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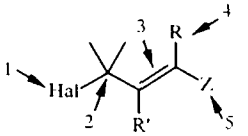
DERIVATIVES OF 4-HALOCROTONIC ACIDS, CONVENIENT REACTANTS IN THE SYNTHESIS OF HETEROCYCLES. (REVIEW)

V. A. Artemov, V. L. Ivanov, and V. P. Litvinov

Literature data are reviewed for the first time on the use of 4-halocrotonic acid derivatives in the synthesis of five- and six-membered heterocycles containing one or several heteroatoms in the ring, and their annelated analogs.

Keywords: enethiolatonitriles, condensed pyridines and pyrimidines, crotonic acid derivatives, cascade heterocyclization.

Functionally substituted crotonic acids possess a high synthetic potential, especially for obtaining various types of heterocycles. In this respect a special place is held by derivatives of 4-halocrotonic acid containing functional groupings Z such as ester, nitrile, or carboxyl, and chlorine or bromine atoms as halogen.



Substituted 4-halocrotonic acids contain several reaction centers predetermining the type of interactions in which they may participate.

1. Halogen atom, readily reacting by nucleophilic substitution.
2. Methylene group in the vinylogic position to an electron-withdrawing Z group.
3. Double bond activated towards nucleophilic addition and cycloaddition by the presence of the conjugated Z group.
4. Substituent R (from hydrogen atom and hydrocarbon radicals to functional groups analogous to the Z group).
5. Electron-withdrawing group Z able to being subjected to nucleophilic attack.

Conversions in which derivatives of 4-halocrotonic acid are involved have been classified by us according to the reaction center participating in the reaction. Since the halogen atom is practically always subjected to nucleophilic substitution the main accent in this review is directed towards the reactions proceeding at other reaction centers.

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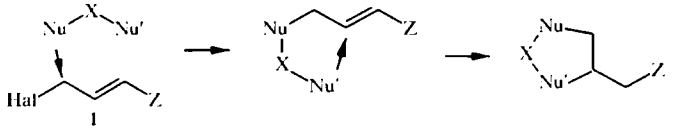
1. REACTIONS INVOLVING THE DOUBLE BOND

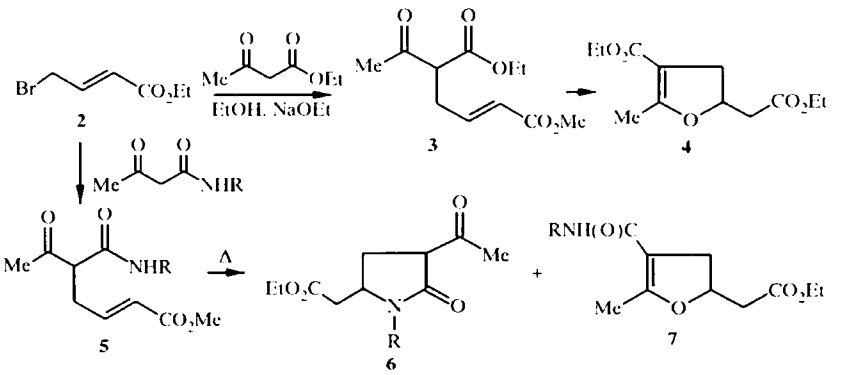
1.1. Nucleophilic Addition at the Double Bond

Approaches to the construction of heterocyclic systems from 4-halocrotonic acid derivatives are widely described in the literature. The key stages of these are the nucleophilic addition at the double bond of the croton fragment. Such a cyclization route is effected on interaction of compound **1** with nucleophiles. As a rule nucleophilic substitution of the halogen atom occurs first and then Michael addition of the second nucleophilic center follows:



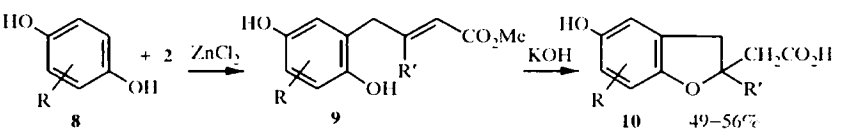
The 4-halocrotonic acid derivative acts as a 1,2-dielectrophile. In the case of 1,3-dinucleophiles five-membered and in the case of 1,4-dinucleophiles six-membered heterocycles are formed. The nucleophilic center attacking the double bond at the key stage may be either a heteroatom (O, S, N) or a carbon atom.

The keto ester **3** obtained from acetoacetic ester and ethyl 4-bromocrotonate **2** is cyclized on heating with the formation of dihydrofuran **4** [1,2]. Reaction proceeds as an intramolecular addition of the OH group of the enol form of compound **3** at the double bond.

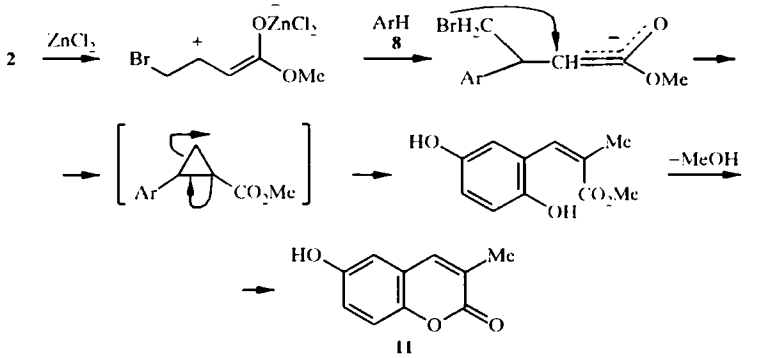


Analogous reactions involving derivatives of acetoacetamide **5** give a mixture of pyrrolidones **6** and dihydrofurans **7** due evidently to competing O- and N-Michael addition [2]. Compounds **5** were successfully isolated only when carrying out the reaction at room temperature. On heating only cyclic products were formed.

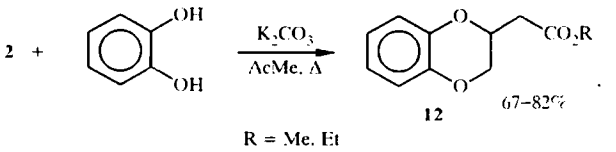
Hydroquinones **8** are alkylated by methyl 4-bromocrotonates **2** under conditions of the Friedel–Crafts reaction with the formation of compounds **9**. On treating the latter with alkali intramolecular addition of the OH group at the double bond occurs leading to benzo[*b*]furans **10** [3].



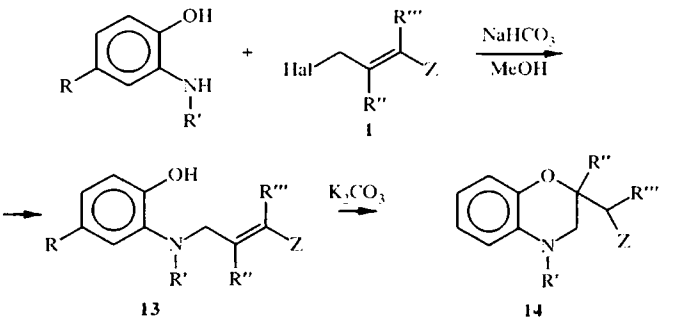
The reaction is accompanied by the subsidiary formation of lactones **11** according to the following scheme:



Alkyl 4-bromocrotonates react with pyrocatechol on boiling in acetone in the presence of potassium carbonate with the formation of benzodioxanes **12** [4,5].

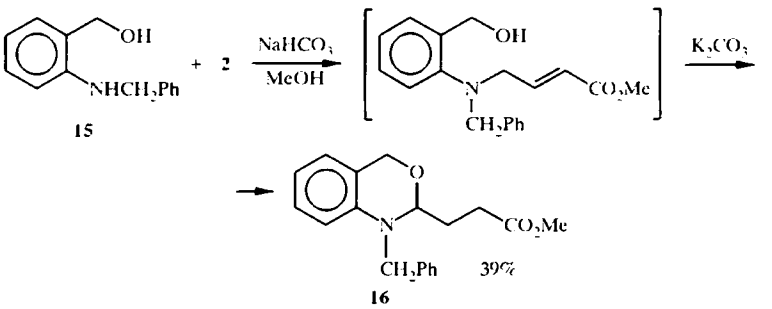


The isolation of monocyclic intermediates **13** when preparing benzoxazine derivatives **14** has been described in a patent [6]. Alkylation of *o*-aminophenol at the nitrogen atom occurs in the first step of the reaction and an intramolecular Michael reaction in the second, leading to closure of the 1,4-oxazine ring with the formation of benzoxazines **14**:

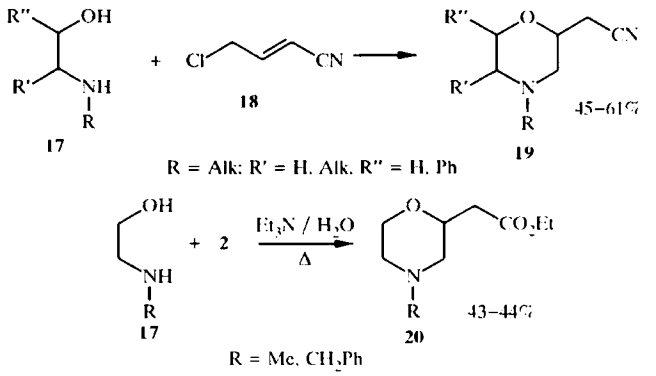


R = H, Me, Cl, NO_2; R', R'' = H, Alk, Ar; R''' = H, Alk, Ar, Z; Z = CO_2Me, CN

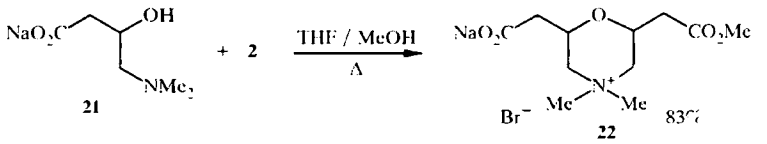
When using compound **15** as substrate reaction occurs analogously in the first step, however no formation of a six-membered ring is observed in the second, but a rearrangement occurs with the formation of the thermodynamically more favored compound **16** [7]:



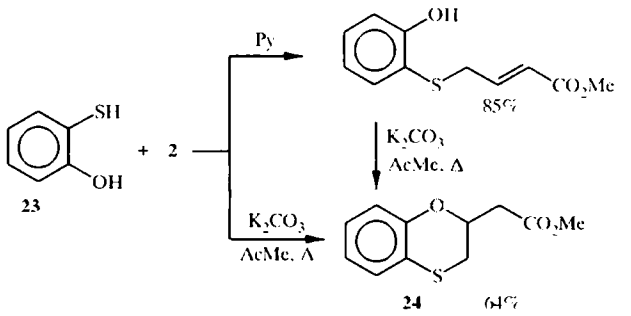
The aliphatic 2-aminoalcohols **17** enter into similar conversions both with 4-chlorocrotononitrile **18** and with ethyl 4-bromocrotonate **2**, tetrahydro-1,4-oxazines **19** or **20** being formed in moderate yield [8,9].



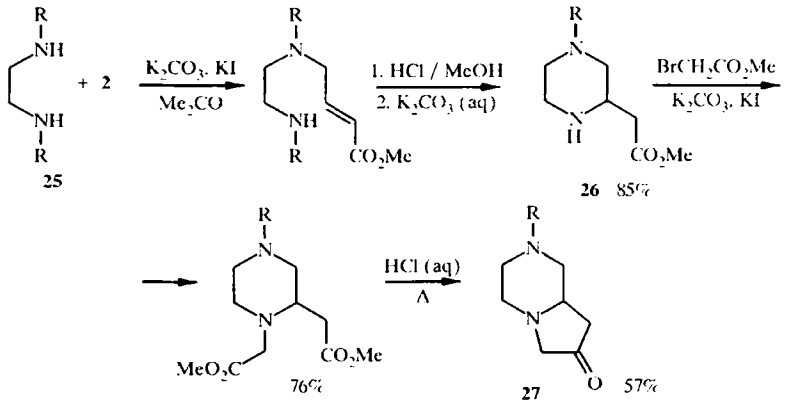
The similarly constructed tertiary amine **21** also reacts with methyl 4-bromocrotonate **2** on boiling in THF/methanol mixture with the formation of the quaternary salt **22** [10]:



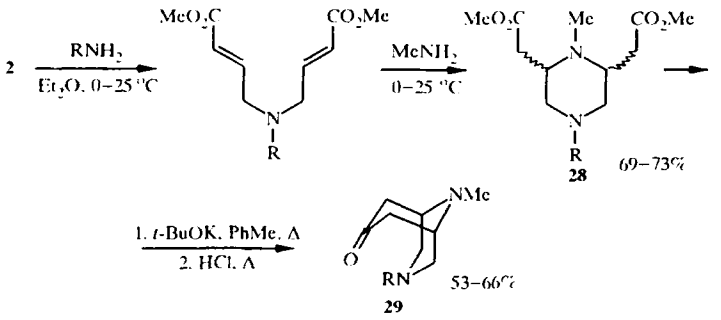
1,4-Benzoxathiin **24** was obtained by the interaction of *o*-mercaptophenol **23** and methyl 4-bromocrotonate **2** [5].



