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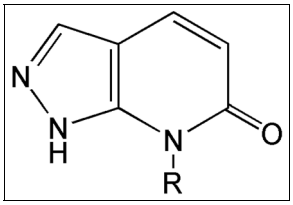

The procedures for the synthesis of substituted pyrazolo[3,4-*b*]pyridine-6-ones and some of their properties are reviewed.

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Contents

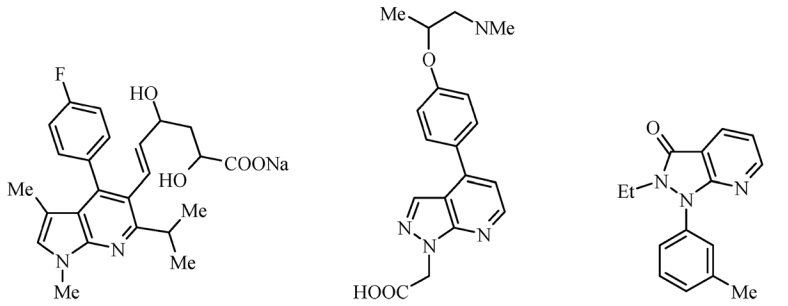
1. INTRODUCTION

Heterocyclic chemistry represents a very important area of organic chemistry. Condensed heterocyclic compounds form the basis of a number of natural and synthetic biologically active substances. In addition, studies of properties and transformations of condensed heterocyclic derivatives are of theoretical interest both for the development of new synthetic methods and for the study of the relationships between chemical structure and reactivity of organic compounds. All this is fully applicable to derivatives of pyrazolo[3,4-*b*]pyridine-6-one, many of which display significant biological activity.

Some of them are being tested and are in different phases of clinical trials for treatment of atherosclerosis [1], as immunosuppressants [2], antiviral agents [3], antidepressants [4], antitumor agents [5], blood-pressure lowering agents [6], so on (Scheme 1).

The interest of researchers in pyrazolo[3,4-*b*]pyridines as potential curative agents has led to numerous

Scheme 1



publications devoted to preparative methods of synthetic chemistry and aimed at creation of compounds of this type with a variety of functional substituents. This review is devoted to the discussion of synthetic methods and some properties of pyrazolo[3,4-*b*]pyridin-6-ones.

2. SYNTHESIS OF PYRAZOLO[3,4-*b*]PYRIDIN-6-ONES, BASED ON ANNELATION OF PYRAZOLE TO THE PYRIDINE RING

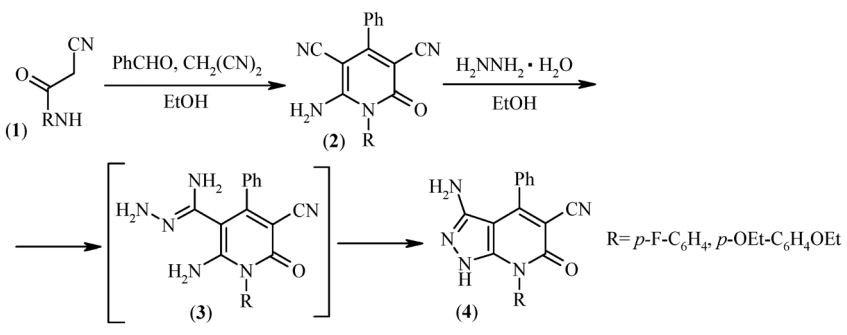
2.1. The fusion of the pyrazole ring to 3-cyanopyridines. The classical method of synthesizing 3-aminopyrazoles is the reaction of closing the pyrazole ring during reaction of hydrazine and *o*-amino cyano derivatives [7–9]. The same approach was used in several studies [10–13] in the synthesis of 6-oxopyrazolo[3,4-*b*]pyridines with the intermediate formation of derivatives of 3-cyano-6-oxopyridine.

Substituted 4-phenyl-2-oxo-1,2-dihydro-3-cyanopyridines (**2**) obtained by condensation and cyclization of cyanoacetanilides (**1**) to benzaldehyde and malononitrile in the presence of piperidine were the starting materials in the hydrazine hydrate synthesis of target pyrazolo [3,4-*b*]pyridones (**4**) [10]. The authors proposed that the initial stage of this transformation was the incorporation of hydrazine into one of the cyano groups of pyridine with the formation of the derivative (**3**; Scheme 2).

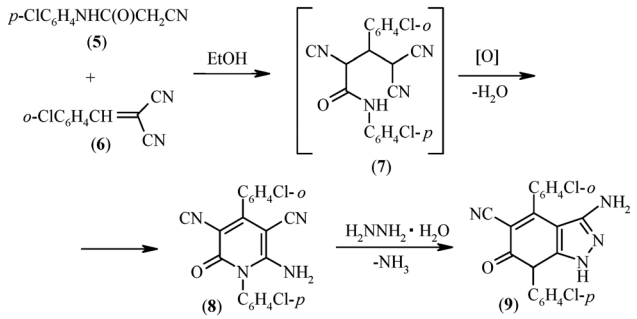
An analogous synthesis of pyrazolopyridinone (**9**) was proposed [11]. The authors showed that the reaction of cyanoacetanilide (**5**) and dinitrile (**6**) in boiling ethanol, in the presence of piperidine, first produced an intermediate, Michael adduct (**7**), which was subjected to cyclization and oxidation, and then formed the pyridine derivative (**8**) in a 70% yield. This derivative used in the reaction with hydrazine hydrate and pyrazolopyridinone (**9**) was obtained in a 65% yield (Scheme 3).

A recent study [12] showed that the reaction of methyl methacrylate (**10**) and malononitrile in the presence of sodium methoxide in boiling methanol resulted in 1,4,5,6-tetrahydropyridine-3-carbonitrile (**11**) in a 50% yield. In this case, the reactants for the synthesis of pyrazolopyridines were not aromatic derivatives; they were cyclic alkoxy enaminonitriles of the type (**11**; the aforementioned dearomatization did not occur). The process of the formation of bicyclic derivatives takes place by the usual pathway—replacement of the methoxy group by the hydrazine group and the cyclization of the latter at the cyano group, ending with pyrazolopyridones (**12**) or (**14**). Surprisingly, acylation of the N1-methyl derivative (**14**) occurs at the exocyclic amino group while the site of acylation of the derivative (**12**) is the N1. It was demonstrated that acylation of the amino group in pyridone (**14**) by different acyl chlorides R^1COCl in the presence of the dimethylaminopyridine

Scheme 2



Scheme 3

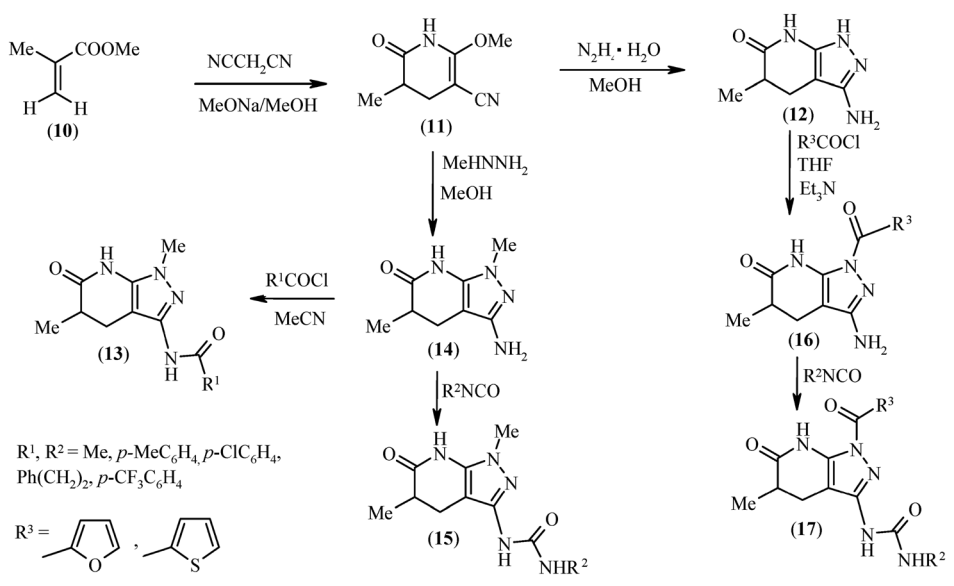


led to the appropriate amides (**13**) with the yield of 26–48%. Also, carbamides (**15**) were synthesized in the reaction of pyridine (**14**) with isocyanates R^2NCO, in a 49–87% yield. The authors of the article [12] note that when pyrazolo[3,4-*b*]pyridine (**12**) reacts with furan-2-carbonyl or thiophene-2-carbonyl chlorides, the reaction takes place selectively with the nitrogen of the pyrazole ring and does not affect the free amino group. The compounds thus obtained (**16**) were introduced into the reaction with isocyanates R^2NCO in the pyridine medium with the formation of carbamide derivatives (**17**; Scheme 4).

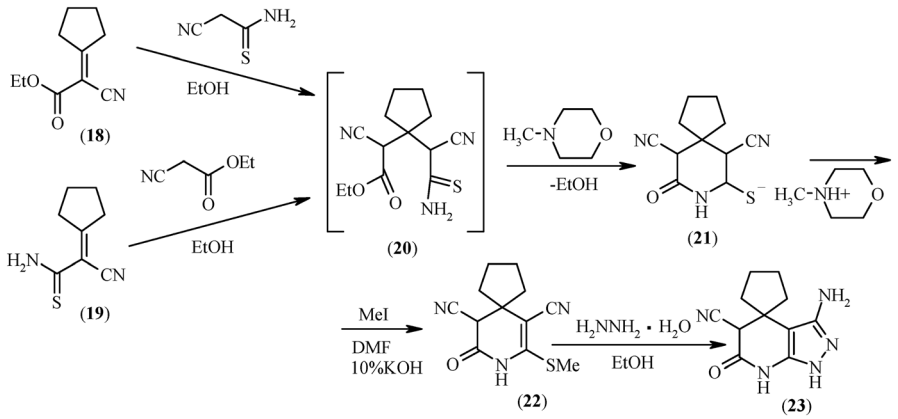
It is widely known that dihydropyridine chalcogenes are possible synthons in the synthesis of heterocyclic compounds with a broad spectrum of biological activity [13]. As a confirmation of these studies, the authors of [14] investigated the reaction of cyclopentylidenecyanoacetic ether (**18**) and cyanothioacetamide in the presence of *N*-methylmorpholine. It was shown that this reaction proceeded initially as Michael reaction with the formation of the adduct (**20**), cyclocondensation of which resulted in the salt (**21**) in a 72% yield. This salt was also obtained in the reaction of cyclopentylidenecyanothioacetamide (**19**) with cyanoacetic ester and *N*-methylmorpholine. The synthesis of the cyclized pyrazolopyridine (**23**) was conducted in the same solution where sulfide (**22**) was formed, with subsequent reaction with hydrazine hydrate (Scheme 5).

4-Methyl-2-methylthio-6-oxo-1-phenyl-5-cyano-3-ethoxycarbonylpyridine (**29**) [15,16] proved to be valuable in the synthesis of heterocyclic compounds. Thus, for example, the ethoxycarbonyl group, located in the ortho position to the methylthio group, allows for various reactions with closing of a new ring. This characteristic was used in the article [17] to synthesize the pyrazolopyridine derivative (**30**), with the closing of the pyrazole ring by hydrazine hydrate. The mechanism of this reaction proposed in ref. 18 is very complex. It assumes the geminal location of two negatively charged fragments near one carbon in one of the stages, which we deem highly improbable. In the scheme below, we assume an equilibrium (resembling that accepted for the Dimroth rearrangement) that preconditions further formation of the pyrazolopyridine bicyclic derivative (Scheme 6).

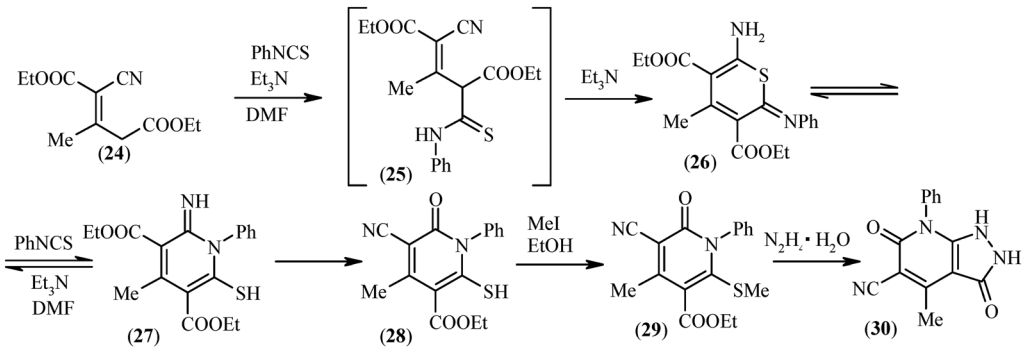
Scheme 4



Scheme 5



Scheme 6



Other authors [19] mention a convenient and simple method of using diethyl 2-phenyl-3-cyanopropene-1,1-dicarboxylate (**33**) as a versatile reagent in the synthesis of a variety of heterocyclic systems, including pyrazolopyridines. Their attempt to get 2-phenyl-3-cyanopropene-1,1-dicarboxylate (**33**) by means of direct condensation of diethyl malonate and benzoyl acetonitrile with the use of various acidic and alkaline agents proved to be unsuccessful. However, this compound was synthesized *via* a series of subsequent chemical transformations. Thus, condensation of diethyl malonate with acetophenone, with the subsequent bromination of the intermediate (**31**) by *N*-bromosuccinimide in the benzene led to the formation of the respective bromomethyl derivative (**32**). The reaction of the latter with sodium cyanide in boiling ethanol led to the substance (**33**), which entered the reaction with trichloroacetonitrile to produce the respective pyridine-3-carbonitrile (**34**). The trichloromethyl group in the latter is a good leaving group in the reaction with nucleophiles, and boiling pyridone (**34**) with phenylhydrazine in dioxane smoothly leads to 5-amino-2-oxopyrazolo[3,4-*b*]pyridine (**35**; Scheme 7).

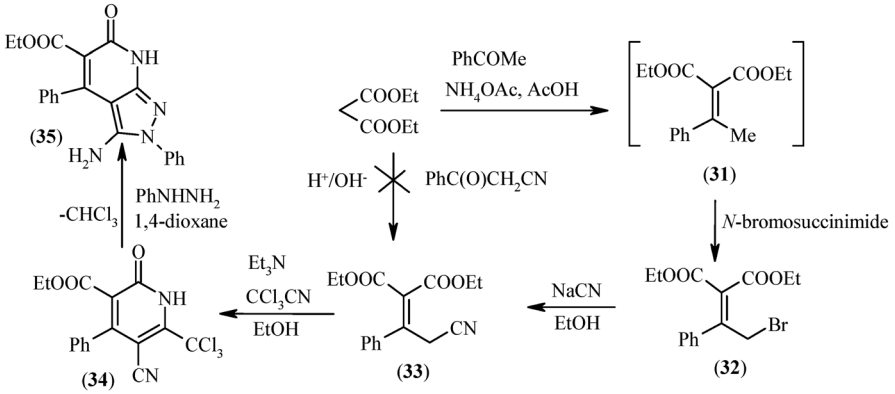
2.2. Annelation of the pyrazole ring to formylpyridines. Closure of the pyrazole ring based on the reaction of a monosubstituted hydrazine with formyl or aldehydic group was also reflected in a series of publications devoted to the synthesis of 2-oxo-pyrazolopyridines.

