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Aminoazoles as Key Reagents in Multicomponent Heterocyclizations

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Abstract Because of the significant role in biological processes in living cells and the diverse types of physiological activities, heterocyclic compounds are in focus of intense investigations by academic and applied-oriented chemists. Considerably, a scientific renaissance of heterocycles during the last decades is closely related to the development of multicomponent approaches to their synthesis. Multicomponent methodology fundamentally different from two-component or sequential processes together with other innovative synthetic methods like microwave- and ultrasonic-assisted reactions offer some new possibilities in constructing heterocyclic systems with high level of molecular diversity and complexity. An overview of known multicomponent heterocyclizations using aminoazoles as a key reagent and their rich synthetic potential for obtaining five-, six-, and seven-membered heterocycles is presented. A special attention is paid to the tuning of chemo- and regio- and positional selectivity of some reactions as well as to the application of nonclassical activation methods based on microwave and ultrasonic irradiation.

Keywords Aminoazole · Heterocyclization · Microwave irradiation · Multicomponent reaction · Selectivity · Ultrasonic irradiation

Contents

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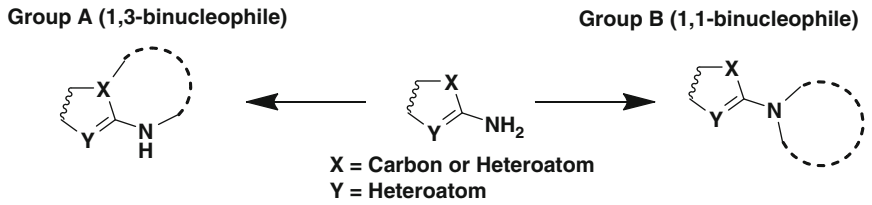
Abbreviations

3-CR	Three-component reaction
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
MCR	Multicomponent reaction
MW	Microwave
NMR	Nuclear magnetic resonance
p-TSA	*para*-Toluene sulfonic acid
RT	Reverse transcriptase
SAR	Structure-activity relationship
US	Ultrasonication

1 Introduction

Binucleophiles of aminoazole-type are quite important reagents in modern heterocyclic chemistry, and their reactions with electrophiles are the most widespread and facile synthetic approach for obtaining diverse heterocyclic systems containing azole moiety [1–3]. An interest on these heterocycles is attributed to their known biological activities: analgetics, cardiovascular vasodilators, calcium channel blocking agents, potassium channel inhibitors, apoptosis-inducers, and so on [4–19]. On the other hand, aminoazoles are usually polyfunctional compounds containing several reactive centers, which make them challenging objectives for studying mechanisms of organic reactions, tuning of their chemo- and regio-selectivity.

The most investigated area of aminoazole chemistry is their two-component reactions with ketoesters, β-dicarbonyls, or α,β-unsaturated aldehydes and ketones yielding fused azoloazines. Besides numerous original articles, several books and reviews were published in this field during recent decades [1–3, 20–24]. At the same time, very promising for combinatorial and medicinal chemistry as well as for diversity-oriented synthesis, multicomponent reactions (MCRs) based on aminoazole building-blocks were covered in literature very restrictedly. Some individual examples are provided, for example, in the following books [1, 21] and reviews



Scheme 1 Two main groups of aminozole MCRs

[2, 25–31]. However, no comprehensive analysis of aminozoles MCRs has been made till date, which afforded the ground for writing the present review.

Generally, multicomponent treatments of aminoazole can be divided into two main groups (Scheme 1):

– Group A: aminoazoles as 1,3-binucleophiles (more diverse)
– Group B: aminoazoles as 1,1-binucleophiles (less diverse)

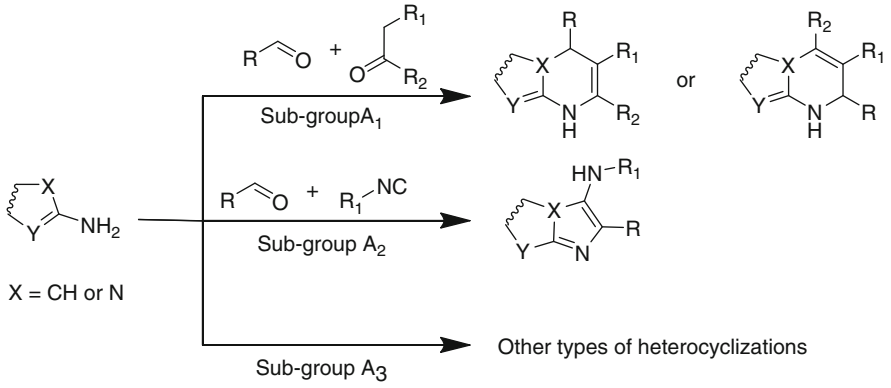
It should be noted that carbonyl compounds, more often aldehydes, are usual second reagent in both the groups. Other building-blocks in these multicomponent processes, leading to the formation of five-, six-, and seven-membered heterocycles, can be numerous acids and their derivatives, β-dicarbonyl compounds or other CH-acids, isocyanides, etc. At this, three-component reactions of ABC and ABB′ types [32] are the most typical for aminoazole, although some four-component ABCC processes were also published.