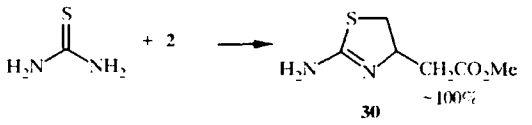
Reactions have also been described in which the nucleophilic center being added at the double bond is nitrogen atom. Diamine **25** reacts with methyl 4-bromocrotonate **2** with the formation of hexahydropyrazine **26** [11], which may be converted into octahydropyrrolo[1,2-*a*]pyrazine **27**:



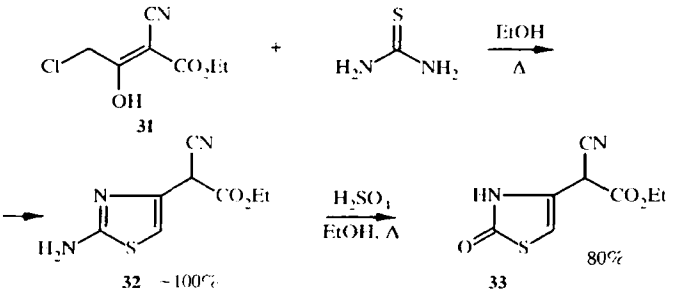
An example is also known of addition of an external nucleophile at two double bonds simultaneously with the formation of hydrogenated pyrazine **28** [12], which was then used for the synthesis of the bicyclic bridge system **29**:



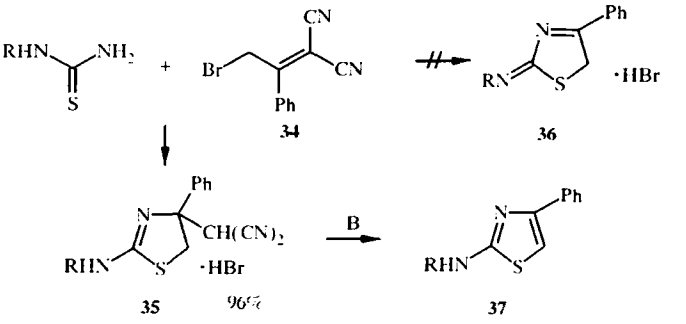
Reactions in which a nitrogen atom acts as the nucleophile in the Michael addition are also characteristic for thiourea and its analogs. In this case alkylation occurs at the sulfur atom with subsequent intramolecular Michael reaction leading to the formation of thiazole ring. Thiourea reacts with methyl 4-bromocrotonate **2** giving dihydrothiazole **30** in quantitative yield [13]:



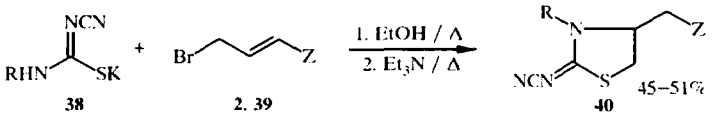
An analogous reaction occurs between thiourea and ethyl ester of 4-chloro-2-cyano-3-hydroxycrotonic acid **31**. In this case dehydration of the cyclic intermediate product leads to thiazole **32**, which in its turn may be hydrolyzed to the corresponding thiazol-2-one **33** [14].



Substituted thioureas react with (2-bromo-1-phenylethylidene)malononitrile **34** with the formation of thiazoline hydrobromides **35** [15]. The initial hypothesis on the formation of imines **36** in this reaction [16] was not confirmed subsequently [15]. On treating with bases salts **35** eliminate malononitrile leading to substituted 2-amino-4-phenylthiazoles **37** [15].

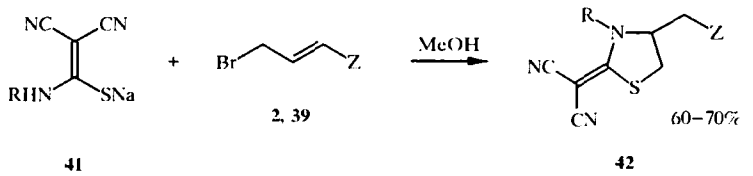


The reaction of N-cyanothioureas **38** containing secondary amino group, with ethyl 4-bromocrotonate **2** or 4-bromocrotononitrile **39** proceeds according to the scheme considered for previous examples and leads to the formation of iminothiazolidines **40** [17]:

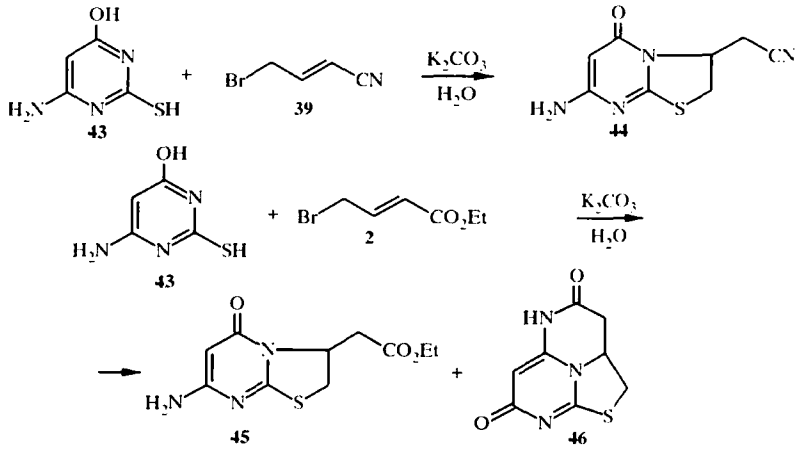


2 Z = CO_2Et, 39 Z = CN

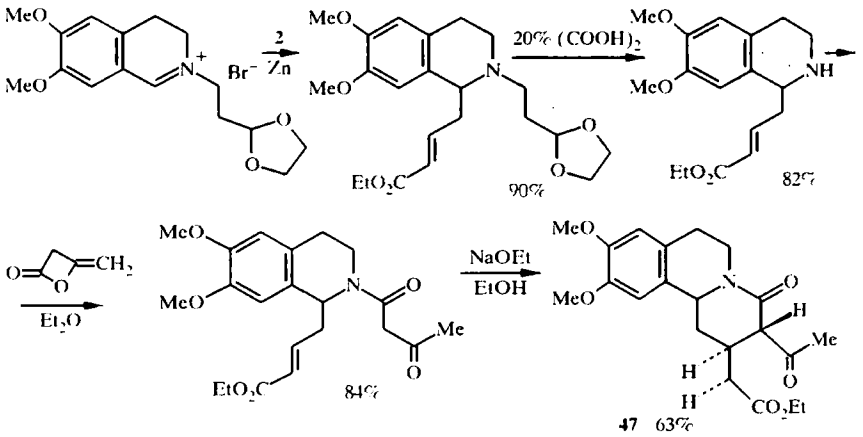
Similar conversions are also characteristic of the adducts of isothiocyanates and malononitrile **41** [18]. Thiazoles **42** are obtained in this case:



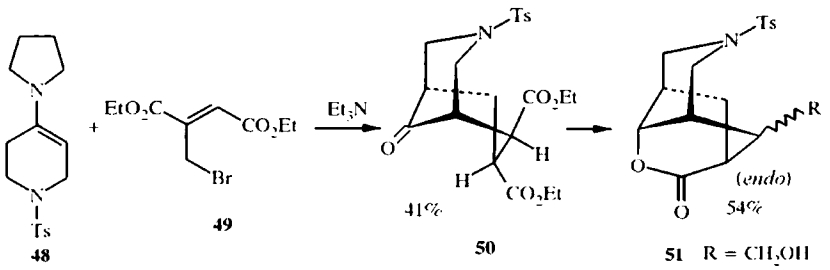
Similarly dihydrothiazolo[3,2-*a*]pyrimidinones **44** and **45** were obtained from 4-amino-6-oxopyrimidine-2-thiones **43** and ethyl 4-bromocrotonate **2** or 4-bromocrotononitrile **39** [19]. In the case of nitrile **39** this reaction proceeds regioselectively. The nitrogen atom of the pyrimidine ring close to the oxygen atom is added at the double bond and the reaction stops at the stage of forming the bicyclic compound **44**. When using ethyl 4-bromocrotonate **2** the Michael reaction is nonregioselective and the isomeric thiazolopyrimidine with a favorable disposition of amino and ethoxycarbonyl groups undergoes intramolecular condensation leading to the tricyclic system **46**:



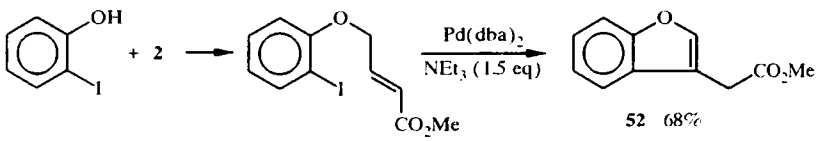
The synthesis of (+)-emetine **47** includes the intramolecular Michael reaction with the participation of the methylene group of the β-dicarbonyl fragment and the double bond of the crotonate residue leading to the formation of piperidine ring [20,21].



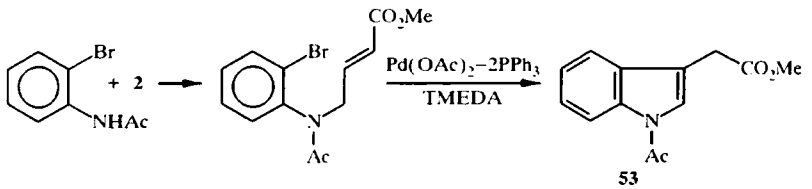
The reaction of N-tosylpiperid-4-one enamine **48** with ethyl 4-bromomesaconate **49** leads to the bicyclic compound **50** [22]. In this case the initial enamine acts as a C,C-1,3-dinucleophile. The bicyclic compound **50** may be converted into the framework lactone **51**:



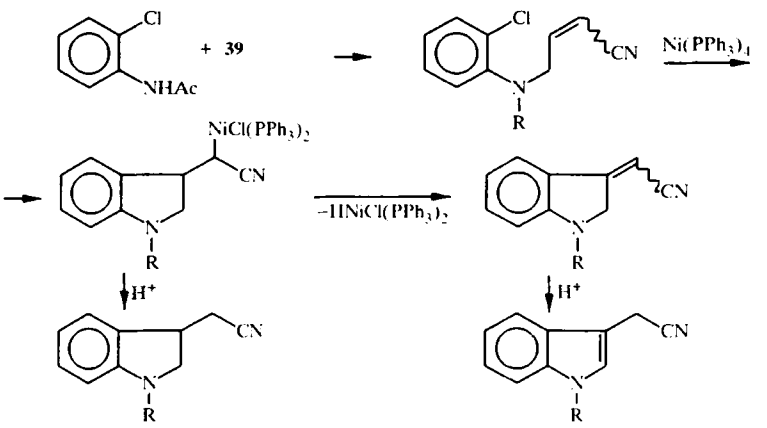
An important approach to the synthesis of benzofurans and indoles is the Heck reaction which comprises an intramolecular combination of aryl halide with double bond disposed in a suitable manner under the action of palladium catalyst. Methyl ester of 3-benzofuranacetic acid **52** was obtained using this approach from *o*-iodophenol and methyl 4-bromocrotonate **2** [23].



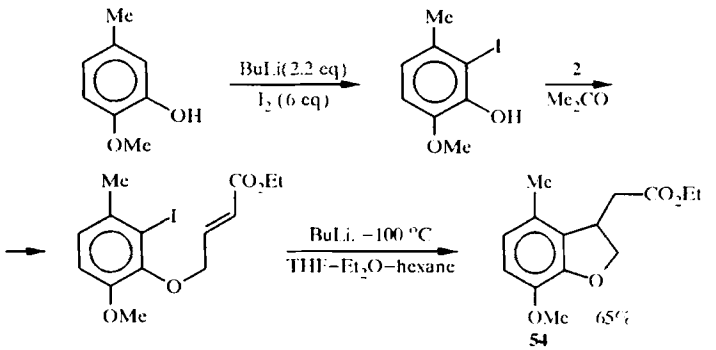
o-Bromoacetanilide is converted under these conditions into a derivative of indolylacetic acid **53** [24].



