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Functionally-substituted Alkoxyethylenes in Reactions with Nucleophiles: Part 2. Synthesis of Noncyclic Structures, Benzene Derivatives, 5-, 7-membered, and Macroheterocycles

V.D. Dyachenko and R.P. Tkachev

Taras Shevchenko Lugansk National Pedagogical University, Lugansk, 91011 Ukraine (0642) 599008
e-mail: dvd_lug@online.lg.ua

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Abstract—The review systematizes and generalizes the published data on the synthesis of cyclic (with the exception of six-membered) and linear structures based on functionally-substituted alkoxyolefins. In some cases the direction of the reaction was demonstrated to depend on its conditions. The data are also presented on the established biological activity of compounds obtained.

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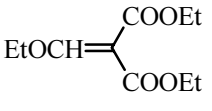
I. INTRODUCTION

This review is a continuation and logical supplement to the first part describing the syntheses of pyridine and quinoline derivatives. The functionally-substituted alkoxyethylenes are more seldom applied to preparation of 5-, 7-membered, and macroheterocycles and also to those of linear and carbocyclic structures than to the synthesis of 6-membered heterocycles. However in recent years the successful search of biologically active substances among these compounds promoted the growth in the number of publications dealing with such problems.

Among the known alkoxyethylenes compounds **1**–**8** are predominantly used in reactions of nucleophilic vinyl substitution for they are easily formed and are sufficiently reactive with respect to nucleophiles.

At the same time the isolation of alkoxyethylenes **1**–**8** in a pure state for performing nucleophilic vinyl substitution is often unfeasible. For instance, the three-component condensation of CH-acid **9**, amine **10**, and triethyl orthoformate (TOF) **11** with intermediate formation of ethoxymethylenes **12** or **13** gave rise to enamines **14**, as a rule, in good yields.



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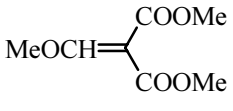

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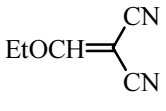

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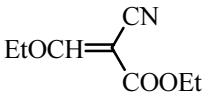

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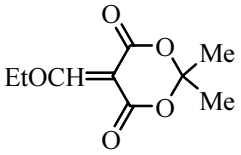

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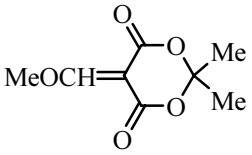

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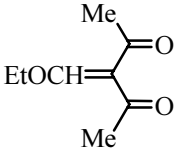

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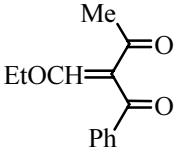

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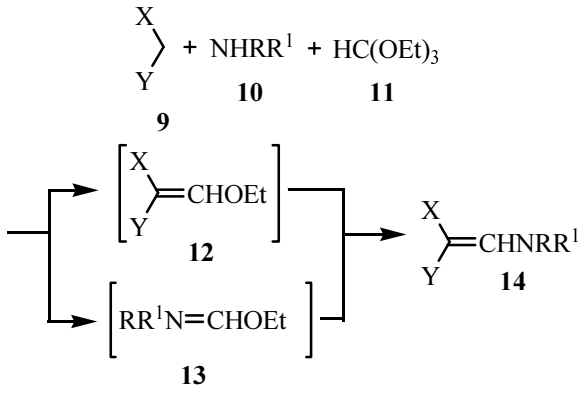
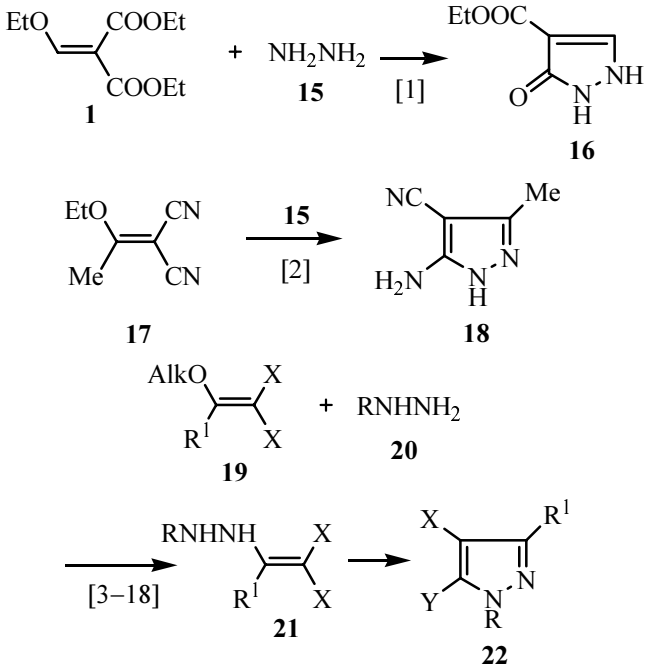


II. SYNTHESIS OF CYCLIC AND OPEN-CHAIN STRUCTURES BASED ON FUNCTIONALLY-SUBSTITUTED ALKOXYETHYLENES

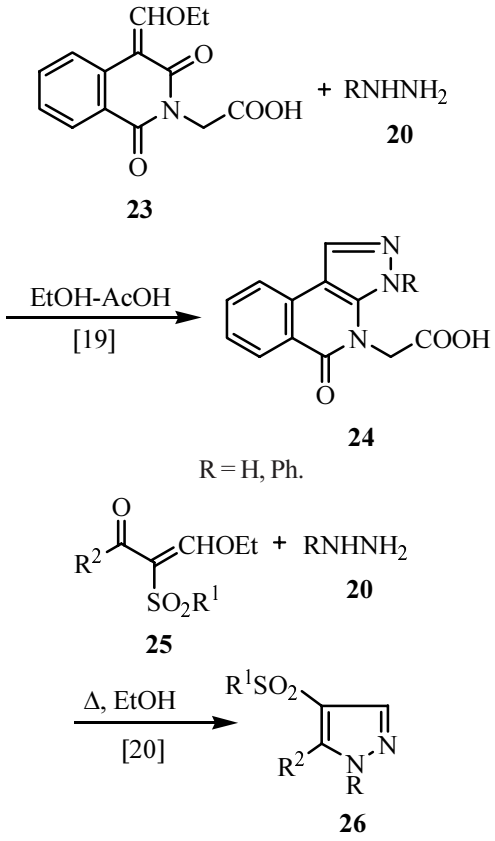
II.1. *Reactions Affording Five-Membered Heterocycles*

II.1.1. Pyrazoles. The classical pyrazole synthesis consists in hydrazine or monosubstituted hydrazine addition to 1,3-dicarbonyl compounds. Hydrazones arise as intermediates in these reactions. The main drawback of this procedure is the current formation of isomeric pyrazoles from unsymmetrical dicarbonyl compounds reacted with hydrazine or monosubstituted hydrazine.

Nowadays reactions of alkoxyethylenes (which are mostly 1,3-dicarbonyl compounds) with hydrazine **15** and its derivatives assume great importance in the pyrazoles synthesis. The advantage of this procedure resides in the frequent possibility of forecasting the reaction product structure. First the nucleophilic vinyl substitution (S_NVin) of the alkoxy group by (as a rule) unsubstituted nitrogen of the hydrazine furnishes the intermadiate product, enamine, which may be often isolated (**21**, **28**, **35**, and **38**). When the initial alkoxyethylenes are derivatives of symmetric CH-acids (compounds **1**, **17**, and **19**) or contain a single electrophilic center capable to enter into further cyclization reaction (compounds **23** and **25**), the structure of pyrazoles to be formed **16**, **18**, **22**, **24**, and **26** is easy to predict. The majority of pyrazoles thus obtained possess biological activity: herbicidal, antimicrobial, anticonvulsive. Some of them may constitute semiproducts in the synthesis of adenosine deaminase inhibitors [7].



R = H, Me, Ph, Ar, Het, perhydroheteryl, $ArSO_2$, COHet, H_2NCS, COOAlk, Bz, CONHPh; R^1 = H, Alk; X = CN, COOAlk, $COCH_3$; Y = NH_2, OH, CH_3.

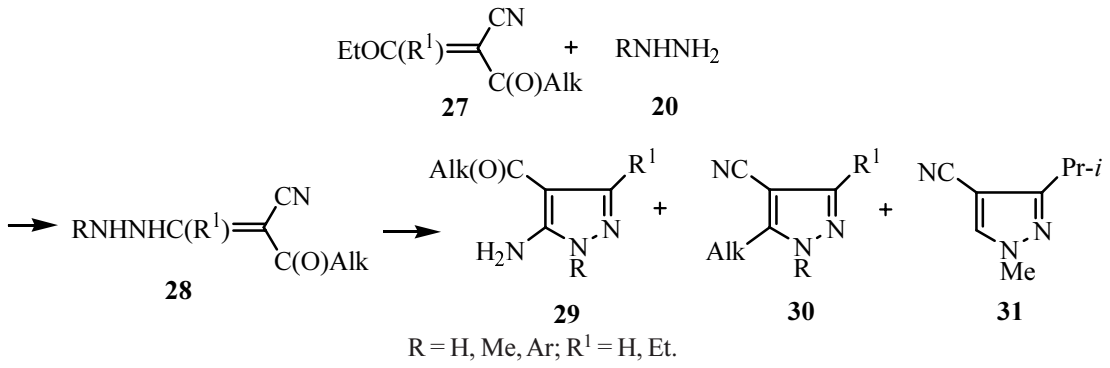


R = H, Ph.

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

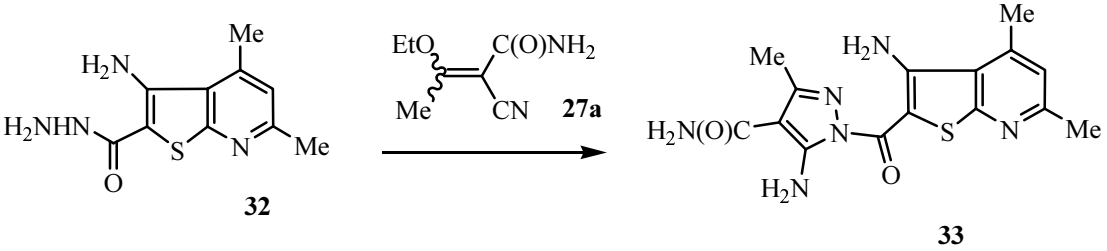
When the initial alkoxyethylene contains two electrophilic centers capable to be involved into further cyclization resulting in pyrazole derivatives the forecasting of the reaction direction may be based on the relative activity of these groups, or the reaction conditions may be varied to achieve predominant occurrence of one or another pathway. For instance, the reaction of ethoxymethylidene(1-ethoxyalkylidene) derivatives of ketonitriles

Scheme 1.



R = H, Me, Ar; R^1 = H, Et.

Scheme 2.



33

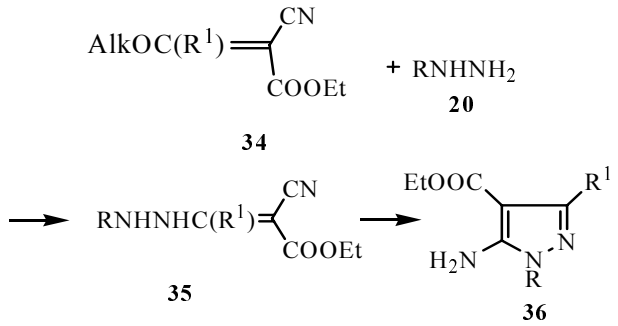
27 with hydrazines **20** afforded 5-aminopyrazoles **29** and 4-cyanopyrazoles **30** and **31** whose ratio depended on the solvent used and on the substituents in both reagents [21].

In general, the factors favoring the formation of pyrazole-4-carbonitriles **30** resulting from the cyclization at the carbonyl carbon are as follows: (a) applying the glacial acetic acid as solvent; (b) using the 3-alkyl-substituted acrylonitrile; (c) bringing into the reaction unsubstituted hydrazine or methylhydrazine. Consequently, for the cyclization at the nitrile group affording pyrazol-4-ylalkan-1-ones **29** are beneficial: (a) ethanol as solvent; (b) a hydrogen present in the position *3* of the acrylonitrile; c) the use of arylhydrazine.