A convenient method for the synthesis of pyrazolopyridones (**39**) is presented in ref. 20; it consists of the initial introduction of the formyl group into pyridine (**36**) *via* heating of the initial compound in triethyl orthoformate and subsequent closure of the pyrazole cycle, with the use of hydrazine hydrate or phenylhydrazine in the presence of acetic acid through the stage of the intermediate (**38**). In the reactions of this type, one should know that they are accompanied by dearomatization of the pyridone cycle, the disadvantage of which in energy terms is compensated for by further generation of the aromatic bicyclic derivatives (Scheme 8).

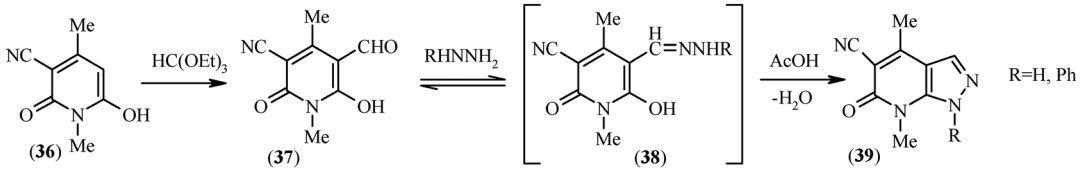
In the refs. 21 and 22, the synthesis of derivatives of pyrazolo[3,4-*b*]pyridin-6-one from the respective amides of the glutaric acid is described. For instance, their heating with the Vilsmeier–Haack reagent resulted in the corresponding N-substituted tetrahydropyridine (**41**) [23], which was subjected to the transformation to the bicyclic product (**42**) in the phenylhydrazine reaction. The reaction of pyrazolopyridine (**42**) with DMF/$POCl_3$ produced chlorosubstituted product (**43**; Scheme 9).

A recent article [24] is devoted to the reaction of *N*-phenyl-3-oxobutanethioamide with 3-phenyl-2-propenoylchloride.

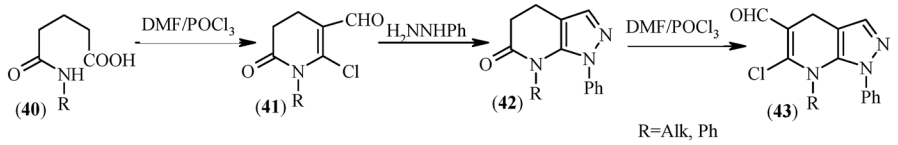
Scheme 7



Scheme 8



Scheme 9



It has been established that, when the reaction is carried out in acetone in the presence of K_2CO_3, it produces 6-thioxopiperidin-2-one (**46**). 6-Thioxopiperidin-2-ones are ß-thioxocarbonyl compounds and can exist in the keto (**46**), enol (**47**), and en-SH (**48**) forms, where the second and the latter forms are likely to be stabilized by an intramolecular H-bond. Crystals of 6-thioxopiperidin-2-ones exist exclusively in the enol form (**47**), which is evidenced by IR-spectroscopy and X-ray diffraction analysis [25]. The authors investigated the reaction of enol (**47**) with hydrazine hydrate in glacial acetic acid and found out that the product of this transformation was pyrazolo[3,4-*b*]pyridin-6-one (**49**; 87% yield; Scheme 10).

3. SYNTHESIS OF PYRAZOLO[3,4-*b*]PYRIDIN-6-ONES, BASED ON ANNELATION OF THE PYRIDINE RING TO THE PYRAZOLE RING

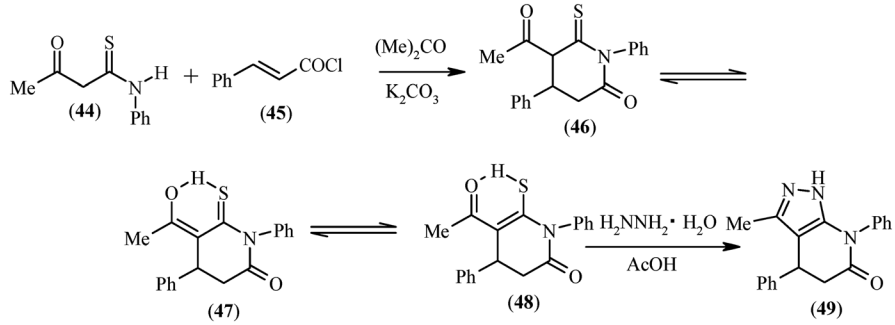
3.1. Annelation of the pyridine ring to pyrazole substituted in the position 4.

3.1.1. Annelation of the pyridine ring to cyanopyrazoles. In the ref. 26, synthesis of derivatives of pyrazolo[3,4-*b*] pyridin-6-ones (**53**), which are inhibitors of receptors of tyrosine kinase [26], crucial for the process of cell fission and apoptosis, is described. Reaction of benzimidazole (**50**) with aminopyrazole (**51**) in the presence of lithium methyl(bis-3-methylsilyl)amide (LMSA) was shown to produce an intermediate amide (**52**), which was isolated and transformed into pyrazolo[3,4-*b*]pyridinone (**53**), in yield lower than 10% (Scheme 11).

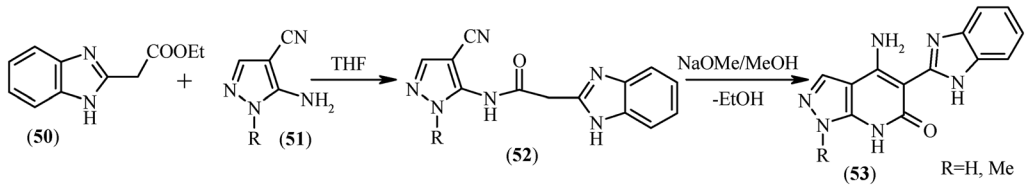
Condensed 4-substituted pyrazolo[3,4-*b*]pyridin-6-ones can be synthesized using the Torp–Ziegler reaction [27,28]. It is well known that such strongly electron-withdrawing substituents as CN and COOAlk in acetamide activate this process [29]. The authors [30] first established that the Torp–Ziegler cyclization occurs even when a morpholine or piperidine substituent was bonded to the methylene group. Thus, derivatives of pyrazolo[3,4-*b*]pyridin-6-one (**58**) were obtained in boiling amines (**57**) in DMSO in the presence of potassium *tert*-butoxide, with yields of 72 and 41%, respectively (Scheme 12).

There is evidence in the literature [31], that metal ions, especially tin(IV), can facilitate the formation of the carbon–carbon bond between the cyano group of

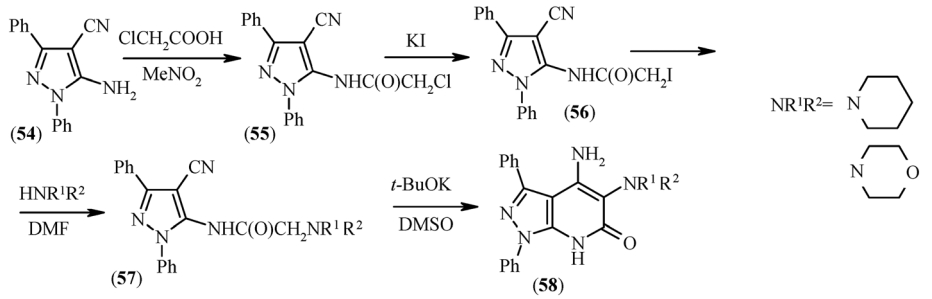
Scheme 10



Scheme 11



Scheme 12



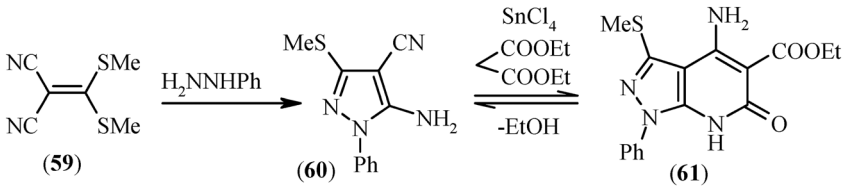
nitriles and methylene group of ß-dicarbonyl compounds *via* formation of complex-coordinated interim compounds with the metal between the nitrile and β-dicarbonyl compounds [32]. Taking this observation into account, the authors [33] presented a new approach to the synthesis of the derivative of pyrazolo[3,4-*b*]pyridone (**61**). It was demonstrated that condensation of pyrazole (**60**), which was previously obtained in the reaction of *S*,*S*-dimethylacetal dicyanoketene (**59**) with phenylhydrazine [34], refluxed with diethyl malonate in toluene in the presence of tin(IV) chloride, resulted in the formation of pyrazolo[3,4-*b*]pyridine carboxylate (**61**), in a low 20% yield (Scheme 13).

In ref. 35, the preparative approach to the synthesis of condensed pyrazolopyridones, allowing one to obtain the target compounds in higher yields (97–98%) was proposed. It is the reaction of aminopyrazoles (**62**) with diethyl malonate in the presence of sodium ethoxide at boiling. Alkaline hydrolysis of pyrazolopyridone (**63**), on treatment with a solution of KOH, leads to the decarboethoxylated derivative of pyridone-2 (**64**), in a 98% yield. Introduction of a nitroso group in the position 5 of the pyridine ring and its further reduction to the amino group result in the formation of the diamino derivative (**66**). The latter reacts with furfural in the presence of ferric chloride with the formation of pyrazoloimidazopyridine (**67**; Scheme 14).

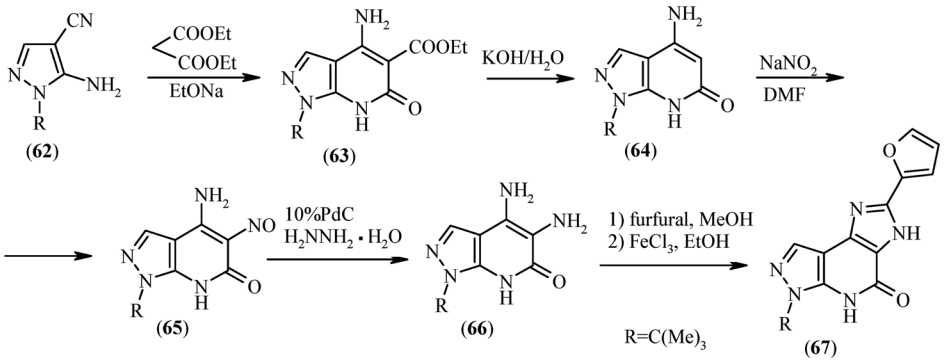
3.1.2. Annelation of the pyridine ring to formylpyrazoles. The authors of ref. 36 present the method for the synthesis of condensed pyrazolo[3,4-*b*]pyridin-6-one (**72**), based on obtaining initially the formyl derivative of 5-aminopyrazole (**70**) *via* Vilsmeier–Haack reaction, and ending in the closure of the pyridine ring after the reaction of formylpyrazole (**70**) with cyanoacetic ether (Scheme 15).

Reference 37 considers the properties of cyanopyrazolopyridine (**72**), synthesized using the above method [36]. It was shown that its treatment by the mixture of the phosphorus oxychloride and phosphorus pentachloride results in a chloro derivative (**73**). The authors attempted

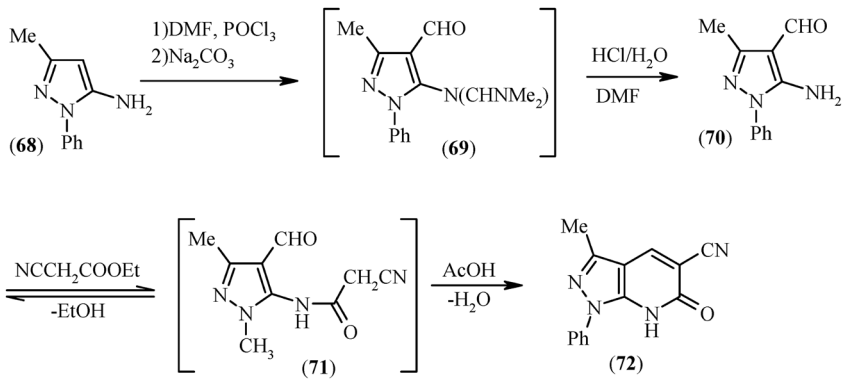
Scheme 13



Scheme 14



Scheme 15

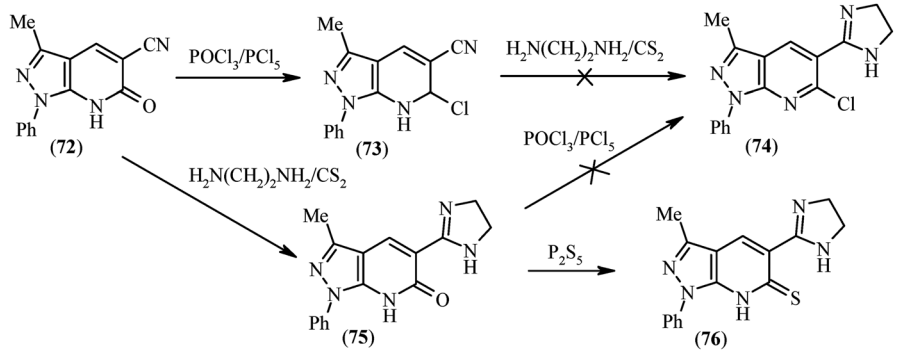


to transform the compound (**73**) into imidazolinyl derivative (**74**) by reaction with ethylenediamine [38] but unsuccessfully. As an alternative approach to obtain pyrazolopyridine (**74**), they suggested the transformation of cyanopyrazolopyridone (**72**), using the aforementioned procedure [38], with the further treatment of the compound (**75**) with phosphorus oxychloride. Imidazolinyl pyrazolopyridone (**75**) was transformed into the corresponding thione (**76**), *via* the reaction with P_2S_5 in pyridine (Scheme 16).

In ref. 39, substituted 4-formylaminopyrazole (75) was synthesized to study its chemical properties. For the synthesis, the Vilsmeier reaction in the presence of 5-aminopyrazole (68) was used. It was shown that, as a result of the reaction, the dimethylaminomethylene derivative of 5-formylpyrazole (78) was obtained. The same compound was formed in the reaction with formylaminopyrazole (77).

Proceeding from the results thus obtained, the authors suggested that in the reaction of 1-phenyl-3-methyl-5-aminopyrazole with the product of the reaction of phosphorus oxychloride with DMF, formylation of the amino group and formation of the compound (77) were the first to occur. This compound further reacts with the second molecule of the reagent, resulting in the formation of the dimethylaminomethylene derivative (78). It was found that, with acidic hydrolysis, the compound (78) turned into the initial aminopyrazole (68), while with alkaline hydrolysis—into 4-formyl-5-aminopyrazole (70) which, undergoing the annelation with the acetic

Scheme 16



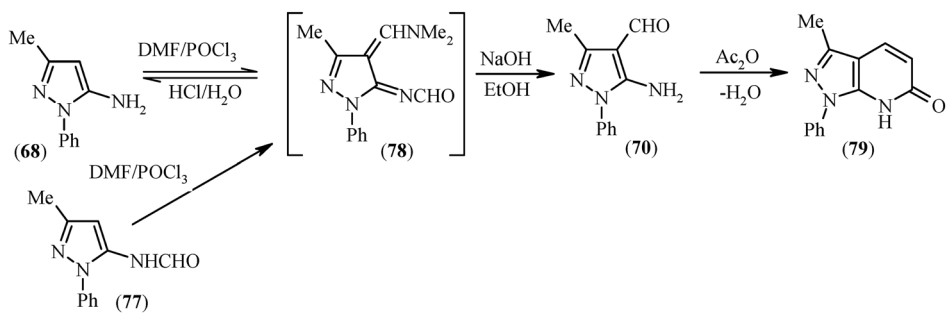
anhydride, was transformed into the derivative of dihydropyrido[3,4-*b*]pyrazole-6-one (79), in a 92% yield (Scheme 17).

