

Heterocyclization Reactions of Pyruvic Acids and Aminoazoles with Controlled Chemoselectivity

Yana I. Sakhno,^a Maryna V. Murlykina,^a Alisa D. Morozova,^a Anton V. Kozyryev,^{a,b}
and Valentin A. Chebanov*^{a,b}

^a *State Scientific Institution "Institute for Single Crystals" NAS of Ukraine, Lenin Ave. 60, 61178, Kharkiv, Ukraine*

^b *V.N. Karazin Kharkiv National University, Svobody sq. 4, UA-61022, Kharkiv, Ukraine*
chebanov@isc.kharkov.com

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The present review includes the analysis of known literature data concerning linear and multicomponent heterocyclizations involving pyruvic acids and aminoazoles. In particular, the review demonstrates the approaches to control regio- and chemoselectivity of these types of treatments and their application to solve the matters of Diversity Oriented Synthesis.

Introduction

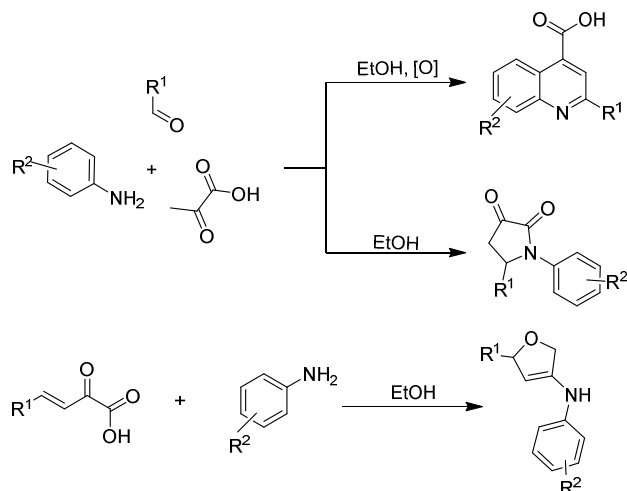
The significance of pyruvic acid in our life can be hardly overestimated. It plays a vital role as one of the most reactive substances among those of important in cellular metabolism. That is why a conclusion may be made that reactions involving pyruvic acid may help to solve some health problems and assist in finding a cure against various diseases today and in future. Heterocyclization reactions of pyruvic acids with nitrogen containing nucleophiles play an important role in the synthesis of heterocyclic compounds having diverse types of physiological activities such as antimalarial [1, 2], antitumor [3], antimicrobial [4], antifungal [5] and analgesic [6–8] activities. Thus, study of

chemical behavior of pyruvic acid and its derivatives in chemical reactions are interesting from several points of view.

The first multicomponent reaction involving pyruvic acid was discovered in the late 19th century [9, 10] by Doebner - the three-component condensation of pyruvic acid, aldehydes and aniline derivatives leading either to quinoline carboxylic acids or to pyrrolidine-2,3-diones (**Scheme 1**). Further this reaction was studied in details in numerous publications [3, 11-22].

Initially, it had been considered that the Doebner reaction proceeded *via* formation of arylidenepyruvic acid [11], however, later that way was refuted and an alternative mechanistic

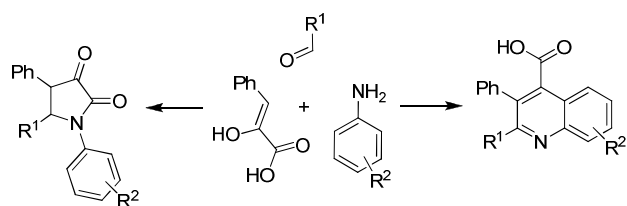
pathway involving the formation of a Schiff base followed by cyclization was proposed [15, 18, 19].



Scheme 1.

On the other hand, reaction of arylidenepyruvic acids and aromatic amines led to 3-arylamino-5-aryl-2(5*H*)furanones [20] but not to pyrrolidine-2,3-diones as it had been reported earlier (**Scheme 1**) [21]. It should be noted that different procedures for Doebner reaction were developed [23-27] based on the variation of solvents, catalysts and activation methods.

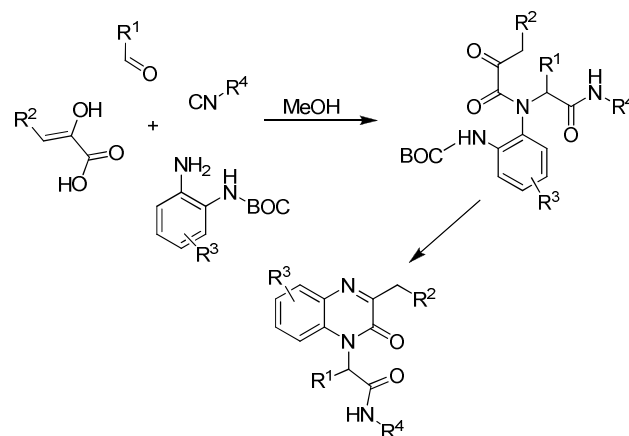
The Doebner-like multicomponent reactions of phenylpyruvic acid with aromatic aldehydes and aromatic amines, also yielded either pyrrolidine-2,3-dione or quinoline-4-carboxylic acid depending on substituents R^1 and R^2 (**Scheme 2**) [12].



Scheme 2.

However, in this case no clear relationship between the electronic character of the substituents and structure of the reaction products was established.

An interesting approach to the synthesis of quinoxaline derivatives *via* Ugi-type reaction was proposed as well (**Scheme 3**) [28]. Thus, the four-component reaction of the starting reagents in MeOH yielded the Ugi adducts, which by means of acid catalysis turned into quinoxalinones.



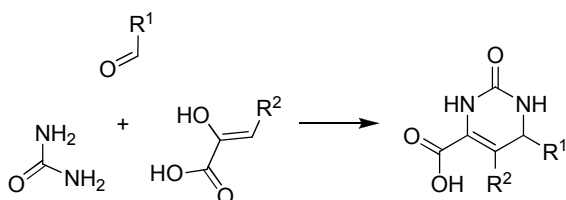
Scheme 3.

Such type of Ugi reaction allowed to synthesize a wide range of quinoxaline derivatives having different types of biological activities: among them inhibitors of various enzymes, as well as benzodiazepine receptor agonists were found [28].

Some publications deal with arylpyruvic acids as α -ketoacids and describe their transformations with 1,2-diamines also yielding quinoxalines or analogous heterocyclic systems. [29-32]

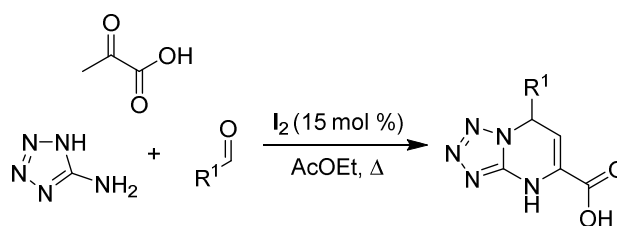
In publication [33] it was shown that Biginelli-like condensation of arylpyruvic acids

with aromatic aldehydes and urea in the presence of catalytic amounts of acid yielded dihydropyrimidine carboxylic acids (**Scheme 4**). Similar pyrimidines were synthesized by using a polymer-supported solid-phase procedure [34].



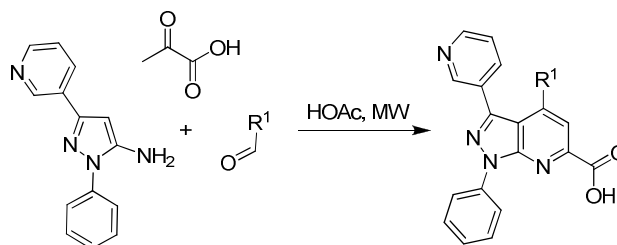
Scheme 4.