It should be also noted that in reaction of 3-ethoxymethylene-2-isopropylcarbonylacrylonitrile and methylhydrazine in every solvent was obtained a side product (30-60%) 3-isopropyl-1-methyl-4-cyanopyrazole **31** originating from the cyclization of compound formed by the replacement S_NVin of ethoxy group with a substituted nitrogen of the hydrazine (Scheme 1) [21].

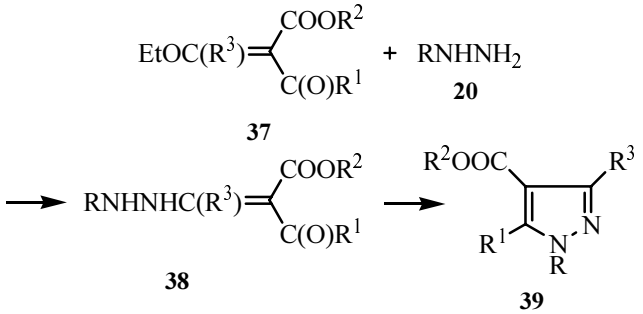
The reaction of alkoxyethylene **27a** with hydrazine derivative **32** gave pyrazole **33** (Scheme 2) [14].

When the structure offers a choice between the ester and cyano groups in compound **34** the cyclization involves exclusively the cyano group affording 5-amino-4-ethoxycarbonylpyrazoles **36** [4, 12-15, 17, 18, 22-32], in the presence of the ester and keto groups (compound **37**) the reaction occurs only at the latter one yielding substituted 4-alkoxycarbonyl-pyrazoles **39** [33-39], and the reaction of 2-ethoxymethyl-ene-1-phenyl-1,3-butan-dione (EMPB) gives rise to a mixture of two isomers, **40** and **41**. In the reaction with the hydrazine formed prevailingly compound **41**, and with phenylhydrazine, isomer **40** [11, 40]. Thus this data suggest a conclusion that in the ring closure occurring in these reaction the alkoxycarbonyl group is the most passive, whereas the process at the cyano or keto group depends on the reaction conditions. It should be indicated that among pyrazoles **36** quite a number of compounds possesses growthcontrol, herbicidal, gametocidal, antitumor, and antiphlogistic activity, and a preparation of xanthine oxidase inhibitor has been reported [22] based on these compounds. Some of pyrazoles **39** are used as

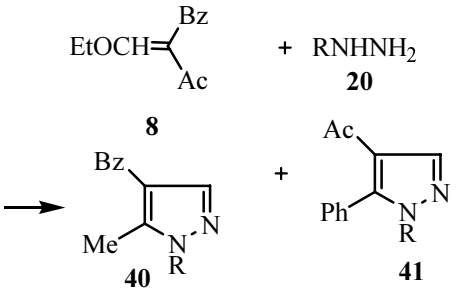


R = Alk, Ph, Ar, Het, CH_2Ph, $CH_2CH(OEt)_2$, $CHPhCH(OEt)_2$, $H_2NC(=S)$, $HetSCH_2C(O)$, $ArOCH_2C(O)$, HetC(O); R^1 = H, Me, CH_2Ph.

semi-products in the synthesis of selective inhibitors of thrombocytes aggregation induced by fibrinogen [39].



R = H, Me, Ph, Ac, aroyl, Ar, $C(S)NH_2$; R^1 = H, Alk, CF_3, CH_2Cl, $CH(OEt)_2$, Ph; R^2 = Me, Et; R^3 = H, Me.

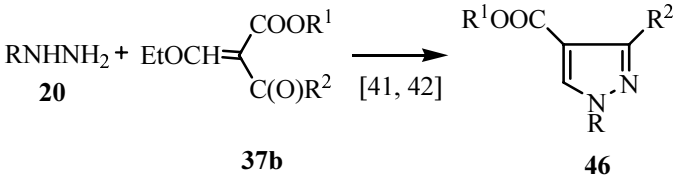


R = H, Ph.

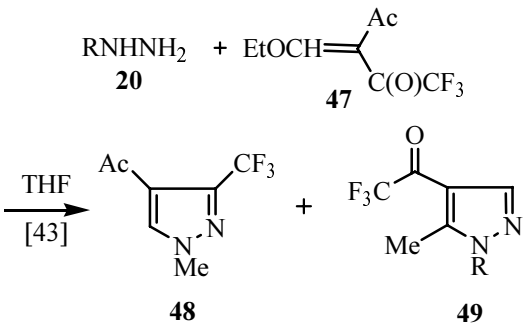
Emelina *et al*. [34, 35] demonstrated that substituted alkoxyethylene **37a** in reaction with the hydrazine alongside the expected pyrazole **42** afforded open-chain product at S_NVin **43**, and the reaction with hydrazine derivative **44** containing a disubstituted nitrogen stopped as expected on the stage of product of S_NVin **45**, and no cyclization occurred (Scheme 3).

As a rule the nucleophile attacking the vinyl carbon atom is the unsubstituted nitrogen of the hydrazine. However in some studies were observed deviations from this rule resulting in compounds **46**, **48**, **50**. Their formation presumably occurs when the vinyl carbon of alkoxyethylene **3**, **4**, **37b**, **47** suffers an attack of the substituted nitrogen of hydrazine **20** where as substituents appear alkyls, substituted alkyls, or heteryl groups, namely the moieties whose migration ability is dubious. Therefore among two presumable pathways leading to these products: an attack by the substituted nitrogen followed by cyclization, or the migration of the substituent to the contiguous nitrogen atom, we consider the former one as more probable. Note that pyrazoles **46** are used in fungicides manufacturing.

In the event of acyl or acylamide (compounds **20b** and **20c**) and -$P(R^1R^2)$=S **20d** substituents the formation of such product (often alongside the common product, e.g., pyrazole **55**) occurred via the second pathway,

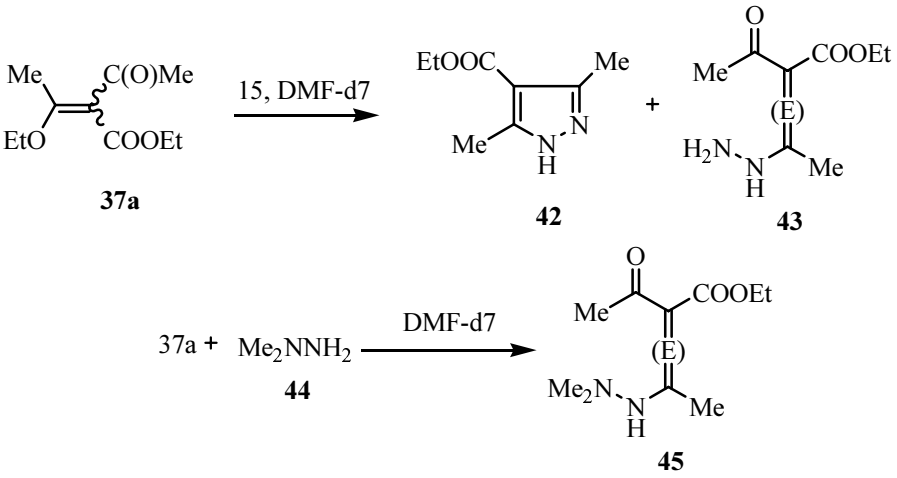


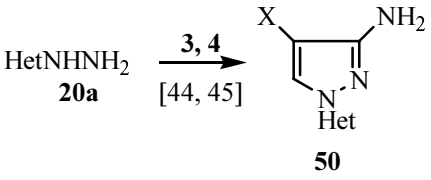
R = Alk, HalAlk, allyl, MeNHCO; R^1 = Alk; R^2 = Alk, fluoroAlk, Ph.



R = Me, Ph, Het.

Scheme 3.





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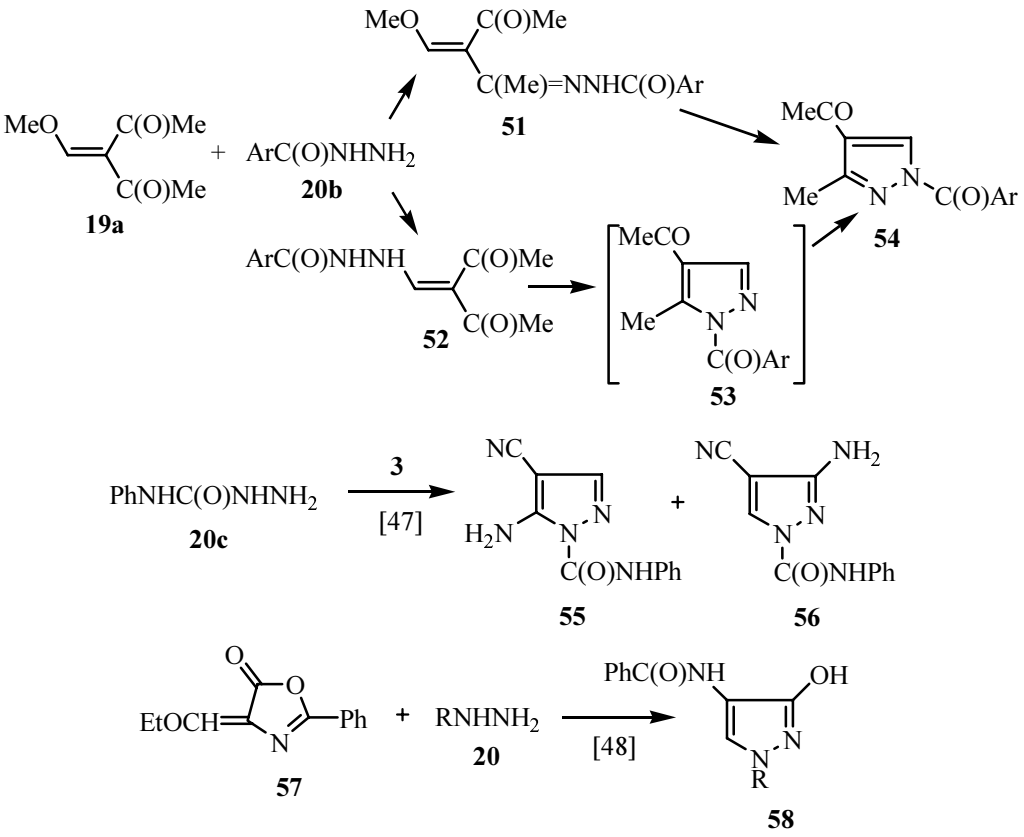
X = CN, COOEt.

by 1,2-migration leading to more sterically feasible pyrazoles **54**, **56**, **58**, **60**. This phenomenon may be comprehended taking into account that the electron pair of the amide nitrogen in azolides in contrast to other amides is involved into the π-system, and therefore the carbonyl carbon possesses a large partial positive charge thus ensuring the mobility of the acyl group. Although among all the azolides the pyrazolides are the least reactive, it is sufficient for the migration of the acyl group.

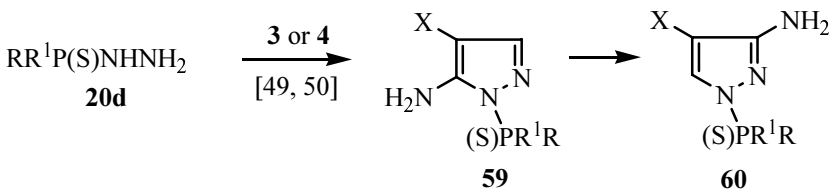
Mitkidou *et al.* [46] alongside the common mechanism of these pyrazoles formation through compounds **52** and **53** suggested without any proofs an alternative way of their building-up involving an attack of aroylhydrazine **20b** on the carbonyl carbon in compound **19a** followed by methanol elimination from intermediate **51** and by cyclization into pyrazole **54** (Scheme 4).

The acyl group migration was assumed in all studies [43–45] on this kind reactions although the primary pyrazole never was isolated and then subjected to the rearrangement yielding the migration product. However

Scheme 4.



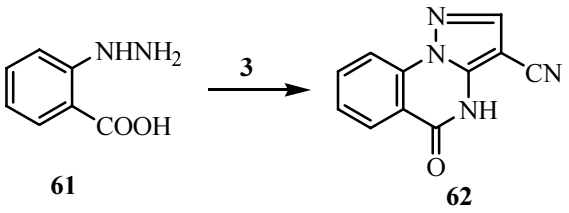
R = ArC(O), HetC(O), $BzNHCH_2C(O)$, PhNHC(O), PhNHC(S), $PhCH_2COO$.