It is known from the literature [40] that condensed pyrazolo[3,4-*b*]pyridones can be conveniently obtained from *o*-aminoaldehydes *via* Friedländer condensation. In the ref. 41, the authors showed a possibility of the synthesis of condensed systems *via* this route. The initial 5-amino-4-formylpyrazole (**82**) used in Friedländer condensation was synthesized by subsequent cyclic condensation of *N*-substituted arylacetonitrile with phenylhydrazine [42] with the formation of aminopyrazole (**83**), which was then formylated under conditions of Vilsmeier–Haack reaction into the dimethylaminoethylene derivative (**81**), in a 72–78% yield. Its hydrolysis under reflux in the presence of NaOH led to the target formyl derivative (**82**), with the yield of 68–70%. It is known [43] that Friedländer condensation may take place in the presence of different alkaline or acidic catalysts. Researchers [41] suggested that the reaction was conducted with diethyl malonate in the presence of piperidine, which permitted the generation of 3-arylpyrazolopyridone (**83**; Scheme 18).

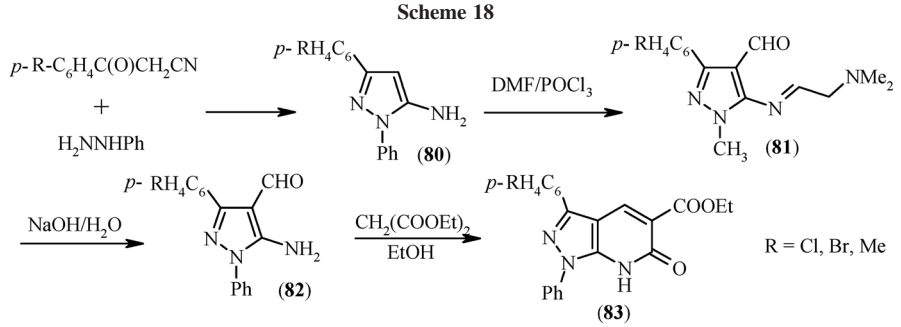
Similar results were obtained when synthesizing 3-methyl(or propyl or phenyl)-5-carboethoxypyrazolopyridines [44].

A similar transformation was described in ref. 45, but, in contrast to the previous publication [41], with 3-aminopyrazole (**84**). Thus, formylation of aminopyrazole

Scheme 17



Scheme 18



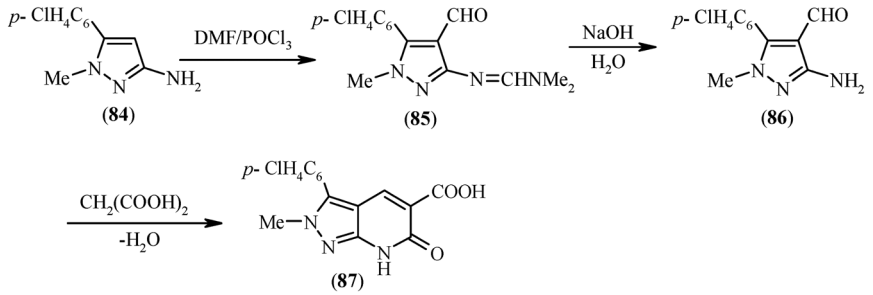
(**84**) by Vilsmeier–Haack reaction resulted in the dimethylaminoethylene derivative (**85**; 62% yield) that, after alkaline hydrolysis, was transformed into aminoformylpyrazole (**86**). The target pyrazolo[3,4-*b*]pyridine (**87**) was obtained from **(86)** in Knoevenagel reaction with the application of malonic acid and piperidine (Scheme 19).

In ref. 46, a possibility of using 3-amino-4-formylpyrazole to synthesize new derivatives of pyrazolo [3,4-*d*]pyridine was reported. The desired substance, 1-phenylpyrazole-4-carboxaldehyde, (**89**) was synthesized by Vilsmeier–Haack formylation of 3-amino-5-pyrazolone (**88**). Its further condensation with hippuric acid resulted in the target 6-oxopyrazolo[3,4-*d*] pyridine (**92**). In addition, it was shown that the reaction of (**89**) with cyanoacetic ester ended in the formation of pyrazolopyridone (**91**; Scheme 20).

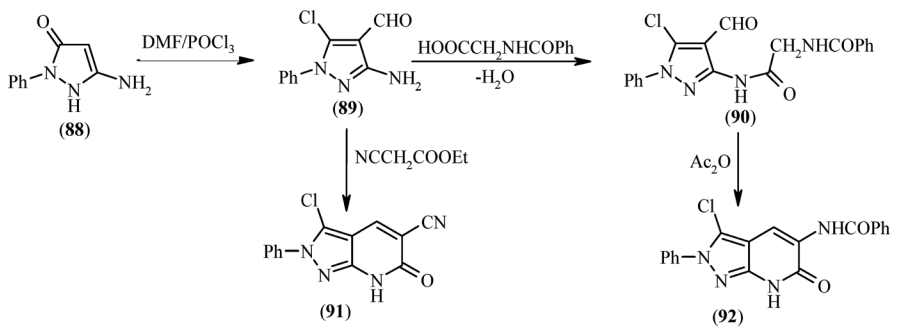
In the report [47], synthesis of pyrazolo[3,4-*b*]pyridin-6-one (**96**) is described. This compound was isolated as a side product in the synthesis of the derivatives of aminopyrazole (**95**) by the reaction of pyrazolyl-2-bromoacetamide (**94**) with 3-(2-methyl-1-piperidyl)propylamine. The authors suggest that the formation of the compound (**96**) is related to the ongoing intramolecular cyclization of pyrazole thus obtained (**95**; Scheme 21).

Authors of the report [48] found out that pyrazolopyridines (**99**) and (**100**) can be obtained in high yields *via*

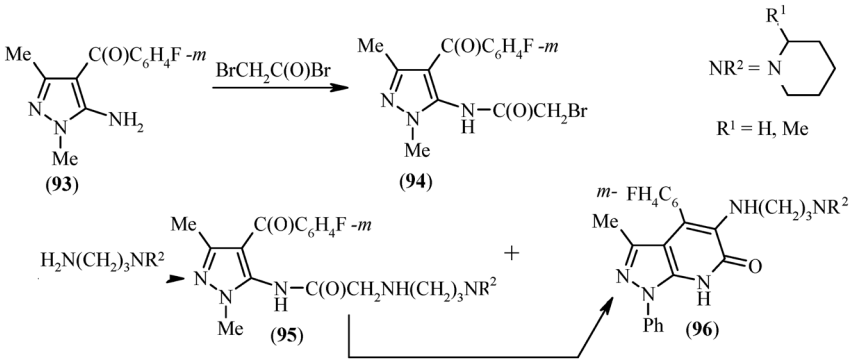
Scheme 19



Scheme 20



Scheme 21

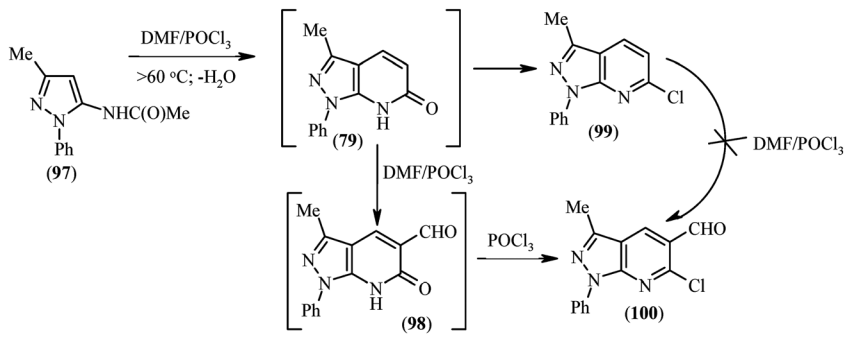


Vilsmeier–Haack reaction with 1-phenyl-5-acetylaminopyrazole (**97**). It was established that cyclization with the formation of condensed pyridines (**99**) and (**100**) took place exclusively at temperatures above 60°C. These researchers suggested that initially, the pyridone cycle was closed with the formation of pyrazole[3,4-*b*] pyridone (**79**), which then reacted with excess of DMF/$POCl_3$. Two competitive reactions, resulting in the formyl derivative of pyrazolopyridine (**98**) and a chlorine derivative of pyrazolopyridine (**99**), were observed. These authors remarked that further formation of 5-formyl-6-chloro derivative (**100**) was the leading process with the 58% yield, facilitated by the *ortho*-position of the formyl group. At the same time, an attempt at formylation of the pyrazolopyridine chloro derivative (**99**) did not result in the formation of the compound (**100**; Scheme 22).

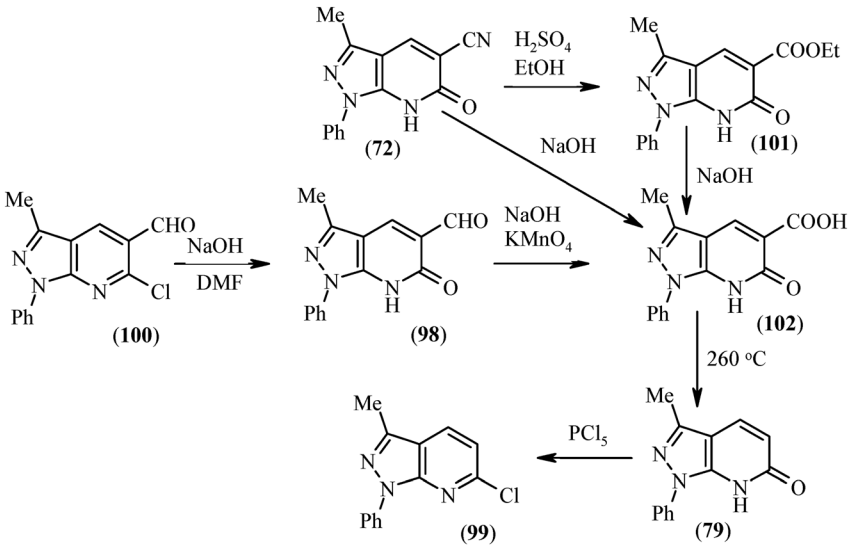
Later, the authors of ref. 48 studied chemical transformations of pyrazolopyridine (**100**) and showed that, as a result of alkaline hydrolysis, it turned into formyl pyrazolopyridone (**98**); subsequent oxidation of its formyl group led to the respective carboxylic acid (**102**). Decarboxylation of the compound (**102**) produced pyrazolopyridinone (**79**), whose reaction with $PhCl_5$ yielded the chloro derivative (**99**), identical to that obtained earlier through the Vilsmeier–Haack reaction. The acid (**102**) was also synthesized by alkaline hydrolysis from carbethoxy pyrazolopyridone (**101**) and cyanopyrazolopyridone (**72**; Scheme 23).

3.1.3. Annelation of the pyridine ring to carbethoxypyrazoles. In the publication [49], the authors reported an approach for the synthesis of some derivatives of pyrazolo[3,4-*b*]pyridin-6-one – prospective ligands of the adenosine receptor A_1 and analogs of the compound (**107**), which might be studied because of their anti-parkinsonian activity. It was shown that the closure of the pyridine ring proceeded smoothly using the well-known reaction of the ethoxycarbonyl derivative of pyrazole (**103**) with diethyl malonate in

Scheme 22



Scheme 23



the presence of sodium ethoxide. Treatment of the compound (**109**) with a mixture of thionyl chloride and DMF led to the dichloro derivative (**105**). Substitution of the chlorine atom at the aromatic carbon atom C-4 in the compound (**105**) for different amines occurs with the formation of pyrazolo[3,4-*b*]pyridones (**106**). Biological studies of synthesized compounds demonstrate that the substitution of the pyridine ring in the structure (**107**) for pyridone is not useful from the point of view of affinity to adenosine receptors A_1 (Scheme 24).

3.1.4. Other methods of synthesis. In the report [50], the authors present the method of synthesis of tetrahydro-1H-pyrazolo[3,4-*b*]pyridine derivatives. Aminopyrazole (**108**) was formylated and treated by Wittig reagent with the subsequent deformylation, hydrogenation, and cyclization that led to the formation of pyrazolopyridine (**112**). This substance was reduced by $LiAlH_4$ to tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine (**113**; Scheme 25).

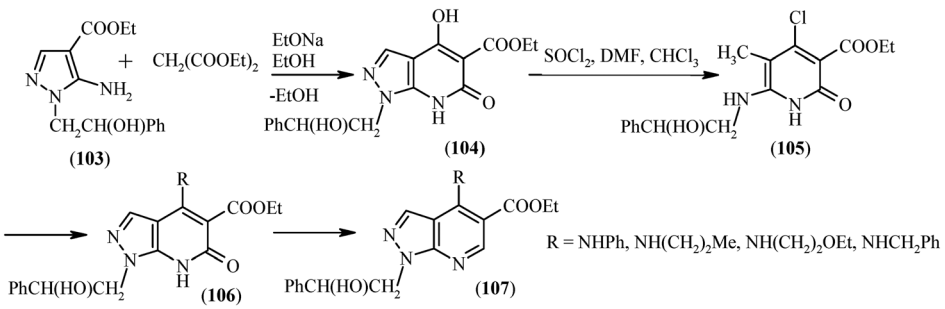
The publication [51] is devoted to a convenient method of synthesizing derivatives of pyrazolo[3,4-*b*]pyridine based on the reaction of imino phosphoranes (**117**) and (**119**). It is shown that iminophosphorane (**116**), synthesized from azidopyrazole (**115**) and triphenylphosphine [52], reacts with nitromethane in the presence of pyrrolidine with the formation of a nitrovinyl derivative (**119**; 55% yield) or it reacts with acetone under similar conditions with the formation of an iminophosporane (**117**; 50%). The authors managed to get target derivatives of pyrazolo[3,4-*b*]pyridone (**118**) and (**120**) by means of the reaction of iminophosphoranes (**117**) and (**119**) with carbon dioxide at 130°C in a sealed tube (Scheme 26).

The authors of the study [53] proposed an approach to the convenient one-phase synthesis of pyrazolo[3,4-*b*] pyridinone from 2-acyl-2′-cyanoacetohydrazides (**121**) and aryl cyano acrylates (**122**). It was shown that the attachment of hydrazide (**121**) to arylidenecyanoacetates (**122**) in ethanol in the presence of piperidine at ambient temperature led to the formation of pyrazolo[3,4-*b*] pyridinone as a piperidinone salt (**125**), in a 25–41% yield. The authors assume that, in the first phase of the reaction, the initial formation of the intermediate (**123**) occurs; then, as a result of a nucleophilic attack of the secondary amide's nitrogen atom on the cyano group, it turns into the aminopyrazole derivative (**124**). The next intermediate (**124**), in turn, is subject to secondary cyclization and spontaneous aromatization with the transformation into pyrazolo[3,4-*b*]pyridin-6-one (**126**; Scheme 27).