A similar reaction also occurs with a nickel catalyst [25]:

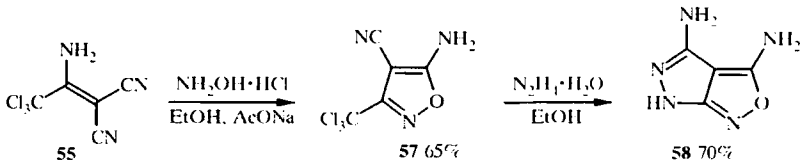


An analogous process may also be carried out with the aid of organolithium compounds, as shown in the example of the synthesis of the substituted benzodihydrofurans **54** [26]:

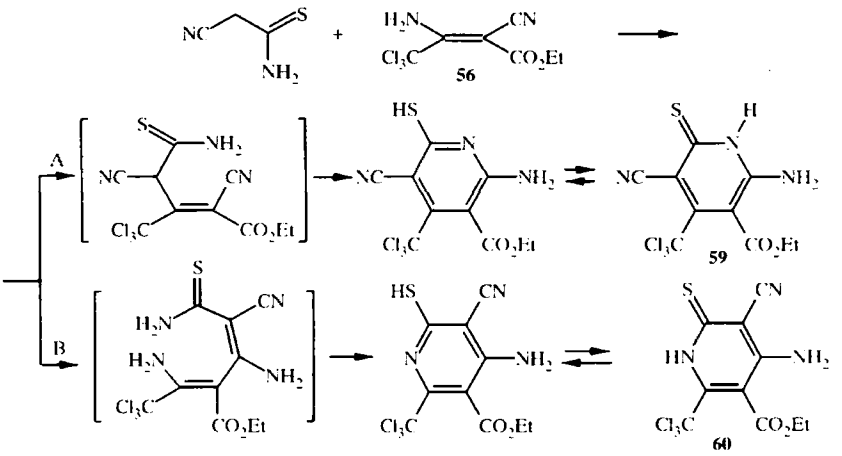


This method was later extended to the synthesis of condensed benzodifuran system [27].

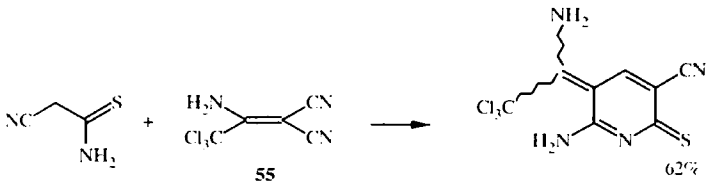
The key stage in the reactions considered is the nucleophilic addition of the crotonate fragment at the double bond. The reactions of 1-amino-2,2,2-trichloroethylidenemalononitrile **55** and the corresponding cyanoacetic ester **56**, which may be considered as Ad_N-E processes with subsequent cyclization, stand quite separately. The halogen atoms are not affected in this case but cyclization occurs at the nitrile group. Compound **55** reacts with hydroxylamine with the formation of isoxazole **57**, which in its turn is converted on reaction with hydrazine hydrate into pyrazoloisoxazole **58** [28]:



On reacting ester **56** with such 1,3-dinucleophiles as cyanothioacetamide, the interaction may proceed as a sequence of stages Ad_N-E and intramolecular condensation of CN and $CSNH_2$ groups (route A) or as addition of the acidic CH_2 group of cyanothioacetamide to the CN group of compound **56** with a subsequent Ad_N-E reaction (route B) with the formation of a mixture of the isomeric pyridinethiones **59** and **60** [29]:

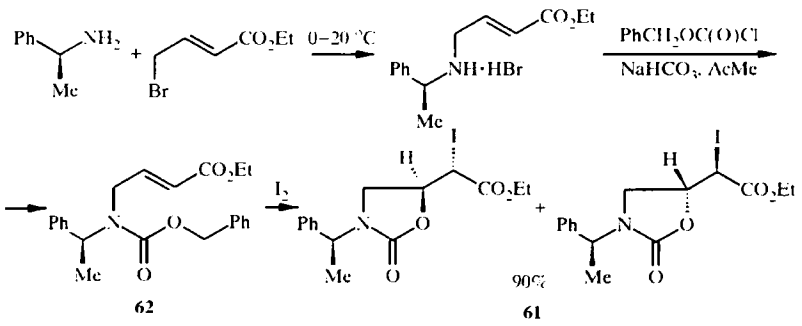


However these results raise serious doubts. And it is not very likely, from our point of view, that malononitrile derivative **55** is converted under these conditions as described in the same paper [29]:

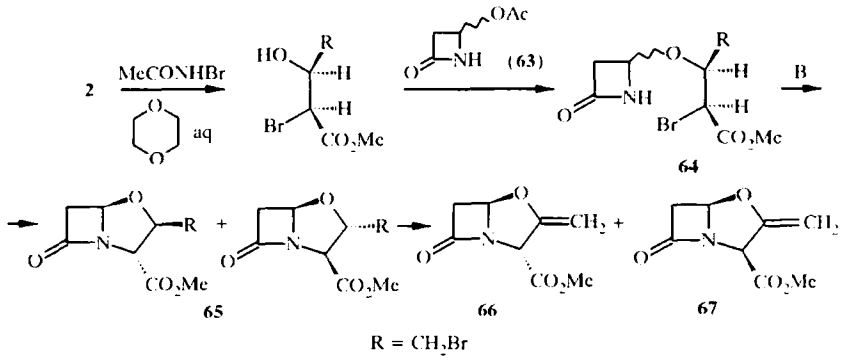


1.2. Electrophilic and Radical Addition at the Double Bond

Electrophilic additions of the crotonic fragment at the double bond leading to heterocyclic compounds are rare. Only one example of such a conversion has been described. (5*S*,*R*)-3-[(1*S*)-Phenylethyl]-5-[(1*S*,*R*)-ethoxycarbonyl(iodo)methyl]oxazolidin-2-one **61** was obtained from the acyclic derivative **62** by electrophilic iodination [30]. The overall yield of product was 90% (ratio of isomers 1 : 1).

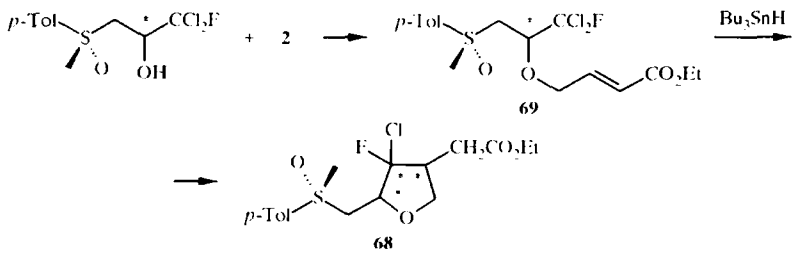


An example is also known of the indirect application of electrophilic addition to the crotonate system for the synthesis of oxazole ring. Hydroxybromination of methyl 4-bromocrotonate **2** with subsequent reaction with lactam **63** leads to the derivative **64**, which undergoes cyclization under basic conditions with the formation of a mixture of stereoisomers **65** [31].



The stereoisomers **65** are spontaneously converted into a mixture of methyl (2*RS*,5*RS*)-3-methylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylates **66** and **67** in ratio of 3 : 7, the overall yield being 48%.

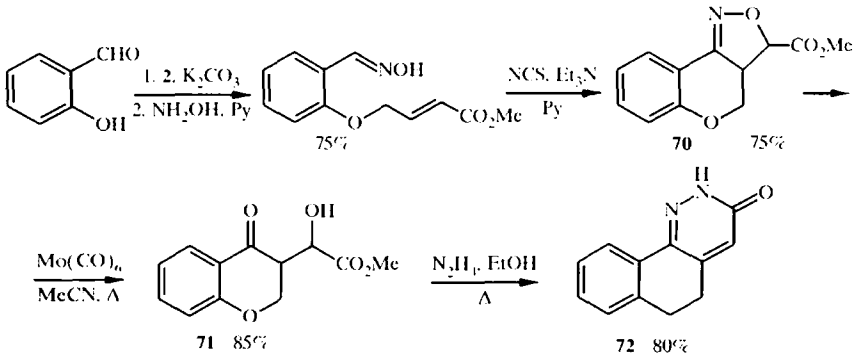
Only one example is known of the formation of a heterocyclic system by radical addition to double bond. Tetrahydrofurans with three asymmetric centers **68** were obtained from compound **69** [32]:



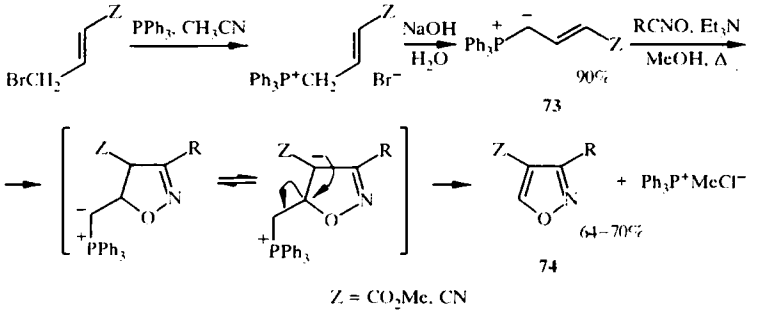
1.3. 1,3-Dipolar Addition at the Double Bond

The 1,3-dipolar cycloaddition reaction holds a special place in the series of cyclizations affecting the double bond. Inter- and intramolecular cycloadditions have been described with such 1,3-dipoles as nitrile oxides, nitrile imines, nitrones, azomethine imides, and diazo compounds.

The nitrile oxide generated from salicylaldehyde oxime, alkylated at the hydroxyl group by methyl 4-bromocrotonate **2**, participates in intramolecular [3+2]-cycloaddition with the formation of 4,5-dihydro-3H-[1]benzopyrano[4,3-*c*]isoxazole-3-carboxylate **70**, which may undergo further conversions with the formation of various heterocyclic systems **71**,**72** [33,34].

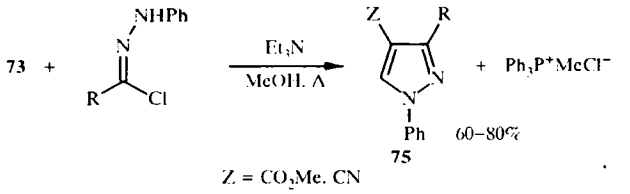


Phosphonium ylides **73** obtained from the corresponding derivatives of 4-bromocrotonic acid enter into 1,3-dipolar addition with nitrile oxides with subsequent elimination of the methylenephosphonium fragment and the formation of isoxazoles **74** by the following scheme [35]:



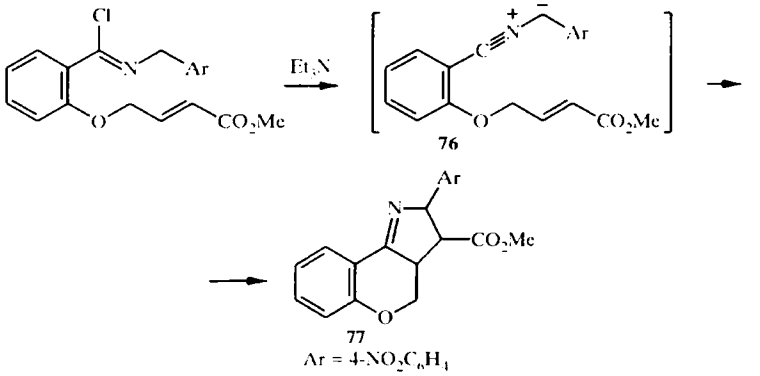
Z = CO_2Me, CN

Pyrazoles **75** are formed in a similar way on reacting phosphonium ylides **73** and nitrile imines [35]:



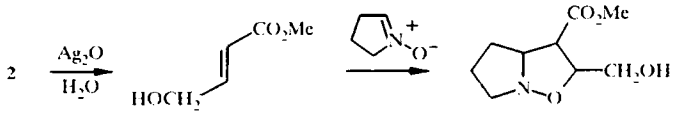
Z = CO_2Me, CN

The addition of nitrile ylide **76** to the double bond of crotonate fragment of salicylic acid derivatives has also been described [36]. Such an addition proceeds in practically quantitative yield and leads to benzopyranopyrroles **77**:

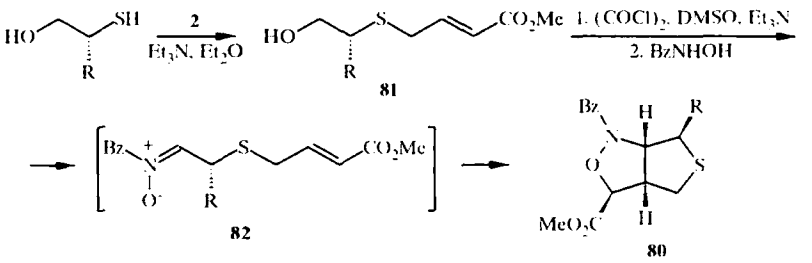


Ar = 4-$NO_2C_6H_4$

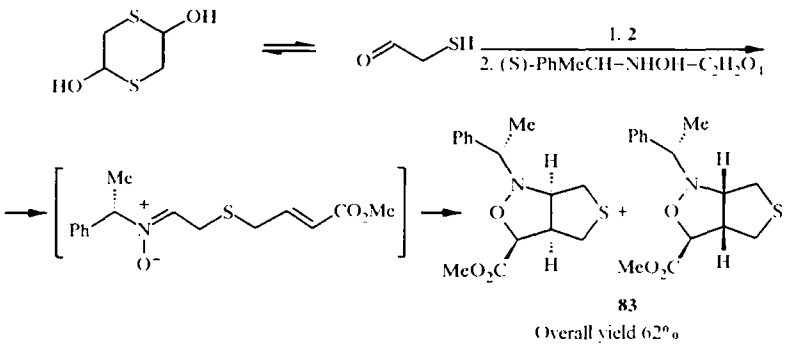
In turn nitrones are added to the double bond of the crotonate fragment with the formation of hydrogenated isoxazoles. 1-Pyrroline 1-oxide reacts with hydroxy derivative **78**, formed from methyl 4-bromocrotonate **2** by the action of silver oxide, with the formation of oxazole **79** [37].