R = Me, PhO; R^1 = PhO, EtO; X = CN, COOEt.

for the compound with the P(R^{1}R^2)=S substituent **20d** that behaved in all instances as acyl group the intermediate product **59** was isolated.

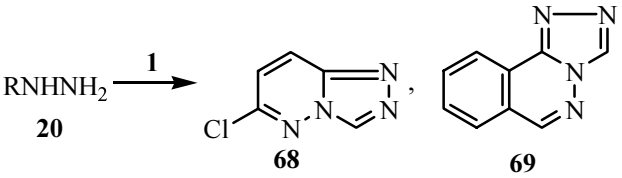
Sometimes the reaction is not terminated at pyrazole formation but continues providing fused derivatives. For instance, if the initial hydrazine molecule contains a phenyl group substituted by 2-carboxyl (compound **61**), the latter is able to react with the amino group of the arising pyrazole, and this one-pot process affords fused system **62**. Neither of the intermediate products was isolated [51].



61 **62**

The reaction of acrylic acid ethoxy derivative **63** with substituted benzimidazol-2-ylhydrazine **64** afforded product of S_NVin **65** which further through pyrazole intermediate **66** underwent cyclization into benzimid-azo[1,2-*a*]pyrazolo[1,5-*c*]quinazoline **67** (Scheme 5) [52].

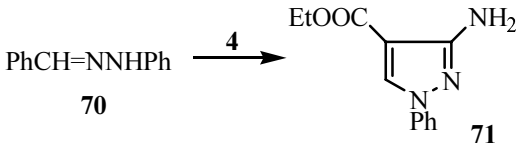
In certain instances, when the substituent in the hydrazine molecule contains a reactive nitrogen, the alkoxyethylene can act as a source of a methylene group and can close a bridge between two nitrogen atoms providing triazoles **68** and **69** [3].



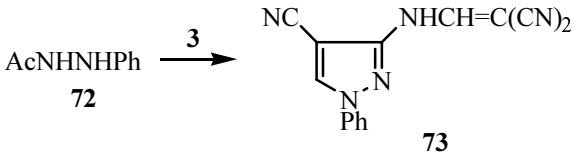
20 **68** **69**

R = 6-chloropyridazin-3-yl, phthalazin-1-yl.

The reaction of alkoxyethylene with 1,2-disubstituted hydrazines **70** and **72** involves a substitution of the acyl or benzylidene moiety, and the subsequent cyclization results in the corresponding pyrazole **71** [53] or compound **73** originating from the reaction between the pyrazole formed with the second molecule of ethoxymethylenemalononitrile (EMMN) [54].



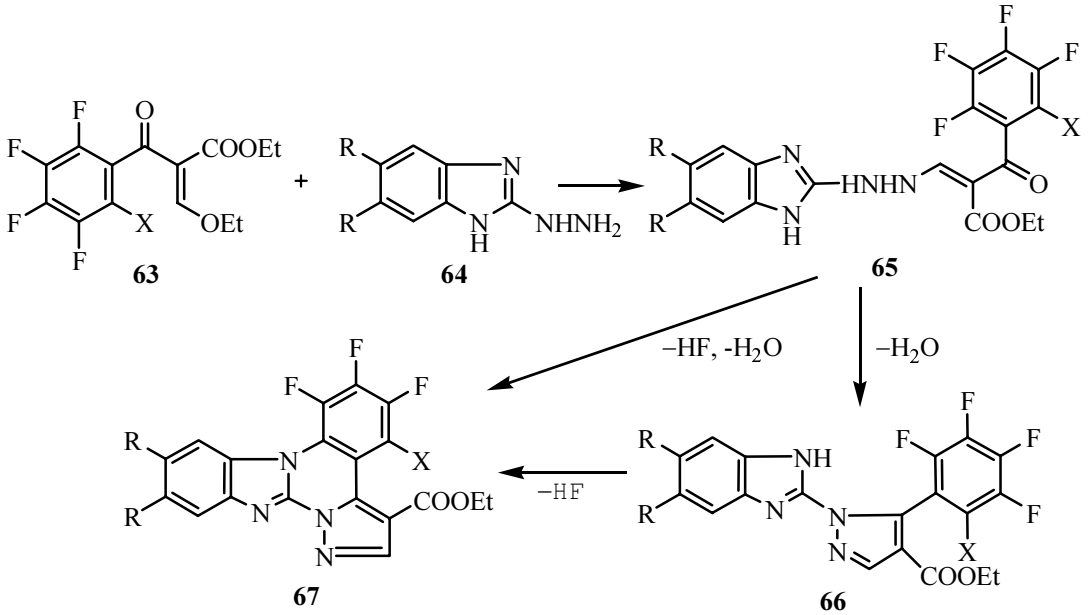
70 **71**



72 **73**

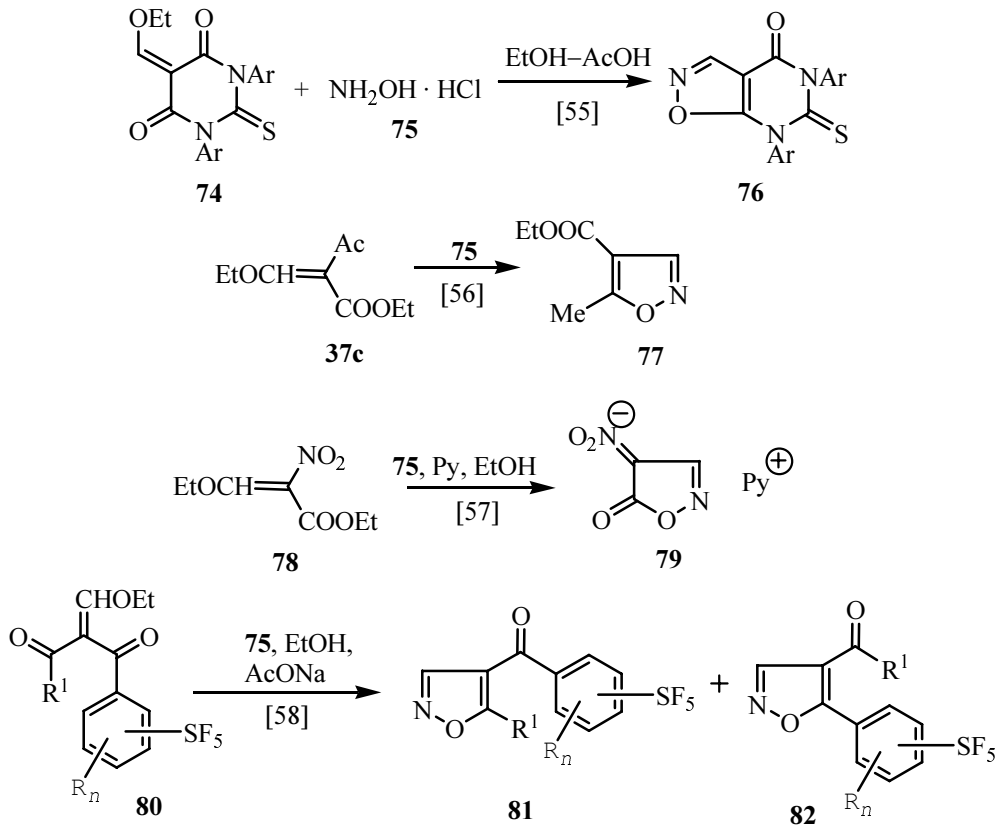
The analysis of the results under consideration suggests a conclusion, that in the synthesis of pyrazole derivatives based on alkoxyethylenes both hydrazine and its

Scheme 5.



X = H, F; R = H, Br, F.

Scheme 6.

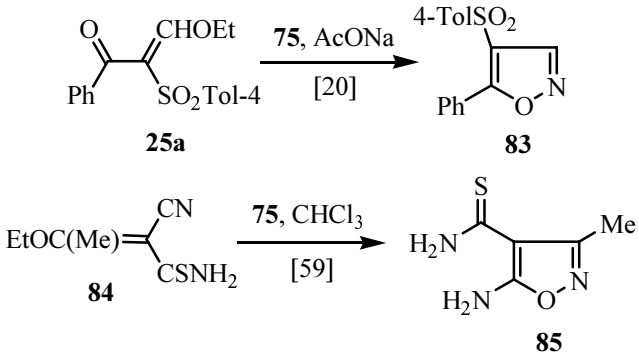


R = Alk, Hal, cycloalkyl; R^1 = Alk, cycloalkyl; n = 0–3.

mono- and disubstituted derivatives can be applied. The pathway taken by the reaction, the structure of arising pyrazoles and their yields depend on the character of substituents both in the hydrazine and alkoxyethyleneas, and also on the reaction conditions. The biological activity inherent to a number of pyrazoles thus obtained suggests that further studies in this field held much promise.

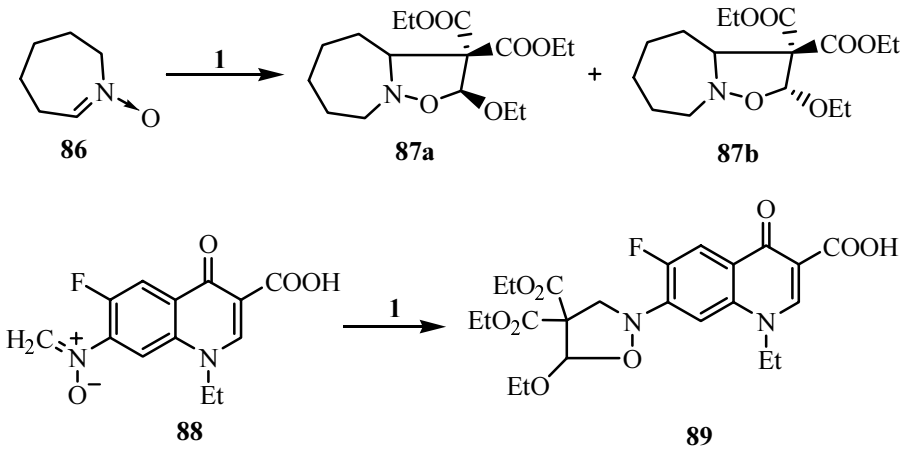
II.1.2. Isoxazoles. Two principal approaches to isoxazole synthesis involve precursors containing either fragments C–C–C and N–O or fragments C–C and C–N–O.

In the alkoxyethylenes chemistry the building up of isoxazole ring from the fragments C–C–C and N–O consist in the condensation with hydroxylamine **75**. The product of the first stage of the reaction, S_NVin of the ethoxy group with the nitrogen of the hydroxylamine commonly are not isolated obviously due to their low stability. Further process, the attack of oxygen on the electron-deficient carbon in a carbonyl or cyano group, results in the ring closure affording substituted isoxazoles **76**, **77**, **79**, **81**, **82**, **83**, and **85**. When the initial alkoxyethylene is symmetric (compound **74**), it is easy to predict the structure of the cyclization product. In the event the alkoxyethylene possesses two different electrophilic centers (compounds **37c**, **78**, **80**, **25a**, and **84**) the exclusive or prevailing formation of one among the two possible products is governed by the extent of the positive polarization of each electrophilic group, and also by sterical factors. Isoxazole **77** is an intermediate product in the synthesis of Thienamycin antibiotic, and compounds **81** and **82** are patented as herbicides.



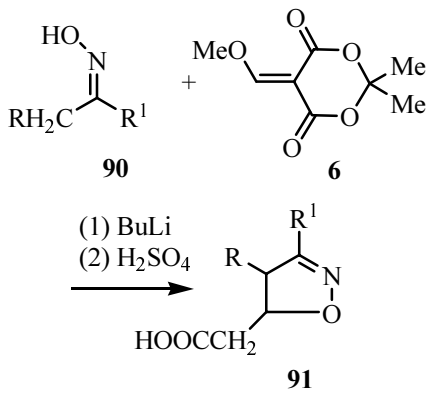
In building up the isoxazole ring from the fragments C–N–O and C–C the nitrogen atom cannot play the role

Scheme 7.



of the nucleophile, and these reactions proceed by another mechanism.