2 Aminoazoles as 1,3-Binucleophiles

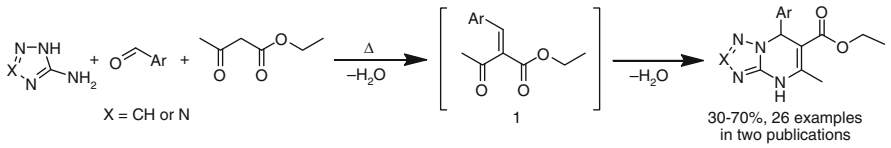
MCRs involving aminoazoles as 1,3-binucleophiles (group A) being the major part of known processes of such type, in turn, can be divided into several additional sub-groups (Scheme 2). The biggest one consists of the treatments of aminoazole with synthetic precursors of α,β-unsaturated carbonyl compounds – aldehydes and CH-acids (Sub-group A_1). They usually lead to partially hydrogenated azolopyridines (X = CH, Hantzsch-type reaction) or azolopyrimidines (X = N, Biginelli-type reaction).

Another type of multicomponent processes is isocyanide-based Groebke hetero-cyclization yielding fused imidazoles (Sub-group A_2). This three-component treatment is close analog of Ugi-reaction, being very promising for combinatorial chemistry aims. And finally, the third and smallest sub-group (A_3) includes other types of MCRs giving rise to fused heterocycles.

In our review we present general and specific examples of all these three types of MCRs, which involve aminoazoles as 1,3-binucleophile reagents. In the following sub-chapters, the most part of published original articles and selected patents in this topic will be observed and discussed.



Scheme 2 Aminoazoles as 1,3-binucleophiles



Scheme 3 MCR of aminoazoles and aldehydes with acetoacetic esters

2.1 Reactions with Synthetic Precursors of α,β-Unsaturated Carbonyls

2.1.1 Noncyclic CH-Acids

The traditional reagents having sufficient importance in multicomponent treatments with aminoazoles and carbonyl compounds are acetoacetic acid and its derivatives. Among these processes, Hantzsch- and Biginelly-type reactions giving highly substituted azolopyridines and azolopyrimidines containing carboxylic, ester, or carboxamide group are the focus of intense research for last decades.

One of the first results in this area concerning MCRs between 3-amino-1,2,4-triazole or 5-aminotetrazole with aromatic aldehydes and acetoacetic esters was published in 2003 independently by Fedorova et al. [33] and Desenko et al. [34]. Target 4,7-dihydroazolo[1,5-a]pyrimidines (Scheme 3) were easily obtained by usual refluxing of the starting materials in ethanol with hydrochloric acid [33] or in dimethylformamide (DMF) [34], however, in moderate yields. The authors of the second publication noted influence of electronic nature of the aldehyde aryl substituent on the reaction efficiency – a presence of strong electron-withdrawing groups (e.g., Ar = 4-$NO_2C_6H_4$) led to the decrease of the MCR's yields.

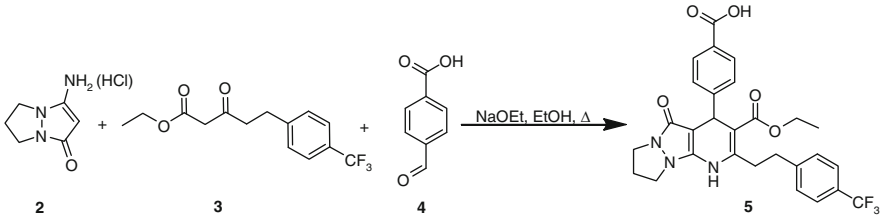
It seems that initial stage of the treatment should be Knoevenagel reaction via the formation of unsaturated derivatives **1** (Scheme 3). This sequence is considered

as standard in the literature, although in several cases the first step of such MCRs can be different, and some corresponding examples will be given below.

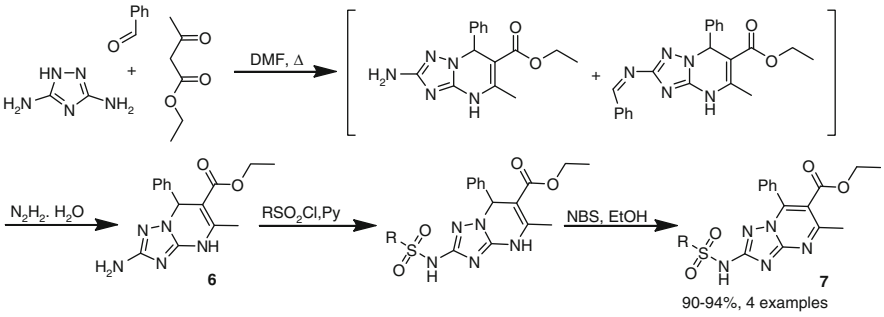
In several subsequent publications, this promising multicomponent synthetic approach was used for the synthesis of certain types of biologically active heterocyclic compounds. For instance, Boros and co-authors [35] reported application of the three-component heterocyclization between bicyclic aminoazole **2**, acetoacetic acid derivatives **3**, and aldehyde **4** to obtain compound **5** being aza-analog of known [36] agonist of the calcetonine receptor (Scheme 4).