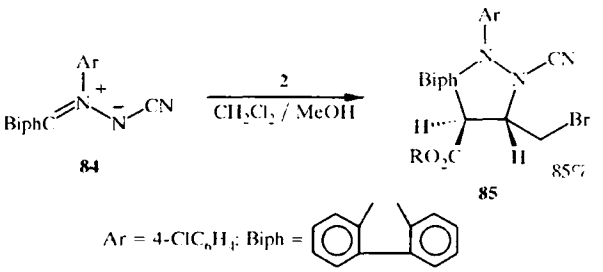
A method has been developed for obtaining hydrogenated thienoisoxazoles **80** from methyl 4-bromocrotonate **2** and thioglycols in two stages. Alcohols **81** formed initially are oxidized to aldehydes according to Kornblum and are converted into nitrones **82**. Nitrones **82** are not isolated under the reaction conditions and enter straight away into dipolar cycloaddition forming thienoisoxazoles **80** [38]. The reaction occurs stereoselectively with the formation of only one isomer:



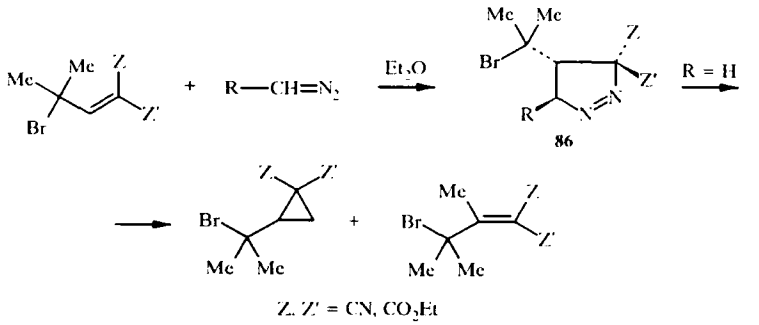
An analogous reaction with mercaptoacetaldehyde leads to a mixture of the stereoisomers **83** in 62% overall yield [38]:



Ylide **84** reacts with methyl 4-bromocrotonate **2** with the formation of tetrahydropyrazole **85** selectively and in high yield [39]:

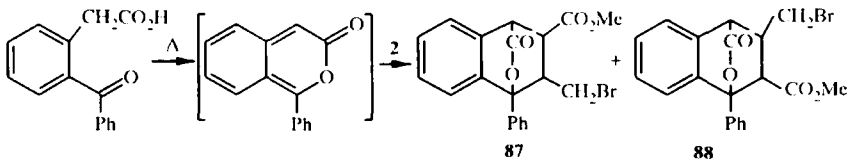


A series of studies has been devoted to the interaction of (2-bromoalkylidene)malononitriles and analogous esters with diazoalkanes [40-43], leading to the formation of products of 1,3-dipolar cycloaddition **86**, which are fairly labile and decompose at room temperature:

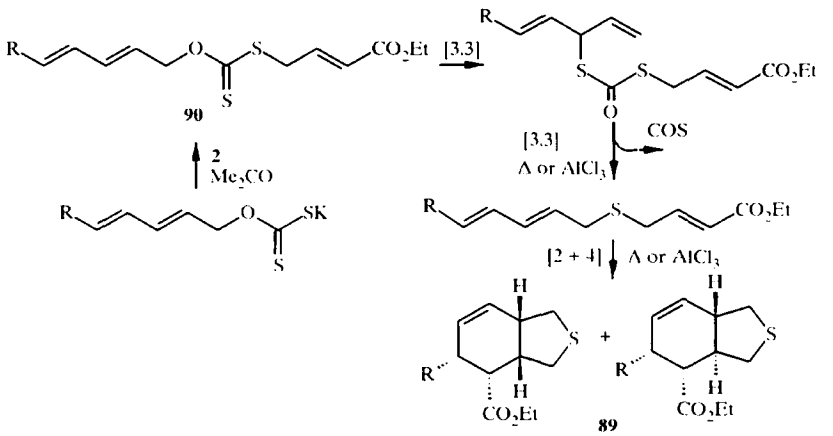


1.4. The Diels–Alder Reaction

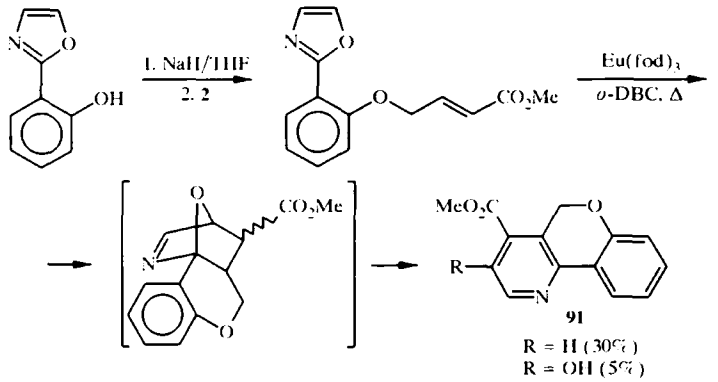
Diels–Alder heterocyclization has been described for derivatives of crotonic acid the double bond of which is activated by the electron-withdrawing influence of ester group. Both inter- and intramolecular variants of this reaction are known.



The Diels–Alder reaction between 1-phenyl-2-benzopyran-3-one and methyl 4-bromocrotonate **2** leads to the polycyclic hydropyranones **87** and **88** [44]. Japanese authors have proposed a procedure for obtaining of hydrogenated benzo[*c*]thiophenes **89**, the key stage of which is an intramolecular [2+4]-cycloaddition. The initial for this conversion xanthogenate **90** was obtained from ethyl 4-bromocrotonate **2**. The one-pot synthesis comprises a cascade of two [3,3]-sigmatropic shifts and intramolecular Diels–Alder reaction which lead to the final bicyclic products **89** [45].



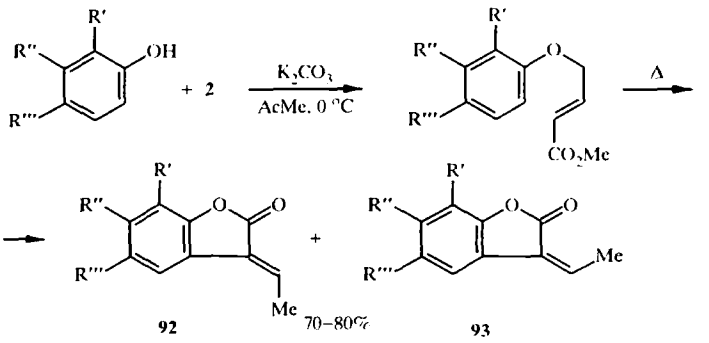
The synthesis of benzopyrano[4,3-*b*]pyridines serves as an interesting example. In this the key stage is the Diels–Alder reaction between the oxazole and crotonate fragments. The subsequent elimination of water from the cycloaddition adduct formed leads to the 1-benzopyrano[4,3-*b*]pyridine system **91** [46].



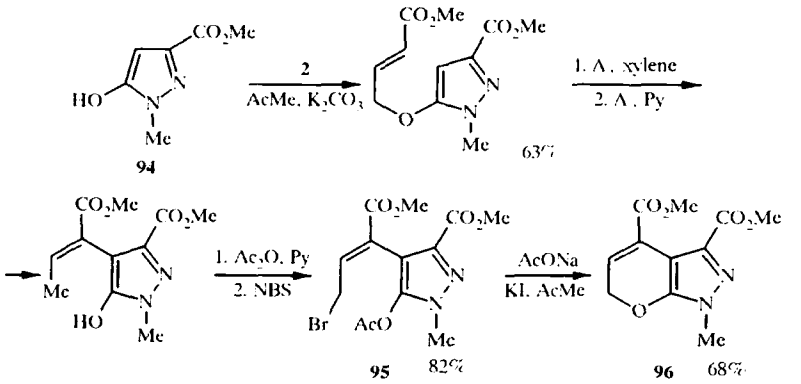
1.5. Sigmatropic Rearrangements Involving the Double Bond of the Crotonate Fragment

[3,3]-Sigmatropic rearrangements (Claisen rearrangement and its thio analog) involving the double bond of the crotonate fragment have been described in the literature. These lead finally to the formation of a heterocyclic system.

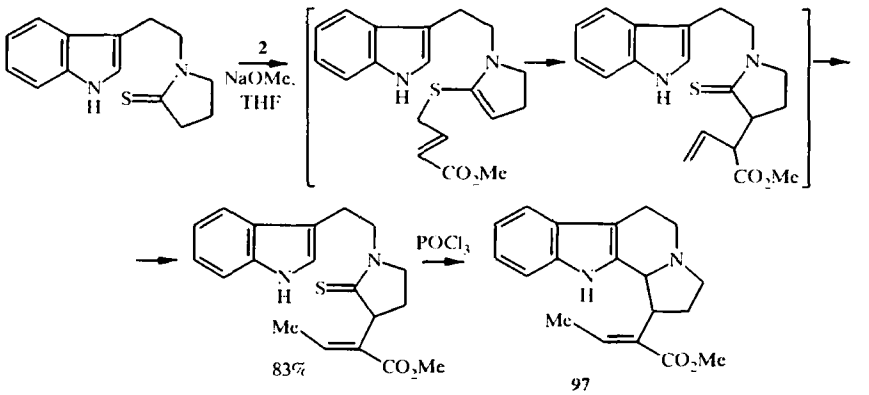
Condensed furans **92**, **93** may be obtained from phenols by reaction with methyl 4-bromocrotonate **2** [47]:



Hydroxypyrazoles **94** serve as starting materials for the preparation of pyranopyrazoles **96** [48]. The synthetic chain includes sequential stages of alkylation at the hydroxyl group of pyrazole **94** by methyl 4-bromocrotonate **2**, Claisen rearrangement, migration of the double bond, acylation of the hydroxyl group, and allylic bromination leading to pyrazole **95**. In the final stage this pyrazole undergoes intramolecular substitution of the bromine atom with the formation of pyranopyrazole **96**:

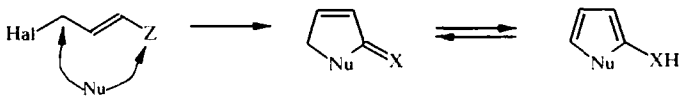


The key step of synthesis [49] is also [3,3]-sigmatropic rearrangement with subsequent electrophilic closure of the six-membered nitrogen-containing ring and the formation of the tetracyclic system **97**.