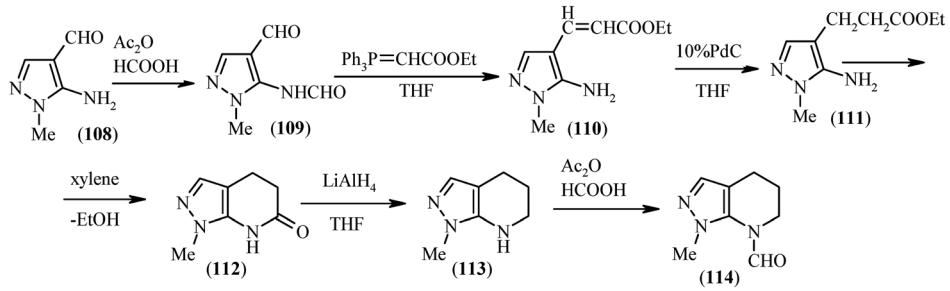
3.2. Annelation of the pyridine ring with 3(5)-aminopyrazoles, not substituted in the position 4.

3.2.1. Annelation based on the reaction of pyrazoles with acetoacetic ester. Most publications highlighting the use of 4-unsubstituted pyrazoles in the synthesis of pyrazolo[3,4-*b*] pyridine system deal with their reaction with derivatives of β-diketones.

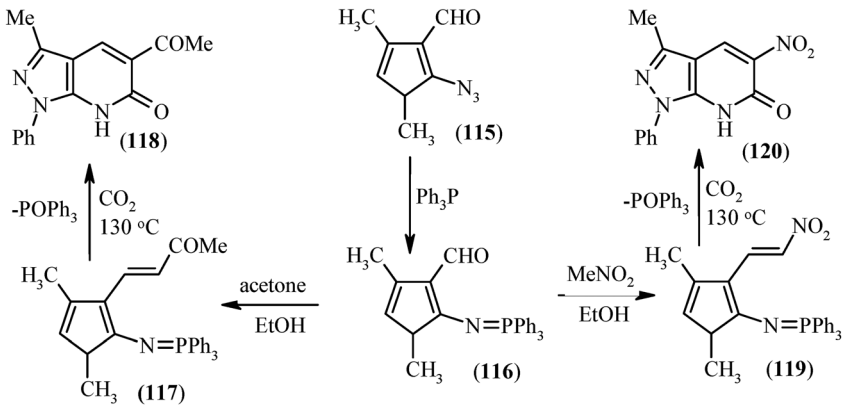
Scheme 24



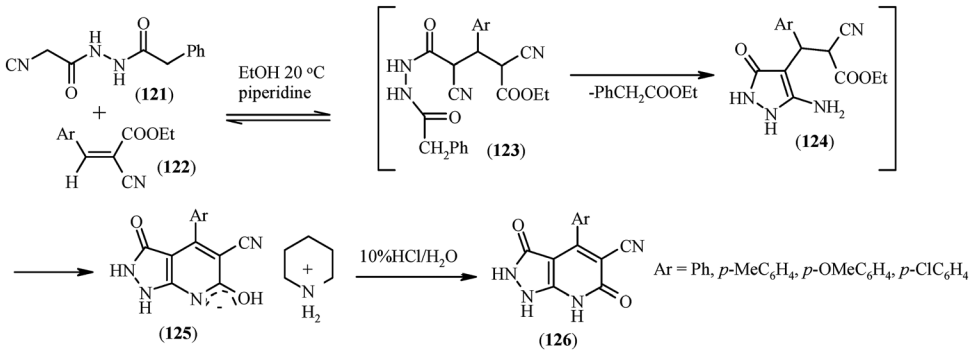
Scheme 25



Scheme 26

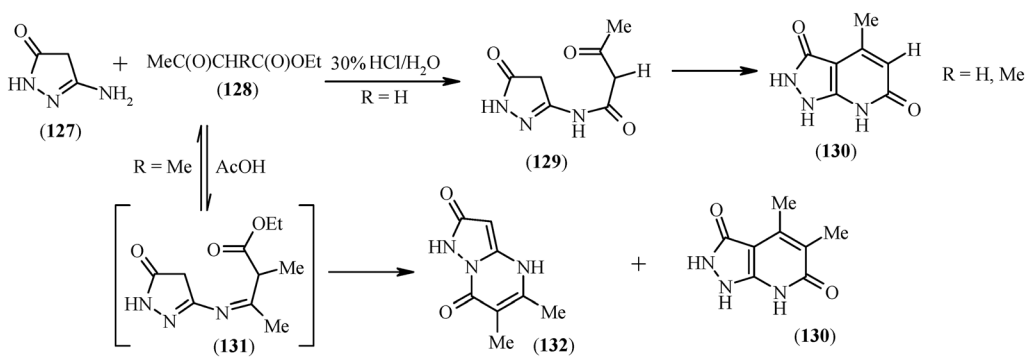


Scheme 27



Numerous articles have been devoted to the reaction of 5-amino-3-pyrazolone with acetoacetic ester, ending in a variety of products [54–62]. The authors [58–60] considered the reaction of 5-amino-3-pyrazolone (**127**) with β-dicarbonyl compounds to find out [60] that refluxing of pyrazolone (**127**) with acetoacetic ester (**128**; R = H) in 30% aqueous HCl [61,62] resulted in the formation of pyrazolo[3,4-*b*]pyridin-6-one (**130**) in a 75% yield. It was also established that condensation of 5-aminopyrazole (**127**) with methyl acetoacetic ester (**128**) (R = Me) proceeded at a slower rate. The bicyclic product (**130**) was extracted with a lower yield. Based on the method described in ref. 59, this reaction in the acetic acid environment takes place with the formation of the mixture of two products: the pyrimidine derivative (**132**) with a 25% yield (cyclization at the pyrazole nitrogen) and pyrazolo[3,4-*b*]pyridin-6-one (**130**) with a 52% yield (cyclization at the methylene group in the ring). In the authors' opinion, the derivative of pyrazolo[1,5-*a*]pyridimine (**132**) is formed *via* the intermediate (**131**; Scheme 28).

Scheme 28



A similar synthesis of pyrazolopyridine (**130**) is described in the report [63].

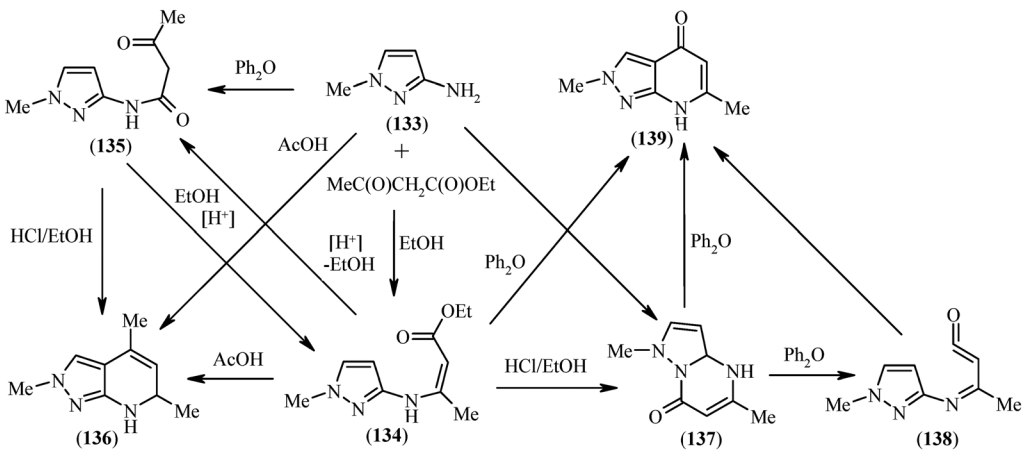
Substituted 3-amino-1-methylpyrazole (**133**) was used in an analogous reaction with acetoacetic ester [64]. The authors found out that refluxing in ethanol led to ethyl-3-(1-methyl-3-pyrazolylamino)crotonate (**134**) in a 62% yield, while refluxing in diphenyl ether—to pyrazole (**135**), in a 67% yield. A 3-h refluxing of (**135**) in ethanol solution of HCl led to the closure of the pyridine ring and extraction of pyrazolo[3,4-*b*]pyridin-6-one (**136**), in a 21% yield. This compound was synthesized in a 50% yield with *via* refluxing of pyrazole (**133**) with acetoacetic ester in acetic acid for 4 hours. Cyclization of crotonate (**134**) in acetic acid within 3 h also ended in the formation of pyrazolo[3,4-*b*]pyridin-6-one (**136**), in a 38% yield. This can be explained by the well-known phenomenon of transformation of crotonate (**134**) into amide (**144**) under acidic conditions [65]. Refluxing of the crotonate (**134**) in the ethanolic solution of HCl or in polyphosphoric acid led to the formation of 1,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-one (**137**). However, refluxing of crotonate (**134**) in diphenyl ether resulted in the formation of the pyrazolo[3,4-*b*]pyridin-4-one derivative (**139**). Heating of pyrazolo[1,5-*a*]pyrimidin-7-one (**137**) at $t > 200$°C in diphenyl ether also led to pyrazolo[3,4-*b*]pyridin-4-one (**139**). It was established that pyrazolo[1,5-*a*]pyrimidin-7-one (**137**) was the first substance to be formed in the temperature range of 140–170°C, and the next was pyrazolo[3,4-*b*]pyridine (**139**)—in the temperature range of 180–200°C. A likely mechanism of this reaction is the attack of the ester group of crotonate (**134**) by the N-2 nitrogen of the pyrazole ring, which is more probable than the attack by carbon C-4 (in this case, pyrazolo[1,5-*a*]pyrimidine (**137**) is formed as the intermediate). Hence, pyrazolo [3,4-*b*]pyridine (**139**) is not directly formed from crotonate (**134**), but it is the final product of the thermal conversion of pyrazolo[1,5-*a*]pyrimidine (**137**). In a similar manner, pyrazolo[3,4-*b*]pyridin-4-one (**139**) was obtained directly from acetoacetic ether and aminopyrazole (**133**) at 240°C (Scheme 29).

In the report [66], the investigators reproduced experiments from earlier trials [67–70] in order to establish the unambiguous structure of products of 4- or 6-oxo derivatives of pyrazolo[3,4-*b*]pyridine obtained during the reaction between aminopyrazole (**140**) and acetoacetic ester in boiling acetic acid. It was shown [66], that refluxing a solution of 1,3-dimethyl-5-amino pyrazole (**140**) in glacial acetic acid led to pyrazole[3,4-*b*]pyridin-6-one in a 53% yield (**143**). The authors coped with the task of synthesizing crotonate (**141**) in boiling benzene in the presence of a catalytic amount of acetic acid [67,71]. The attempt at cyclization *via* boiling in diphenyl ether did not lead to the expected pyrazolopyridine (**143**), but it resulted in the isomeric form – pyrazolo [3,4-*b*]pyridin-4-one (**144**). However, its heating in acetic acid or in ethylene glycol results in the formation of the target pyrazolo[3,4-*b*]pyridin-6-one (**143**). According to the authors, under these conditions, crotonate (**141**) first turns into amide (**142**), and then the amide cyclizes into pyrazolo[3,4-*b*]pyridin-6-one (**143**; Scheme 30).

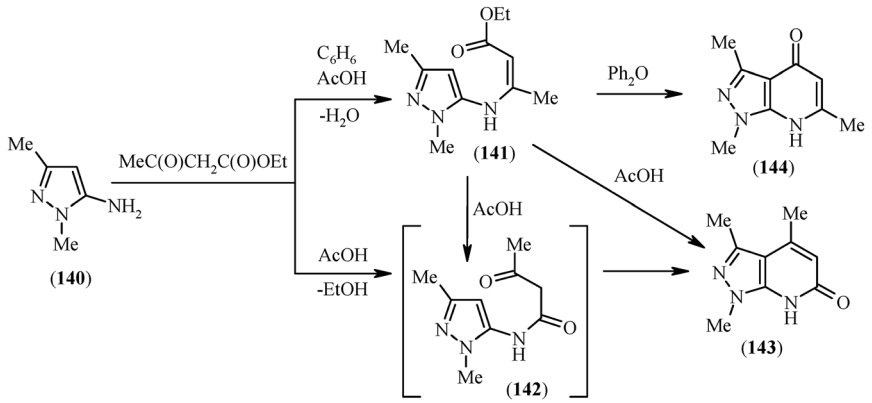
Pyrazolo[3,4-*b*]pyridin-6-one (**143**) was converted into the corresponding tetrahydro derivative (**147**) *via* the chloro derivative (**150**) which, after catalytic hydrogenolysis, was transformed into the pyrazolotetrahydropyridine derivative (**147**) in a 55% yield (Scheme 31).

A similar dependence of the structure of products, formed in the reaction of 5-aminopyrazoles (**148**) with acetoacetic ester, is described in ref. 72. It was demonstrated that aminopyrazoles (**148**) formed crotonates (**149**) in this reaction at room temperature, while at 80–150°C, they were converted into the amide (**151**). According to the authors, the determining factor in the

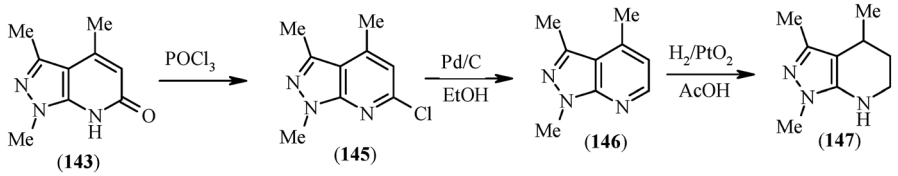
Scheme 29



Scheme 30



Scheme 31

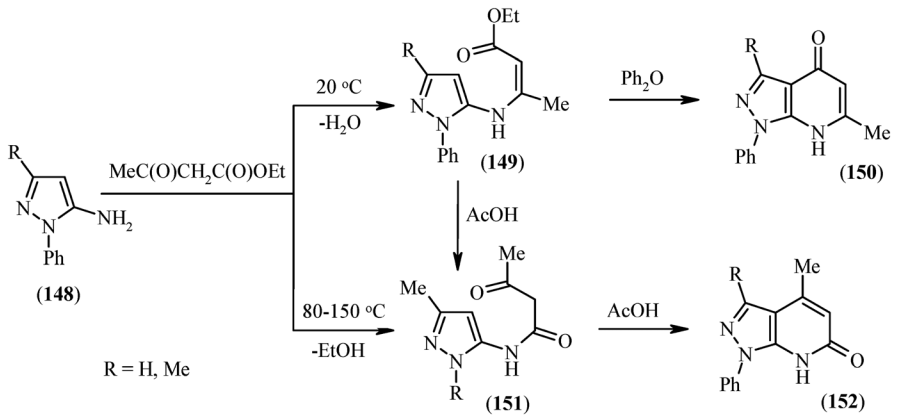


reaction direction was the temperature. It was found out that heating of crotonate (**149**) at 130°C for 40 min without the solvent or in diphenyl ether at 210°C, pyrazolo[3,4-*b*]pyridin-4-one was formed (**150**). Cyclization of acetoacetamide (**151**) in acetic acid at 120°C, yielded pyrazolo[3,4-*b*]pyridin-6-one (**152**). Crotonate (**149**) was shown to partly convert into amide (**151**) on heating in the acetic acid [65]. The study of IR spectra [73] of pyrazolopyridones (**150**) and (**152**), in which absorption bands at 1680 cm^{-1} are observed, allows for a conclusion that these compounds are in their oxo form (Scheme 32).