To synthesize azolopyrimidines **7**, containing sulfonylamino-group and promising in agriculture as herbicides and plant growth regulators, the authors of article [37] used three-component heterocyclization of 3,5-diamino-1,2,4-triazole, benzaldehyde, and acetoacetic ester in boiling DMF (Scheme 5). The MCR at the first stage yielded two compounds, which without separation in one-pot way manner were treated with hydrazine hydrate to obtain pure intermediate **6**. Further sulfonylation and oxidation was carried out sequentially in pyridine and ethanol, correspondingly, with separation of each reaction products.

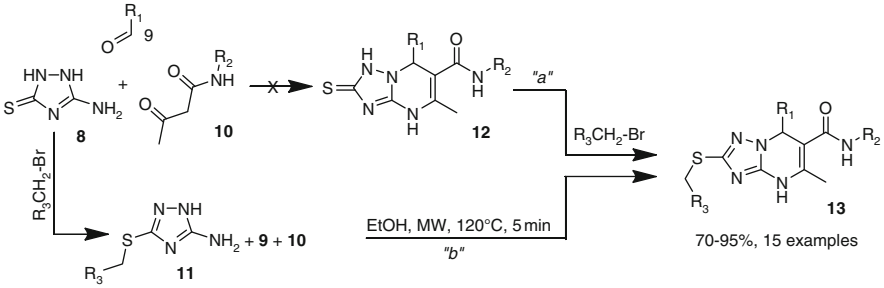
MCRs of aminoazoles and aldehydes with acetoacetamides are also known. For example, combinatorial-oriented synthesis of potentially pharmacologically active dihydrotriazolopyrimidines **13** was described in [38].The authors considered that carrying out S-alkylation at the last step of pathway "a" (Scheme 6) was more convenient for the combinatorial procedure; however, all attempts to realize three-component condensation of 3-amino-1,2,4-triazolo-5-thione **8** with aldehydes **9** and



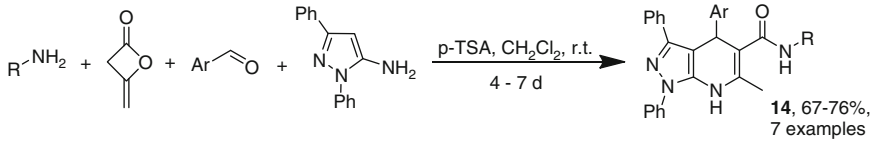
Scheme 4 Synthesis of aza-analog of agonist of the calcetonine receptor



Scheme 5 Synthesis of azolopyrimidines promising in agriculture



Scheme 6 Three-component synthesis of triazolopyrimidinecaroxamides



Scheme 7 Alternative four-component synthesis of carboxamide derivatives of azoloazines

acetoacetamides **10** were unsuccessful – only the starting materials were reisolated from the reaction mixture quantitatively.

As an alternative, initial S-alkylation of aminoazole **8** with appropriate alkylbromides (R_3CH_2Br) was performed. Then 3-amino-5-alkylthio-1,2,4-triazoles **11** were introduced into the MCRs with aromatic aldehydes and acetoacetamides (pathway "b"). To sufficiently increase yields of target heterocycles **13**, the cyclocondensations were performed under microwave irradiation in ethanol at 120°C.

In some cases synthesis of starting materials for MCRs is also a difficult task, which sometimes complicates greatly application of procedures involving commercially inaccessible reagents. In the previous example, both acetoacetamides and animoazole building-blocks were hardly available by synthetic methods. In this context, to avoid laborious stage of acetoacetamide synthesis, Shaabani et al. [39] suggested four-component procedure for obtaining similar carboxamide derivatives. It was shown that room temperature treatment of equimolar mixture of primary amines, diketene, 5-amino-1,3-diphenylpyrazole and aldehydes, containing both electron-withdrawing and electron-donating substituents, in CH_2Cl_2 in the presence of *p*-TSA gave pyrazolo[3,4-b]pyridine-5-carboxamides **14** in good yields (Scheme 7). In this MCR acetoacetamide formed in situ by the addition of amine to diketene molecule.

This procedure can be used for the MCRs based on other 1,3-binucleophiles. For example, the same authors applied it to form pyrido[2,3-d]pyrimidine-6-carboxamide derivatives from 6-aminouracile [40].

However, the main disadvantage of the new multicomponent procedure consists in a very long duration of the treatment to reach the required level of conversion.

Thus, reaction of 5-aminopyrazole should be carried out for 4–7 days, while in the case of 6-aminouracile the process lasts even longer – up to 13 days.

In some cases special synthetic methodologies were applied to increase reactions yields or to satisfy "green chemistry" requirements. For example, Yao and co-authors [41] successfully carried out solvent-free three-component reaction of 5-aminotetrazole, aromatic aldehydes, and acetoacetic acid in the presence of inexpensive and commercially available sulfamic acid as catalyst. The yields of the MCRs were rather low but the whole procedure was facile, economic, and eco-friendly.

Over the last decades in organic chemistry and, particularly, in heterocyclic synthesis, the popularity of nonclassical activation methods has been growing continually. Microwave-assisted methodologies are the most promising among them and intensively used in different fields of up-to-date chemistry [42–45]. In the most cases, the combination of multicomponent approaches with microwave technologies and "green chemistry" solvents and catalytic systems gives a possibility to reach high criteria of "ideal synthesis" [46].