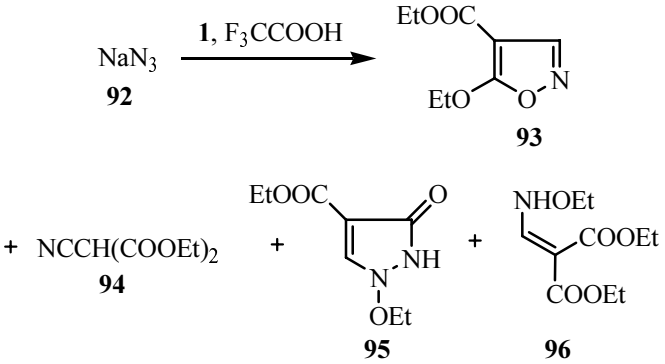
For instance, the reaction between 3,4,5,6-tetrahydro-2H-azepine 1-oxide **86** and substituted quinolin-7-yl-azomethine oxide **88** with diethyl ethoxymethylene-malonate occurred regioselectively and afforded the products of 1,3-dipolar cycloaddition: 3-ethoxy-4,4-diethoxycarbonylisoxazoles, a mixture of **87a** and **87b** [60], and compound **89** [61] respectively. As shown in [61] for compound **89**, this reorientation of the adduct is consistent with the theory of the frontier molecular orbitals which assumes that this type reaction is governed by the interaction of dipole **88** HUMO and LUMO of the electron-deficient alkene **1**. The bond formation between the carbon atom of azomethine oxide **88** and the disubstituted end of the alkene is due to the enhanced charge density and atomic orbital factor in the LUMO on the most substituted carbon atom in the olefin owing to the electron-donor alkoxy group (Scheme 7).



R = H, SPh, OPh, Ar; R^1 = Me, Ph, Ar; R + R^1 = 1,2,3,4-tetrahydronaphtho-1,2-diyl, $(CH_2)_4$, $(CH_2)_{10}$.

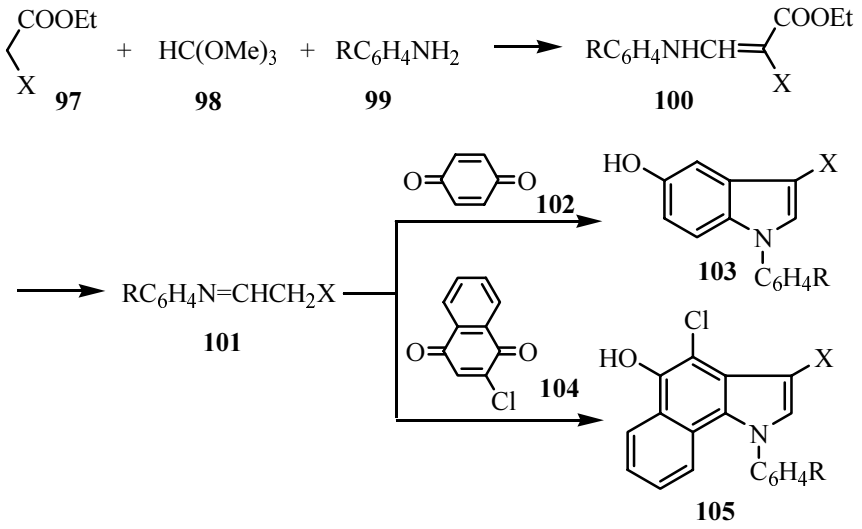
The reaction of ketone oximes **90** with olefin **6** in the presence of butyllithium followed by treating with H_2SO_4 and boiling in DMF furnished [(+,-)-4,5-dihydroisoxazol-5-yl]acetic acids **91** in 35-79% yields [62].

The reaction of sodium azide **92** with diethyl ethoxymethylenemalonate in the trifluoroacetic acid gave rise to a mixture of compounds **93-96**, isoxazole **93** prevailing [63].



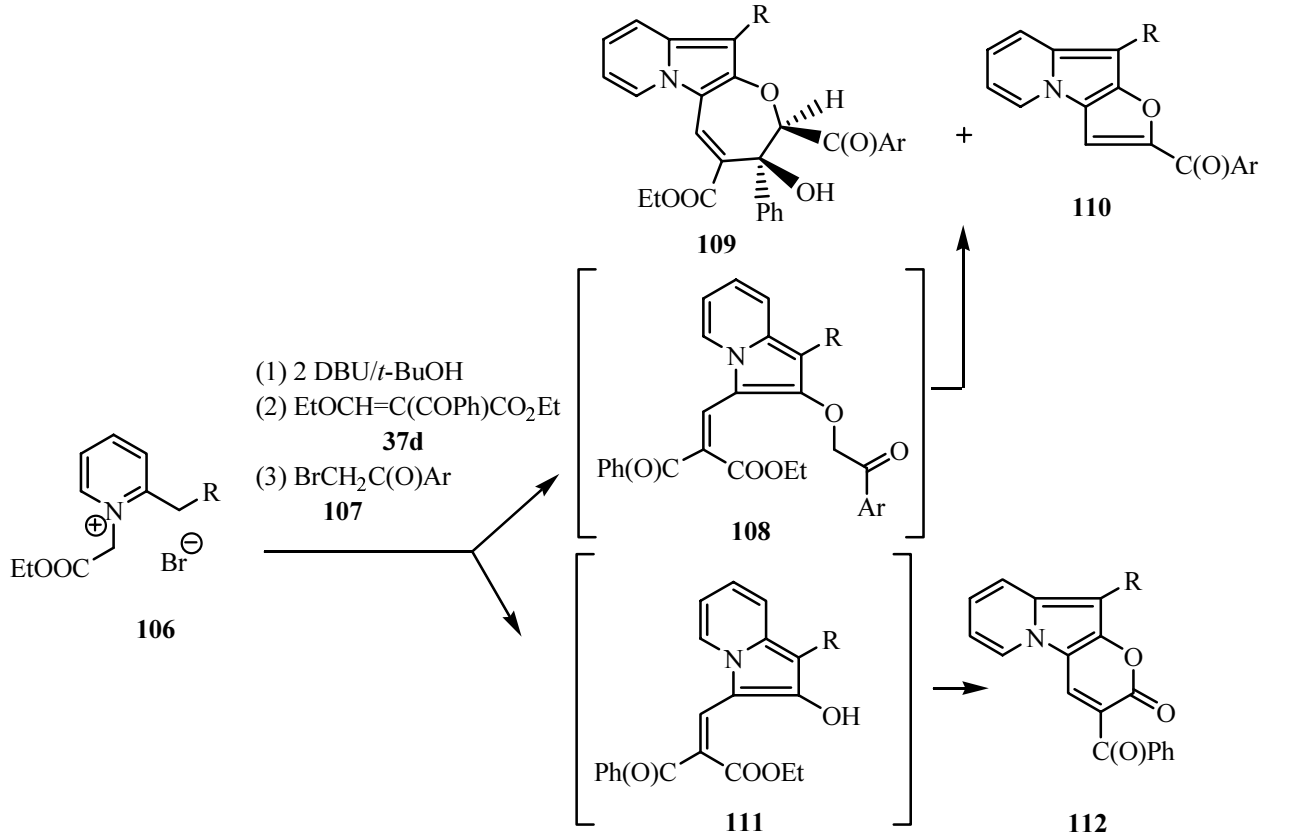
Hence the synthesis of isoxazoles based on alkoxyethylenes can be performed either by reactions with hydroxylamine and N-oxides (classical methods) or involving ketone oximes and sodium azides which are particular procedures for constructing the target compounds.

II.1.3. Other five-membered heterocycles. Pyrroles can be obtained using alkoxyethylenes by several routes. The reaction of methylene-active compound **97** with triethyl orthoformate **98** and amines **99** affords enamines **100** that by heating in DMF in the presence of water undergo decarboethoxylation converting into intermediate compound **101**; the reaction of the latter *in situ* with *p*-benzoquinone **102** or with 2-chloro-1,4-naphthoquinone**104** in DMF results respectively in 1-(R-phenyl)-3-X-5-hydroxyindoles **103** or in fused indoles **105** [64].



X = CN, COOMe, COOEt, Ac; R = 3-MeO, 2-Cl, H.

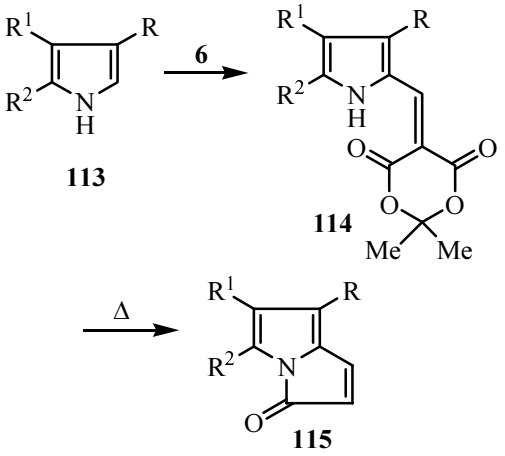
The synthesis of indolisines fused with oxorings of various size was performed by treating pyridinium bromide **106** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by reaction of the arising 2(3H)-indolisinone with ethyl ethoxymethylenebenzoylacetate **37d** and further with phenacyl bromide **107** in the presence of a base [65]. In this way were obtained 2,3-dihydrooxepino[2,3-b]indolisines of *cis*-configuration in positions *2* and *3* **109** (yield 2-5%), 2H-pyrano[2,3-b]indolisin-2-ones **112** (yield 4-10%), and furo[2,3-b]indolisines **110** (yield 3-10%).



R = Me, Et; Ar = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4.

Products **109** and **110** form through a common intermediate, 2-arylcarbonylmethoxy-3-[2-benzoyl-2-(ethoxycarbonyl)vinyl]indolisine **108**, and product **112** is generated obviously by an intermolecular nucleophilic attack of oxygen from 2-hydroxy group on the ester carbonyl carbon in 3-[2-benzoyl-2-(ethoxycarbonyl)vinyl]-2-indolisinol **111**.

Olefin **6** with substituted pyrrole **113** in MeCN provide products of methoxy group replacement **114** which on the flash-thermolysis afford pyrrolisine-3-ones **115** [66].



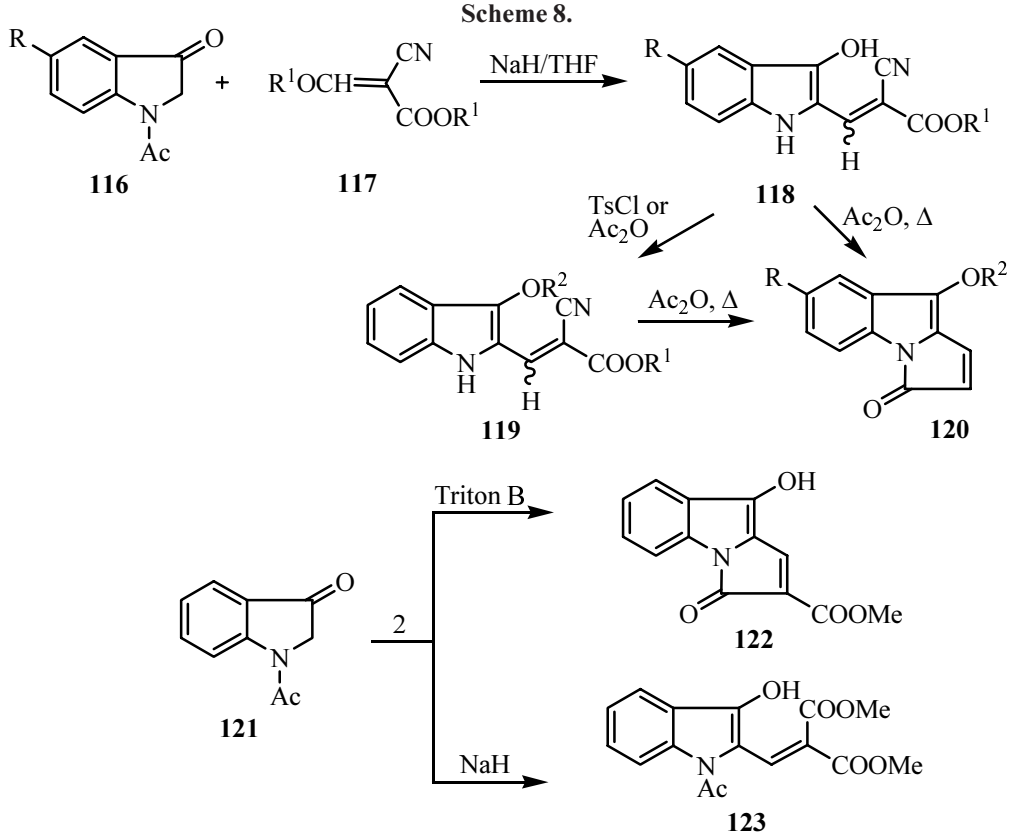
R = H, Ph; R^1 = H, Ph; R^2 = H, Me, Ph.

