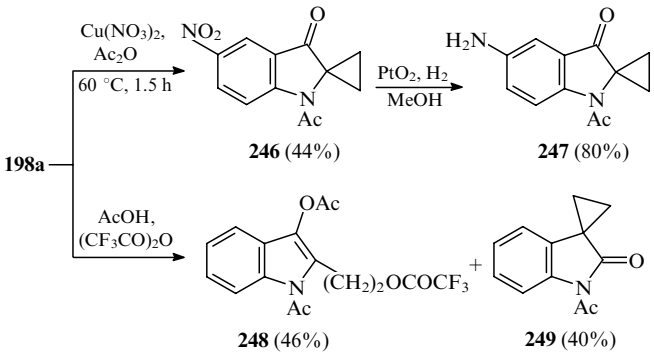
Certain transformations of spiro[cyclopropane-1,2′-indolin]-3-one derivatives, in particular of compounds **198**, also occur with retention of the cyclopropane fragment; some functional derivatives showing antiinflammatory and analgesic activities were synthesised from them.[100, 128] For example, the reduction of compound **198a** with sodium borohydride results in the hydroxy derivative **243**; its reactions with Grignard reagents give alcohols **244a**,**b**.

Saponification of *N*-acetylindolinone **198a** on treatment with MeONa or KOH in methanol results in unsubstituted spiro[cyclopropane-1,2′-indolin]-3-one **245** in an almost quantitative yield. The latter was used as the starting compound for the syntheses of alkyl-, acyl-, alkoxycarbonyl- and sulfonylspiro[cyclopropane-1,2′-indolin]-3-ones.[128]



R = Ph (**244a**, 67%), Bn (**244b**, 79%).

Nitration of compounds **198a** with copper nitrate gives the 5-nitro derivative **246**, catalytic hydrogenation of which affords 5-aminoindolinone **247**. The acetylamino and mesitylamino derivatives of the latter show biological activities. It is of note that treatment of the spirane compound **198a** with trifluoroacetic anhydride in acetic acid results not only in cyclopropane ring opening to give substituted indole **248**, but also in skeletal isomerisation of compound **198a**, probably through Wagner – Meerwein rearrangement. The rearrangement product **249** is formed in 40% yield.[100]



V. Conclusion

It is evident from this review that the methods for the synthesis of nitrogenous heterocycles containing a spirocyclopropane fragment are quite diverse though rather laborious; this restricts considerably the study of the properties of these compounds. The interest in heterocyclic compounds incorporating a spirofused cyclopropane fragment stems from the search for new medicines and biologically active compounds. Some heterocycles with a spirocyclopropane fragment, such as derivatives of dihydroisoxazoles, indoline-2(3)-ones, cephalosporins and penicillanates, are of interest as potential pharmaceutical compounds.