There are a lot of papers about already known and currently studied biological activity of azoloazine structures, *e.g.* antifungal [35] and antimicrobial [35, 36], hypoglycemic activity [37], in particular, (DPP4) inhibition [38], cardiovascular activity [39], *etc.* However, multicomponent procedures involving pyruvic acid or its derivatives, aromatic aldehydes, and heterocyclic amines, for example aminoazoles, have been previously rarely investigated. Aside from our publications which are discussed in the General part of the review, recently, we have found some publications in the literature devoted to the reactions involving pyruvic acid and its derivatives with aminoazoles. Li-Yan Zeng and coworkers reported one-pot treatment of pyruvic acid with 5-aminotetrazole and structurally diverse aryl aldehydes which gave 5-aryl-5,8-dihydropyrimidopyridine-7-carboxylic acids (**Scheme 5**) [40, 41].



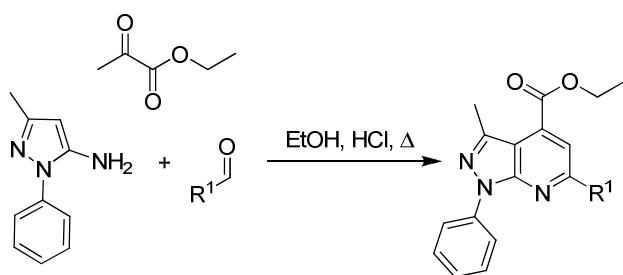
Scheme 5.

In publication [42] it was considered that multicomponent reaction involving pyruvic acid and 5-amino-1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazole with aromatic aldehydes in boiling acetic acid gave 4-substituted-1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxylic acids in 54-75% yields (**Scheme 6**). The reactions were carried out by two different techniques – by conventional heating and under microwave irradiation. The compounds obtained were screened for their antibacterial and anti-tumor activities with positive results.



Scheme 6.

It should be noted, that multicomponent cyclization of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole with aromatic aldehydes and ethyl pyruvate led to the formation of a different set of pyrazolo[3,4-*b*]pyridine-4-carboxylates as reaction product [43] (**Scheme 7**), instead of pyrazolopyridines described above [42].

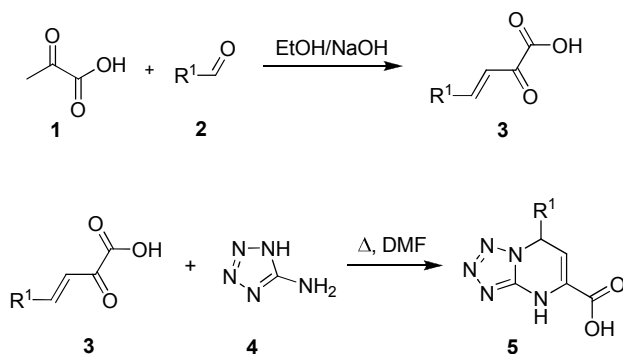


Scheme 7.

In vitro biological evaluation of pyrazole[3,4-*b*]pyridine derivatives, as a new antichagasic agent series, were carried out [43].

General part

One of the first reactions [44] involving pyruvic acids and aminoazoles was two-component condensation (Scheme 8). The preliminary treatment of pyruvic acid (**1**) and aldehydes **2** gave the starting arylidenepyruvic acids **3** which further reacted with 5-aminotetrazole (**4**) upon heating in DMF leading to dihydro-tetrazolopyrimidine carboxylic acids **5** (Scheme 8).



2, 3: R¹ = C₆H₅, 4-CH₃OC₆H₄, 4-ClC₆H₄, 4-FC₆H₄

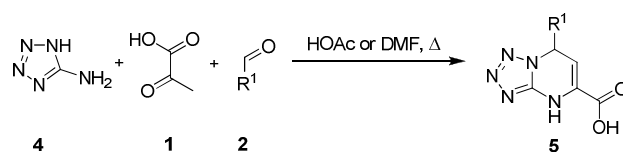
Scheme 8.

Afterwards the potential biological activity of the compounds **5** was studied with the help of computational analysis using the system

PASS-C&T 4.00. The results of the screening showed that dihydro-tetrazolopyrimidines **5** might possess cardiovascular, anticonvulsant, cardioprotector and fibrinolytic types of activity.

However, the authors [45] mentioned about one significant drawback in the described reaction. The first stage of that procedure gave arylidenepyruvic acids **3** in very low yields (15–30%) while the second stage yields were within 40–60% range and the general efficiency of this two-staged reaction was unsatisfactory. Thereby, the next publications were dedicated to the applying multicomponent reactions as an alternative pathway for the synthesis of azolopyrimidine carboxylic acid derivatives from appropriate aminoazoles, aromatic aldehydes and pyruvic acids.

Refluxing 5-aminotetrazole (**4**), aromatic aldehydes **2** and pyruvic acid (**1**) in DMF or glacial acetic acid led to the formation of the same fused dihydropyrimidines **5** (Scheme 9) that allowed to save time, reagents and to enhance the yields [45].



2: R¹ = C₆H₅, 4-CH₃OC₆H₄, 4-BrC₆H₄, 4-FC₆H₄, 4-CH₃OCOC₆H₄

Scheme 9.

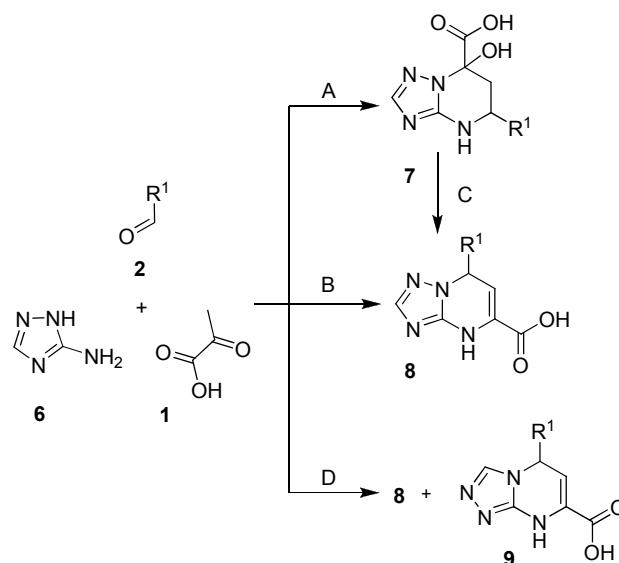
Nowadays there is a wide set of approaches for controlling the selectivity of multicomponent reactions such as classical ones like variation of the parameters of the reaction me-

dium (*e.g.* the solvent and catalyst types, time regime *etc.*) and non-classical methods like microwave and ultrasonic irradiation, *etc.* Moreover, modification of the structures of the starting reagents, thereby increasing their polyfunctionality, may also considerably influence the reaction proceeding and cause the formation of different types of final heterocycles [46-51].

In the publications [45, 52, 53] an influence of substituents in the aldehyde and pyruvic acid components on a proceeding their heterocyclizations with 3-amino-1,2,4-triazole derivatives was studied. Particularly, variation of the temperature regime together with applying non-classical activation methods (ultrasonic and microwave irradiation) allowed to switch the reaction between several directions and to obtain selectively several chemotypes of final structures.