1-Acetyl-3-oxo-2,3-dihydroindoles **116** and **121** reacted with alkoxymethylene derivatives of ethyl cyanoacetete **117** and dimethyl methoxymethylenemalonate in the presence of sodium hydride to give products of alkoxy group substitution **118** and **123**. The boiling of compound **118** or its acetyl (tosyl) derivatives **119** in acetic anhydride resulted in the cyano group elimination and cyclization into (3H)-pyrrolo[1,2-*a*]indol-3-ones **120**. The reaction of 2,3-dihydroindole **121** with alkoxyethylene **2** in the presence of triton B gave rise to fused pyrrole **122** (Scheme 8) [67].

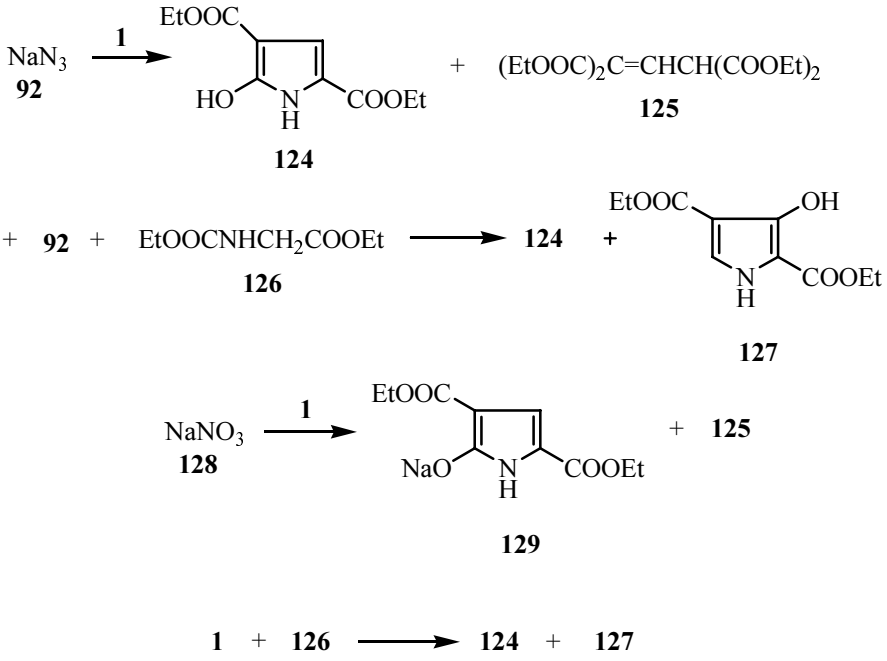
The preparation of substituted pyrroles by reactions with diethyl ethoxymethylenemalonate with various nitrogen-containing compounds was investigated [68]. It was shown that the reaction with sodium azide **92** in DMSO at 100°C afforded a mixture of products **124** and **125**, pyrrole **124** prevailing, and at adding to the reaction mixture diester **126** led to formation also of pyrrole **127**.

The reaction of sodium nitrite **128** with diethyl ethoxymethylenemalonate at boiling in ethanol afforded sodium salt **129** and an open-chain substance **125**, and with ester **126** pyrroles **124** and **127** were obtained [68].

Scheme 8.



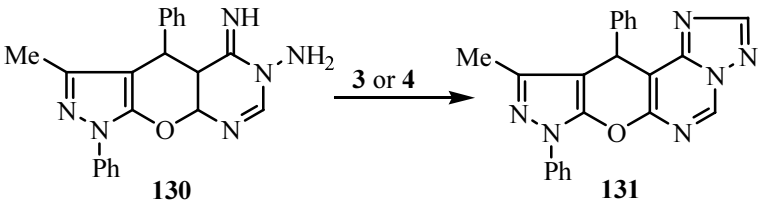
R = H, OCH_3; R^1 = Me, Et; R^2 = Ac, Ts.



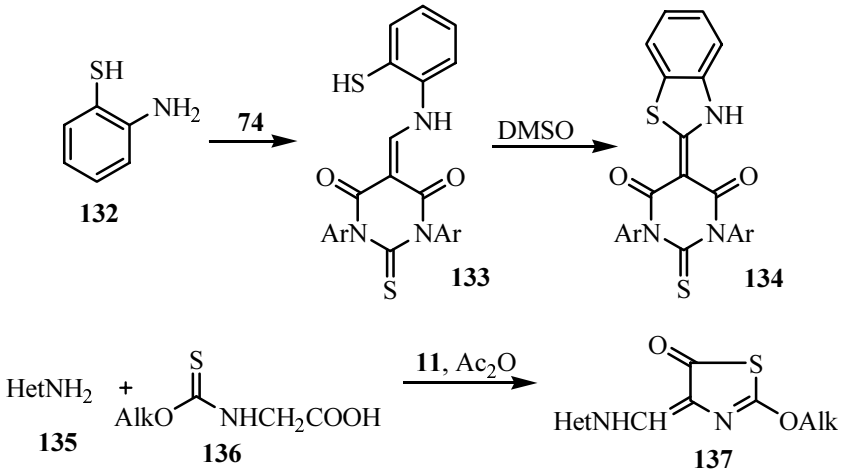
In reaction with fused 1-amino-6-iminopyrimidine **130** ethyl ethoxymethylenecyanoacetate or EMMN served as a source of methylene group to close the ring between two nitrogen atoms by a carbon bridge giving in a 84% yield fused 1,2,4-triazole **131** possessing a physiological activity (Scheme 9) [69].

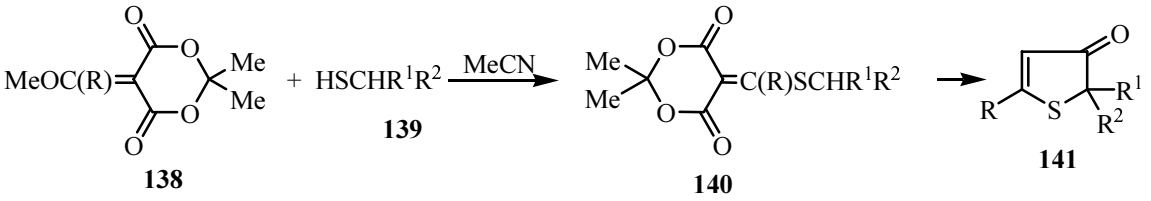
Thiazole derivative **134** was obtained by condensation of alkoxyethylene **74** with 2-aminothiophenol **132** followed by oxidation of the formed enamine **133** with DMSO [70]. Thiasole structure **137** was prepared by one-pot reaction of heteroaromatic amines **135** with ethers **136** in the presence of $HC(OEt)_3$ and Ac_2O [71] (Scheme 10) .

Scheme 9.



Scheme 10.

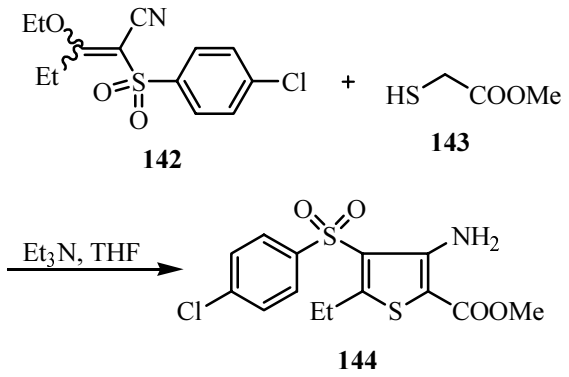




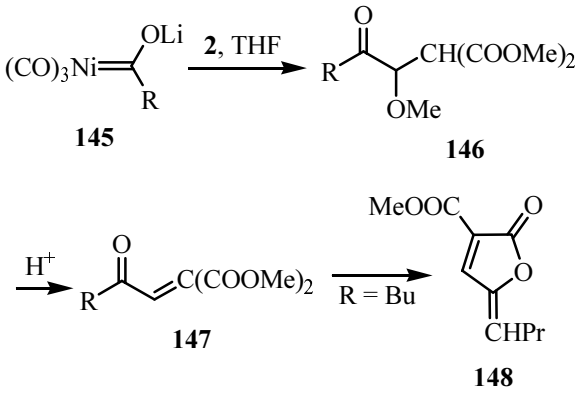
R = H, Me, Ph, 4-t-BuC_6H_4, MeS; R^1 = H, Me; R^2 = H, Me, Ph, COOMe; R^1R^2 = C_5H_{10}.

1-Methoxyalkylidene derivatives of Meldrum's acid **138** react with thiols **139** in MeCN furnishing the product of S_NVin of the methoxy group by a sulfur atom **140** whose subsequent pyrolysis afford thiophenes **141** [72].

The reaction of ethoxyalkylidene derivative of CH-acid **142** with ester **143** in the presence of triethylamine in THF gave rise to thiophene **144** [73].



Treating compound **2** with nickel acylate complex **145** in THF gave a product of conjugate addition **146** in 89% yield; the reaction of the latter with sulfuric acid afforded in high yield olefin **147**, which at R = Bu under the reaction conditions underwent cyclization in 95% yield into furan-2-one derivative **148** [74].



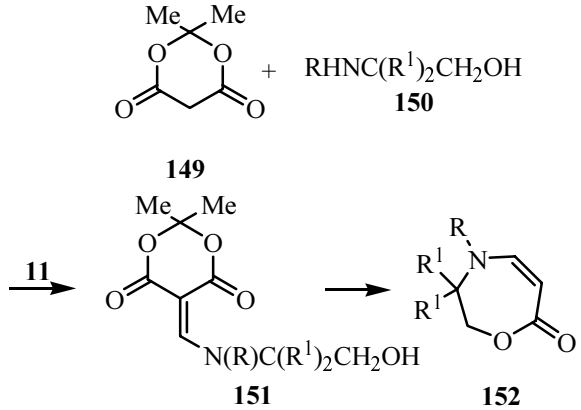
R = Bu, Ph.

Thus in the ring closure of five-membered heterocycles the alkoxyethylenes most frequently play the role of a source of a three-carbon block C–C–C (synthesis of pyrazoles, isoxazoles, pyrroles, thiophenes, and furanes). They can also supply one- two-, and four-carbon blocks. The alkoxyethylenes can also initiate the ring closure of a heterocycle not being directly involved in the building up of its structure (synthesis of pyrroles and thiazoles).

II.2. *Synthesis of Seven-Membered and Macroheterocycles*

The majority of the syntheses of large and medium rings occurs as an intramolecular cyclization of very reactive ketones containing nucleophilic groups situated at a distance corresponding to the desired number of atoms in the ring.

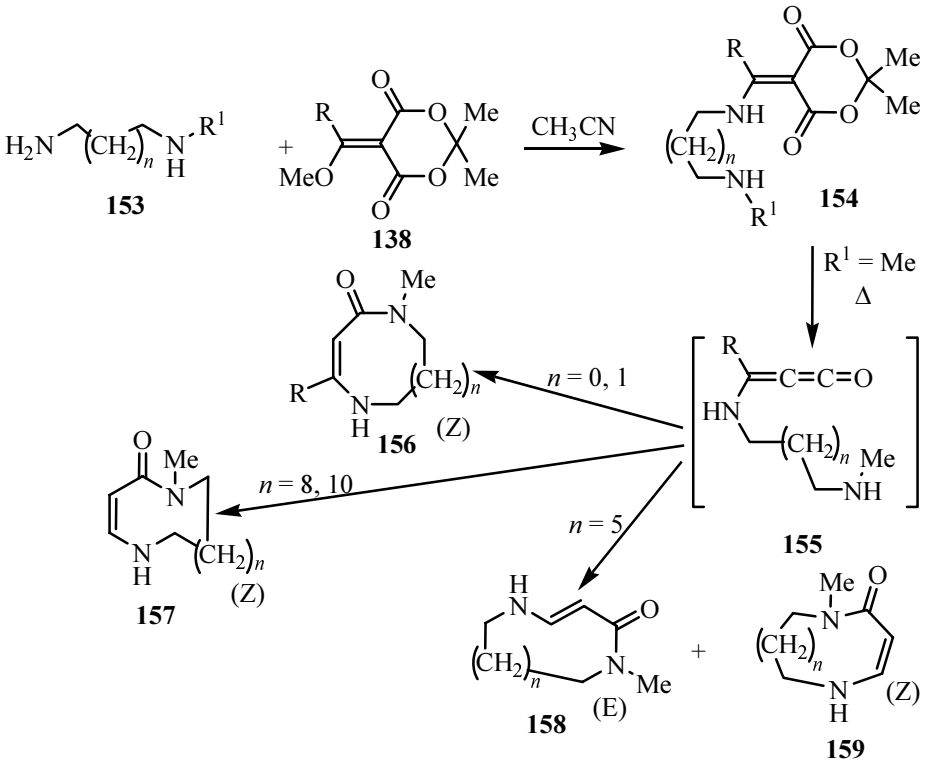
Thus a one-pot synthesis using Meldrum's acid **149**, triethyl orthoformate, and aminoalcohol **150** gave a product of S_NVin **151** whose thermolysis via an intermediate aminomethyleneketene led to 2,3-dihydro-1,4-oxazepin-7-one **152** [75].