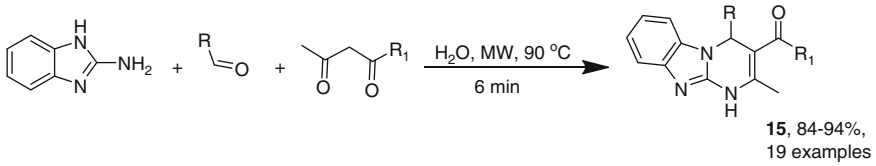
In addition to the abovementioned results consisting only the increasing yields (Scheme 6) [38], another example of effective microwave-assisted synthesis of azolopyrimidine carboxamides should be described. Tu et al. [47] reported eco-friendly three-component reaction of 2-aminobenzimidazole, aromatic aldehydes, and some β-dicarbonyl compounds under microwave irradiation (Scheme 8). It was shown that the treatment of the starting materials can be most efficiently carried out at 90°C (200 W MW power) in water medium instead of traditional organic solvents like ethanol, acetic acid, or DMF.

Nonclassical synthetic methods can also be used for tuning MCRs selectivity, and several successful examples will be reflected somewhat lower in our review.

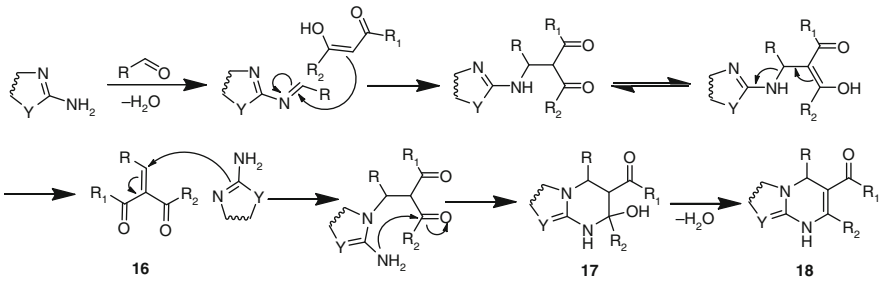
Generally, MCRs based on aminoazoles and synthetic precursors of α,β-unsaturated carbonyl compounds proceed via a sequence of Knoevenagel-type condensation, which was already mentioned (see Scheme 3), Michael-like addition, cyclization, and water elimination. For example, the authors of [47] considered the following mechanism (Scheme 9).

Some steps of the sequence proposed, of course, may be others, but key stages including formation of α,β-unsaturated dicarbonyl derivative **16**, cyclization into tetrahydropyrimidine **17**, and dehydration are common in the most cases.

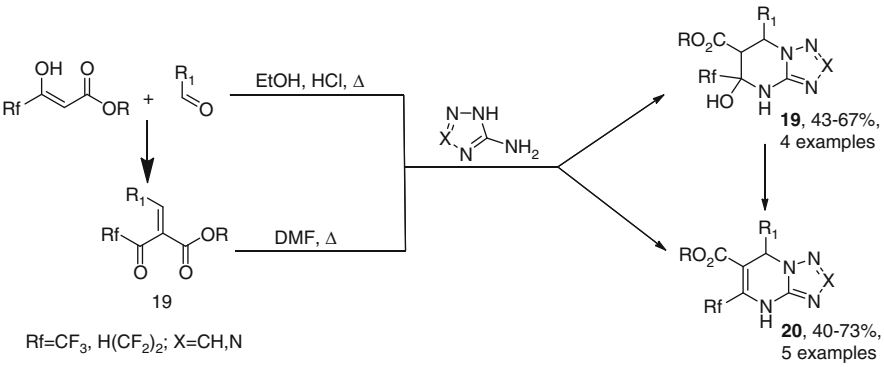
It should be noted that in the most cases MCRs of aminoazoles with CH-acids and aldehydes and linear reactions including preliminary synthesis of α,β-unsaturated carbonyl compounds like **16** yield the same reaction products.



Scheme 8 Eco-friendly MW-assisted MCR of aminobenzimidazole, aldehydes and 1,3-dicarbonyls



Scheme 9 Possible mechanism of MCRs between aminoazoles, aldehydes and CH-acids



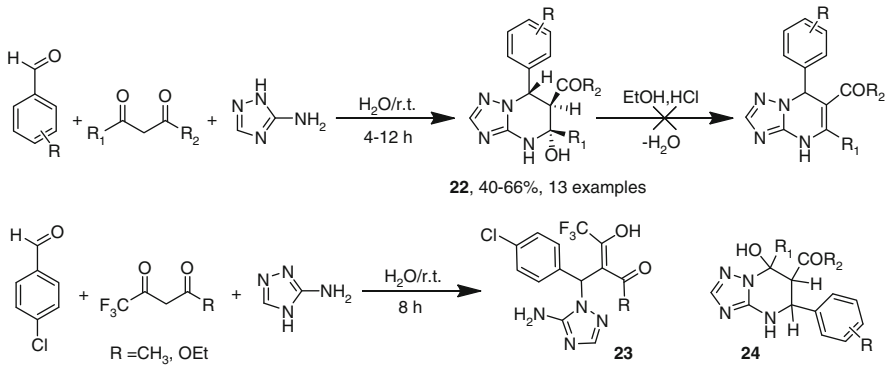
Scheme 10 MCRs of fluorinated 1,3-dicarbonyls

However, there are numerous examples when both these synthetic approaches give different heterocyclic systems, which lets additional powerful tool for tuning of reactions selectivity.