Thus, the behavior of 3-amino-1,2,4-triazole (**6**) in the three-component condensation with aromatic aldehydes **2** and pyruvic acid (**1**) turned up to be quite the same to the 5-aminotriazole (**4**) reactivity [45]. Refluxing 3-amino-1,2,4-triazole (**6**) and aromatic aldehydes **2** with pyruvic acid (**1**) in glacial acetic acid allowed to isolate from the reaction mixtures the pure acids **8** with good yields (**Pathway B, Scheme 10**). At the same time, heating the starting compounds **1**, **2** and **6** in DMF led to mixtures of two regioisomeric dihydrotriazolopyrimidines **8** and **9** (**Pathway D, Scheme 10**). All attempts to separate these mixtures by crystalli-

zation or using HPLC were unsuccessful [45, 53].



A: HOAc, Δ, 65 °C, 48h
 B: HOAc, Δ, 118 °C, 4h
 C: HOAc, Δ, 118 °C, 4h
 D: DMF, Δ, 153 °C, 1,5h

2: R¹ = C₆H₅, 3-OHC₆H₄, 4-OHC₆H₄, 2-CH₃OC₆H₄, 3-CH₃OC₆H₄, 4-CH₃OC₆H₄, 4-BrC₆H₄, 4-FC₆H₄, 4-CH₃COC₆H₄

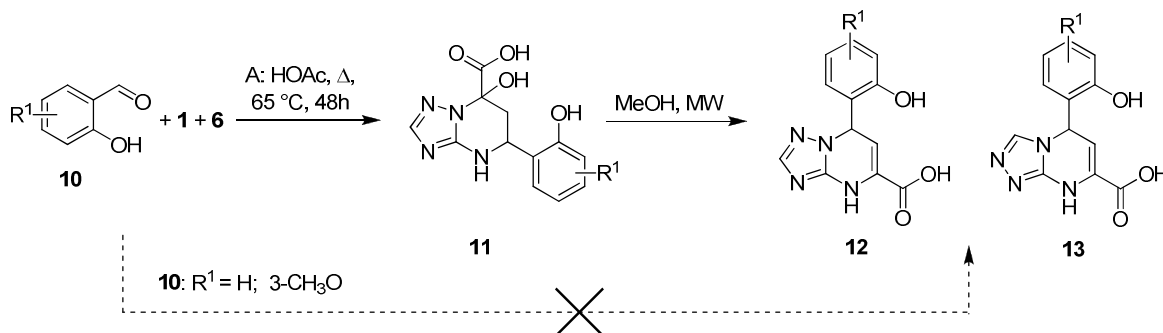
Scheme 10.

Over time, Murlykina *et al.* [53] discovered that decreasing the temperature up to 65 °C in the reaction of the same starting materials **1**, **2** and **6** led to the formation of tetrahydropyrimidines **7** (**Pathway A, Scheme 10**). It should be noted that boiling the compounds **7** in acetic acid for 4 hours *via* decomposition / heterocyclization / dehydration sequence [45] also led to the formation of heterocycles **8** (**Pathway C, Scheme 10**).

On the contrary, heating the compounds **11**, derived from 2-hydroxybenzaldehyde **10**, in HOAc led to the tarring of the reaction mixture, and no individual product was isolated. However, their MW irradiating in MeOH (140 °C, 50 min) finally allowed to get dihydropyrimidines

12 (Scheme 11). Decreasing the reaction temperature up to 130 °C yielded the mixture of two regioisomeric compounds **12** and **13** [53]. The authors [53] varied the temperature, solvents and different catalysts, however, neither an in-

creasing the yield of **12** nor a selective isolation of compounds **13** was achieved. All attempts to obtain dihydropyrimidines **12** or **13** in the three-component condensation were also unsuccessful.

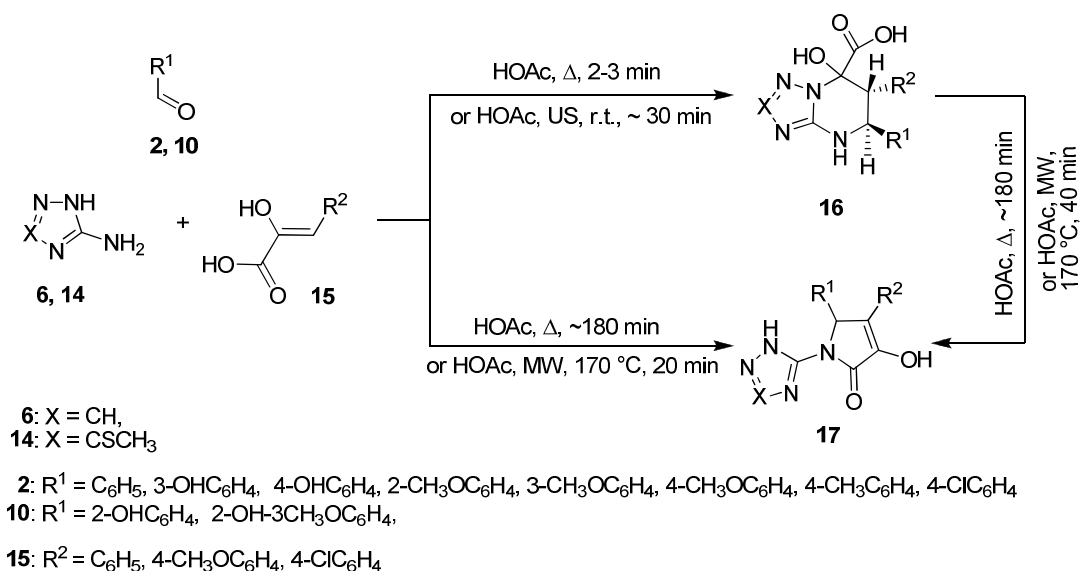


Scheme 11.

As it was mentioned before multicomponent reactions involving arylpyruvic acids and aminoazoles leading to heterocyclic compounds have been rarely investigated, thereby, it was interesting to disclose an influence of an introduction of a β -aryl substituent into pyruvic acid on the reaction proceeding. Thus, the authors [52, 53] disclosed the results on the tuning multicomponent condensation reactions of 5-aminotriazole (**4**) or 3-amino-1,2,4-triazole derivatives **6** and **14** with aldehydes and arylpyruvic acids using both traditional and non-classical activation methods. It was found that the condensation of aminotriazoles **6**, **14** with arylpyruvic acids **15** and aromatic aldehydes **2** in boiling acetic acid led to different products depending on the reaction conditions. Particularly, tetrahydrotriazolopyrimidine carboxylic acids **16** were isolated after refluxing equimolar amounts of the starting materials **2**, **15** and **6** or **14** in acetic acid for 2-3 minutes while reaction

for 180 minutes provided pyrrolones **17**. Reaction times within those extremes in most cases led to the formation of both heterocycles **16** and **17** (**Scheme 12**).

The experimental data obtained [52] indicated that in this three-component condensation (**Scheme 12**) the fused pyrimidines **16** were the kinetically controlled reaction products while pyrrolones **17** might be considered as the thermodynamically controlled products. In addition, the authors applied ultrasonic and microwave irradiation: treatment the starting materials **2**, **15** and **6** or **14** for *ca.* 30 minutes under ultrasonication yielded exclusively fused triazolopyrimidinecarboxylic acids **16** and these conditions were chosen as the optimal ones; on the other hand, MW irradiating the mixture of the same starting materials in acetic acid at 170 °C allowed to obtain pyrrolones **17** with almost 9-fold time reduction as compared with the thermal heating [52, 53].