References

1. W Kirmse, H Schütte *Chem. Ber.* **101** 1674 (1968)
2. P Bladon, D R Rae *J. Chem. Soc., Perkin Trans. 1* 1468 (1974)
3. P Bladon, D R Rae, A D Tait *J. Chem. Soc., Perkin Trans. 1* 2240 (1974)
4. Yu V Tomilov, E V Shulishov, O M Nefedov *Izv. Akad. Nauk SSSR, Ser. Khim.* 1057 (1991) [a]
5. M Regitz, G Maas *Diazo Compounds. Properties and Synthesis* (New York: Academic Press, 1986) p. 301
6. *Methoden der Organischen Chemie (Houben-Weyl)* Vol. E19b/1 (Stuttgart: Georg Thime, 1989) p. 491
7. W M Jones, M H Crasley, W S Brey Jr *J. Am. Chem. Soc.* **85** 2754 (1963)
8. Yu V Tomilov, E V Shulishov, I P Klimenko, O M Nefedov *Izv. Akad. Nauk, Ser. Khim.* 2698 (1996) [a]
9. Yu V Tomilov, E V Shulishov, G P Okonnishnikova, O M Nefedov *Mendeleev Commun.* **5** 200 (1997)
10. A Sandoval, G Rosenkranz, K Djerassi *J. Am. Chem. Soc.* **73** 2383 (1951)
11. H Gutsche, in *Organic Reactions* (New York: Wiley; Translation into Russian, Moscow: Inostr. Lit., 1956) Vol. 8
12. C J Rostek, W M Jones *Tetrahedron Lett.* 3957 (1969)
13. L Fitjer, J-M Conia *Angew. Chem.* **85** 349 (1973)
14. S Zöllner, H Buchholz, R Gleiter, A de Meijere *Angew. Chem.* **103** 1544 (1991)
15. N S Zefirov, S I Kozhushkov, B I Ugrak, K A Lukin, O V Kokoreva, D S Yufit, Yu T Struchkov, S Zoellner, R Boese, A de Meijere *J. Org. Chem.* **57** 701 (1992)
16. A de Meijere, S I Kozhushkov *Adv. Strain Org. Chem.* **4** 225 (1998)
17. W Kirmse, G Wächtershäuser *Liebigs Ann. Chem.* **707** 44 (1967)
18. W Kirmse, U Seipp *Chem. Ber.* **107** 745 (1974)
19. W Kirmse, F Scheidt *Chem. Ber.* **103** 3711 (1970)
20. W Kirmse, G Hellwig *Chem. Ber.* **115** 2744 (1982)
21. W Kirmse *Carbene Chemistry* (New York: Academic Press, 1971)
22. W Kirmse, P van Chiem, P G Henning *J. Am. Chem. Soc.* **105** 1695 (1983)
23. W Kirmse, P Chiem, P G Henning *Tetrahedron* **41** 1441 (1985)
24. W Kirmse, F Scheidt *Angew. Chem.* **83** 251 (1971)
25. W Kirmse, H Jendralla *Chem. Ber.* **111** 1873 (1978)
26. W Kirmse, U Richarz *Chem. Ber.* **111** 1883 (1978)
27. W Kirmse, U Richarz *Chem. Ber.* **111** 1895 (1978)
28. Yu V Tomilov, E V Shulishov, G P Okonnishnikova, O M Nefedov *Izv. Akad. Nauk, Ser. Khim.* 2199 (1995) [a]
29. I D Kuchuk, Candidate Thesis in Chemical Sciences (St Petersburg: St Petersburg State University, 1996)
30. Yu V Tomilov, E V Shulishov, A B Kostitsyn, O M Nefedov *Izv. Akad. Nauk, Ser. Khim.* 662 (1994) [a]
31. M Regitz, H Heydt *1,3-Dipolar Cycloaddition Chemistry* Vol.1 (Ed. A Padwa) (New York: Wiley-Interscience, 1984) p. 393
32. Yu V Tomilov, I V Kostyuchenko, E V Shulishov, B B Averkiev, M Yu Antipin, O M Nefedov *Izv. Akad. Nauk, Ser. Khim.* 1328 (1999) [a]
33. Yu V Tomilov, I V Kostyuchenko, E V Shulishov, O M Nefedov *Izv. Akad. Nauk, Ser. Khim.* 688 (1998) [a]
34. E Oliveri-Mandala *Gazz. Chim. Ital.* **40** 117 (1910)
35. Yu V Tomilov, E V Shulishov, S A Yarygin, O M Nefedov *Izv. Akad. Nauk, Ser. Khim.* 2203 (1995) [a]