When R_2 substituent is flourocontaining alkyl group, the transformation **17** → **18** becomes hindered and its proceeding requires some special methods. For example, in [48] Biginelli-like cyclocondensations based on three-component treatment of 3-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and fluorinated 1,3-dicarbonyl compounds were investigated. It was shown that the reaction can directly lead to dihydroazolopyrimidines **20**, but in the most cases intermediate tetrahydroderivatives **19** were obtained (Scheme 10). To carry out dehydration reaction, refluxing of tetrahydroderivatives **19** in toluene in the presence of *p*-TSA with removal of the liberated water by azeotropic distillation was used. The same situation was observed for the linear reaction proceeding via the formation of unsaturated esters **21**.

It is interesting that hindered elimination of water for the MCR of flourocontaining acetoacitic acid derivatives was not observed in [36].

Another example of the formation of hydroxyl-containing tetrahydropyrimidenes was described by Shaabani et al. in their publication concerning "green



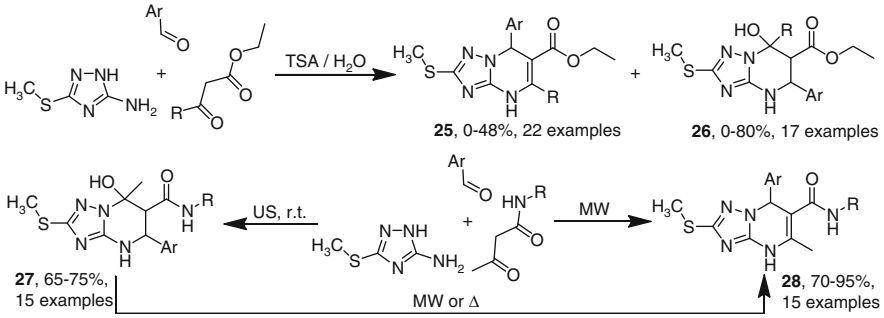
Scheme 11 Unusual directions of aminoazole MCRs

chemistry" matters [49]. It was established that three-component reaction of some CH-acids and aromatic aldehydes with 3-amino-1,2,4-triazole in water at room temperature allowed isolation of triazolopyrimidines **22**, as sole diastereomere, which were not able to eliminate water during their heating in EtOH with HCl (Scheme 11).

On the other hand, similar treatment of flourocontaining dicarbonyl compound gave up no tetrahydropyrimidine, as it was expected, but noncyclic reaction product **23** was isolated. The formation of compound **23** is in good correlation with the mechanism offered in [47] (Scheme 9). However, we should note that structure of compounds **22**, established in [49] by means of IR, NMR, and mass-spectra, can be wrong. In several other works, it was shown that similar MCRs had another positional direction with the formation of compounds type **24** [50–54].

For instance, Chen and co-authors [50] reported MCRs of 3-amino-5-alkylthio-1,2,4-triazole with aromatic aldehydes and β-ketoesters. For the development of regioselective and eco-friendly procedure to the Biginelli-like tetrahydropyrimidines they applied water medium and *p*-TSA catalysis. It was surprisingly established that conventional heated or microwave-assisted reaction of the starting materials both in water and in organic solvents yielded a mixture of two heterocyclic compounds **25** and **26** in various ratios (Scheme 12). The structures of the reaction products were proven by X-ray analysis and NMR study.

To elaborate selective approach to the compounds **25** and to increase their yields, the authors of [50] applied microwave-assisted reaction in ethanol as described earlier in [38] (see Scheme 6). However, the selective procedure for the synthesis of the heterocycles **26** was not published in this article. It was achieved by other authors [54] with the help of ultrasonication, being equally with microwave-assisted synthesis as one of the most facile tool in the modern organic chemistry [55–57]. It was established that three-component reaction of 3-amino-5-alkylthio-1,2,4-triazole with aldehydes and acetoacetamides under ultrasonic irradiation at room temperature led exclusively to tetrahydrotrialopyrimidines **27**, while the same



Scheme 12 Controlled MCRs of 3-amino-5-alkylthio-1,2,4-triazoles

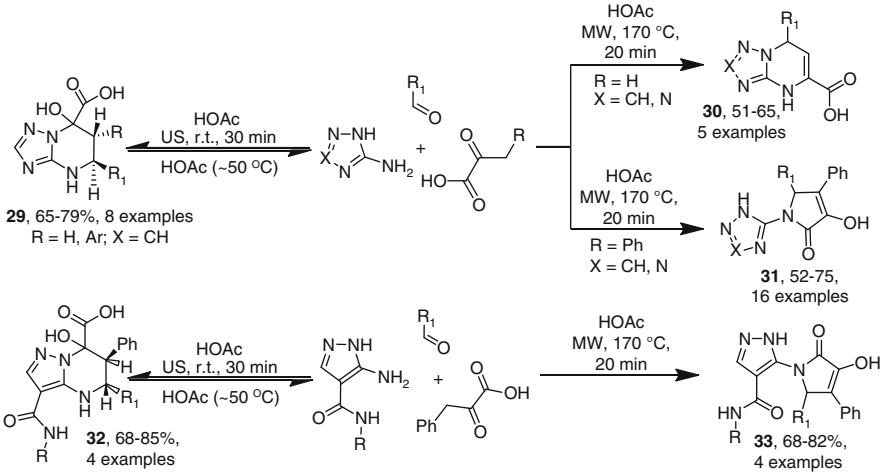
treatment in microwave field at higher temperatures yielded "classical" Biginelli-like heterocycles **28** (Scheme 12). Moreover, compounds **27** can be easily converted into **28** by heating in ethanol.