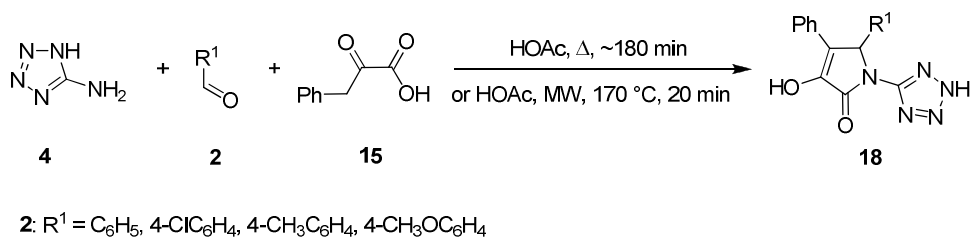


Scheme 12.

Afterwards the studies of antibacterial and antiviral activities of the compounds synthesized were carried out *in vitro* [53]. The tested substances didn't show high antibacterial activity, however, for several of them sufficient increase in biomass of test-cultures compared with control was found. The promising result was also obtained for pyrrolone **17** (R¹ = 2-CH₃OC₆H₄). This compound showed high activity against influenza A/H1N1 with an average IC₅₀ value of 0.57 μM and a CC₅₀ >100 μM.

The reference compound amantadine had an IC₅₀ of 13.5 μM, demonstrating that compound **17** was at least 20-fold more active than the reference drug.

Multicomponent condensations involving 5-aminotetrazole (**4**) in boiling acetic acid (or with applying MW irradiation) provided the formation of only pyrrolones **18** being analogous to **17** and all the attempts to get fused pyrimidines of type **16** remained unsuccessful [52] (**Scheme 13**).



Scheme 13.

This fact was explained by Sakhno *et al.* [52] regarding the mechanistic aspects of these reactions (**Scheme 14**). Thus, the three-component reaction of the starting materials **2**, **15** and **6** or **14** at room temperature giving triazolopyrimidines **16** most probably proceeded

via the initial formation of azomethines **19** and their subsequent reaction with arylpyruvic acids **15** which was not a synchronous process (**pathway "a"**, **Scheme 14**). The authors [52] indirectly proved this assumption by the treatment of preliminary synthesized Schiff base **19**

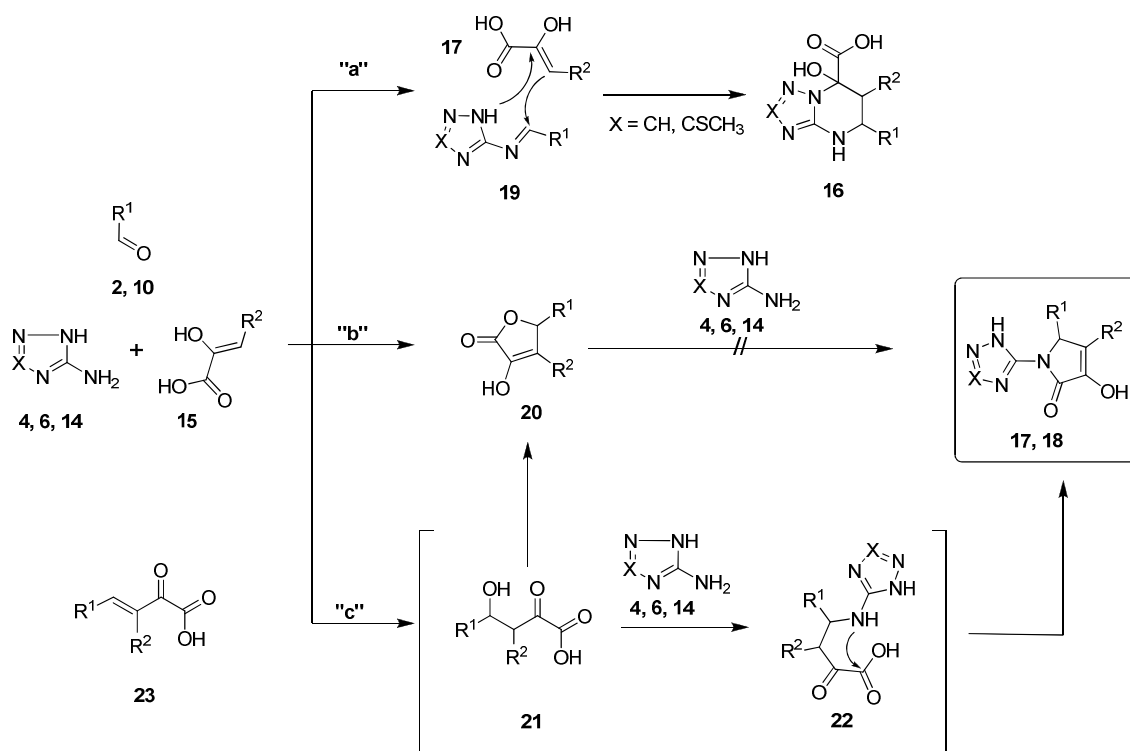
with arylpyruvic acids **15** yielding triazolopyrimidines **16** and by observation of compounds of type **19** in trace amounts in the mother liquor of the multicomponent reaction.

According to the hypothesis [52] 5-aminotetrazole (**4**) formed no azomethine with aldehydes and, therefore, the appropriate tetrazolopyrimidines were not isolated.

The pathway of high-temperature reaction leading to pyrrolones **17** and **18** is also unusual and its mechanism seems unclear. In this condensation aminoazoles **4**, **6**, **14** act as mononucleophiles like anilines [54, 55]. Described in the literature [56] related three-component reaction of anilines, pyruvic acids and aldehydes proceeds through the formation of furanone derivatives like **20** (pathway "b", Scheme 14).

However, it was established that compounds **20**, synthesized by reaction of arylpyruvic acids and aldehydes [57], did not react with aminoazoles **4**, **6**, **14** and, therefore, could not be intermediates in that multicomponent process.

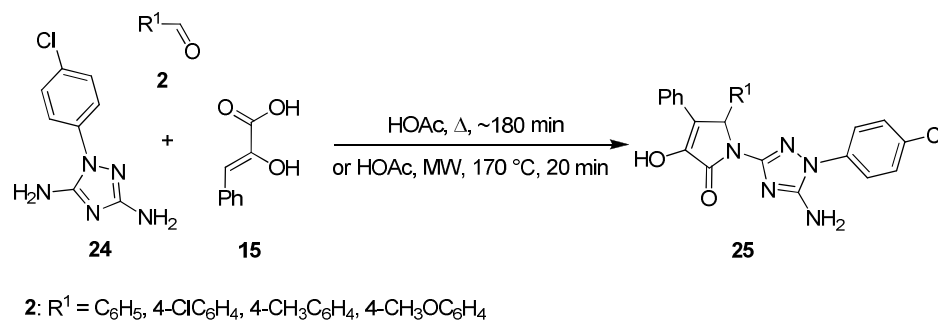
The authors [52] proposed the probable sequence that might include formation of aldols **21** at the first stage of the high-temperature three-component reaction, subsequent nucleophilic substitution of the hydroxyl group with aminoazole (intermediate **22**) and, ultimately, an intramolecular condensation (pathway "c", Scheme 14). The other mechanisms cannot be also excluded, *e.g.*, via arylidenepyruvic acids **23** formed by water elimination from aldols **21**.



Scheme 14

However, Sakhno *et al.* [52] didn't succeed in the attempts to synthesize the compounds **23** by the direct reaction of arylpyruvic acids **15** and aldehydes **2** under different condition which was in good agreement with the literature data for the synthesis of similar unsaturated acids [58].