36. Yu V Tomilov, I V Kostyuchenko, E V Shulishov, O M Nefedov *Izv. Akad. Nauk, Ser. Khim.* 532 (1997) [a]
37. I V Kostyuchenko, Candidate Thesis in Chemical Sciences, Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 1999
38. I V Kostyuchenko, E V Shulishov, Yu V Tomilov, in *Khimiya Karbenov i Rodstvennykh Intermediatov (Tez. Dokl.), S.-Peterburg 1998* [The Chemistry of Carbenes and Related Intermediates (Abstracts of Reports), St Petersburg, 1998] p. 85
39. W M Jones *J. Am. Chem. Soc.* **82** 6200 (1960)
40. W M Jones, M H Crasley, D G Baarda *J. Am. Chem. Soc.* **86** 912 (1964)
41. E V Shulishov, G P Okonnishnikova, Yu V Tomilov, in *Khimiya Karbenov i Rodstvennykh Intermediatov (Tez. Dokl.), S.-Peterburg 1998* [The Chemistry of Carbenes and Related Intermediates (Abstracts of Reports), St Petersburg, 1998] p. 106
42. Yu V Tomilov, I V Kostyuchenko, E V Shulishov, O M Nefedov, in *XVI Mendeleevskii S'ezd po Obshchei i Prikladnoi Khimii (Tez. Dokl.), Moskva, 1998* [The XVIth Mendeleev Congress on General and Applied Chemistry (Abstracts of Reports), Moscow, 1998] p. 301
43. S I Kozhushkov, T Haumann, R Boese, A de Meijere *Angew. Chem., Int. Ed. Engl.* **32** 401 (1993)
44. S Tratteberg, A Simon, A de Meijere *J. Mol. Struct.* **118** 333 (1984)
45. K K Shen, R G Bergman *J. Am. Chem. Soc.* **99** 1655 (1977)
46. W R Dolbier Jr , M J Seabury *Tetrahedron* **43** 2437 (1987)
47. J K Crandall, W W Conover *J. Org. Chem.* **39** 63 (1974)
48. D H Aue, R B Lorens, G S Helwig *J. Org. Chem.* **44** 1202 (1979)
49. J E McMurry, A P Coppolino *J. Org. Chem.* **38** 2821 (1973)
50. L Fitjer *Angew. Chem.* **88** 803 (1976)
51. L Fitjer *Chem. Ber.* **115** 1047 (1982)
52. L Fitjer, D Wehle *Chem. Ber.* **115** 1061 (1982)
53. D J Pasto, Fu-Tai Chen *Tetrahedron Lett.* 2995 (1972)
54. W Weber, I Erden, A de Meijere *Angew. Chem.* **92** 387 (1980)
55. T Tsuji, R Kikuchi, S Nishida *Bull. Chem. Soc. Jpn.* **58** 1603 (1985)
56. T Thiemann, S Kohlstruk, G Schwir, A de Meijere *Tetrahedron Lett.* **32** 3483 (1991)
57. M Oda, R Breslow *Tetrahedron Lett.* 2537 (1973)
58. D Kaufmann, A de Meijere *Chem. Ber.* **116** 1897 (1983)
59. D Kaufmann, A de Meijere *Tetrahedron Lett.* 779 (1979)
60. A de Meijere *Chem. Ber.* **107** 1684 (1974)
61. W-D Schröer, W Friedrichsen *Liebiqs Ann. Chem.* 1648 (1978)
62. A Brandi, A Guarna, A Goti, F De Sarlo *Tetrahedron Lett.* **27** 1727 (1986)
63. A Brandi, S Carli, A Goti *Heterocycles* **27** 17 (1988)
64. A Brandi, S Garro, A Guarna, A Goti, F Cordero, F De Sarlo *J. Org. Chem.* **53** 2430 (1988)
65. A Brandi, F M Cordero, F De Sarlo, A Goti, A Guarna *Synlett* 1 (1993)
66. F M Cordero, B Anichini, A Goti, A Brandi *Tetrahedron* **49** 9867 (1993)
67. F M Cordero, A Brandi, C Querci, A Goti, F De Sarlo, A Guarna *J. Org. Chem.* **55** 1762 (1990)
68. A Brandi, Y Dürüst, F M Cordero, F De Sarlo *J. Org. Chem.* **55** 5666 (1992)
69. F M Cordero, S Cicchi, A Goti, A Brandi *Tetrahedron Lett.* **35** 949 (1994)
70. A Brandi, F M Cordero, F De Sarlo, R Gandolfi, A Rastelli, M Bagatti *Tetrahedron* **48** 3323 (1992)
71. S Cicchi, A Goti, A Brandi *J. Org. Chem.* **60** 4743 (1995)
72. M Mauduit, C Kouklovsky, Y Langlois *Tetrahedron Lett.* **39** 6857 (1998)
73. A Brandi, A Goti, S Kozhushkov, A de Meijere *J. Chem. Soc., Chem. Commun.* 2185 (1994)
74. A Goti, B Anichini, A Brandi, S Kozhushkov, C Gratkowski, A de Meijere *J. Org. Chem.* **61** 1665 (1996)
75. F M Cordero, A Brandi *Tetrahedron Lett.* **36** 1343 (1995)
76. A Guarna, A Brandi, A Goti, F De Sarlo *J. Chem. Soc., Chem. Commun.* 1518 (1985)
77. E G Occhiato, A Guarna, A Brandi, A Goti, F De Sarlo *J. Org. Chem.* **57** 4206 (1992)
78. B Anichini, A Goti, A Brandi, S I Kozhushkov, A de Meijere *J. Chem. Soc.* 261 (1997)