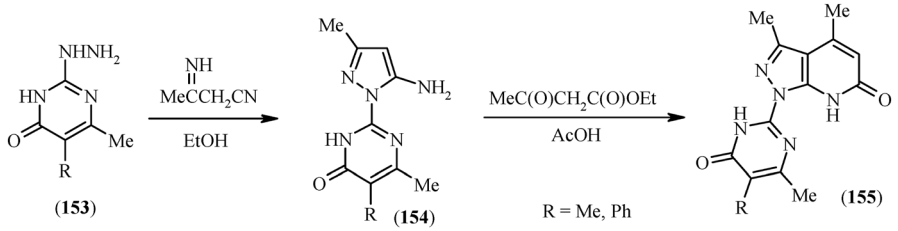
The above-noted dualism of the reactions passing between 5-amino pyrazoles and acetoacetic ester [72,74] was not observed in the case of pyrazole (**154**) in boiling acetic acid [75] (Scheme 33).

Dorn and coworkers [76–80] considered transformations of 1-substituted 3-amino and 5-aminopyrazoles (**156**) taking place with acetoacetic ester. They showed [78,79] that at boiling in xylene at 150°C, the reaction of 1-substituted 3-aminopyrazole (**156**) with acetoacetic ester produced acetoacetamide (**157**) in 81% yield. Esters (**158**) can be obtained by reaction of 1-substituted 3- and 5-aminopyrazoles (**156**) by heating in ethanol. The reaction rate accelerates both in the presence of a catalytic amount of acids (AcOH, H_2SO_4) and with amines present in excess [70,81]. Condensed pyrazolo [3,4-*b*]pyridin-6-ones (**160**) were synthesized by heating of crotonate (**158**) in acetic acid or (directly) from aminopyrazole (**156**) and acetoacetic ester in acetic acid. The authors of ref. 76 managed to extract the

Scheme 32



Scheme 33



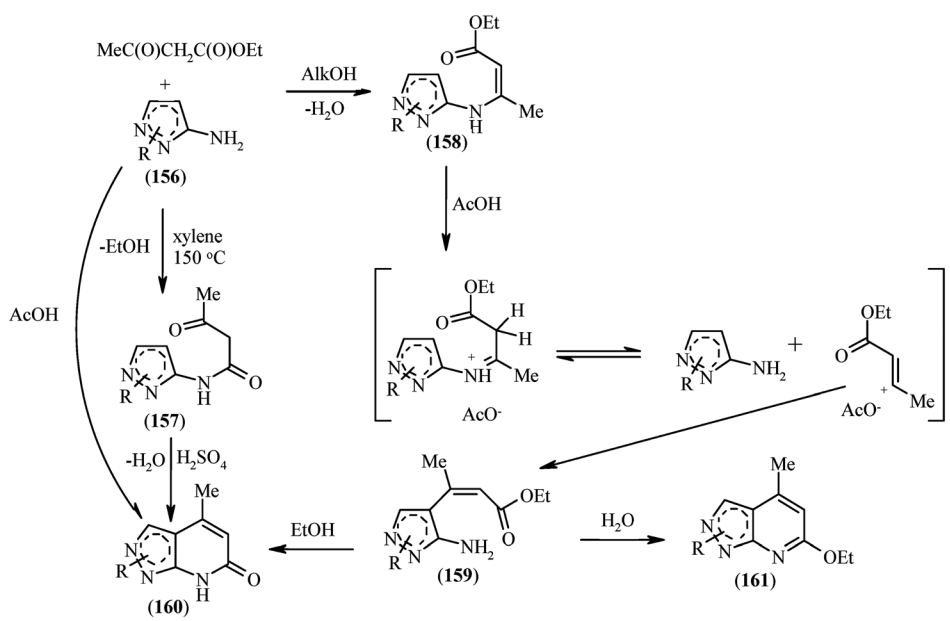
intermediate compound (**159**). In connection with the increased electron density at carbon C-4 in 1-substituted 5-aminopyrazoles, 1-substituted pyrazolo[3,4-*b*]pyridin-6-ones (**160**) were synthesized faster and with a greater yield than those formed from derivatives of 3-aminopyrazole. It was observed that with the increasing concentration of acid, there was an intramolecular reaction leading to the formation of 6-ethoxy pyrazolo[3,4-*b*]pyridinones (**161**). In the authors' opinion, it is the compound (**159**) that is an intermediate in the of formation of pyrazolopyridinones (**160**); this is confirmed by the fact that condensation of acetoamides (**157**) in sulfuric acid gives only traces of pyrazolo[3,4-*b*]pyridin-6-ones (**160**; Scheme 34).

3.2.2. Synthesis of pyrazolo[3,4-b]pyridin-6-ones, based on reaction of pyrazoles with other ketoesters. Because of considerable interest of the researchers in different fluorine-containing heterocyclic compounds, authors of ref. 82 considered methods of synthesis of fluorine derivatives of pyrazolo[3,4-*b*]pyridinone. Earlier [66], it was noted that condensation of 5-amino-1,3-dimethylpyrazole (**140**) with acetoacetic ester in benzene led to the formation of a crotonate. Contrary to these results [82], the reaction of ethyl 4,4,4-trifluoroacetoacetate with 5-amino-1,3-dimethylpyrazole (**140**) in benzene in the presence of a catalytic amount of acetic acid resulted in the stable tetrahydropyrazolo[3,4-*b*]pyridin-6-one (**162**), heating of which in diphenyl ether yielded the desired product (**163**) in 93% yield (Scheme 35).

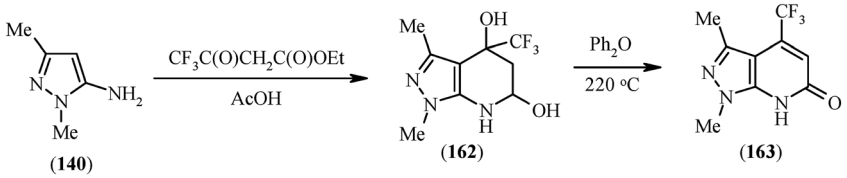
They also studied the condensation of ethyl 4,4,4-trifluoroacetate with aminopyrazole (**140**) in boiling ethanol and established that this reaction proceeded with the formation of a mixture of 5-amino-1,3-dimethyl-4-substituted pyrazole (**164**), in a 52% yield, and tetrahydropyridone (**162**), in a 19% yield. The formation of the aminopyrazole derivative (**164**), which is a likely intermediate in the reaction, demonstrated that the carbonyl group of trifluoroacetoacetic ester was attacked by the nucleophilic C-4 center of pyrazole (**140**). Further boiling of pyrazole (**164**) in diphenyl ether or in acetic acid led to the formation of condensed pyrazolo[3,4-*b*] pyridin-6-one (**163**). Direct condensation of aminopyrazole (**140**) with trifluoroacetoacetic ester in boiling acetic acid also led to the mixture of these compounds (Scheme 36).

A similar transformation with the use of trifluoroacetoacetic ester was considered in ref. 83, where the

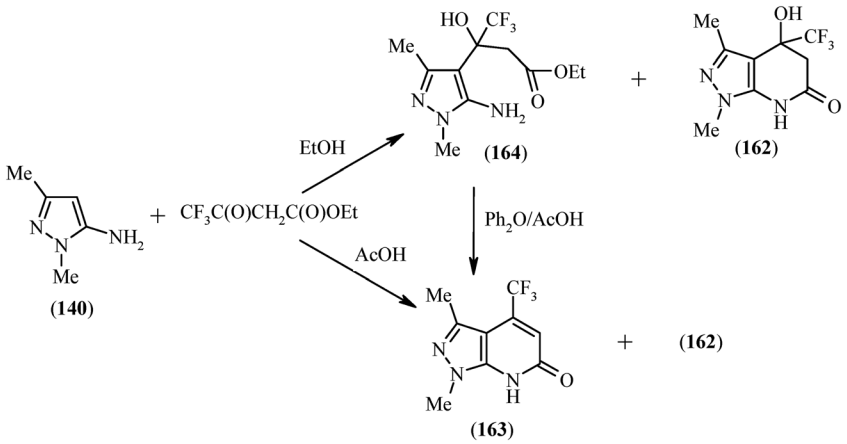
Scheme 34



Scheme 35



Scheme 36

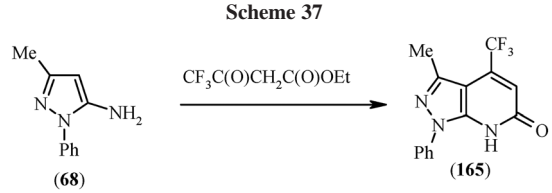


derivative of pyrazolo[3,4-*b*]pyridine (**165**) was synthesized from 1-phenyl-3-methyl-5-aminopyrazole (**70**) in trifluoroacetic acid (Scheme 37).

This reaction proceeds in a slightly different way with nonsubstituted aminopyrazoles (**166**) [82]. Thus, reaction of trifluoroacetoacetic ester with aminopyrazoles (**166**) leads, in addition to the earlier described tetrahydro derivative (**167**), to pyrazoles (**168**), which undergo transformations to the respective pyrazolo[3,4-*b*]pyridinones (**169**) in diphenyl ether and acetic acid, respectively. The extraction of a small amount of amide (**168**) evidenced that the most likely pathway of condensation was the route presuming a nucleophilic attack by the amino group of aminopyrazole (**166**) on the carbonyl group of the ester. The reaction of trifluoroacetic ester with aminopyrazoles in boiling acetic acid results in pyrazolo[3,4-*b*] pyridinones (Scheme 38).

Condensation of 1,3-dimethyl-5-aminopyrazole (**140**) with esters (**170**) at reflux in acetic acid was described in ref. 84. Similarly as before, formation of the intermediate

Scheme 37



(**171**) was observed. The intermediate was obtained when the reaction was conducted in benzene in the presence of a catalytic amount of acetic acid (Scheme 39).

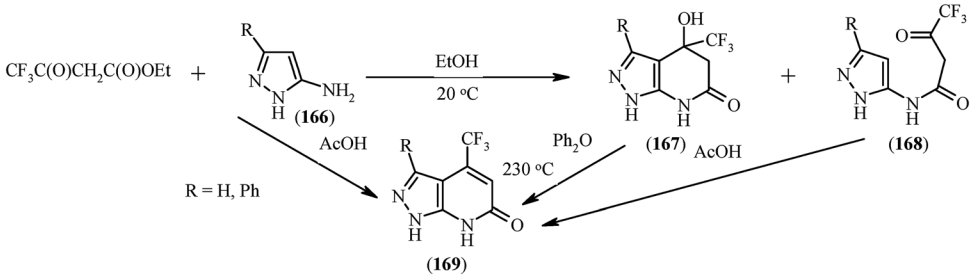
It was shown [85] that the reaction of amine (**133**) with malonic ester in boiling acetic acid or without a solvent at room temperature led to the target pyrazolopyridone (**173**), in a 42–31% yield (Scheme 40).

It was demonstrated in reports [80,86] that the reaction of 1-benzyl-5-aminopyrazole (**174**) with β-diketones in benzene at room temperature afforded derivatives of 5-aminopyrazole (**175**), which turned into pyrazolo[3,4-*b*]pyridin-6-ones (**176**) in a 90% yield, when being heated in acetic acid or ethanol in the presence of an acid (Scheme 41).

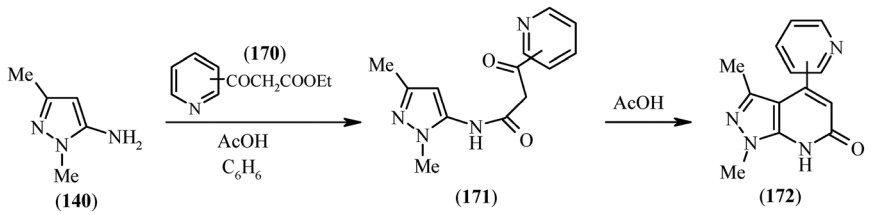
Hoehn [87] described the method of synthesis of new 1,4,5,7-tetrahydropyrazolo[3,4-*b*]pyridin-6-ones (**180**), which possess anti-inflammatory activity. 5-Aminopyrazoles (**177**) reacted with β-ketoesters in benzene to yield hydroxy esters (**178**). In them, the intramolecular closure of the pyridine ring takes place in acetic acid and results in pyrazolo[3,4-*b*]pyridin-6-ones (**179**). The hydrogenation of the latter led to the desired 1,4,5,7-tetrahydropyrazolo [3,4-*b*]pyridines (**180**; Scheme 42).

In the same publication [87], formation of tetrahydropyrazolo[3,4-*b*]pyridin-6-ones (**180**) was studied by heating aminopyrazole (**177**) with alkylidene or arylidene malonic esters in DMF through the intermediate formation of the acid (**181**) and ester (**182**). Varying

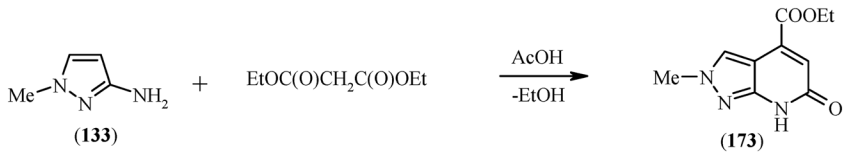
Scheme 38



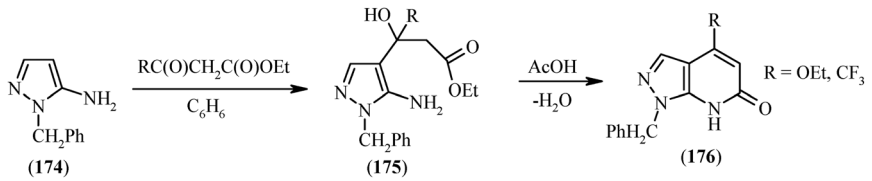
Scheme 39



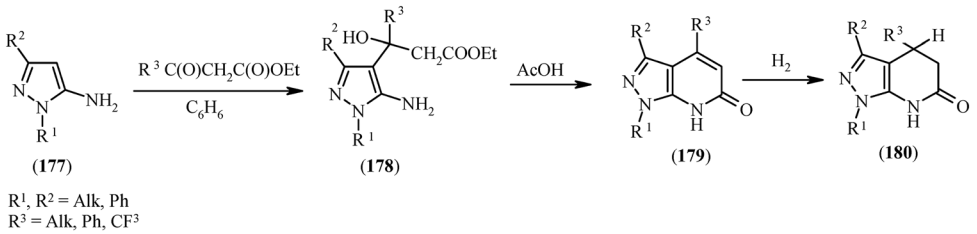
Scheme 40



Scheme 41



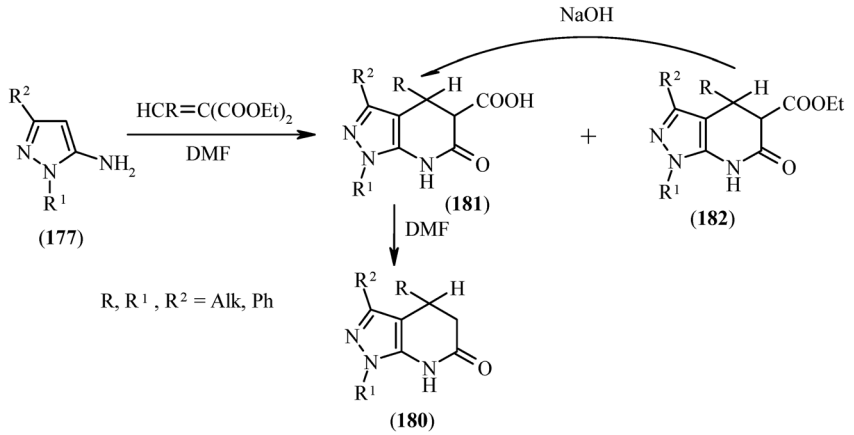
Scheme 42



temperature and time of the reaction, the author managed to obtain both the acid (**181**) and the ester (**182**; Scheme 43).