R = H, Me, Et, Ph; R^1 = H, Me.

A fast preparation of large enaminolactams was described in [76]. The reaction of secondary ω-aminoalkylamines **153** with alkoxyethylene **138** in acetonitrile afforded Meldrum's acid derivatives **154**. In some cases in low yield formed also bis-derivatives of Meldrim's acid as reaction products of both amino and N-methylamino group with two equiv of alkoxyethylenes. The thermolysis of compound **154** occurred through intermediate for-

Scheme 11.



R = H, Me; R^1 = Me, Bz, *t*-butoxycarbonyl

mation of ketenes **155** that under the reaction conditions transform into the corresponding macrocycles **156-159**.

It was shown that the decomposition of the Meldrum's acid derivatives containing *tert*-butoxycarbonyl and benzyl substituents at the terminal nitrogen atom did not afford the expected macrocycles. This result is due to the difficulties arising for the attack on the ketene because of low nucleophilicity of the NH–CO–O–*t*-Bu group and sterical hindrances created by the benzyl group. The thermolysis of methyl derivatives **155**, except for the diamine with $n = 3$, proceeded with intramolecular nucleophilic addition of the terminal $NHCH_3$ group to the central double bond resulting in enaminolactams possessing as a rule the Z-configuration. Their yield depends on the ring size: The seven- and eight-membered rings were obtained in 70-75% yield, whereas their fifteen- and seventeen-membered homologs formed in 40–50% yield (Scheme 11).

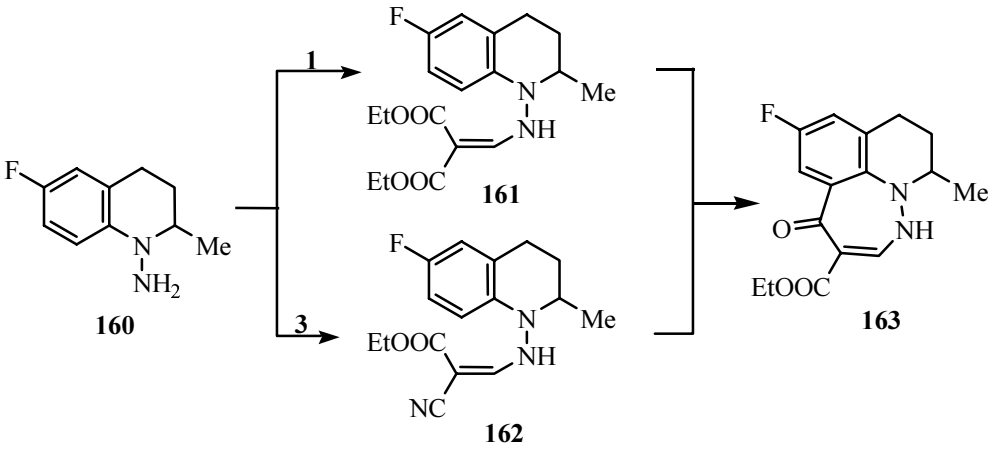
3,4-Dihydro-2*H*-quinoline **160** at boiling in toluene with diethyl ethoxymethylenemalonate or ethyl ethoxymethylenecyanoacetate furnished products of S_NVin **161** and **162** in a quantitative yield; these compounds through an intramolecular cyclization gave ethyl 1-oxo-4,5-benzidiazepine-2-carboxylate **163** in respective yields 11 and 12% [77]. This process should be mentioned as an analog of the Gould–Jacobs reaction where because of an "additional" nitrogen atom forms not a six-membered but a seven-membered ring.

II.3. *Synthesis of Benzene Derivatives*

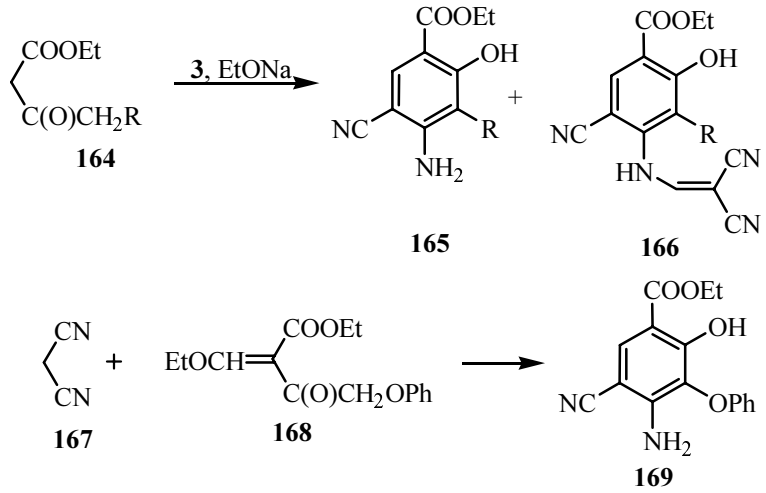
The alkoxyethylenes may take part in constructing aromatic systems lacking heteroatoms. These reactions are infrequent. They consist in S_NVin of an ethoxy group with a methylene-active fragment of some CH-acid followed by cyclization with a C–C bond formation. For instance, a reaction of two CH-acids, **164** and **167** with an ethoxymethylene derivative of another was studied, and it was demonstrated that EMMN with CH-acid **164** in the presence of sodium ethylate afforded a mixture of substituted aniline **165** with a product of its reaction with the second EMMN molecule **166**, whereas from malononitrile **167** and alkoxyethylene **168** formed only substituted aniline **169** [78].

The heating of CH-acid **170** with diethyl ethoxymethylenemalonate provided acridone **171** [79]. It should be mentioned that this process is quite similar to Gould–

Scheme 12.

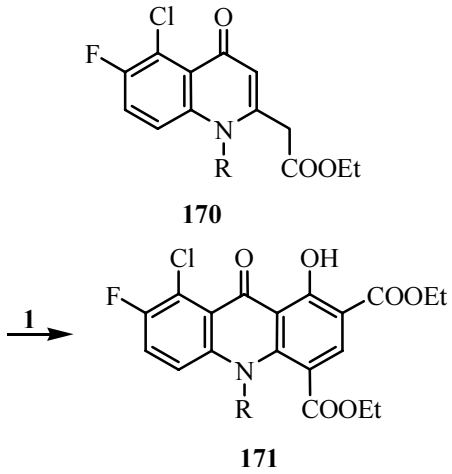


Scheme 13.



R = Alk, cycloalkyl, AlkO, ArO, cycloalkoxy.

Jacobs reaction where not nitrogen but a methylene-active fragment acts as a nucleophile.

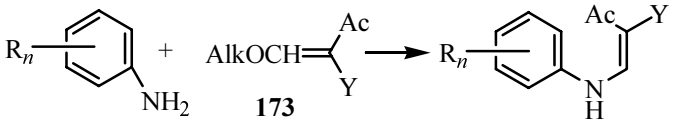


R = H, Et.

II.4. *Alkoxyethylenes Reactions without Cyclization*

These reactions are well documented and often constitute a first stage in the synthesis of various heterocycles. A nitrogen atom acting as a nucleophile may be acquired from aromatic or aliphatic amines, amides, or be a part of a ring of a nonaromatic heterocycle. In the first case the product of S_NVin undergoes further the cyclization into pyrimidines, fused pyridines, or quinolines. However the cyclization of these products is sometimes impossible, or just they are the target compounds.

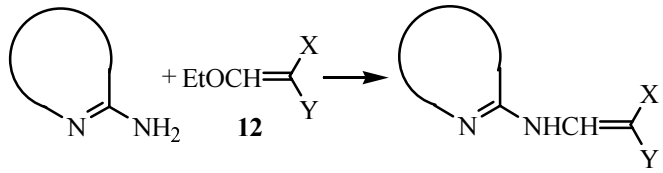
For instance, the reaction of aromatic amines **172** with alkoxyethylene **173** gave rise to enamines **14a** which did not suffer further cyclization if in the alkoxyethylene at least one of the electron-acceptor groups was not an alkoxycarbonyl [80–84]. Enamines **14a** are a new class of protein tyrosine kinase inhibitors of low molecular weight.



172 **14a**

R = H, Alk, Ar, Het; Y = Ac, CN; *n* = 1–4.

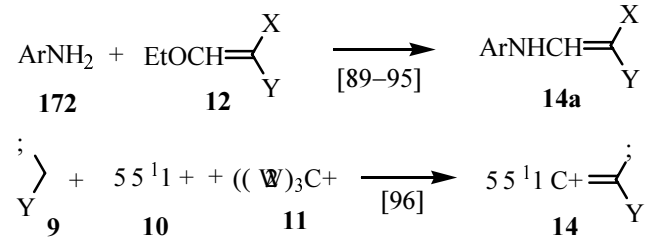
The reaction of nitrogen-containing heterocycles containing an amino group in the *ortho*-position with respect to the endocyclic nitrogen **135a** with alkoxyethylene **12** afforded products of S_NVin **14b** whose cyclization can provide fused pyrimidines. However some of these products are cardioactive, or are applied to dyeing polymer fibers and thus are target compounds [85–88].



135a **14b**

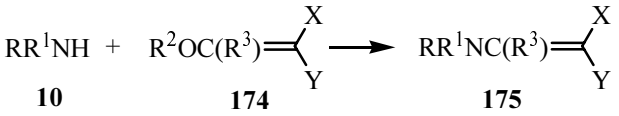
X, Y = COOEt, CN, $C(O)COCH_2C(CH_3)_2CH_2OC(O)$, $C(O)C_6H_4C(O)$.

Products of S_NVin **14**, **14a** are also target substances, intermediates in the synthesis of fused pyridines by Gould–Jackson reaction, and therewith instead of alkoxyethylene **12** and amine **172** in some cases a mixture of CH-acid **9**, triethyl orthoformate, and amine **10** were used. Enamines **14a** possess antiphlogistic and analgesic action at low toxicity, they are used as nonsteroid inhibitors for androgen binding, and also are applied as semiproducts in the synthesis of antimicrobial, antitumor, and antiviral drugs.



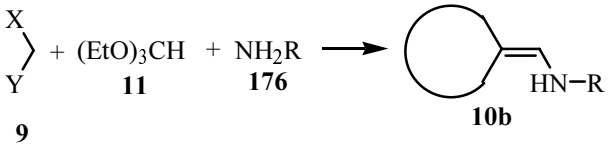
X = Bz, Y = COOEt, X + Y = C(O)OC(CH$_3$)OC(O) R = Ph, Ar, 1-naphthyl; R^1 = H, Me.

At the use in the S_NVin reactions with alkoxyethylene **174** of various amines, ammonia, and amides **10** formed enamines **175**, which were as a rule prepared for medicinal applications against bacterial and micotic infections [33, 36, 54, 97–108].



R, R^1 = H, Alk, PhC(O), Ar; X, Y = COOAlk, CN, SO_2, Alk, COAlk, SO_2Ph, $COCF_3$, NO_2; R^2 = Alk C_1–C_4;

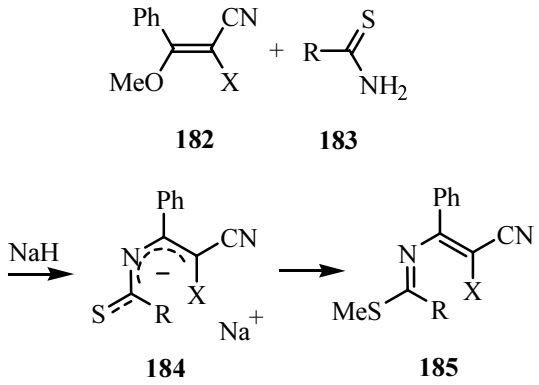
In a one-pot process using CH-acid **9**, TOF, and various amines and hydrazines **176** also formation of similar enamines **10b** is possible which showed an aldose reductase activity [109–114].