Based on the results obtained revealing several rules in the proceeding condensations of aminoazoles and arylidenepyruvic acids (or their synthetic precursors) the influence of the modifying aminoazole on the reaction behavior was studied as well. Among the polyfunctional



Scheme 15.

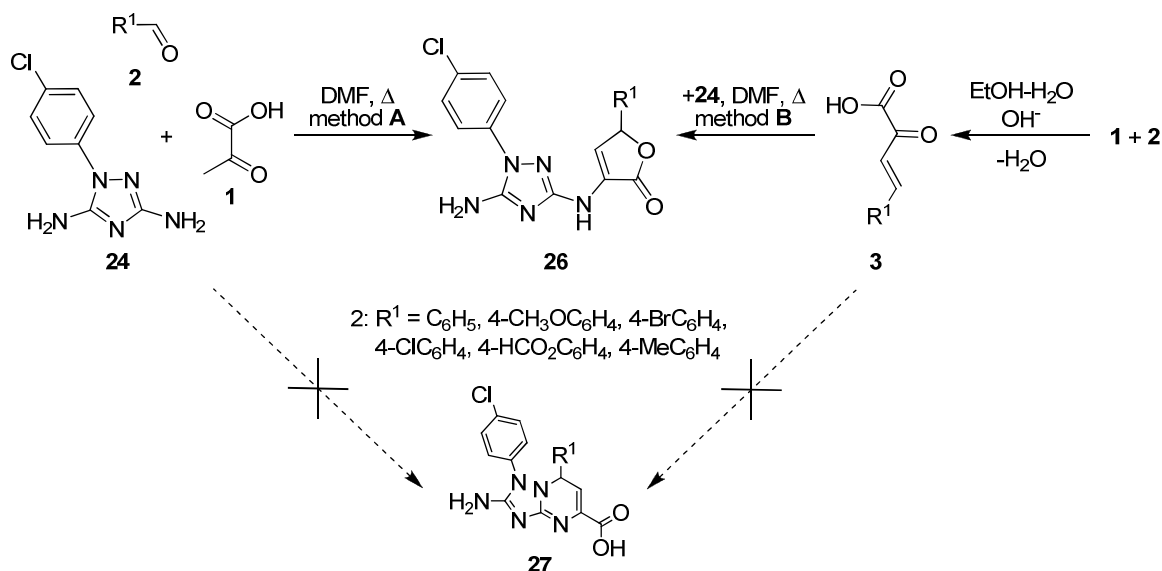
However, 1-(4-chlorophenyl)-3,5-diamino-1,2,4-triazole (**24**) in the reaction with phenylpyruvic acid (**15**) and aromatic aldehydes **2** showed the similar to aminotetrazole **4** behavior: after the heating or MW irradiating the starting materials (**Scheme 15**) in acetic acid corresponding pyrrolones **25** were synthesized while all the attempts to isolate tetrahydropyrimidines like **16** (**Scheme 12**) were unsuccessful [52].

The analogous multicomponent condensation involving unsubstituted pyruvic acid (**1**) proceeded in an unusual direction. It was established [68] that three-component treatment of

aminoazoles, applied in the heterocyclizations with carbonyl compounds, 3,5-diamino-1,2,4-triazole is of an interest due to the presence of several alternative reaction centers which usually results in formation of pyrimidine structures with additional possibility of further modification of the cyclization products. Moreover, introduction of an aryl substituent at position 1 of the diaminotriazole gives rise to specific properties that have been studied in details by Chernyshev *et al.* [59-63], Papini *et al.* [64-66] and other authors [67].

diaminotriazole **24**, aromatic aldehydes **2** and pyruvic acid (**1**) in boiling DMF gave unexpected 3-[5-amino-1-(4-chlorophenyl)-1H-1,2,4-triazol-3-ylamino]-5-arylfuran-2-ones **26** (**Method A, Scheme 16**). The authors [68] emphasize that neither triazolopyrimidines like **16** (**Scheme 12**) nor pyrrolone derivatives of type **25** (**Scheme 15**) were isolated or even chromatographically detected in the mother liquor.

The direction of the sequential reaction (**Scheme 16, method B**) *via* preliminary synthesis of arylidenepyruvic acids **3** was identical to the multicomponent procedure.



Scheme 16.

It was found that refluxing diaminotriazole **24** and unsaturated acids **3** in DMF led to the formation of the same triazolofuranones **26**, however the yields were smaller [68].

An alternative direction leading to triazolopyrimidines **27** was disfavored owing to the fact of a loss of aromaticity by the aminoazole moiety during the reaction (**Scheme 16**).

The most probable way for the formation of triazolylfuranones **26** was suggested in publication [68] and included the attack of one of the NH₂ groups of diaminotriazole **24** on the β-carbonyl group of pyruvic acid (**1**) with formation of azometines **28** followed by the cyclization with an aldehyde component **2** into the corresponding furanones **26** (**Scheme 17**). Formation of imines like **28** in analogues heterocyclizations involving aromatic or heterocyclic amines and pyruvic acids was previously described and discussed in several works [69-73]. According to the authors [68], other possible pathways, *e.g.*, *via* preliminary *in situ* formation

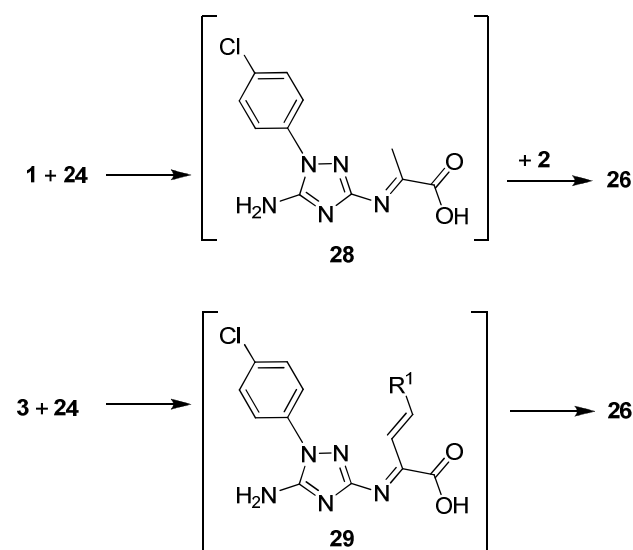
of arylidenepyruvic acids **3** or even whole furanone moiety were doubtful because of the previous negative results obtained for analogues multicomponent reactions (**Scheme 14**) [45, 52].

On the other hand, the fact of isolation of triazolopyrrolones **25** in the reaction involving phenylpyruvic acid (**15**) [52] (**Scheme 15**) can be explained by the specific influence of the phenyl substituent preventing the formation of the intermediate like **29**.

Similarly, the mechanism of the sequential reaction (**Scheme 17**) leading to the furanones **26** can take place *via* formation of imines **29** and their further cyclization into the final compounds **26**.

Reactions of 5-aminopyrazoles with pyruvic acids can also proceed in several directions and lead to fused pyridine or pyrimidine carboxylic acids; therefore, they are interesting from the point of view of chemo- and regioselectivity. In addition, high interest in the study

of pyridine and pyrimidine heterocycles containing fused pyrazole rings is mainly caused by the known biological activity of these systems reported in the literature [74-77].



Scheme 17.