With the purpose of production of pyrazolo[3,4-*b*]pyridines, which are of interest as physiologically active compounds, the method of their synthesis was considered in the report [88] proceeding from aminopyrazole (**183**) and various β-diketones and esters of β-ketoacids. The formation of derivatives of pyrazolo[3,4-*b*]pyridin-6-ones (**185**) takes place on boiling of the amides (**184**)

Scheme 43



or the original amines (**183**) in acetic acid, and the formation of pyrazolo[3,4-*b*]pyridine-4-ones (**187**) is observed with heating of the crotonate (**186**) in diphenyl ether (Scheme 44).

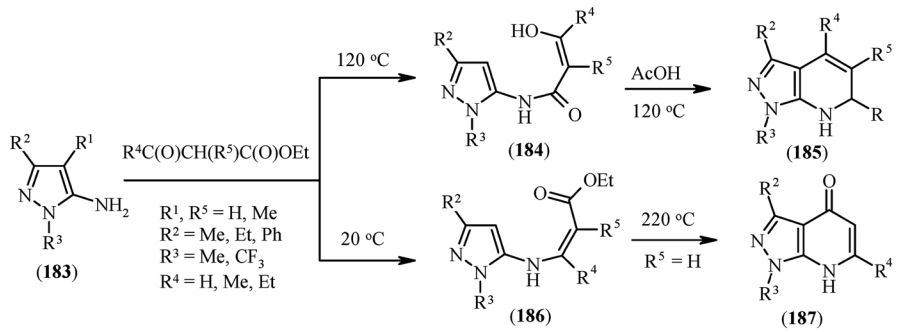
It was shown [89] that 1-benzylpyrazolo[3,4-*b*]pyridin-6(7*H*)-one (**191**) was obtained from aminopyrazole (**174**). Thus at the first stage, Skraup reaction [90] with the formation of pyrazolopyridine (**188**) was carried out, and pyrazolopyridine was converted into the appropriate *N*-oxide (**189**). Irradiation of the latter leads to the desired product (**191**). The derivative was also obtained by heating of the amide (**190**) in acetic acid. The authors established that reaction of aminopyrazole (**174**) with the diethyl ester of malonic acid in the presence of sodium ethoxide gives 4-hydroxy-pyrazolo[3,4-*b*]pyridine-6-one (**193**) in a 38% yield. When this reaction was attempted in acetic acid, it was not possible to get the condensed derivative. 4-Methylpyrazolo[3,4-*b*]pyridinone (**192**) was synthesized by heating of pyrazole (**174**) with acetoacetic ester in acetic acid (Scheme 45).

In ref. 91, the authors studied the possibility of synthesizing the derivative of pyrazolo[3,4-*b*]pyridin-6-one (**199**) as the analog of the isomeric guanosine. Condensation of aminopyrazole (**194**) with diethyl ester of malonic acid in glacial acetic acid, and the subsequent reaction of the condensed compound (**195**) with hydrazine hydrate led to hydrazide (**196**) that was converted into azido derivative (**197**). The latter, in the course of the Curtius rearrangement [92] in acetic acid, was converted into nucleoside (**198**), the hydrolysis of which resulted in the desired product (**199**), in a 50% yield. Unfortunately, the authors [91] did not investigate the stereochemistry of obtained compounds (Scheme 46).

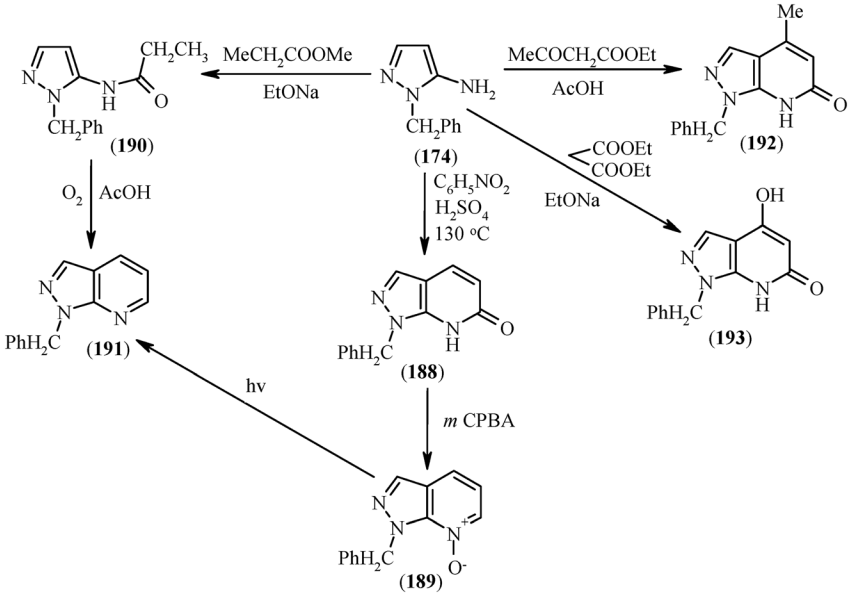
The reactivity of polystyrene was studied and it proved to be possible to use this substance in the synthesis of 6-oxopyrazolo[3,4-*b*]pyridines (**200**) and (**202**) [93] (Scheme 47).

The convenient method of synthesis of 4,5-dihydropyrazolo[3,4-*b*]pyridin-6-ones was presented in ref. 94. The interest in these compounds is due to their potential properties as calcium antagonists. Dihydropyrazolo[3,4-*b*]pyridin-6-ones (**206**) were synthesized by heating of equimolar amounts of aminopyrazole (**203**) and the arylidene derivative of Meldrum acid (**204**) in nitrobenzene [95]. The authors assume that the first stage consists of the bonding of the C-4 carbon of pyrazole (**203**) to the β-carbon of cyclic ether with further loss of one molecule of acetone and CO_2 through formation and subsequent

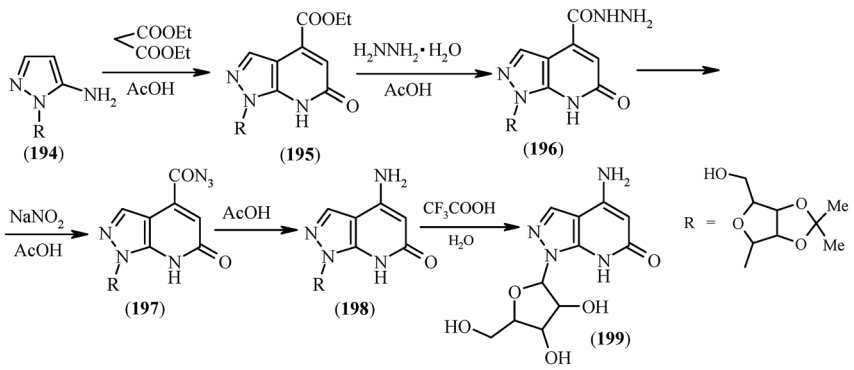
Scheme 44



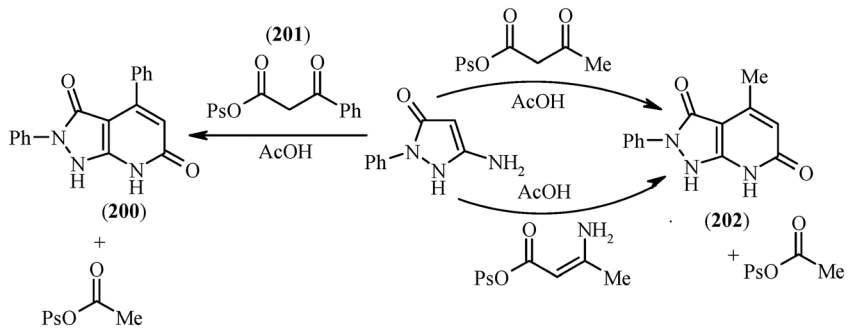
Scheme 45



Scheme 46



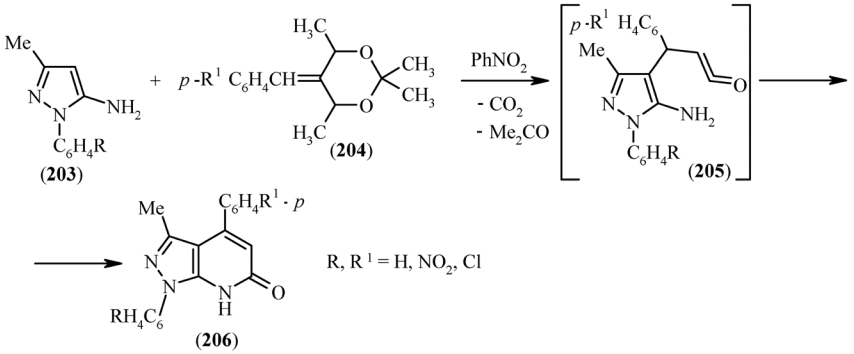
Scheme 47



cyclization of the ketene (**205**). This assumption is in agreement with the data obtained from the literature [96,97], describing properties of derivatives of Meldrum acid (Scheme 48).

In the ref. 98, authors showed the formation of the derivative (**210**) by reaction of 1-substituted 3- and 5-aminopyrazolones (**208**) both with acetoacetic ester and with 3-amino crotonates (**207**). The reaction was so

Scheme 48



intense that is was impossible to identify the intermediate (**209**; Scheme 49).

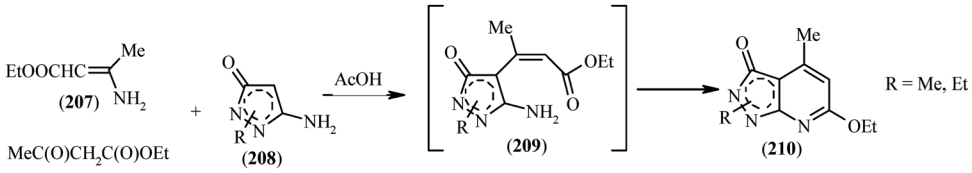
Some chemists also considered [99] the behavior of pyrazolin-5-one regarding reagents with the double bond. It was established that the reaction of pyrazolin-5-one (**88**) with ethyl crotonate (**211**), carried out in the presence of sodium ethoxide, produced the pyrazolo[3,4-*b*] pyridine derivative (**213**), in a 17% yield. The same compound was obtained by the cross synthesis from α-ethoxycarbonyl-β-methylglutamonitrile (**212**) and phenylhydrazine, in a 35% yield (Scheme 50).

The method for the synthesis of 6-oxopyrazolo [3,4-*b*]pyridin-5-carbonitrile (**215**) via the condensation of pyrazoline-5-one (**88**) with methyl-2-cyano-3,3-bis (methyl thio)acrylate (**214**) when sulfuric acid was added in the course of the reaction [100] was also presented (Scheme 51).

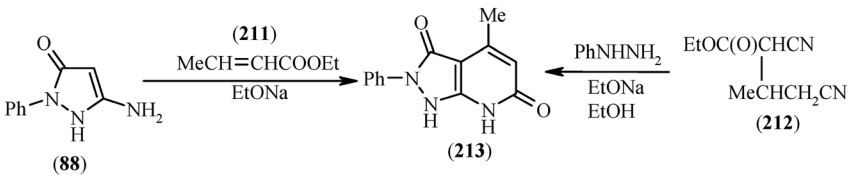
3.3. Synthesis of pyrazolo[3,4-*b*]pyridin-6-ones from pyrazolones. Other authors [101] described cyclic condensation of 1,3-disubstituted 2-pyrazolin-5-one (**216**) with acetoacetic ester, which took place in glacial acetic acid to produce pyrano[2,3-*c*]pyrazolin-6-one (**225**), the latter being transformed into pyridone (**218**) in two ways: by fusion of the compound (**217**) with ammonium carbonate or by passing ammonia through the solution of (**217**; Scheme 52).

In the publication [102], the authors describe the synthetic method for producing a derivative of pyrazolo

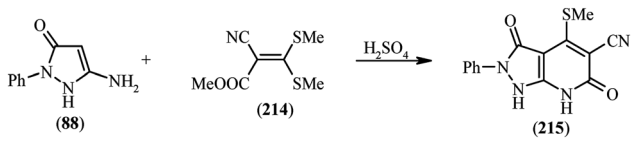
Scheme 49



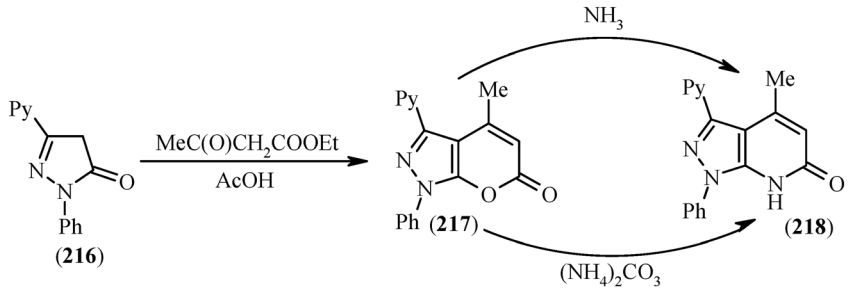
Scheme 50



Scheme 51



Scheme 52

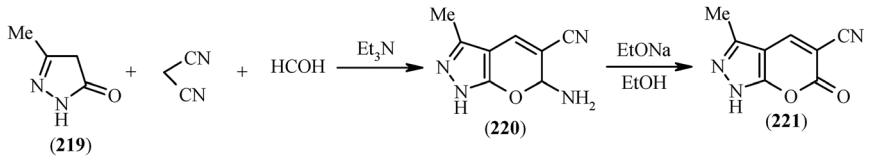


[3,4-*b*]pyridine (**221**), based on the reaction of 5-methyl-2,4-dihydropyrazole-5-one (**219**) with formaldehyde and malononitrile (Scheme 53).

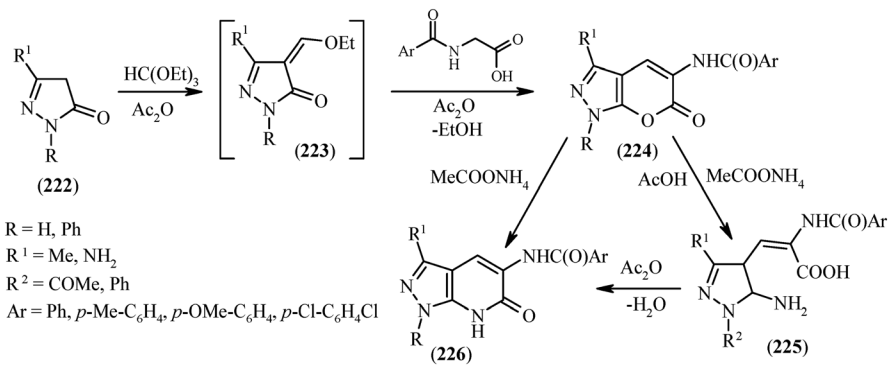
There was a report [103] about the synthesis of pyrano [2,3-*c*]pyrazoles and pyrazolo[3,4-*b*]pyridones through the reaction of pyrazolones with triethyl orthoformate and derivatives of hippuric acid. It is highly probable that the formation of (**224**) goes through the intermediate stage (**223**), which is subjected to Michael cyclization. It has been determined that the pyrone (**224**) in boiling acetic acid in the presence of ammonium acetate undergoes acid-catalyzed transformation with the formation of the acyclic compound (**225**). When (**225**) is refluxed in acetic anhydride, one gets the appropriate pyrazolo[3,4-*b*] pyridines (**226**). The compound (**226**) was also obtained by cross synthesis from pyrone (**224**) and ammonium acetate (Scheme 54).