79. A de Meijere, I Erden, W Weber, D Kaufmann *J. Org.Chem.* **53** 152 (1988)
80. L Wessjohann, L Skattebol, A de Meijere *J. Chem. Soc., Chem. Commun* 574 (1990)
81. K Giller, M S Baird, A de Meijere *Synlett* 524 (1992)
82. D J Pasto, J K Borchardt *J. Am. Chem. Soc.* **96** 6937, 6944 (1974)
83. A Battaglia, G Barbaro, P Giorgianni, E Foresti, P Sobatino, A Dondoni *J. Org. Chem.* **50** 5368 (1985)
84. F-P Dubau, G Zinner *Chem. Ber.* **108** 2189 (1975)
85. R C Petter, S Banerjee, S Englard *J. Org. Chem.* **55** 3088 (1990)
86. J Haddow, C J Suckling, H C S Wood *J. Chem. Soc. Chem. Commun.* 478 (1987)
87. F H C Stewart *Aust. J. Chem.* **36** 1629 1983)
88. M C Venuti, G H Jones, R Alvarez, J J Bruno *J. Med. Chem.* **30** 303 (1987)
89. M J Rance, J C Ruddock, M S Pacey, W P Cullen, L H Huang, M T Jefferson, E B Whipple, H Maeda, J Tone *J. Antibiot.* **42** 206 (1989)
90. K R Fox *J. Antibiot.* **43** 1307 (1990)
91. J S Kiely, M C Schroeder, J C Sesnie *J. Med. Chem.* **31** 2004 (1988)
92. G Vaidyanathan, J W Wilson *J. Org. Chem.* **54** 1810 (1989)
93. Br. P. 2 049 660; *Chem. Abstr.* **95** 62 190 (1981)
94. N F Osborne *J. Chem. Soc., Perkin Trans. 1* 1435 (1982)
95. D J Anderson, A Hassner *Synthesis* 483 (1975)
96. H J Bestmann, R Kustmann *Chem. Ber.* **102** 1816 (1969)
97. O Tsuge, H Watanabe, Y Kiryu *Bull. Chem. Soc. Jpn.* **52** 3387 (1979)
98. O Yu Magidson *Zh. Obshch. Khim.* **33** 2173 (1963) [b]
99. BRD P. 2 653 477; *Chem. Abstr.* **87** 117 781 (1977)
100. M Kawada, Y Kawano, H Sugihara, S Takei, I Imada *Chem. Pharm. Bull.* **29** 1900 (1981)
101. Eur. P. 287 196; *Chem. Abstr.* **110** 94 998 (1989)
102. A Franke *Liebigs Ann. Chem.* 717 (1978)
103. H Otomasu, T Tanaka, M Aoyagi *Chem. Pharm. Bull.* **24** 787 (1976)
104. K C Joshi, R Jain, S Arora *Heterocycles* **26** 1835 (1987)
105. W I Awad, A K Fateen, M A Zayed *Tetrahedron* **20** 891 (1964)
106. I Arenal, M Bernabe, E Fernandez-Alvarez, S Penades *Synthesis* 773 (1985)
107. J M Bland, C H Stammer, K I Varughese *J. Org. Chem.* **49** 1634 (1984)
108. J M Bland, A Shah, A Bortolussi, C H Stammer *J. Org. Chem.* **53** 992 (1988)
109. I Arenal, M Bernabe, O Cuevas, E Fernandez-Alvarez *Tetrahedron* **39** 1387 (1983)
110. S Alcaraz, A Herrero, J L Marco, E Fernandez-Alvarez, M Bernabe *Tetrahedron Lett.* **33** 5605 (1992)
111. M D Fernandez, M P de Frutos, J L Marco, E Fernandez-Alvarez, M Bernabe *Tetrahedron Lett.* **30** 3101 (1989)
112. N A Anisimova, L I Deiko, T V Mandel'shtam, in *Sovremennye Problemy Organicheskoi Khimii* (Modern Problems of Organic Chemistry) (St Petersburg: St Petersburg State University, 1996) Vol. 11, p. 136
113. J W Hines Jr , E G Breitholle, M Sato, C H Stammer *J. Org. Chem.* **41** 1466 (1976)
114. J Pitlik, J C Jaszberenyi *Acta Chim. Hung.* **126** 847 (1989)
115. J E Baldwin, J Pitlik *Tetrahedron Lett.* **31** 2483 (1990)
116. J C Sheehan, E Chacko, Y S Lo, D R Ponzi, E Sato *J. Org.Chem.* **43** 4856 (1978)
117. C Galvez, A Gonzalez, A Serra *J. Chem. Res. (S)* 402 (1985)
118. M Schneider, O Schuster, H Rau *Chem. Ber.* **110** 2180 (1977)
119. P Battioni, L Vo-Quang, Y Vo-Quang *Bull. Soc. Chim. Fr.* 401 (1978)
120. M M Campbell, R G Harcus, S J Ray *Tetrahedron Lett.* **16** 1441 (1979)
121. S E Kondrat'eva, S I Burmistrov *Zh. Org. Khim.* **11** 197 (1975) [c]
122. U Schöllkopf, M Houptreif, J Dippel, M Nieger, E Egert *Angew. Chem.* **98** 187 (1986)
123. Y Hamada, M Sugiura *Yakugaku Zasshi* **100** 168 (1980); *Chem. Abstr.* **93** 71 510 (1980)
124. B M Trost, L S Melvin *Sulfur Ylides. Emerging Synthetic Intermediates* (New York: Academic Press, 1975) Vol. 31, p. 42
125. D O Spry *Tetrahedron Lett.* **26** 2413 (1973)