2. DERIVATIVES OF 4-HALOCROTONIC ACIDS AS 1,4-DIELECTROPHILIC SUBSTRATES

In contrast to the interaction with 1,3- and 1,4-dinucleophiles the reaction of 4-halocrotonic acid derivatives with mononucleophiles proceeds by a different scheme and with another reaction centers:



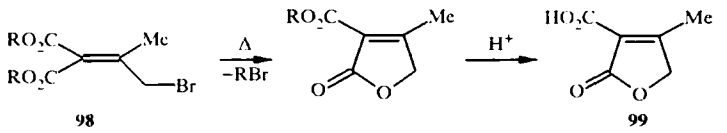
Z = COOR, X = O; Z = CN, X = NH

The cyclization proceeds as 1,4-dinucleophilic attack – S_N2 substitution of the halogen atom and nucleophilic interaction with the group Z. These processes have different rates as indicated by the possibility of isolating one or other of the intermediates in many cases. The sequence of their formation depends markedly on conditions of the synthesis. For the formation of a heterocyclic compound by such a scheme *cis* disposition of the substituents at the double bond of the crotonate fragment is usually required. Since derivatives of *cis*-crotonic acid are poorly available and are readily rearranged into *trans* isomers, the majority of the cyclizations of this type are carried out on substrates containing two Z groups (derivatives of malonic and fumaric acids). However occasionally cyclization is successfully carried out with *trans* derivatives. In these cases the reaction requires the use of catalysts such as metal ions.

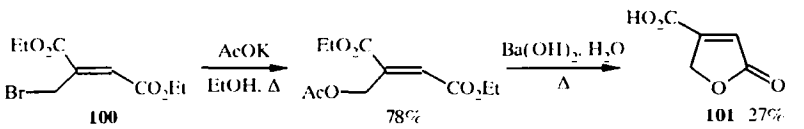
In conversions of this type nucleophiles may be oxygen (internal nucleophile), nitrogen (NH_3, RNH_2), or sulfur (NaSH, KSAc) atoms, which lead respectively to furans, pyrroles, and thiophenes.

For nucleophilic attack by oxygen the only reactions described are those in which the attacking oxygen atom is already present in the molecule of the initial substrate (COOR group) and in this way is the internal nucleophile. Cyclization proceeds according to the following scheme:

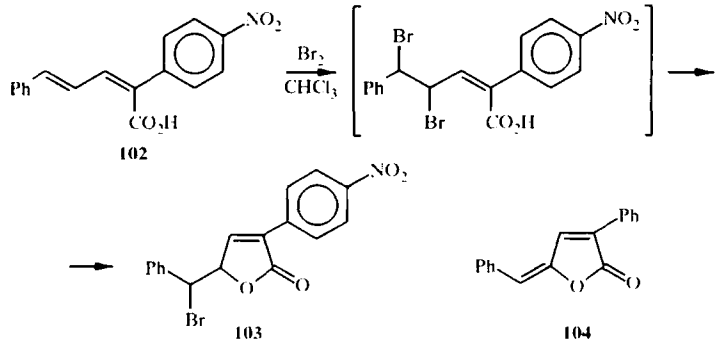
Various substituted butenolides **99** were synthesized by heating (2-bromo-1-methylethylidene)malonates **98** at 150-160°C with subsequent modification of the carbalkoxy group [50].



Aconic acid **101** was also obtained from ethyl 4-bromo-3-ethoxycarbonylcrotonate **100** [51]. Initially the bromine atom is nucleophilically substituted by acetoxy group and lactonization occurs in the second stage comprising sequential stages of hydrolysis and dehydration.

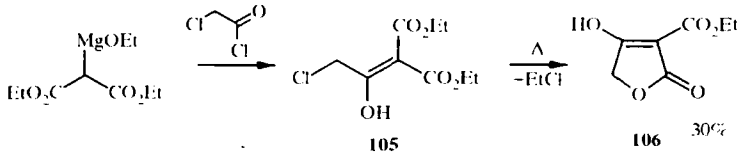


On brominating diene **102** polysubstituted derivative of 4-bromocrotonic acid is formed *in situ*, which is then lactonized with the formation of butenolide **103** [52].

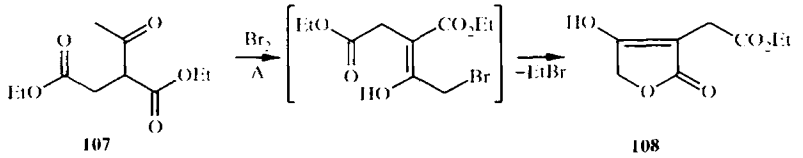


An analogous reaction in the presence of Et_3N was described previously [53]. In this case the dehydrobromination product **104** was also isolated.

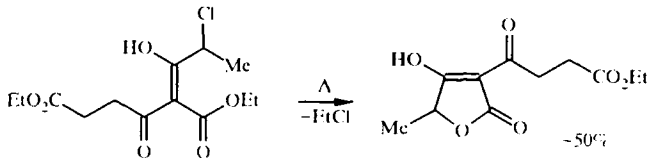
Ethyl (2-chloro-1-hydroxyethylidene)malonate **105** undergoes thermal cyclization with the formation of 3-carbethoxytetronic acid **106** accompanied by the elimination of ethyl chloride [54].



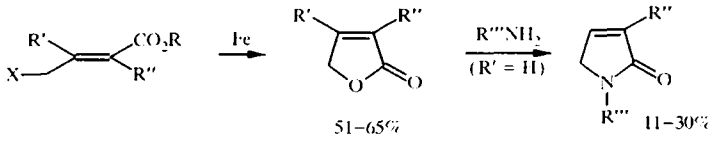
The homolog of compound **105** containing bromine atom in place of chlorine obtained *in situ* by the halogenation of acetoacetic ester derivative **107**, was subjected to lactonization with the formation of tetronic acid derivative **108** [55].



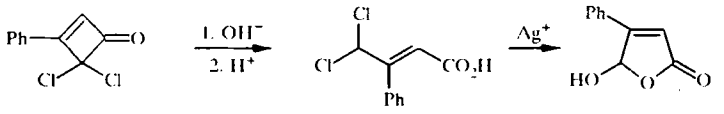
This method was extended to the synthesis of substituted in a different way tetronic acids [54] and also to tetrinic and phenyltetrinic acids [55], for example:



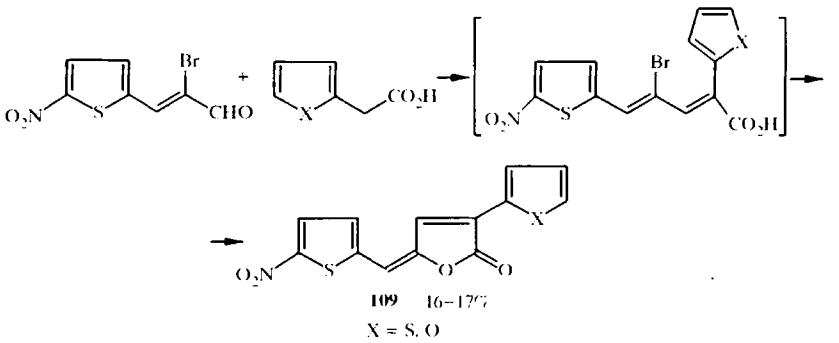
Such an intramolecular cyclization was also successfully carried out in the case of derivatives of *trans*-crotonic acids. Iron powder was used as catalyst for such conversions [56]:



Silver salts have also been used as ring closure catalysts [57]:



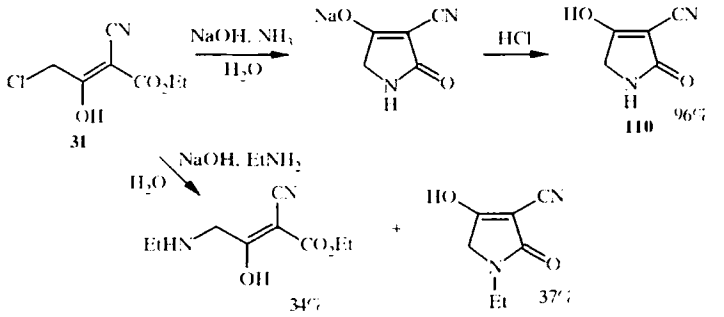
The synthesis of the polyheterocyclic system **109** is an interesting example of intramolecular closure of the furan ring with *trans* configuration of the double bond [58]. In these cases cyclization probably occurs as an Ad_E-E process:



109 16–17%

X = S, O

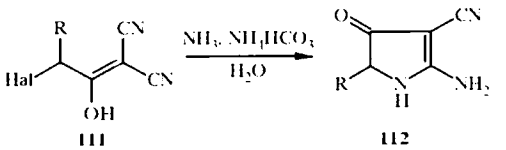
There is a large group of syntheses based on the interaction of ammonia (or primary amines) with 4-halocrotonic acid derivatives. Pyrrol-2-ones **110** may be obtained by reacting ethyl ester of 4-chloro-2-cyano-3-hydroxycrotonic acid **31** with ammonia under strongly alkaline conditions [59]:



31

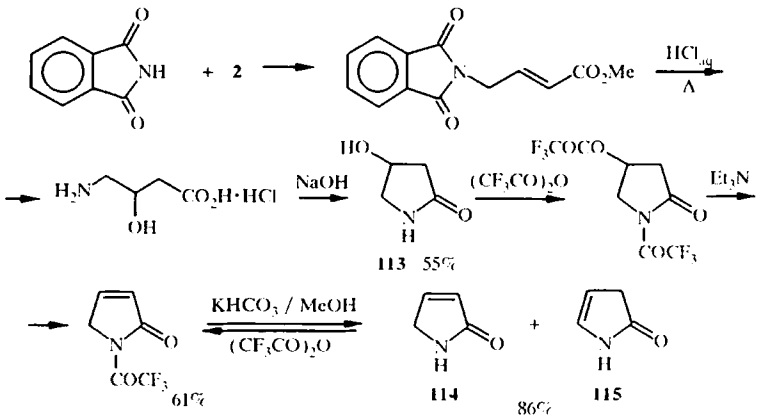
110 96%

On using malononitrile derivative **111** in analogous reactions pyrrole derivative **112** with amino group in position 2 is formed [60]:

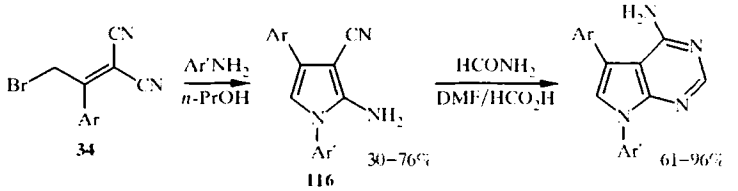


111 **112**

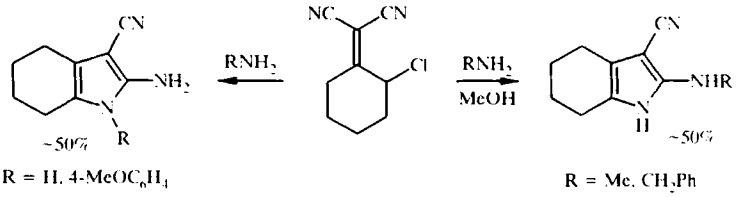
An analog of this reaction is the synthesis of the pyrrole ring using phthalimide according to the scheme given below [61]. The resulting dihydropyrrol-2-one **113** may be dehydrated to a mixture of compounds **114** and **115** through the formation of trifluoroacetyl intermediates:



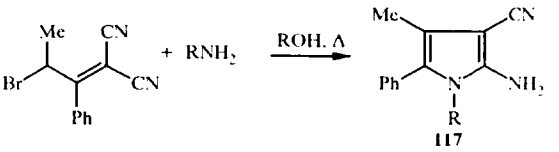
A series of studies has been devoted to the synthesis of pyrroles from 2-bromo-1-arylethylidenemalononitriles and primary amines. Compound **34** reacts with aniline by the conventional scheme with the formation of 2-amino-3-cyanopyrrole **116** [62]:



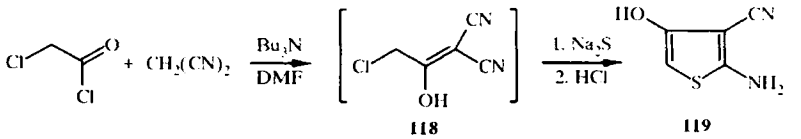
Depending on the conditions and the nature of amine used the reaction may proceed via various routes (initial substitution of halogen or initial reaction of amine and the nitrile group) [63]:



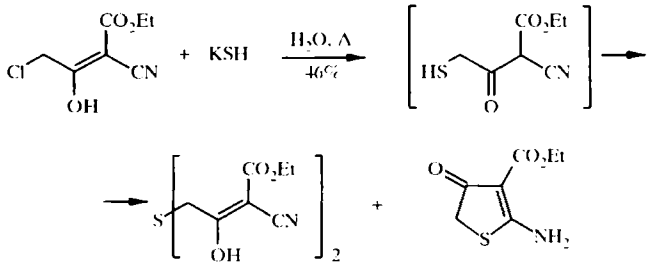
The reaction with amines may also proceed in another direction with the formation of pyrrole **117** [63]:



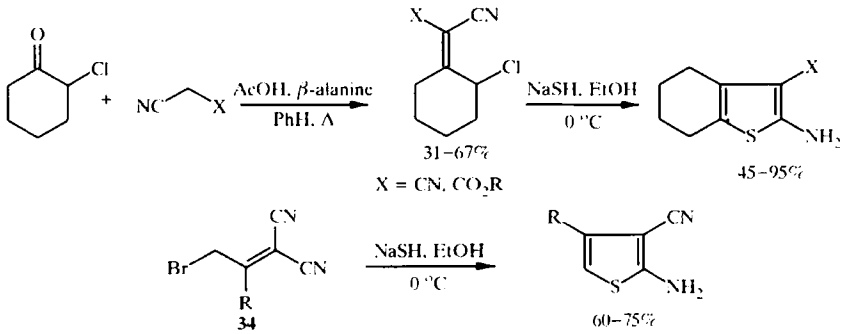
Cyclizations of this type are also fairly widely used for sulfur-containing nucleophiles. The simplest example of such reaction is the interaction of (2-chloro-1-hydroxyethylidene)malononitrile **118,** generated *in situ*, with sodium sulfide leading to thiophene **119** [64]. The reaction probably includes intramolecular interaction of the thiolate and nitrile groups.