A simple and convenient method of synthesis of pyrazolo[3,4-*b*]pyridine from 1,3-diphenylpyrazolin-5-one (**227**) by Vilsmeier–Haack reaction [105,106] and Knoevenagel condensation of aldehyde (**228**) with acetophenone or *p*-methylacetophenone was presented in ref. 104. Condensed derivatives of pyrazolo[3,4-*b*]pyridine (**230**) were synthesized as a result of Michael reaction of diethyl ester of malonic acid with the pyrazole derivative (**229**) with subsequent cyclization (Scheme 55).

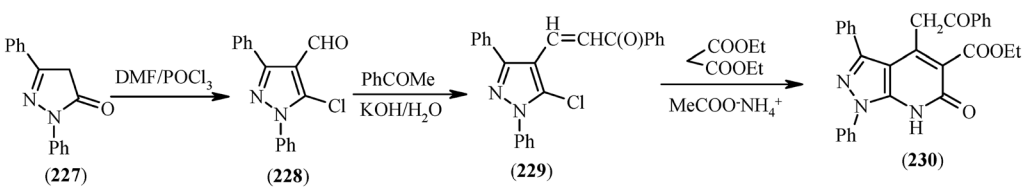
Scheme 53



Scheme 54



Scheme 55



The synthesis of pyrazolo[3,4-*b*]pyridine (**232**) was described in ref. 107, where the key substance, 3-methyl-1-thiocarbamoylpyrazol-5-one (**231**) was obtained by cyclization of thiosemicarbazide with acetoacetic ester in ethanolic solution of ammonia [108]. By fusion of pyrazolone (**231**) with acetoacetic ester in the presence of ammonium acetate, the target pyrazolo[3,4-*b*]pyridinone (**232**) was synthesized in a 85% yield (Scheme 56).

Condensation of pyrazolones (**233**) with aromatic aldehydes in the Knoevenagel reaction was considered [109] to result in the formation of arylidene derivatives (**234**). It was shown that their use in Michael reaction with cyanoacetic ester and subsequent cyclodehydrogenation produced the appropriate compounds (**235**; Scheme 57).

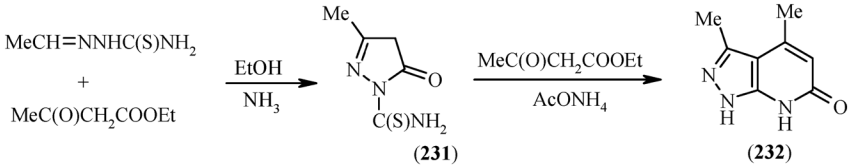
4. OTHER METHODS OF SYNTHESIS OF PYRAZOLO[3,4-*b*]PYRIDIN-6-ONES

An unusual method of synthesis of the pyrazolo[3,4-*b*]pyridinone system, based on the application of the derivative of isothiocarbamide, is presented in ref. 110. The derivative of phenylpropiolamide (**236**) was reacted with thiocarbamide and yielded the respective isothiocarbamide (**237**). It was ascertained that its alkaline hydrolysis resulted in a mercapto derivative (**238**), in an 86% yield. Treatment of the latter with excess sodium hydroxide leads to the closure of the pyridine ring and formation the of target pyrazolopyridine (**239**; Scheme 58).

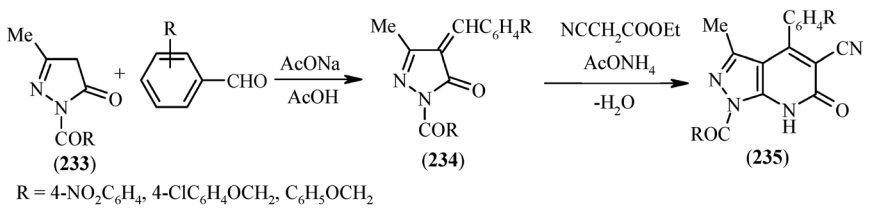
From 5-amino-1,3-dimethylpyrazole (**140**), *p*-chlorobenzaldehyde, and mercaptoacetic acid, thiazepines (**240**) were synthesized with the purpose of studying their biological activity [111]. The attempt of their alkylation by methyl iodide in DMF or DMSO, in the presence of sodium hydride ended in the contraction of the ring with the elimination of sulfur and formation of pyrazolo[3,4-*b*]pyridin-6-one (**241**; Scheme 59).

Dihydropyrazolo[3,4-*b*]pyridinones were synthesized by heating of aminopyrazole (**68**) with different benzylidene derivatives of ethyl cyanoacetate (**242**) in the presence of triethylamine [112]. It was proven that the

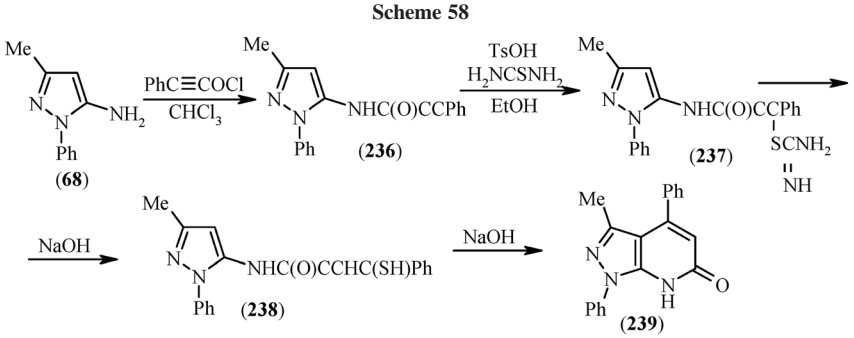
Scheme 56



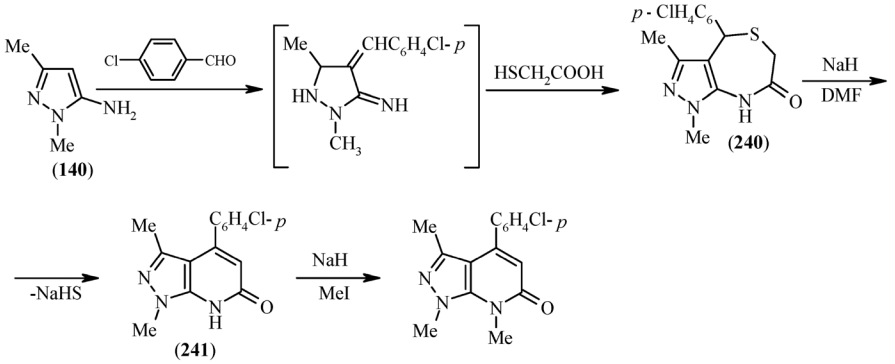
Scheme 57



Scheme 58



Scheme 59



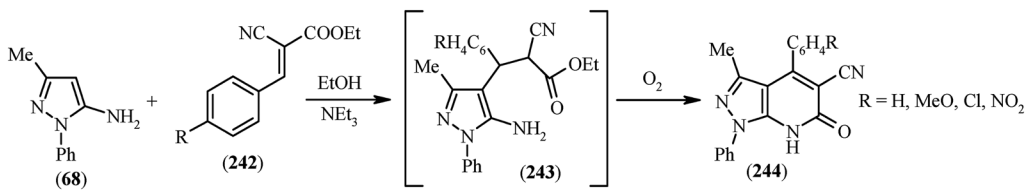
formation of the bicyclic product (**244**) occurred by oxidation of the intermediate (**243**; Scheme 60) [113–116].

Short and efficient synthesis of pyrazolo[3,4-*b*] pyridine (**72**) was presented in ref. 117. In this work, aldehyde was used as the starting material (**245**). Its reaction with 2-cyanoacetamide in the presence of triethylamine produced the derivative of pyrazoline (**246**; the 60% yield). The product, when heated in pyridine, undergoes easy cyclization with the formation of 1-phenylpyrazolo[3,4-*b*]pyridin-6-one (**72**), in a 55% yield (Scheme 61).

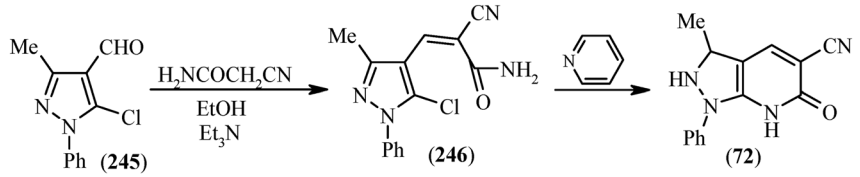
An unusual method of synthesis of a polysubstituted pyrazolopyridine (**249**) was presented in [118]. Initially, the formation of 5-phenylpent-3-enoate (**247**) occurred in the presence of triethylamine, with the conversion of the former by a phenyldiazonium salt into phenylhydrazone (**248**), in a 80% yield. The latter was reacted with phenylhydrazine, which led directly to the target 1,3-diphenylpyrazolo[3,4-*b*]pyridine (**249**; Scheme 62).

In the report [119], potential synthesis of 6-oxo derivative of pyrazolopyridine (**253**) was presented by means of oxidation of the appropriate mercapto derivative (**250**). It was also

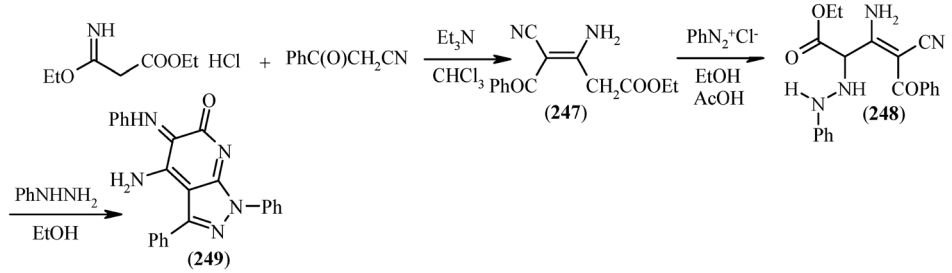
Scheme 60



Scheme 61



Scheme 62

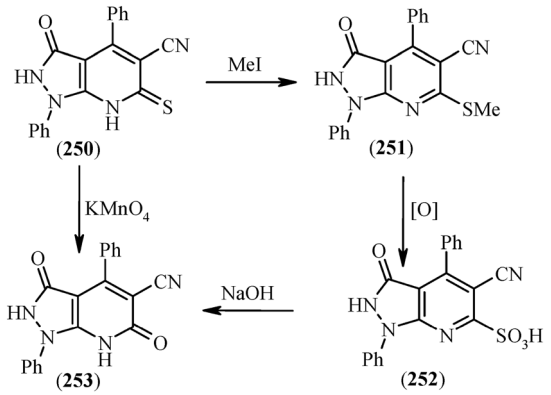


shown that its methylthio derivative (**251**) could be oxidized into the acid (**252**), the alkaline hydrolysis of which resulted in pyrazolopyridin-6-one (**253**; Scheme 63).

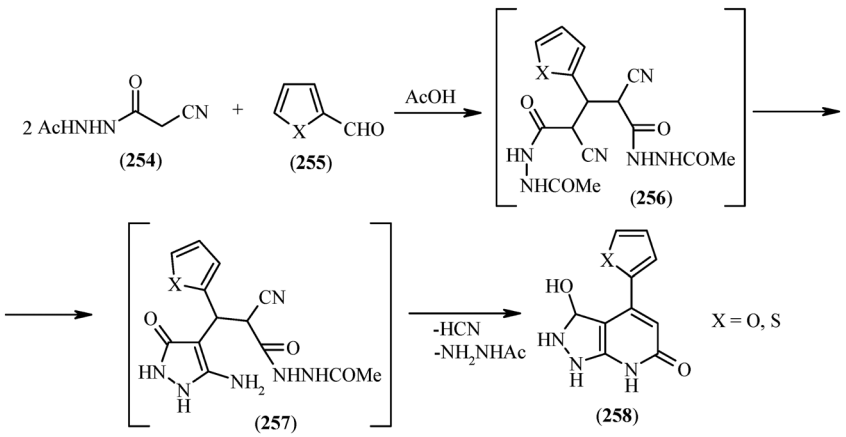
Pyrazolopyridin-6-ones, containing a thiophene or furan ring in the position 4, were synthesized by authors of ref. 120. It was shown that in the first stage of this reaction, acetylhydrazide (**254**) was attached to aldehyde (**255**) to form the adduct (**256**), which, with the separation of the acyl residue, was transformed into the intermediate (**257**). The latter, in turn, was subjected to cyclization with the formation of derivatives of pyrazolo[3,4-*b*]pyridone (**258**; Scheme 64).

An interesting method of synthesizing pyrazolopyridones was discussed in the article [121]. The authors determined that condensation of ß-ketoesters with cyanoacetylhydrazide in the ethanol solution of KOH produced potassium salts of appropriate substituted 2-pyridones (**259**). It was also stated that the direction of the reaction depended on the nature of the substituent in the position 4 of the potassium salt. When the molecule has electron-acceptor substituents such as $-CF_3$ and COOEt groups, on acidification of the salt solution (**259**), a rearrangement is observed with the formation of pyrazolo[3,4-*b*]pyridones (**263**). At the same time, acidification of the solution of the salt (**259**; R = *p*-$C_6H_4NO_2$) leads to the formation of a mixture of the bicyclic product (**263**) and pyridone (**264**), in a 4:1 ratio (Scheme 65).

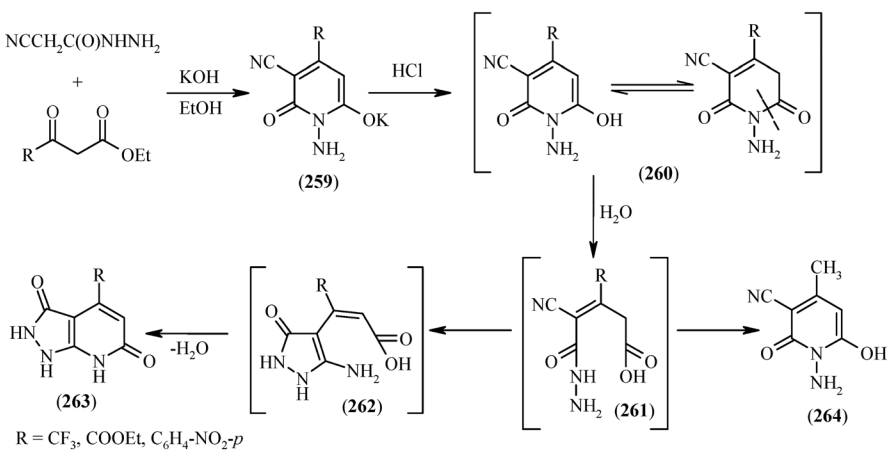
Scheme 63



Scheme 64



Scheme 65



The conversion of the salt (**259**) into pyrazolopyridone (**263**) most likely requires the cleavage of the N1–C6 bond in the pyridone ring of the compound (**260**). The electron-acceptor group in the position 4 of pyridone causes an increase of the bond polarization in the molecule, and this can be the reason for the hydrolytic cleavage of the bond, leading to the formation of the intermediate. Cyclization of the intermediate (**261**) passes immediately through the attack of the carbon in the CN group directed toward NH_2, and this results in the intermediate (**262**), which is subjected to cyclization into pyrazolo[3,4-*b*]pyridone (**263**).