126. P D Croce, D D Monaco, C La Rosa *J. Chem. Soc., Perkin Trans. 1* 299 (1986)
127. R M Williams, G J Fegley *J. Am. Chem. Soc*. **113** 8796 (1991)
128. M Kawada, H Sugihara, I Mikami, K Kawai, S Kuzuna, S Noguchi, Y Sanno *Chem. Pharm. Bull*. **29** 1912 (1981)
129. D W Robertson, J H Krushinski, G Don Pollock, H Wilson, R F Kauffman, J S Hayes *J. Med. Chem*. **30** 824 (1987)
130. J R Bagley, S A Thomas, F G Rudo, H K Spencer, B M Doorley, M H Ossipov, T P Jerussi, M J Benvenga, T Spaulding *J. Med. Chem*. **34** 827 (1991)
131. H Tawada, Y Sugiyama, Y Ikeda, Y Yamamoto, K Meguro *Chem. Pharm. Bull*. **38** 1238 (1990)
132. R W Woodard, P K Subramanian *J. Org. Chem*. **52** 15 (1987)
133. P K Subramanian, D M Kalvin, K Pamalingam, R W Woodard *J. Org. Chem*. **54** 270 (1989)
134. T Okawara, K Nakayama, Y Honda, T Yamasaki, M Furukawa *J. Chem. Soc., Perkin Trans. 1* 1733 (1986)
135. T Kataoka, Y Nakamura, H Matsumoto, T Iwama, H Kondo, H Shimizu, O Muraoka, G Tanabe *J. Chem. Soc., Perkin Trans. 1* 309 (1997)
136. A K El-Shafei, A M M El-Saghier, E A Ahmed *Synthesis* 152 (1994)
137. G Kalaus, J Galambos, M Kajtar-Peredy, L Radics, L Szabo, C Szantay *Heterocycles* **15** 1109 (1981)
138. G Kalaus, J Galambos, M Kajtar-Peredy, L Szabo, C Szantay *Acta Chim. Hung*. **124** 707 (1987)
139. M Machida, K Oda, E Yoshida, Y Kanaoka *Tetrahedron* **42** 4691 (1986)
140. I V Kostyuchenko, E V Shulishov, Yu V Tomilov, O M Nefedov, in *The 17th International Congress of Heterocyclic Chemistry (Abstracts of Reports), Vienna, 1999* PO-293
141. C Leuenberger, M Karpf, L Hoesch, A S Dreiding *Helv. Chim. Acta* **60** 831 (1977)
142. Yu V Tomilov, I V Kostyuchenko, G P Okonnishnikova, E V Shulishov, E A Yagodkin, O M Nefedov *Izv. Akad. Nauk, Ser. Khim*. 471 (2000) [a]
143. G F Duffin, J D Kendall *J. Chem. Soc*. 408 (1954)
144. P S Engel, D B Gerth *J. Am. Chem. Soc*. **103** 7689 (1981)
145. H J Rosenkranz, H Schmid *Helv. Chim. Acta* **51** 1628 (1968)
146. Y Hamada, M Sugiura, M Hirota *Tetrahedron Lett*. **22** 2893 (1981)

[a] — *Russ. Chem. Bull. (Engl. Transl.)*
[b] — *Russ. J. Gen. Chem. (Engl. Transl.)*
[c] — *Russ. J. Org. Chem. (Engl. Transl.)*