Generally, an application of room temperature reactions carried out under ultrasonication or high-temperature heating proceeding in microwave field can be a very powerful methodology for tuning chemo-, regio-, or positional selectivity of organic reactions. Precise control of the reaction parameters within these technologies gives a possibility to direct process along kinetically or thermodynamically controlled pathways, which allows in obtaining different reaction products selectively. In addition to the above-mentioned works [51–54], several examples of the application of this strategy were recently published [58–61] and will be discussed in this review.

For example, an application of this strategy was successful for a three-component reactions involving pyruvic acids, aldehydes, and 3-amino-1,2,4-triasole, which allowed to develop preparative and high-selective procedures for the synthesis of three different classes of heterocycles [51–53, 62]. Thus, heterocyclization of pyruvic or arylpyruvic acids with 3-amino-1,2,4-triazole and aromatic aldehydes in acetic acid at room temperature under ultrasonication gave triazolopyrimidine carboxylic acids **29** [51] (Scheme 13). It is interesting that the same reaction with 5-aminotetrazole cannot be carried out. On the other hand, MCRs of both aminotriazole or aminotetrazole with aldehydes and arylpyruvic acid at 170°C under microwave irradiation yielded exclusively triazolylpyrrolones **31** [51], while the high-temperature treatment involving pyruvic acid led to other heterocyclic system – dihydroazolopyrimidines **30** [62].

Very similar directions of the MCRs were found for another starting aminoazole – 5-amino-*N*-aryl-1H-pyrazole-4-carboxamide [52]. Its ultrasonic-assisted treatment with phenylpyruvic acid and aldehydes at room temperature gave partially hydrogenated azolopyrimidines **32** (Scheme 13). Heating of the same starting materials up to 170°C in microwave field allowed isolating pyrrolones **33**.

The formation of tetrahydropyrimidines **29** and **32** is reversible and their heating at ca. 50°C for 30 min leads to decomposition into starting compounds, while



Scheme 13 MCRs under kinetic and thermodynamic control

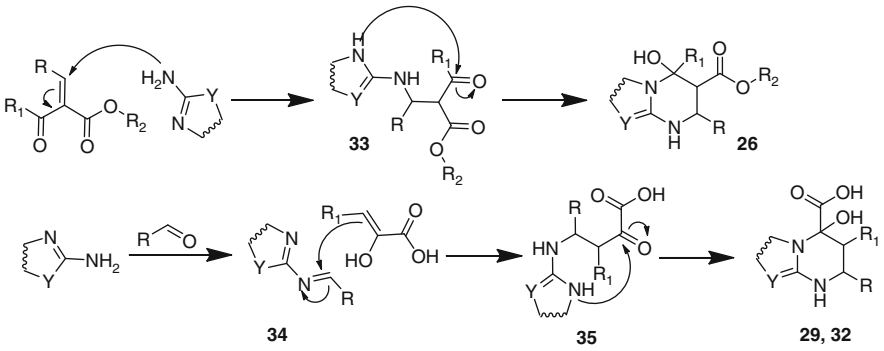
refluxing in acetic acid yields (depending on R substituent) ether carboxylic acids **30** (R = H) or pyrrolones **31**, **33** (R = Ph) [51–53].

As described earlier for compounds **22** (Scheme 11), attempts to carry out dehydration of tetrahydropyrimidines **29**, **32** were unsuccessful under various reaction conditions.

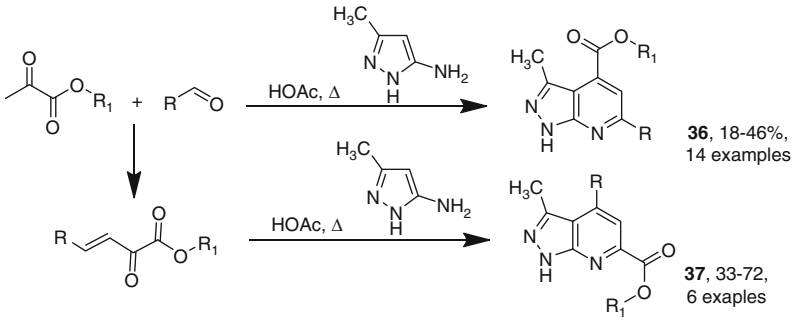
Chen and co-authors in their work [50] offered key stages for mechanism of heterocyclization leading to compounds **25** and **26** (Scheme 12). The reaction sequence for azolopyrimidines **25** formation is very similar to that published in [47] and presented in Scheme 9. Pathway to tetrahydroderivatives **26**, in opinion of [50], also includes at the beginning Knoevenagel condensation. Further step of the reaction in this case should be the addition of exocyclic NH_2 group of aminoazole to enone fragment of unsaturated ester, with subsequent cyclization of the adduct formed into final tetrahydropyrimidine (Scheme 14).