R = Alk, Ar, NHAr, NMePh.

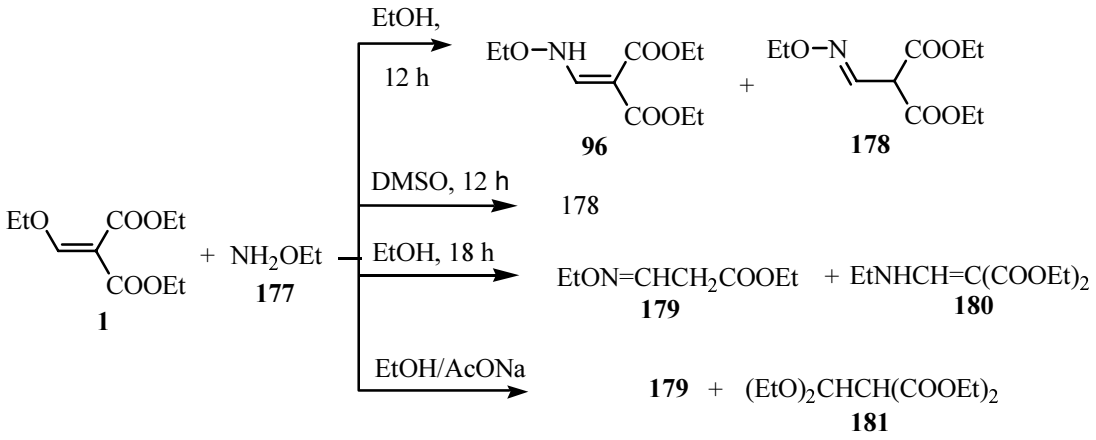
The reaction between diethyl ethoxymethylenemalonate with hydroxylamine ethyl ether **177** was investigated under various conditions. The boiling in ethanol for 12 h yielded an isomer mixture **96** and **178**, and in DMSO formed only ester **178**. The boiling in ethanol for 18 h resulted in azomethine **179** and olefin **180**, and boiling for 12 h in ethanol in the presence of AcONa furnished a mixture of ester **179** and acetal **181** (Scheme 14) [63].

The reaction of alkoxyethylene **182** with thioamides **183** in DMF in the presence of NaH as base proceeded in the first stage by the type of Michael addition with subsequent formation of a salt **184** methylated into 1-methylthio-2-azabuta-1,3-diene-4-carbonitrile **185**, and therewith always occurred the regioselective methylation of sulfur and E-stereoselectivity in the formation of the double C=N bond [115].

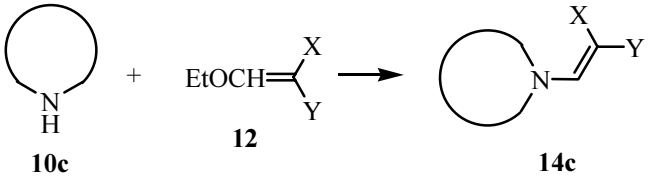


X = CN, CO_2Me; R = Me, Ph.

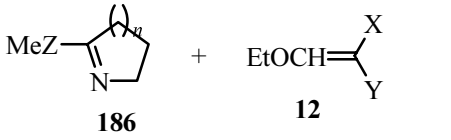
Scheme 14.

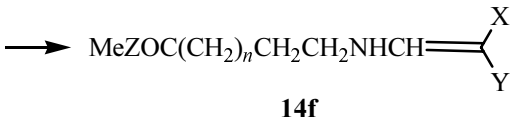


When the nucleophile in the S_NVin reaction is a nitrogen atom included into a nonaromatic cyclic system **10c** the process results in N-(X,Y-2,2-vinyl)-substiturted heterocycles **14c** [116]. A ring opening is also possible. For instance, the reaction of lactim (thio)ethers **186** with alkoxyethylene **12** involves rings opening to afford products of substitution by nitrogen-containing moieties **14f** [117].



X, Y = CN, COOEt, X + Y = SC(S)N(CH_2COOMe)C(O), C(O)COC(Ph)N.

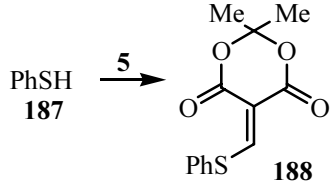




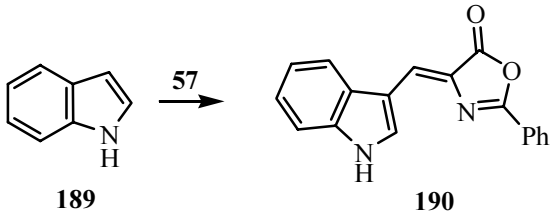
14f

Z = O, S; X,Y = Ac, COOEt.

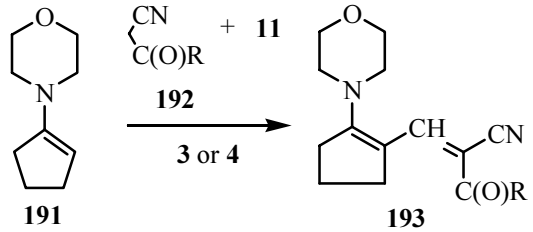
The sulfur atom also can play the role of a nucleophile. For instance, under the effect of the microwave irradiation olefin **5** reacted with thiophenol **187** to give a product of S_NVin **188** [118].



Enamines containing a reactive methylene group yield with alkoxyethylenes diene(polyene)amines. For instance, on condensation of imidazole **189** with 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one **57** in the glacial acetic acid olefin **190** of the *Z*-configuration was obtained [119].

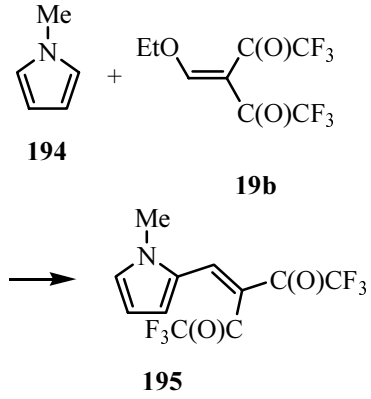


By reaction of *N*-(cyclopent-1-enyl)morpholine **191** with CH-acids **192** and TOF or with a prefabricated ethyl ethoxymethylenecyanoacetate at heating the corresponding products of S_NVin **193** were obtained in moderate yields (31–77%) [120].

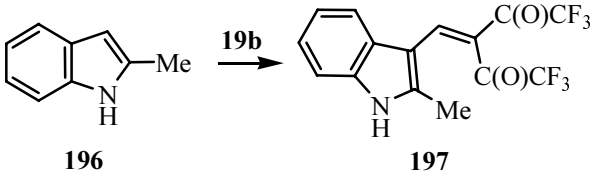


R = OEt, NHMe.

By reaction of pyrroles **194** and indoles **196** with alkoxyethylene **19b** in the presence of a Lewis acid ($ZnCl_2$) heteryl-substituted enones **195** and **197** were obtained in respective yields 88 and 84% [121].

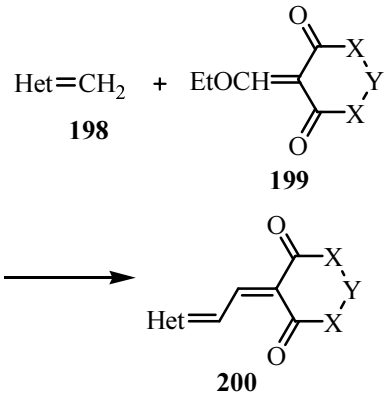


194 **19b** **195**



196 **197**

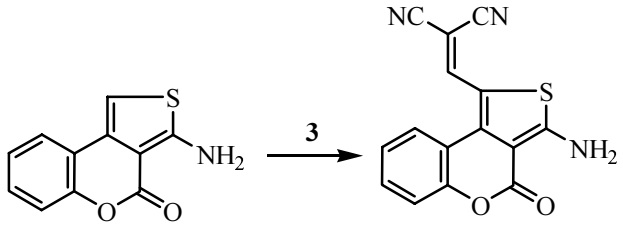
Methylene-*N*-heterocycles of enamine type **198** reacted with cyclic 2-ethoxymethylene-1,3-dicarbonyl compounds **199** in toluene to furnish 2-[2-(heterylidene)-ethylidene]-1,3-dicarbonyl compounds **200** [122].



198 **199** **200**

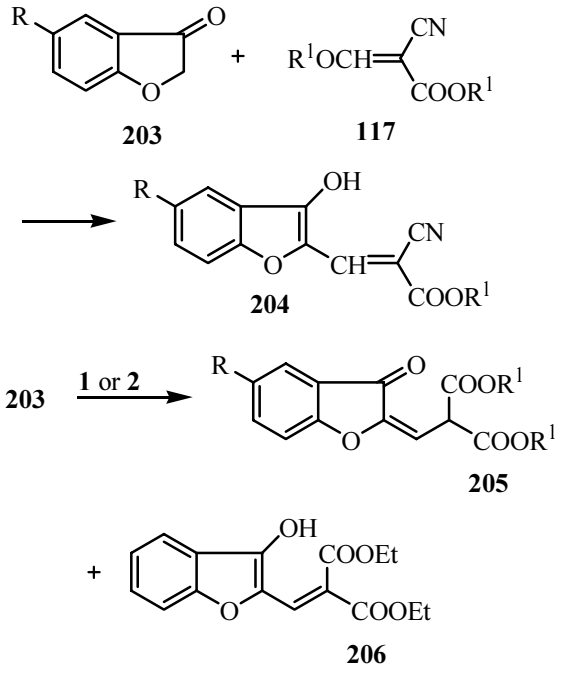
X = O, NMe , CH_2; Y = CMe_2, CO.

The reaction with EMMN of fused **201** possessing a reactive hydrogen atom in the *2* position belongs to a similar type. Thus system **202** was synthesized [123].



201 **202**

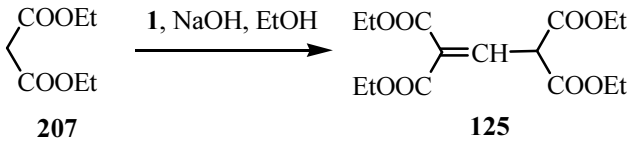
By reaction with alkoxyethylene of a heterocycle having in the ring a methyle-active group a product of S_NVin was obtained. For instance, by condensation with alkoxyethylenes of 3-oxo-2,3-dihydrobenzofuran **203** in the presence of a base 2-vinylbenzofuran derivatives **204** (a mixture of *E*- and *Z*-isomers) were prepared at the use of alkoxymethylenecyanoacetates **117**, and with alkoxymethylenemalonates **1** or **2** the corresponding 2-ethylidene-3-oxo-2,3-dihydrobenzofurans **205** (a mixture of *E*- and *Z*-isomers) and also compound **206** (in reaction with diethyl ethoxymethylenemalonate) were obtained [124].



203 **117** **204** **205** **206**

R = H, Cl; R^1 = Me, Et.

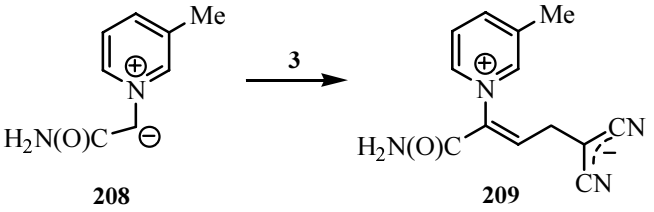
The diethyl ethoxymethylenemalonate reacted with diethyl malonate **207** in the presence of alkali affording a product of S_NVin, olefin **125** [68].