The article [78] described the treatment of arylidenepyruvic acids or pyruvic acids with aromatic aldehydes and substituted 5-aminopyrazoles (Scheme 18). Under thermal or microwave heating, these cyclocondensations led to fused pyridine or pyrimidine carboxylic acids. It was shown that refluxing on an oil bath of equimolar mixtures of 5-amino-3-methylpyrazole (30) with unsaturated acids 3 in DMF or acetic acid allowed to obtain 4-aryl-3-methylpyrazolo[3,4-*b*]pyridine-6-carboxylic acids 33 (Scheme 18).

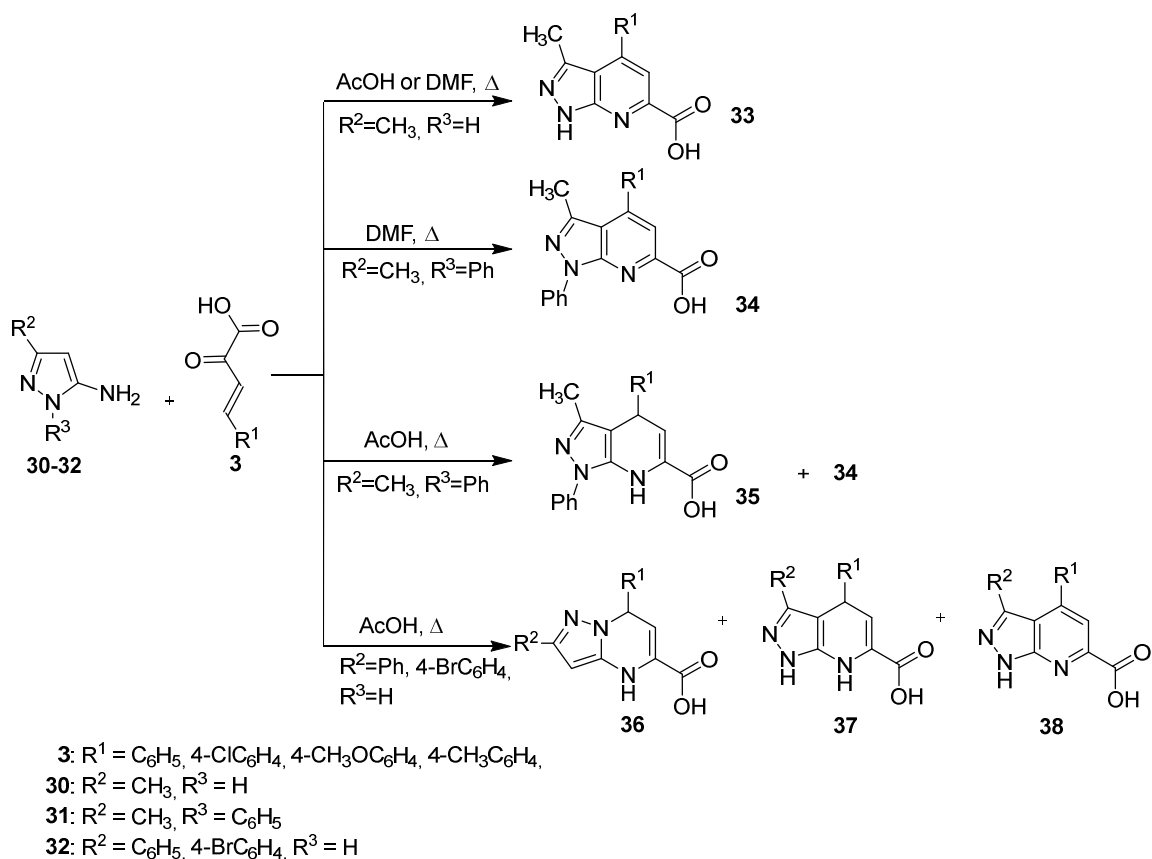
It should be noted that heterocyclic products in these reactions were not isolable as

dihydroderivatives, which indicate the high propensity of the expected 4-aryl-3-methyl-4,7-dihydropyrazolo[3,4-*b*]pyridine intermediates to oxidation.

Treatment of 5-amino-3-methyl-1-phenylpyrazole (31) with arylidenepyruvic acids 3 in boiling DMF led to 4-aryl-3-methyl-1-phenylpyrazolo[3,4-*b*]pyridine-6-carboxylic acids 34. However, the authors showed that refluxing the starting materials in boiling acetic acid allowed obtaining their dihydroanalogs 35, which were accompanied by only small amounts of heterocycles 34. Exposure of dihydropyridines 35 on air resulted in their oxidation to products 34.

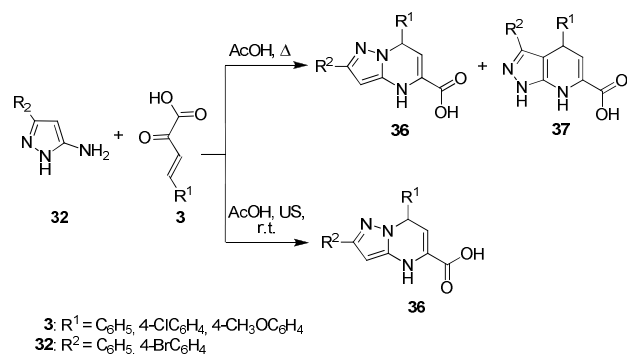
Refluxing arylidenepyruvic acids 3 with 5-amino-3-arylpyrazoles 32 allowed to isolate the mixtures of several regioisomers and products of their heteroaromatization (36, 37 and 38) as the reaction was not regioselective in most cases.

It should also be noted that condensation of 5-aminopyrazoles 30-32 with the unsaturated acids 3 have never yielded isomers with opposite location of the aryl and carboxyl groups at the pyridine or pyrimidine rings.



Scheme 18.

To solve the dilemma of obtaining the mixture of two regioisomers when 3-aryl-5-aminopyrazoles **32** reacted with arylidenepyruvic acids **3** in boiling acetic acid the authors of the article [78] applied ultrasonication to this reaction (**Scheme 19**).



Scheme 19.

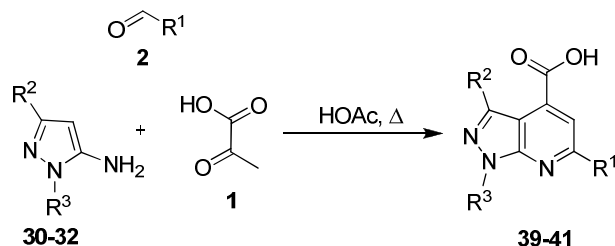
It was determined that cyclocondensation of the starting materials in acetic acid under

ultrasonic irradiation at room temperature caused the formation of exclusively 2,7-diaryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids **36**.

In the case of multicomponent reactions of pyrazoles **30-32** with pyruvic acid (**1**) and aromatic aldehydes **2** corresponding 6-aryl-3-methylpyrazolo[3,4-*b*]pyridine-4-carboxylic acids **39**, 1,6-diaryl-3-methylpyrazolo[3,4-*b*]pyridine-4-carboxylic acids **40** or 3,6-diarylpyrazolo[3,4-*b*]pyridine-4-carboxylic acids **41** were formed (**Scheme 20**) [78].

It was a very surprising discovery that reactions of 3-substituted 5-aminopyrazoles **30-32** with arylidenepyruvic acids **3** and the three-component cyclocondensation of the same pyra-

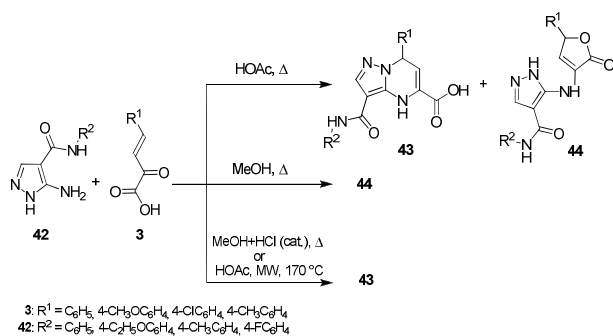
zoles with pyruvic acids **1** and aldehydes **2** led to the formation of different reaction products, which differ in the location of the carboxylic and R¹ substituents. It is also very important to mention that heteroaromatized compounds were formed as the result of the three-component reactions even under inert conditions.