However, in MCRs based on pyruvic acids no formation of α,β-unsaturated carbonyl compounds was observed. Instead of Knoevenagel condensation, the first step of the process was the formation of the corresponding azolmethine **34**, which when treated with enole form of pyruvic acid gave adduct **35**. The final stage was cyclization into compounds **29** or **32** [51, 53] (Scheme 14).

Generally, MCRs of pyruvic acids with nitrogen containing binucleophiles are challenging objectives for detailed study. On the one hand, heterocycles formed in such reactions can possess numerous types of biological activities [4, 63–67] and their synthesis is very promising from the viewpoint of medicinal chemistry. Moreover, as it follows from the several abovementioned publications, these multicomponent processes yielding diverse heterocyclic systems are very interesting for the development of strategy for chemo- and regio-selective organic reactions – even just changing temperature regime gives a possibility to obtain several different final products (Scheme 13).



Scheme 14 Mechanisms of tetrahydroazolopyrimidines formation



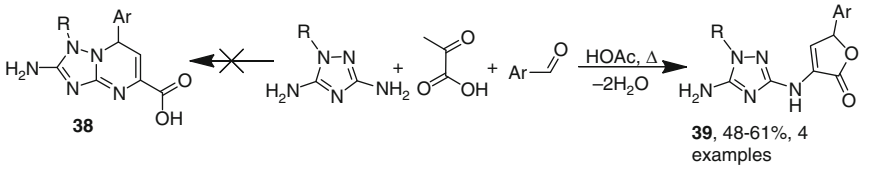
Scheme 15 Synthesis of positional isomers of pyrazolopyridine carboxylic acid derivatives

In some cases a choice of multicomponent or linear protocol for the treatment of pyruvic acids, aminoazole, and aldehydes allows obtaining different heterocycles. For instance, MCR involving 5-aminopyrazoles or sequence pathway via preliminary synthesis of arylidenpyruvic acids led to positional isomers **36** and **37**, respectively (Scheme 15) [4, 61, 68]. It is interesting to note that the same strategy applied to 3-amino-1,2,4-triazole or to amino-*N*-aryl-1H-pyrazole-4-carboxamide reactions gave no effect and the final compound for both the protocols were the same [52, 61, 62].

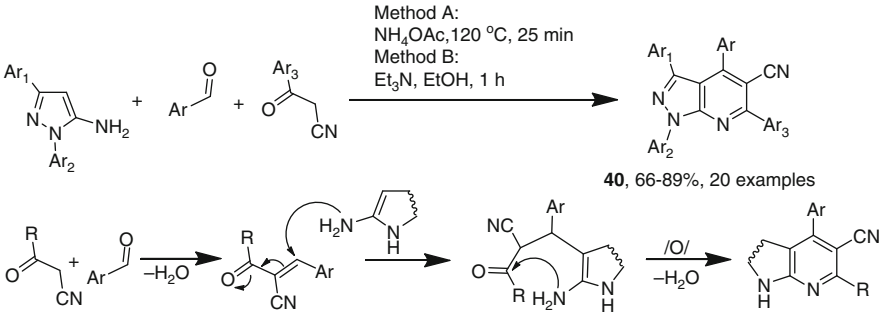
Different products of the three-component and linear treatments in the case of 5-aminopyrazole can be the evidence that this MCR follows independent pathway without formation of in situ α,β-unsaturated carbonyl compound.

The direction of MCR involving pyruvic acid, aldehyde, and 1-aryl substituted 1,2,4-triazole-3,5-diamine was different from the directions of all other processes that were discussed earlier. It was established [53] that this treatment yielded 3-(5-amino-1H-1,2,4-triazol-3-ylamino)furan-2(5H)-one **39** instead of triazolopyrimidine carboxylic acids **38** (Scheme 16).

This unusual direction of the MCR is connected with the loss of aromaticity following the pathway, giving carboxylic acids **38**. It can lead to the increase in the



Scheme 16 Unusual direction of MCR involving 1,2,3-triazole-3,5-diamine



Scheme 17 Benzoylacetonitriles in MCRs with aminopyrazoles

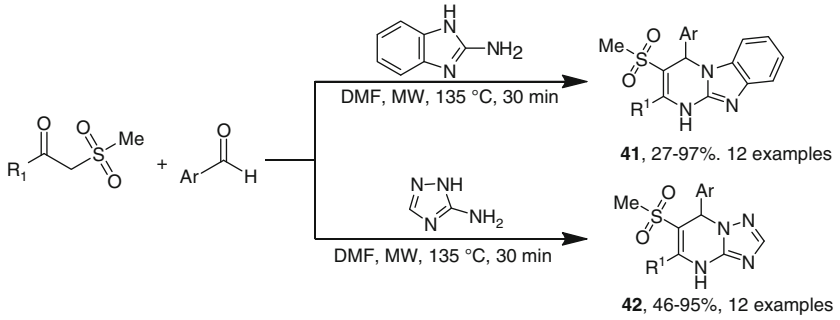
transition states energy or to the decrease in thermodynamic stability of the final heterocycles. Both these factors should favor formation of furanones **39**.