An analogous reaction was described even in 1910, however a high yield was not achieved and thiophenes were isolated as side products [65]:

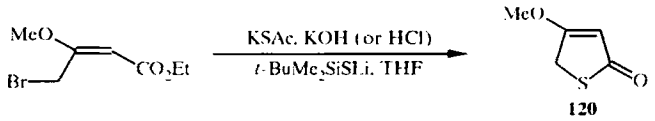


One of the methods of thiophene synthesis used by Gewald is an interesting example of such an approach [66]:

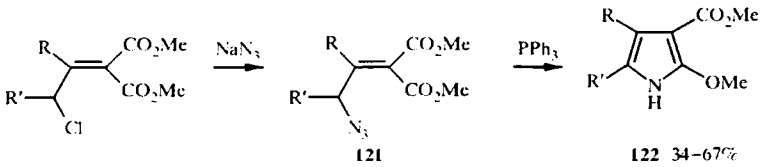


The intermediates in this reaction are probably the corresponding 1,4-mercaptonitriles.

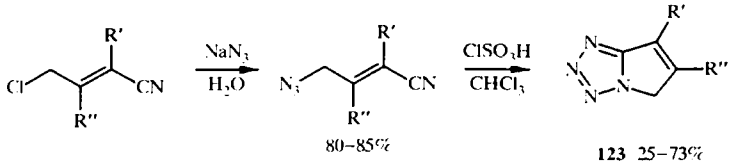
The synthesis of thiophen-2-one **120** using such synthon equivalents of HS⁻ as KSAc and *t*-BuMe$_2$SiSLi has also been described [67].



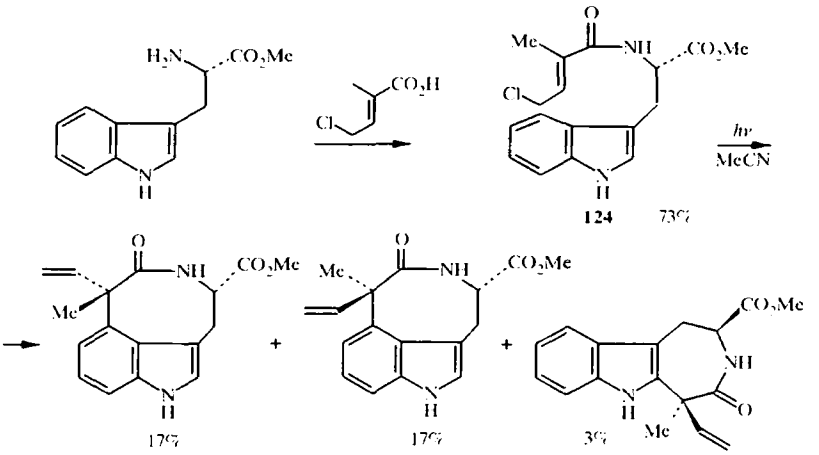
Several reactions, which are essentially analogs of the examples enumerated above, differ from them formally. In particular, this concerns syntheses using azides for the initial nucleophilic substitution of the halogen atom. Pyrroles **122** may be obtained from compounds containing azide group **121** by condensation in the presence of triphenylphosphine [68]:



Intramolecular 1,3-dipolar cycloaddition leading to 5H-pyrrolo[1,2-*d*]tetrazoles **123** has also been described [69]:

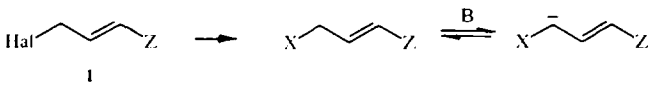


The preparation of methyl ester of N-(4-chlorotiglyl)-L-tryptophan **124** is an example of reaction where the group Z reacts in the initial stage. Subsequent photocyclization leads to closure of the eight-membered nitrogen-containing ring [70]:



3. REACTIONS BASED ON DEPROTONATION OF THE METHYLENE GROUP OF THE CROTONATE FRAGMENT

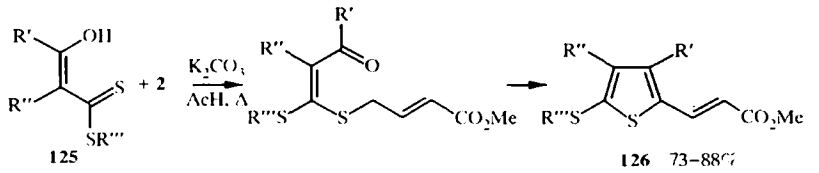
The reactions considered previously refer to processes in which derivatives of 4-halocrotonic acids either play the role of dielectrophilic substrates or the double bond of the crotonate fragment participates in synchronous conversions. The reactions discussed in this section differ in that, in addition to the electrophilic centers in the crotonate fragment, a nucleophilic center is generated in the reaction process. This center determines the direction of subsequent conversions. In all the reactions described in the literature nucleophilic center of such type is generated by deprotonation of the CH_2 group of compounds **1**. In reality the protons of this group are acidic (vinylogic position relative to electron-withdrawing group), however this acidity is insufficient for the majority of reactions. The main method of increasing the acidity of these protons consists of substituting the halogen atom in compound **1** by a group stabilizing the neighboring anion:



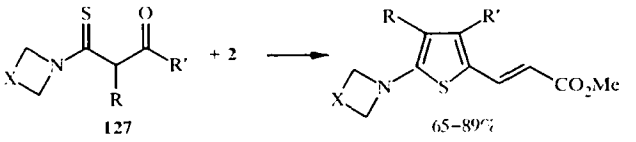
Two ways of such increasing the acidity have been described: substitution of halogen atom by sulfur atom and quaternization of pyridines by halides **1**.

Derivatives of 4-halocrotonic acids may act as substrates having both electrophilic and nucleophilic centers.

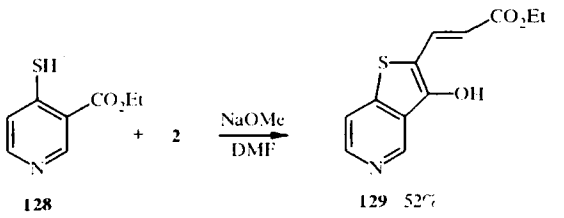
Syntheses of heterocycles have been described the key stage of which is deprotonation of the CH_2 group activated by the vinylogous group Z and the sulfur atom. The anion formed on deprotonation reacts by nucleophilic addition at multiple C–heteroatom bond (C=O, C=N, C=N), which as a rule is contained in the residue X and leads to closure of thiophene or thiazole ring. On reacting methyl 4-bromocrotonate **2** with compounds **125** alkylation at the sulfur atom occurs initially. Subsequent deprotonation leads to condensation of the CH_2 and CO groups and the formation of thiophenes **126** [71]:



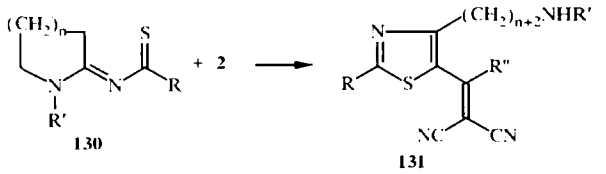
Thioamides **127** also undergo this reaction [71]:



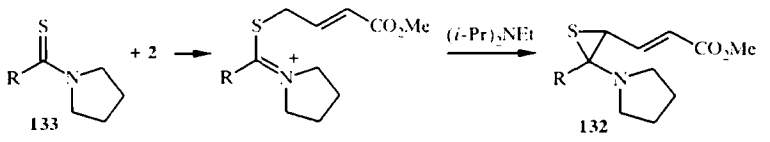
A similar cyclization was also carried out with ester group. Thienopyridine **129** was obtained from ethyl 4-mercaptonicotinate **128** [72]:



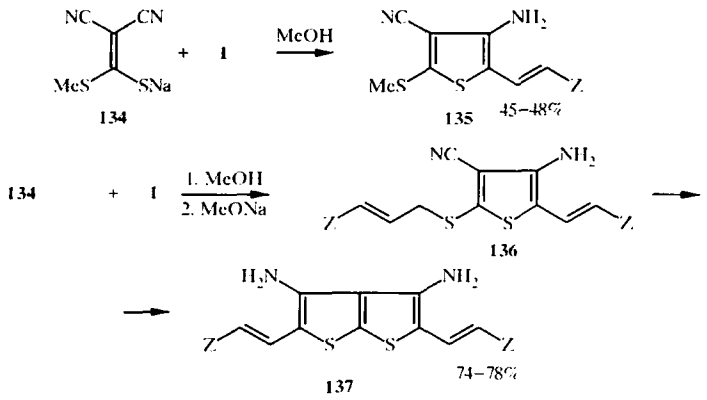
Reactions are known in which nucleophilic addition at the C=N bond of iminium salts occur in the second stage. Reaction between thioamides **130** and (2-bromo-1-arylethylidene)malononitriles proceeds fairly unusually with the formation of thiazole **131** [73,74].



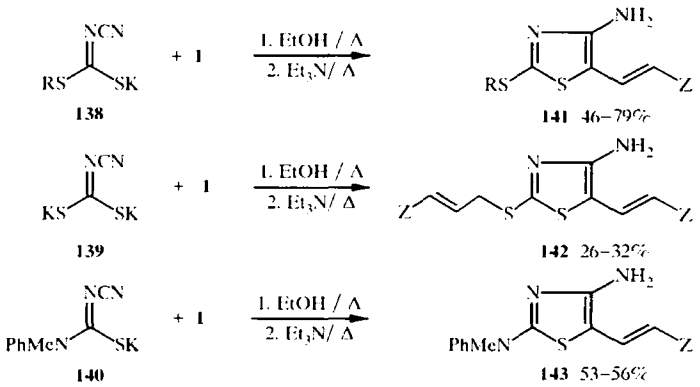
The preparation of thiiranes **132** from thioamides **133** has also been described by the following scheme [75]:



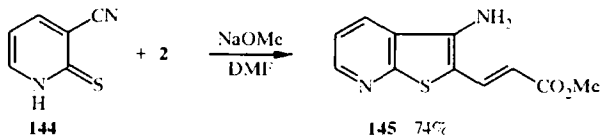
A series of studies has been devoted to conversions in which intramolecular condensation occurs between the methylene and nitrile groups. The interaction of 4-halocrotonic acid derivatives with adducts **134** of malononitrile and carbon disulfide has been investigated. Depending on the experimental conditions both the monocyclic thiophenes **135** and **136** and thienothiophenes **137** were successfully isolated from the reaction mixture. The reaction occurs as a sequence of stages of alkylation at the sulfur atom and the formation of the thiophene ring by a Thorpe–Ziegler reaction [18]:



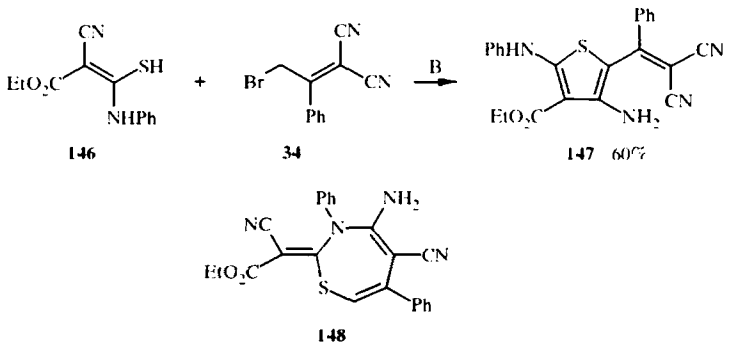
A series of syntheses has been carried out with adducts of carbon disulfide (isothiocyanates) and cyanamide **138-140** [17]. The reaction mechanism comprises sequential stages of alkylation at the sulfur atom and Thorpe–Ziegler reaction between the acidic methylene group and the cyano group, leading to the formation of thiazoles **141-143** respectively.