- 2:** R¹ = Ar
30: R² = CH₃, R³ = H
31: R² = CH₃, R³ = C₆H₅
32: R² = C₆H₅, 4-BrC₆H₄, R³ = H

Scheme 20.

However, the treatment of 5-aminopyrazoles with arylidenepyruvic acids not necessary leads to the formation of pyrazoloazines.



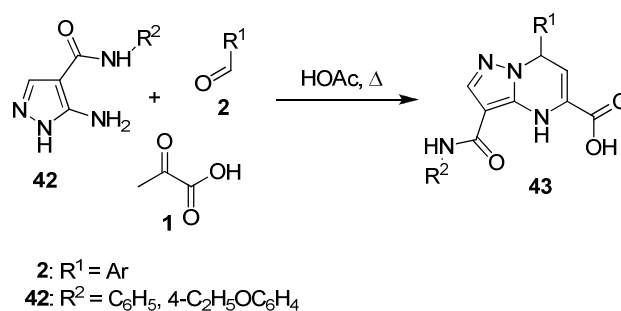
Scheme 21.

The authors of the article [80] showed that refluxing pyrazoles **42** with unsaturated acids **3** in acetic acid allowed to obtain the mixture of pyrazolopyrimidine-5-carboxylic acids **43** and pyrazolylaminofuranones **44** (**Scheme 21**)

while heating the starting materials **3** and **42** in boiling methanol resulted in the formation of solely compounds **44** in high yields.

It is important to point out that the addition of catalytic amounts of HCl had a strong effect on this reaction. Thus, in contrast to the above observation where **44** was selectively obtained, addition of hydrochloric acid changed the direction towards compounds **43**. However, using HCl in methanol medium has a serious drawback: it causes the esterification of acids **43**. To overcome this obstacle the authors [80] searched for the different reaction conditions and it was established that microwave irradiation (2 min at 170°C) in acetic acid of the starting materials yielded only the acids **43**.

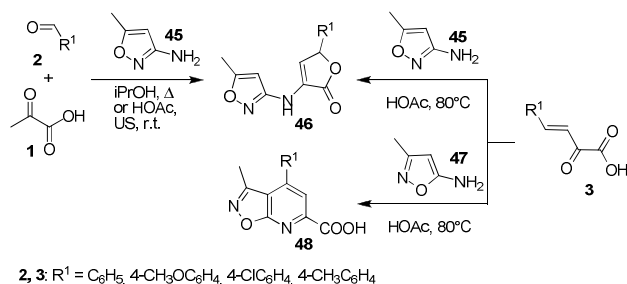
The multicomponent reactions of pyrazoles **42** with pyruvic acid (**1**), and aldehydes **2** led to pyrimidines **43** (**Scheme 22**), which were identical to the compounds isolated as the products of the two-component cyclocondensations (**Scheme 21**).



Scheme 22.

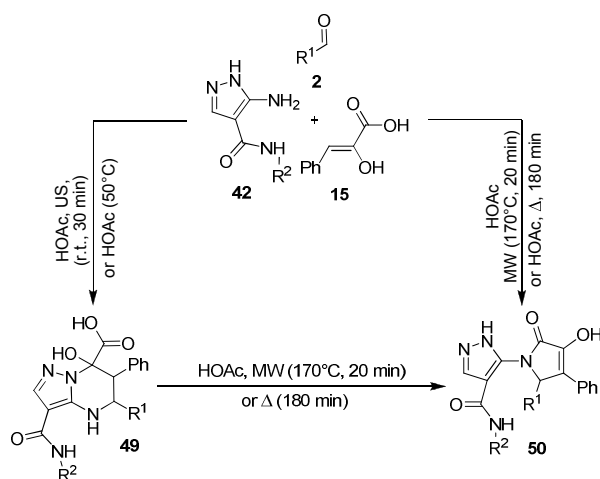
The interactions involving 3-amino-5-methylisoxazole (**45**) with arylidenepyruvic acids **3** or their synthetic precursors, pyruvic acid (**1**) and aromatic aldehydes **2**, resulted in the

formation of furanones **46** similar to compounds **44**. At the same time heating (80°C) 5-amino-3-methylisoxazole (**47**), arylidenepyruvic acids **3** in AcOH allowed to obtain only isoxazolopyridinecarboxylic acids **48** (Scheme 23) [81].



Scheme 23.

The influence of temperature regime on three-component reaction of pyrazole **42**, phenylpyruvic acid (**15**), and aromatic aldehydes **2** was explored in publication [80]. Under ultrasonication of starting materials in acetic acid at room temperature tetrahydropyrazolopyrimidine-7-carboxylic acids **49** were only formed (Scheme 24).

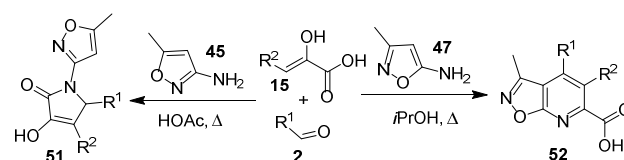


Scheme 24.

On the other hand, refluxing pyrazole **42**, phenylpyruvic acid (**15**), and aromatic alde-

hydes **2** in acetic acid or their heating in the microwave reactor led to the formation of pyrrolones **50**. The authors of articles [80, 81] concluded that compounds **49** were the kinetically controlled products, while compounds **50** were thermodynamically controlled ones.

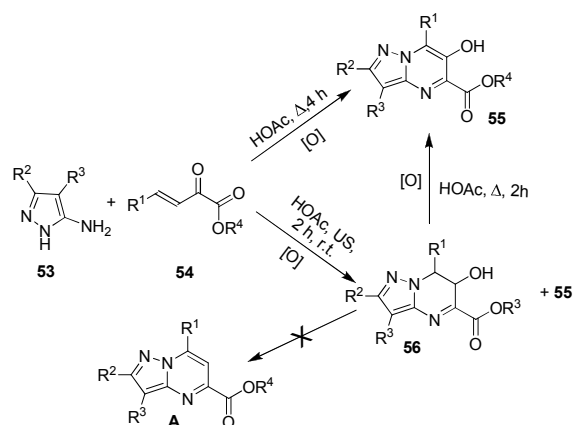
Pyrrolones **51**, similar to **50**, were also obtained under refluxing 3-amino-5-methylisoxazole (**45**) with aromatic aldehydes and arylpyruvic acid in HOAc, while the same three-component reaction involving isomeric 5-amino-3-methylisoxazole (**47**) proceeded with the formation of the carboxylic acids **52** (Scheme 25) [81].



Scheme 25.