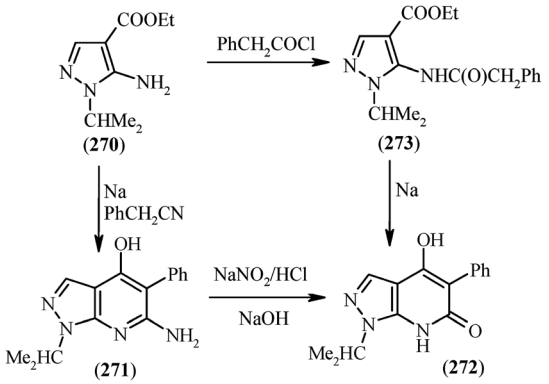
5. SYNTHESIS OF PYRAZOLO [3,4-*b*]PYRIDINE-4,6-DIONES

A new three-step of synthesis of 4-hydroxypyrazolo [3,4-*b*]pyridin-6-one (**268**) with the use of aminopyrazole (**265**) and diketene as the starting materials was presented in ref. [123]. It was determined that the amino group of the compound (**265**) could not react with diketene directly or in the presence of Et_3N, but in acetic acid or when catalyzed by DMAP in CH_2Cl_2, the reaction proceeded smoothly and pyrazolocarboxylate (**266**) was extracted with a 78% yield. Pyrazolopyridone (**267**) was synthesized from (**266**) by Dieckmann cyclization by heating in ethanol in the presence of sodium ethoxide. Treatment of 4-hydroxy derivative of pyridine (**267**) with sulfuric acid was shown to end in the transformation into pyrazolopyridone (**268**). Amino methylene derivatives of pyrazolopyridine (**269**) were produced from the latter in the ≪one-pot≫ reaction with triethyl formate and substituted anilines, in ∼90% yield (Scheme 66).

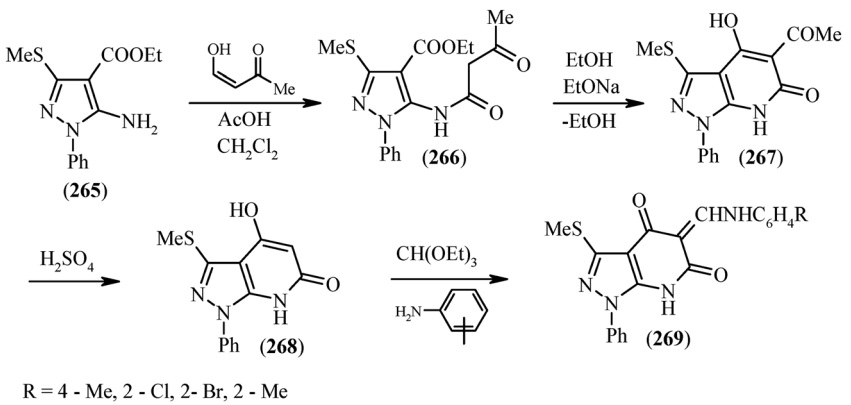
Two other methods of synthesis of 4-substituted pyrazolo[3,4-*b*]pyridines are described in the report [124]. The authors showed that reaction of aminopyrazole (**270**) with phenylacetonitrile in the presence of Na led to the closing of the pyridine ring and formation of the compound (**271**). Substitution of the amino group in the pyridine nucleus and formation of the oxo derivative of pyrazolopyridine (**272**), in a 62.5% yield, is carried out *via* diazotization, followed by alkaline hydrolysis. Another approach to the synthesis of the compound (**272**) was made by the authors by reaction of aminopyrazole with phenylacetyl chloride with the formation of the acyl derivative (**273**). Its cyclization in the presence of Na in toluene leads to pyrazolo[3,4-*b*]pyridone (**272**), in a 23% yield (Scheme 67).

In the article [125], the authors describe the method of synthesis of 4-substituted pyrazolo[3,4-*b*]pyridine. Condensation of diethyl malonate with 5-aminopyrazole in ethanol in the presence of sodium ethoxide [126] led to 4-hydroxypyrazolopyridone (**274**), in a 82% yield. The conversion of (**274**) into the chloro derivative (**275**) was performed using the method described in [127]. The authors were interested in obtaining tricyclic dihydrodipyrazolo[3,4-*b*:3′,4′-*d*]pyridine (**278**) with the purpose of studying its immunosuppressant activity, based

Scheme 67



Scheme 66

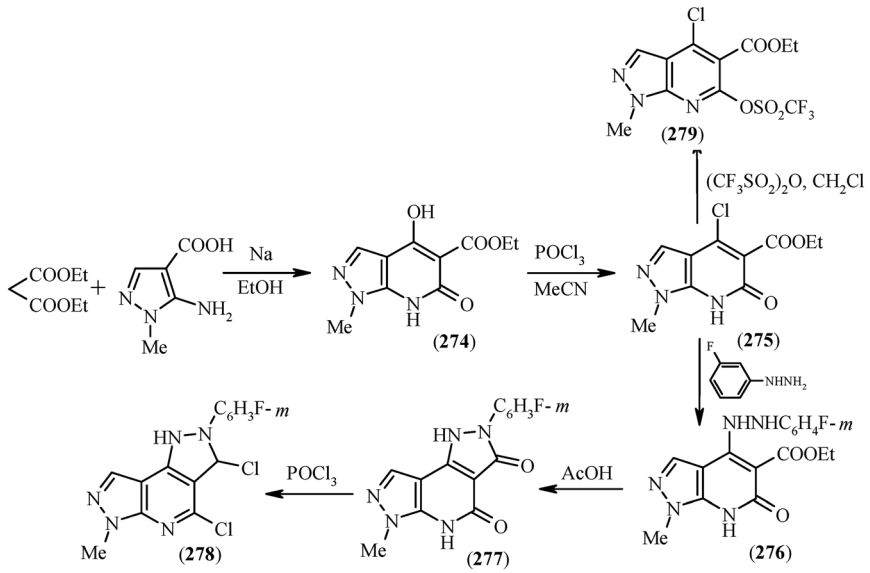


on the similarity of its structure with well-known immunosuppressants [128]. It was shown that the synthesis of the target compound (**278**) was conducted *via* the substitution of chlorine in (**275**) by the hydrazine group in a reaction with 3-fluorophenylhydrazine, cyclization of the obtained compound (**276**) in hot acetic acid, and treatment of the latter with phosphorus oxychloride. It was also established that the reaction of pyrazolopyridone (**275**) with anhydride of trifluoromethanesulfonic acid led to the formation of the corresponding derivative of pyridine (**279**), in a 92% yield (Scheme 68).

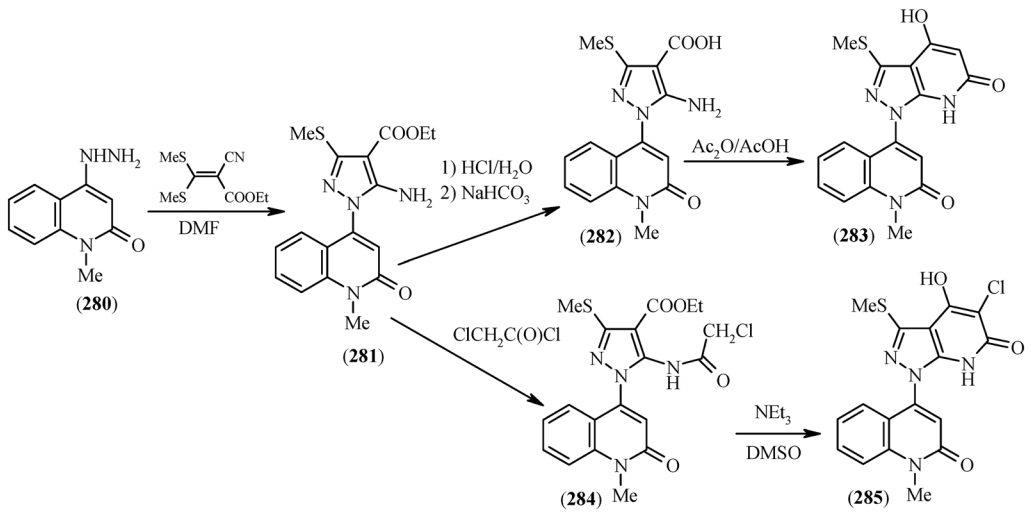
In the article [129], synthesis of pyridin-6-ones (**283**) and (**285**) was described. 4-Ethoxycarbonylpyrazole (**281**) was synthesized in the reaction of quinolinone (**280**) with bis-methyl thioacrylate in boiling DMF [130]. Hydrolysis of (**281**) in the acidic environment led to the formation of amino acid (**282**), the treatment of which by the mixture of acetic acid and acetic anhydride ended in the formation of pyrazolopyridinone (**283**) [131]. 5-Chloro derivative of pyrazolopyridinone (**285**) was formed by chloroacetylation of amino ether (**281**) and subsequent intramolecular cyclization of the synthesized chloroacyl derivative (**284**) in boiling DMSO and in the presence of thiethylamine (Scheme 69).

Authors of the publication [132] consider the possibility of the reaction of cyclocondensation of 1-phenyl-3-

Scheme 68

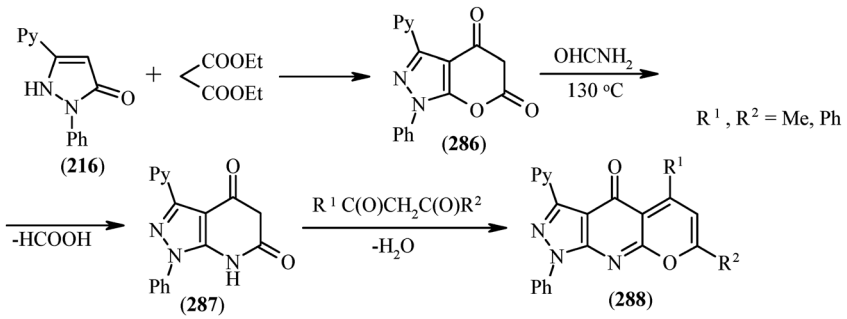


Scheme 69

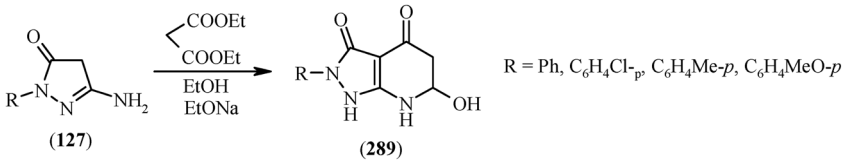


(3-pyridyl)-3-pyrazolin-5-one (**216**) with diethyl malonate in polyphosphoric acid. To confirm the structure, the compound (**286**) was converted into the corresponding pyridinone derivative (**287**). It was shown that heating of dihydropyronopyrazolidone (**286**) in formamide led to the tetrahydropyridinopyrazolodione derivative (**287**), in a 63% yield. There was the evidence that 1,3-diketones such as acetylacetone, dibenzoylmethane, and

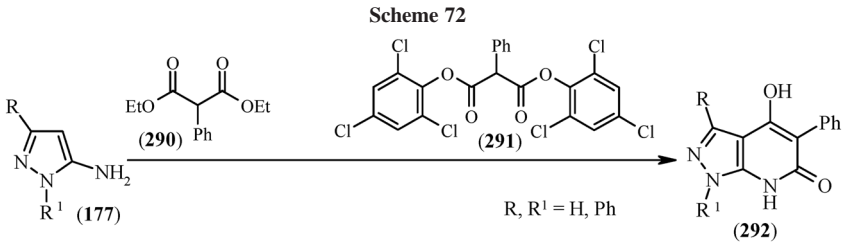
Scheme 70



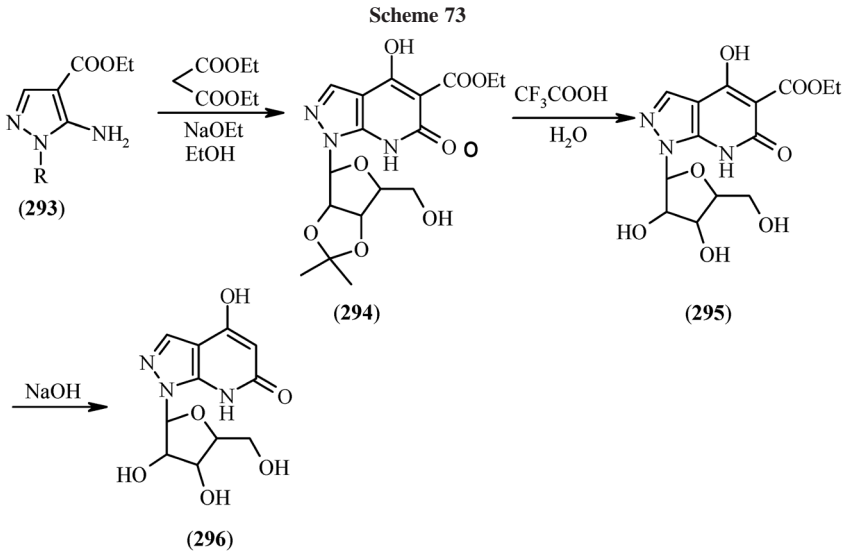
Scheme 71



Scheme 72



Scheme 73



benzoylacetone easily enter the reaction with pyridinedione (**287**) in the presence of pyridine with the formation of pyrano[2,3-*b*]pyrazolo[4,3-*e*]pyridine-4(1*H*)-one (**288**; Scheme 70).

In a U.S. patent [133], the method of synthesis of new dyes—derivatives of 2-arylhexahydropyrazolopyridine, with the common formula (**289**) has been described. It was determined that heating of 3-amino-1-aryl-5-pyrazolone (**127**) with diethyl malonate in ethanol, in the presence of sodium ethoxide for 20 h, led to the derivatives of hexahydropyrazolopyridine in a satisfactory yield. Compounds (**289**) have a reactive methylene group in the position 5 of the pyridine ring, activated by two carbonyl groups in the positions 4 and 6. Such derivatives are of value in the production of azo dyes and are also used in color photography (Scheme 71).

The report [134] describes advantages of the use of commercially available, activated di(2, 4, 6-trichlorophenyl)-2-phenylmalonate (**291**) instead of the compound (**290**) leading to derivatives of 4-hydroxy-3-phenylpyridine-2(1*H*)-one (**292**) by means of microwave reaction of condensation without a solvent. It was shown that the malonate (**291**) was subjected by electrophilic aromatic cyclization with greater efficiency than (**290**). The side product on irradiation might be 2,4,6-trichlorophenol, which can decrease the internal pressure in the sealed reaction vessel in contrast to the alcohol produced when using **(290)** and permitting the more effective course of the reaction. Thus, a short reaction time, high yield, and simple extraction of the end product are clear advantages of the use of activated malonate (**291**) compared with (**290**; Scheme 72).

For the synthesis of an analog of xanthosine (**296**), authors used the method [135]. It was demonstrated that the treatment of amine (**293**) with diethyl malonate in ethanol, in the presence of sodium ethoxide led to the formation of the ester (**294**) in a 62% yield. The product (**295**) was synthesized in a similar manner as the analog of isoguanosine (**199**) [91] and subjected to alkaline hydrolysis. The, decarboxylation with the formation of 4-hydroxy derivative of pyrazolo[3,4-*b*] pyridine-6-one (**296**) was observed, in a 42% yield but authors did not describe stereochemistry of the substitute (Scheme 73).

6. CONCLUSION

This review highlights the importance of pyrazolo[3,4-*b*]pyridine-6-ones as compounds with different types of biological activity and presents the various methods leading to their synthesis. It is clear that additional publications can be expected in the near future, describing new compounds of this type possessing interesting biological activity.

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