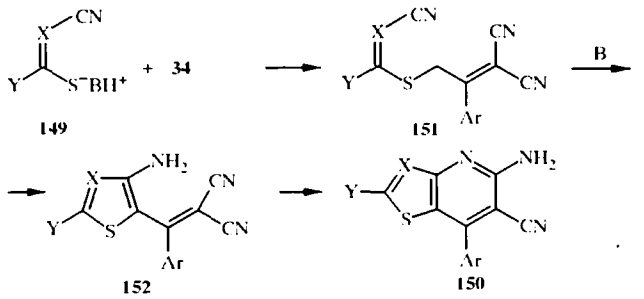
Thienopyridine **145** was obtained in this reaction on using 3-cyanothiopyridine **144** [72].



Thiophene **147** to which the thiazepine structure **148** was previously assigned erroneously [78] is formed on reacting adducts of isothiocyanates and cyanoacetic ester **146** with (2-bromo-1-phenylethylidene)malononitrile **34** [76,77].

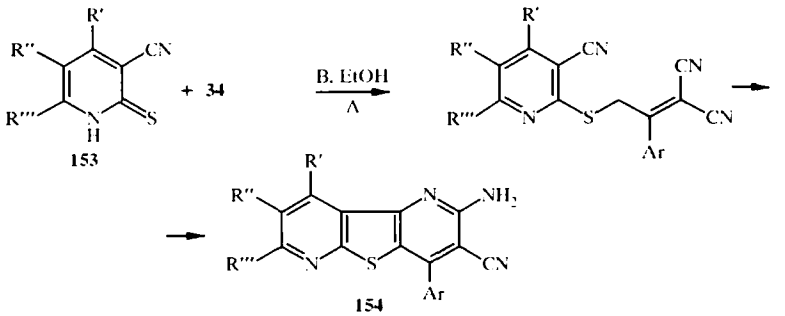


As was shown by our investigations the type of reactions under consideration is not completed by the formation of the thiophene structure **147**. In basic medium a further intramolecular interaction occurs between the NH_2 and CN groups in this compound which leads finally to an annelated heterocyclic system. It was discovered that (2-bromo-1-arylethylidene)malononitriles **34** reacts with enethiolates **149** in alcohol in the presence of an organic base with the formation of the annelated heterocyclic compounds **150** in high yield [79-83]. The reaction proceeds by cascade heterocyclization mechanism, including in the first stage the regioselective alkylation of thiolate **149** at the sulfur atom with the formation of acyclic product **151**, which is cyclized under the reaction conditions according to Thorpe into derivative of thiophene or thiazole **152**, and then undergoes an intramolecular cyclization with the formation of condensed pyridines **150**.



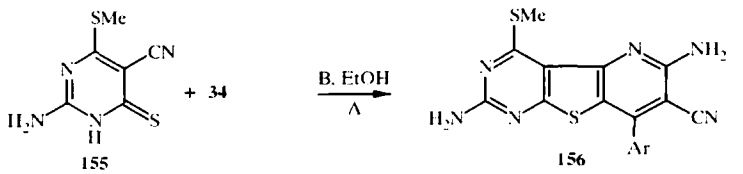
B = piperidine; X = N, CR'; Y = NHR', SR'

Cascade heterocyclization, in our opinion the directed heterocyclic synthesis of the future, has also proved to be extremely fruitful for the synthesis of annelated systems with three heterocyclic rings. Pyrido[3',2':3,2]thieno[2,3-*b*]pyridines **154** were formed in high yield as a result of the interaction of (2-bromo-1-arylethylidene)malononitrile **34** with pyridinethiones **153** under analogous conditions [79,81-83].

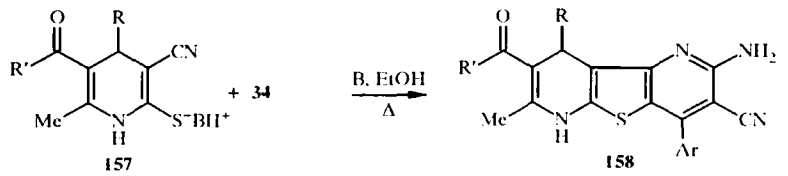


R', R'', R''' = Alk, Ar, Het

The use of pyrimidinethione **155** as substrate in this reaction leads to the preparation of pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **156** [79,82,83].

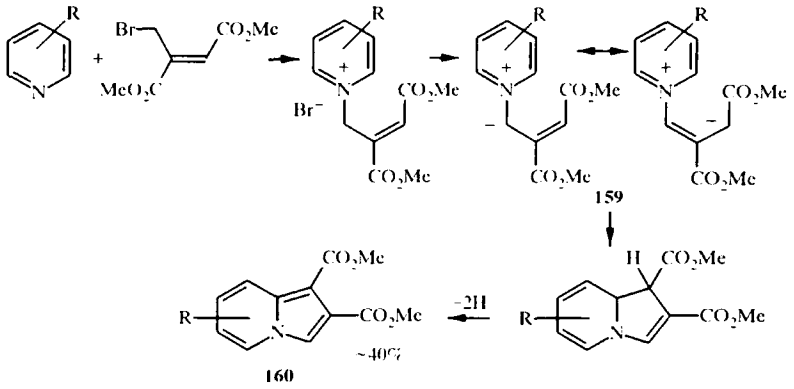


The present approach also proved to be promising in the synthesis of partially hydrogenated annelated heterocyclic compounds. 6,9-Dihydropyrido-[3',2':4,5]thieno[2,3-*b*]pyridines **158** was obtained by the reaction of 3-cyano-1,4-dihydropyridine-2-thiolates **157** with (2-bromo-1-arylethylidene)malononitrile **34** [80,82,83].

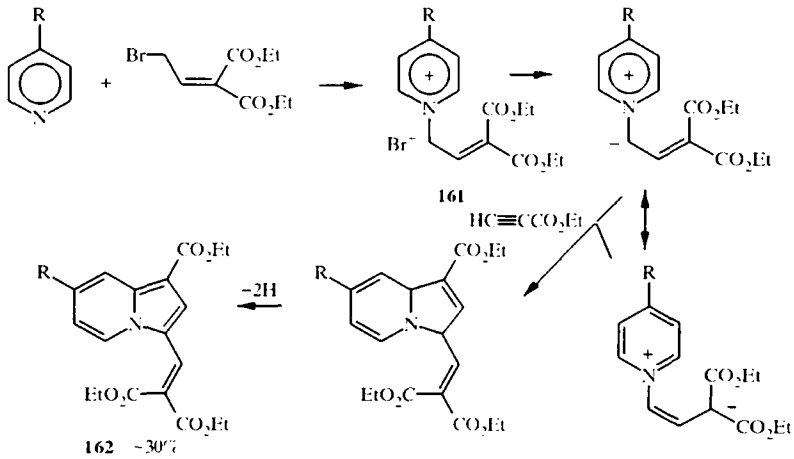


R = Ar, Het; R' = Me, OEt

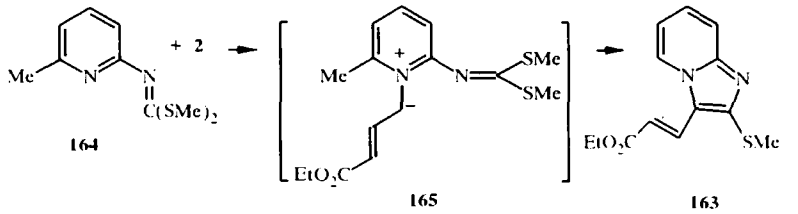
Another method of increasing the acidity of the methylene unit in 4-halocrotonic acid derivatives is the quaternization of pyridines by these compounds. The resulting salts readily undergo deprotonation with the formation of the corresponding pyridinium ylides, which take part in further conversions. Ylide formed from pyridine and mesaconic acid derivative **159** undergoes intramolecular cyclization, which is accompanied by dehydrogenation leading finally to indolizines **160** [84]:



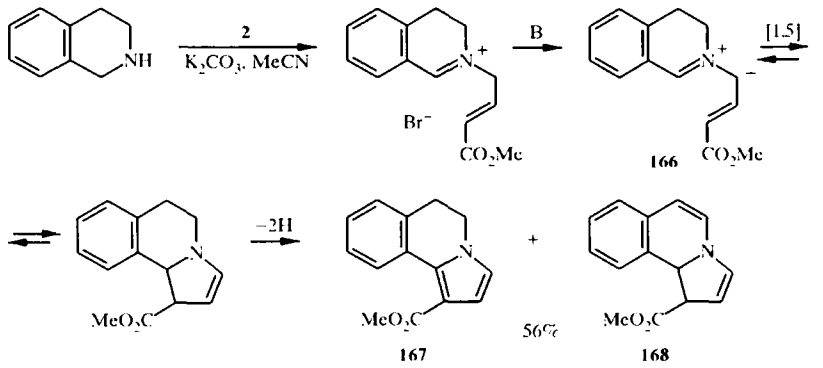
In difference to this, ylide obtained from malonic acid derivative **161** does not take part in spontaneous intramolecular cyclization. Such stability may be explained by the significantly greater delocalization of the negative charge on the crotonate fragment. 1,3-Dipolar cycloaddition reaction has been described for this ylide with ethyl acetylenecarboxylate leading finally to indolizines **162** [84]:



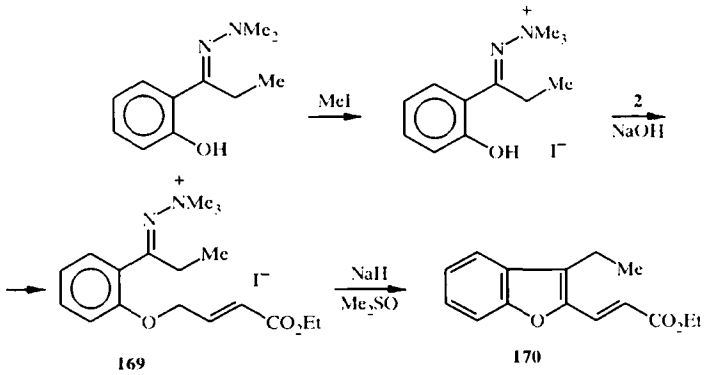
Imidazopyridines **163** were obtained from pyridines **164** and ethyl 4-bromocrotonate **2** [85]. The reaction probably occurs as a sequence of stages of alkylation at the nitrogen atom of the pyridine ring, the formation of ylide **165**, and subsequent closure of the imidazole ring according to the Ad_N-E mechanism.



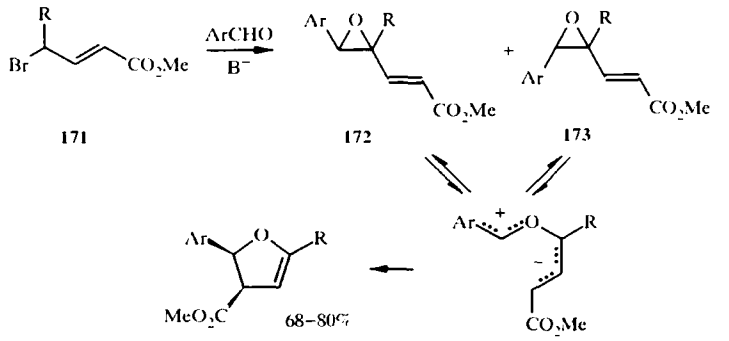
Ylide **166** obtained from tetrahydroisoquinoline alkylated at the nitrogen atom with methyl 4-bromocrotonate **2** may undergo 1,5-dipolar electrocyclization leading to a mixture of pyrroloisoquinolines **167** and **168** [86].