Some interesting results were found when 3-aryl-4-alkyl-5-aminopyrazoles **53** reacted with several esters of arylidenepyruvic acids **54** – the treatment yielded esters of 6-hydroxy-2,7-diarylpirazolo[1,5-*a*]pyrimidine-5-carboxylic acids **55** (Scheme 26) [81]. In contrast, carrying out the same reaction under ultrasonication at room temperature caused the formation of the esters of 6-hydroxy-2,7-diaryldihydropyrazolo[1,5-*a*]pyrimidine-5-carboxylic acids **56** in mixtures with some amounts of compounds **55**. It should be mentioned that further refluxing of compounds **56** in acetic acid allowed to obtain heterocycles **55**; all

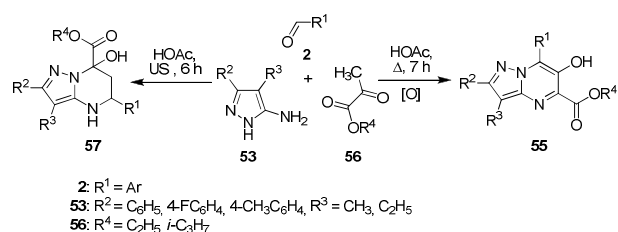
the efforts to carry out the dehydration of esters **56** were *in vain*.



53: R² = C₆H₅, 4-FC₆H₄, R³ = C₂H₅
54: R¹ = 4-CH₃OC₆H₄, 4-ClC₆H₄, R⁴ = C₂H₅, *i*-C₃H₇

Scheme 26.

The multicomponent reactions of pyrazoles **53** with ethyl pyruvate (**56**) and aromatic aldehydes **2** in boiling acetic acid also led to pyrimidines **55** (**Scheme 27**) [81]. On the other hand, the same interaction under ultrasonication allowed obtaining 7-hydroxytetrahydropyrazolopyrimidines **57**.



2: R¹ = Ar
53: R² = C₆H₅, 4-FC₆H₄, 4-CH₃C₆H₄, R³ = CH₃, C₂H₅
56: R⁴ = C₂H₅, *i*-C₃H₇

Scheme 27.

There were a lot of examples when the introduction of *ortho*-OH-group into aromatic ring of the aldehyde allowed the formation of several different chemotypes of final structures, *i.e.* oxygen-bridged [82-88], spiroheterocyclic compounds [89], lactones [85] and the other structures [82]. In continuation of the recent research [44, 45, 52, 58, 78-80] dedicated to the

tuning the selectivity of the reactions involving aminoazoles, aromatic aldehydes and pyruvic acids, the similar MCRs with the participation of *ortho*-hydroxybenzaldehydes were chosen as a challenging object for the study. It was found that variation of the temperature regime together with applying non-classical activation methods (ultrasonic and microwave irradiation) allowed to switch such reaction as well.

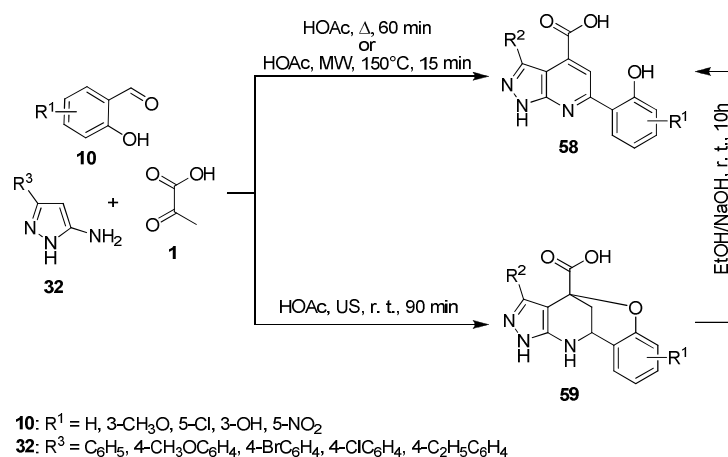
Thus, the condensation of pyruvic acid (**1**) with *ortho*-hydroxybenzaldehydes **10** and 5-amino-3-arylpzrazoles **32** under conventional refluxing in acetic acid led to the pyrazolo[3,4-*b*]pyridine-4-carboxylic acids **58** (**Scheme 28**) similar to those obtained in the reactions involving other aldehydes (**Scheme 20**) [90]. The substances **58** might also be obtained under microwave irradiation (AcOH, 150 °C, 20 min) that allowed a 4-fold reduction in the time of the process due to the higher reaction temperature [90].

However, the treatment of the same starting materials **1**, **10** and **32** in acetic acid at room temperature with application of ultrasonic irradiation gave benzoxazocine-4-carboxylic acids **59** (**Scheme 28**). These oxygen-bridged heterocycles were stable upon boiling in a series of solvents (acetic acid, methanol, ethanol and butanol). However, their stirring in ethanol with addition of sodium hydroxide led to cleavage of the bridged fragment, oxidation and the formation of compounds **58** in 90% yields. MW irradiating compounds **59** in HOAc (150 °C, 15

min) or heating them in DMSO for 48 hours also caused the formation of heteroaromatic carboxylic acids **58** (Scheme 28) [90].

The authors [90] considered azomethines as the intermediates of both heterocyclizations

mentioned above. Indeed, treatment of the corresponding preliminary obtained imines with pyruvic acid led to the formation of compounds **58** and **59**, respectively.



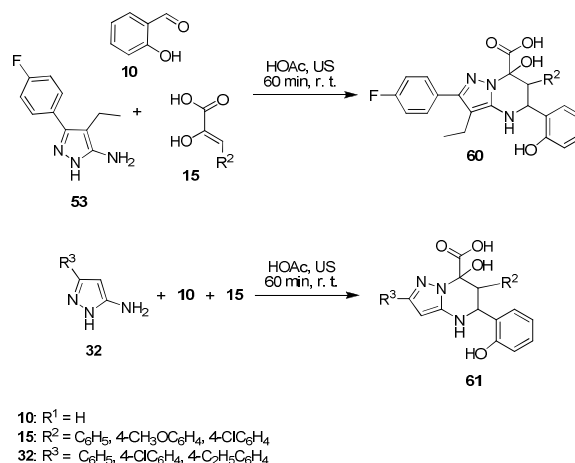
Scheme 28.

The possibility of the transformation of the azomethines into pyrazolopyridines like **58** by refluxing with pyruvic acid had been described in the earlier works [78].

As it was mentioned above, 5-aminopyrazoles containing a substituent in the fourth position sometimes possessed specific properties and exhibited unusual behavior in multicomponent reactions [80, 91, 92].

However, it was found that heterocyclization of 5-amino-4-ethyl-3-(4-fluorophenyl)pyrazole (**53**) and salicylaldehyde (**10**) both with pyruvic acid (**1**) and with arylpyruvic acids **15** in acetic acid under ultrasonication at room temperature led to the tetrahydroderivatives **60** similar to the reaction presented on Scheme 27 and no formation of bridged structures was observed (Scheme 29) [90].

Heterocyclization of pyrazoles **32** and salicylaldehyde (**10**) with arylpyruvic acids **15** under ultrasonic irradiation, in contrast to the multicomponent reactions involving pyruvic acid, proceeded with the formation of a pyrimidine ring instead of a pyridine one (carboxylic acids **61**, Scheme 29).



Scheme 29.

Compounds **60** and **61** were also obtained in the reaction of the corresponding azomethines with arylpyruvic acids [90].

Antimicrobial activity of the heterocycles obtained was studied as well. For several of the compounds tested a sufficient increase in biomass of cultures compared with control was found [90].

Conclusions

Thus, the known literature data demonstrate high potential of linear and multicomponent heterocyclizations involving aminoazoles, aldehydes and pyruvic acids or its derivatives for organic synthesis and, in particular, for Diversity Oriented Synthesis. Switchable character of such reactions and possibility to tune their selectivity by variation of the reaction parameters opens the pathway to obtain diverse heterocyclic scaffolds from a limited set of starting materials.

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