207 **125**

The regioselectivity of various methyl-substituted ylides with alkoxyethylene was studied, and it was shown to depend on the methyl group position in the pyridine ring [125]. The reaction of ylides **208** containing the methyl group in the position *3* with EMMN in methanol proceeds

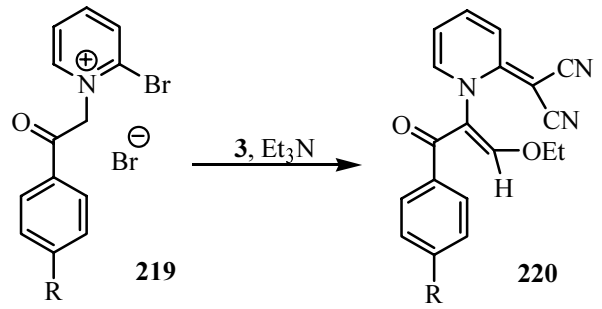
exclusively with the formation of zwitter-ions **209**. The cause of this result is presumably the impossibility for ylide with a substituent in the position *3* to form anhydrobases with an exocyclic methyl group that occurs for 2- and 4- substituted ylides (structures **211** and **214**).



In the case of 2- or 4-substituted ylides **210** and **213**, the reaction as a rule occurs at the methyl group affording in good yields the corresponding 1-R-2(4)-(3-X-3-Y-prop-2-en-1-ylidene)-1,2(1,4)-dihydropyridines (qiunolines) **212** and **215** (Scheme 15).

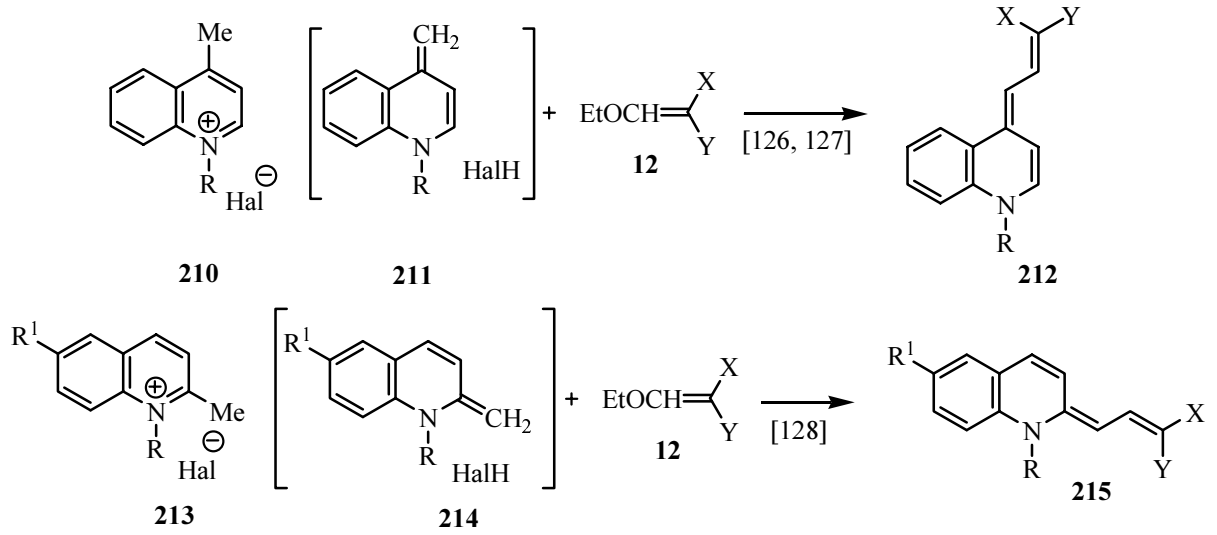
However bringing into this reaction 1-(4-R-phenacyl)-4-methylquinolinium bromides **216** resulted in formation of merocyanine **217** in a mixture with zwitter-ions (Scheme 16) **218**.

The reaction of 2-bromopyridinium bromides **219** with EMMN in the presence of excess triethylamine was also studied providing 2-dicyanomethylene-1-[1-(4-R-benzoyl)-2-ethoxyvinyl]-1,2-dihydropyridines **220** whose



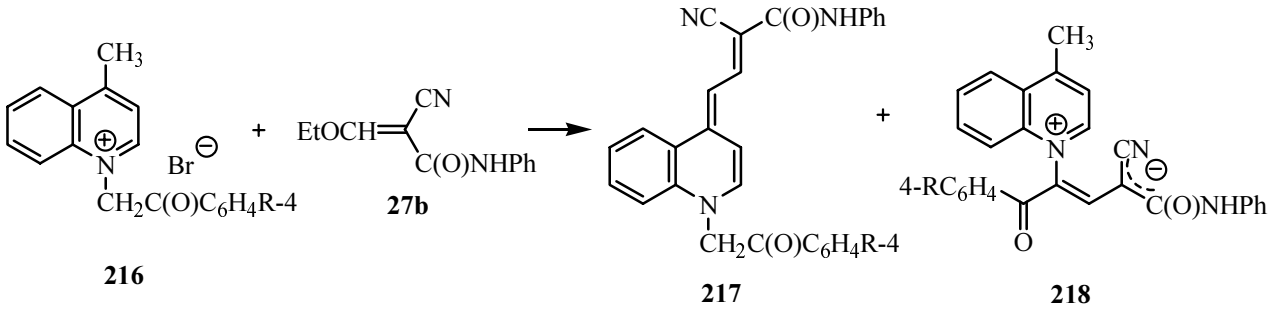
R = H, Cl.

Scheme 15.



R = Me, Et, CH_2=CH–CH_2; R^1 = H, Me; X, Y = CN, PhNHCO.

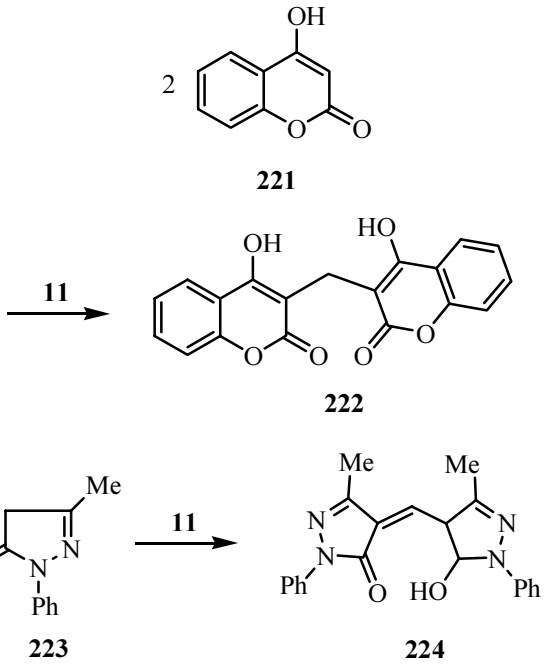
Scheme 16.



R = H, Cl, Br.

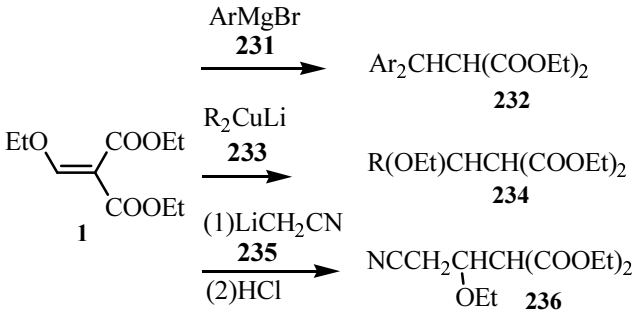
structure was established by X-ray diffraction analysis [129].

Obviously two molecules of CH-acids are linked via intermediate formation of an alkoxyethylene by transfer of one carbon from triethyl orthoformate. Thus reactions with TOF of 4-hydroxycoumarin **221** and pyrazolone **223** afforded respectively structure **222** [130] and dipyrazolylmethane **224** [131].



Considering the wide practical applications of alkoxyethylenes in the S_NVin reactions, stands out the relatively small number of syntheses proceeding with the alteration in the hybridization of the carbon atom at the double bond from sp^2 to sp^3. The reaction of unsaturated alcohol **225** [132] and cyclophosphite **227** [133] with diethyl ethoxymethylenemalonate occurred affording the corresponding products of addition to the double C=C bond, systems **226** and **228**, and the reaction of 1-phenyl-*o*-carboran-2-yllithium **229** [134] with alkoxyethylene **78** followed by acidification resulted in saturated system (Scheme 17) **230**.

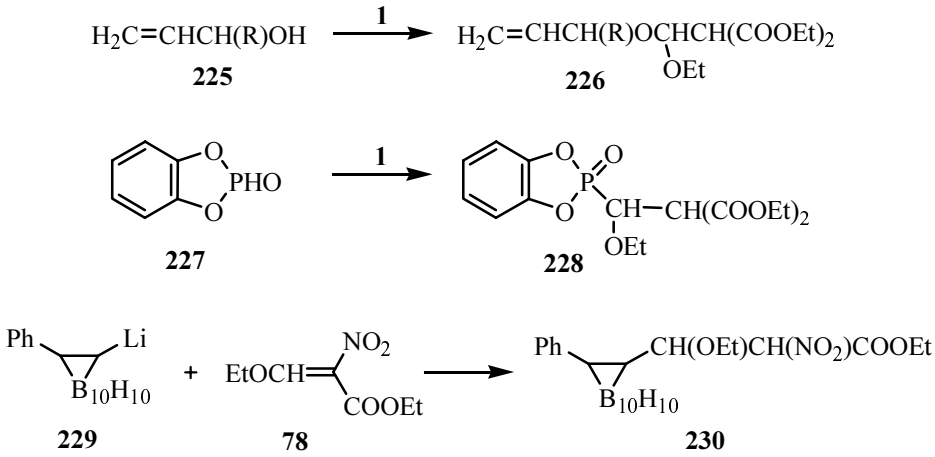
The diethyl ethoxymethylenemalonate was converted into derivatives of diethyl 2-(1,1-diarylmethyl)malonate **232** by treating with arylmagnesium bromide **231** [108], namely, by the classic Grignard reaction (no formation of the presumed product of S_NVin was observed), and the reactions with organocuprates **233** and cyanomethyllithium **235** afforded derivatives of diethyl 2-(1-ethoxyalkyl)malonates, **234** [108] and **236** respectively [135].

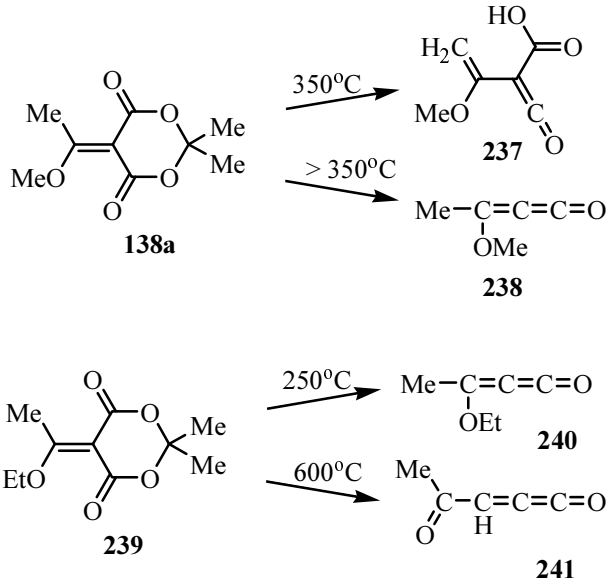


R = Ph, Bu, *t*-Bu.

Alkoxyethylenes can undergo transformations without an attack of a nucleophile. In a vacuum flash-thermolysis of olefin **138a** with matrix separation at 350°C a conjugated system **237** was obtained, and at higher temperature formed system **238**. Compound **239** at 250°C furnished ketene **240**, and at 600°C, s-*trans*- and s-*cis*-ketenes **241** [136].

Scheme 17.





Thus alkoxyethylenes can give rise to open-chain products both through the S_NVin of the alkoxy group with N, S, or C atoms and via addition across the double bond either with retention or elimination of the ethoxy group. The alkoxyethylenes undergo vacuum flash-thermolysis giving various unsaturated systems. Inasmuch as the alkoxy group in the alkoxyethylenes is prone to elimination the methods of preparation of saturated addition products are seldom used and have no preparative importance.

III. CONCLUSIONS

The above reported suggests that the reaction of the functionally substituted alkoxyethylenes with nucleophilic reagents occurs mostly by the type of nucleophilic vinyl substitution. When several reaction products are expected, the selection of appropriate conditions may make these reactions regiocontrlled. Variation of functional groups in the alkoxyethylenes permits preparation under sufficiently mild conditions of desired cyclic and linear biologically active substances.

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