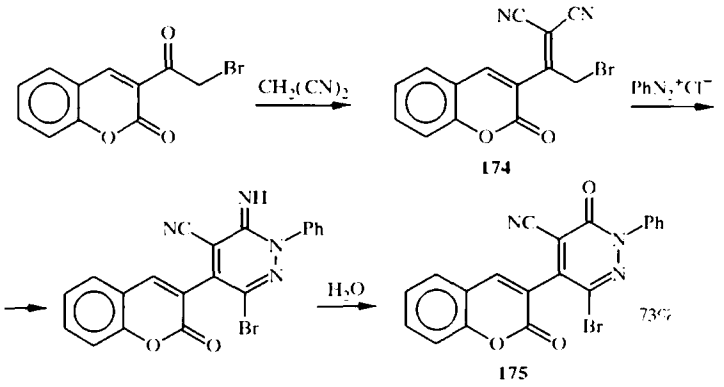
Cases of deprotonation of the crotonate methylene group without prior activation have also been described. The methylene group of compound **169** was successfully deprotonated by dimethyl anion which enables an intramolecular condensation with the formation of benzofuran **170** [36].



Methyl 4-bromocrotonates **171** undergoe Darzens reaction under normal conditions with the formation of the corresponding oxiranes **172** and **173** used for the synthesis of various hydrogenated furans [87]:

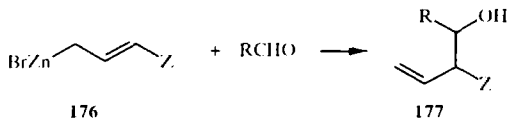


Japp–Klingemann reaction has been described for the malonic acid derivatives **174** leading to the substituted pyrazines **175** [88]:



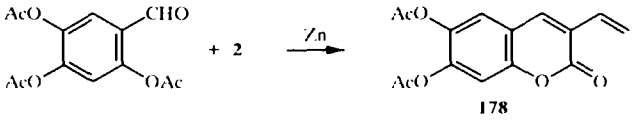
4. ORGANOMETALLIC COMPOUNDS ON THE BASIS OF 4-HALOCROTONIC ACID DERIVATIVES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

The described organometallic compounds generated from 4-halocrotonic acid derivatives are mainly organozinc compounds, intermediates in the Reformatsky reaction. The halogen (Br but not Cl) atom in position 4 of the initial substrate proves to be fairly reactive for the direct formation of organozinc compounds. The resulting compound **176** has two nucleophilic centers, *viz.* the carbon atom directly bound to zinc atom, and the carbon atom vinylogic to it, linked to electron-withdrawing group. Probably due to the steric requirements of the Reformatsky reaction the second nucleophilic center reacts usually with the formation of the adduct **177**:

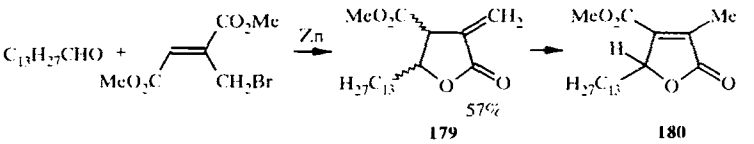


Further conversions of adducts **177** may lead to various heterocyclic compounds.

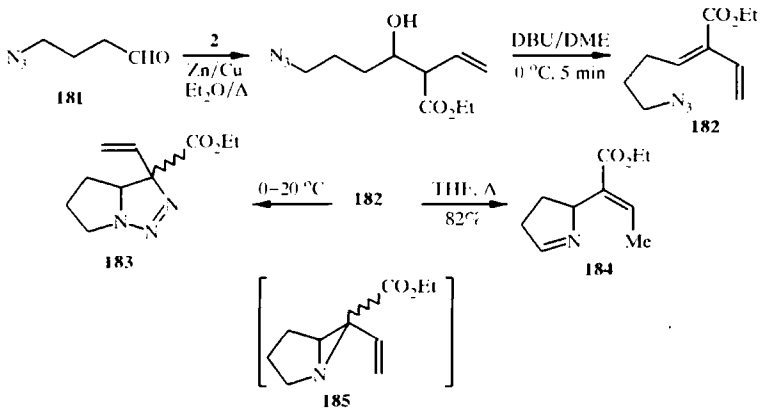
Benzopyranone **178** was obtained by the Reformatsky reaction from 2,4,5-triacetoxybenzaldehyde [89]:



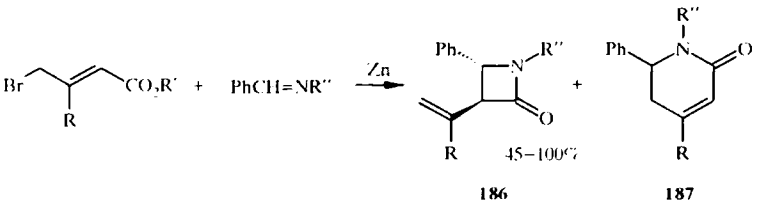
Long-chain aldehydes have been introduced into the Reformatsky reaction with methyl 4-bromo-3-methoxycarbonylcrotonate [90]. The resulting mixture of diastereoisomers **179** was then isomerized into aconic acid derivative **180**.



Azidodiene **182** was formed by an analogous reaction with azidoaldehyde **181** and subsequent elimination of water. Compound **182** may undergo conversion in two directions depending on the temperature conditions. Under mild conditions (room temperature) an intramolecular 1,3-dipolar cycloaddition of the azide fragment occurs at the activated double bond with the formation of pyrrolotriazole **183**. Under more drastic conditions (boiling in THF) substituted dihydropyrrole **184** is formed. The mechanism of this conversion comprises addition of nitrene formed on decomposition of azide to the double bond, which leads to the intermediate **185**, recorded in the reaction mixture by NMR. Further isomerization of vinylaziridine **185** leads to the reaction product **184** [91]:

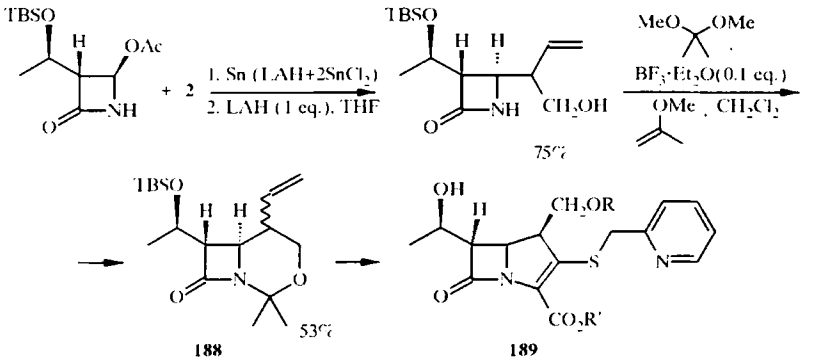


The Reformatsky reaction with Schiff's bases leads to lactams **186**, which were isolated as the main products. Pyridones **187** are also formed as by-products in this reaction [92].



This conversion obviously illustrates the ambident character of organozinc compounds. Lactam **189** is the product of reaction at the second and pyridine **187** – at the first reaction center.

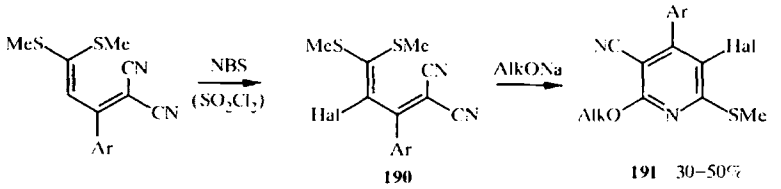
The organotin derivative of methyl 4-bromocrotonate **2** has been used in the synthesis of antibiotics. 7-Oxo-3-oxa-1-azabicyclo[4.2.0]octane **188** was obtained in three stages from 4-acetoxyazetidinone when using a reaction close to the Reformatsky reaction at the first stage [93]:



The condensed 1,3-oxazine **188** obtained was then converted into an analog of thienamycin **189**.

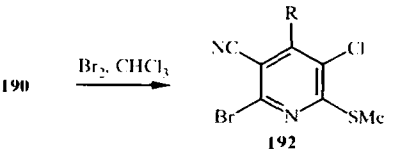
5. OTHER REACTIONS

Other methods have been described in the literature for the synthesis of heterocyclic compounds from derivatives of 4-halocrotonic acids including cyclization with the participation of side substituents. Compounds **190** react with alcoholates with the formation of alkoxypyridines **191** [94,95]:

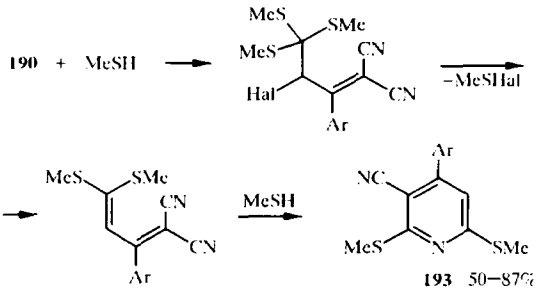


The mechanism of this reaction includes addition of alcoholate to the nitrile group with subsequent replacement of the SMe group according to Ad_N-E mechanism.

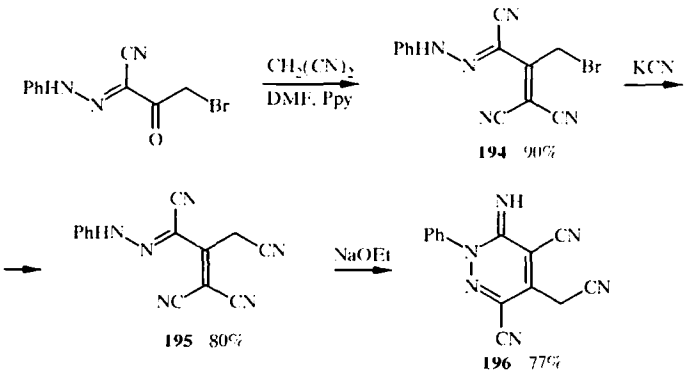
Substituted pyridines **192** may also be obtained on using bromine in place of alcoholate [96].



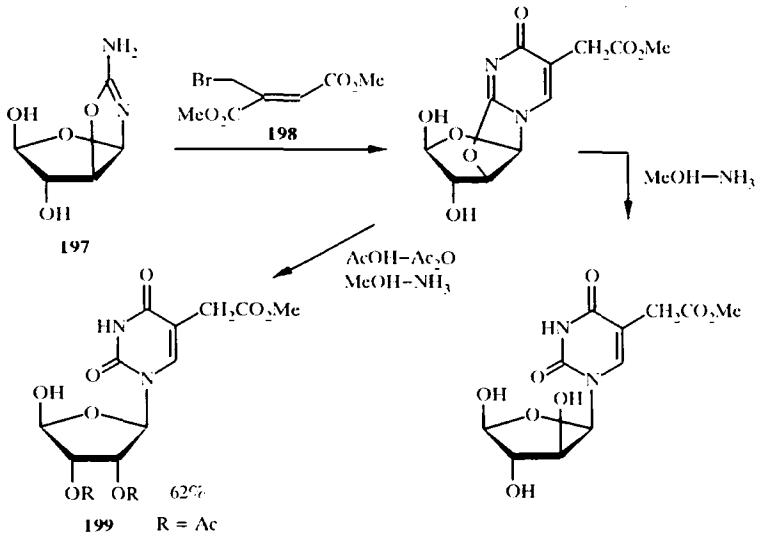
When using MeSH in a similar conversion the reaction proceeds anomalously [94,97]. Attack does not occur initially at the CN group but Michael addition of methanethiol takes place with subsequent elimination of MeSHal, which leads finally to pyridine **193**:



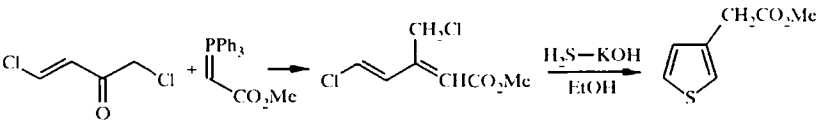
In [98] compound **194** containing 2-ethylidenemalononitrile fragment served as the precursor for the polycyano-substituted compound **195**. This compound is cyclized under the action of sodium ethoxide with the formation of pyridazine **196**:



The reaction of isourea **197** with dimethyl bromomethylfumarate **198** leads to pyrimidine **199**. The reaction comprises nucleophilic substitution of the bromine atom and subsequent condensation of the amino and methoxycarbonyl groups situated side-by-side with the bromomethyl substituent [99]:



An example has also been described of the formation of thiophene ring as a result of double nucleophilic substitution of chlorine atom by sulfur atom [100,101].



CONCLUSION

The given analysis of literature data on the conversions of 4-halocrotonic acids indicates the high, frequently unique synthetic potential of these compounds to obtain functionally substituted heterocyclic compounds, potentially possessing various forms of biological activity.

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