As CH-acids in the MCRs with aldehydes and aminoazoles, other classes of organic compounds were used as well. Cyanoacetic acid derivatives, acetoyl(aroyl) acetonitriles, ketosulfones, acetophenones, and other reagents were successfully introduced into these three-component heterocyclizations. For example, synthesis of pyrazolo[3,4-b]pyridine-5-carbonitriles **40** was carried out as the multicomponent treatment of 5-aminopyrazole, aldehyde, and benzoylacetonitriles solvent-free by fusion either in ammonium acetate at 120°C or in boiling ethanol with Et_3N (Scheme 17) [69]. The second approach gave the worst results from the viewpoint of yields and purity of the target compounds.

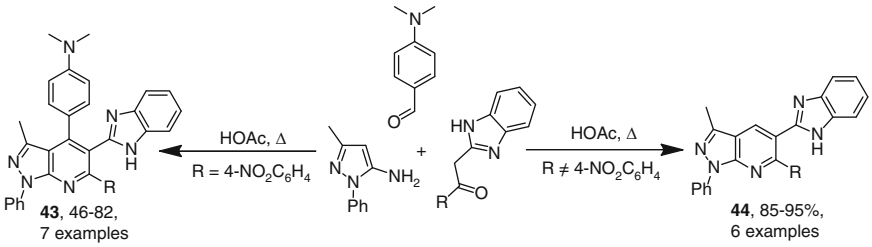
To carry out the similar MCR involving 5-amino-3-methyl-1-phenylpyrazole, aromatic aldehydes, and 3-cyanoacetyl indoles, Zhu et al. [70] used microwave-assisted synthesis in glygol at 150°C. Application of other solvents was less effective and gave either no reaction products (water medium) or led to the sufficient yield decreasing (EtOH, HOAc, DMF). Microwave irradiation was also used by Quiroga et al. [71] to synthesize ether 4-aryl-5-cyano-6-phenylpyrazolo[3,4-b]pyridine-3-ones or their dihydroderivatives under argone atmosphere.

The mechanism of these MCRs, according to [70], should include formation of unsaturated nitrile, its treatment with aminopyrazole and cyclization following with water elimination and, sometimes, oxidation (Scheme 17).

Three-component treatments of ketosulfones and aldehydes with 2-aminobenzimidazole or 3-amino-1,2,3-triazole were carried out in microwave reactor as well



Scheme 18 Ketosulfones in MCRs with aminoazoles



Scheme 19 Elimination of 4-dimethylaminophenyl substituent

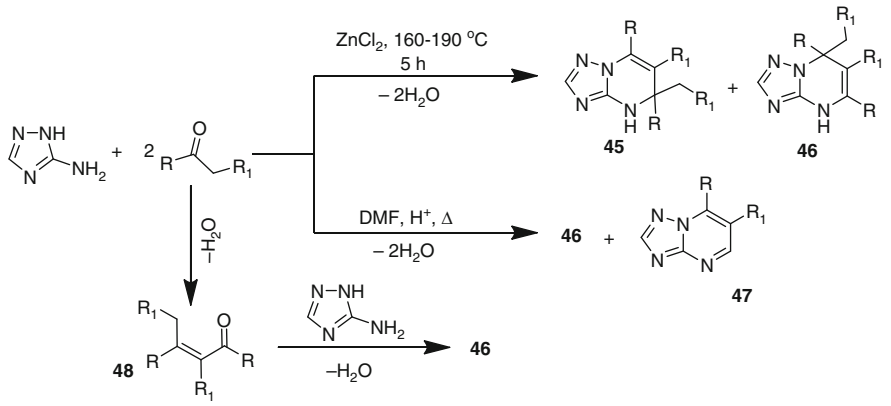
(Scheme 18) [72]. It is interesting to note that this MCR involving 5-aminotetrazole was unsuccessful and only the starting materials were reisolated from the reaction mixture. An explanation for this unreactivity could be the decrease in nucleophilicity comparing 3-amino-1,2,4-triazole and 2-aminobenzimidazole with 5-aminotetrazole. The same observations regarding the reactivity characteristics for these aminoazoles have already been reported before [73].

Three-component treatment of ketosulfones and related CH-acids with aldehydes and 5-aminopyrazoles was also patented by Han and Hu [74]. They used stirring of the starting materials in THF at 70°C and HPLC purification to synthesize biologically active pyrazolopyrimidines containing sulfonic group.

Hantzsch-type reaction between 5-amino-3-methyl-1-phenylpyrazole, 4-dimethylaminobenzaldehyde, and 2-aroylbenzimidazole is followed by elimination of 4-dimethylaminophelyl substituent [75]. The treatments that were carried out in boiling glacial acetic acids for 2 h yielded pyrazolopyridines **44** when R≠4-$NO_2C_6H_4$ (Scheme 19).

Similar elimination of electron-rich aryl substituents was also described for other heterocyclic systems [76–78].

In some cases, the question of positional and regioselectivity arises for MCR based on aminoazole. Regioselectivity problem concerning the presence of non-equivalent reaction centers in 1,3-binucleophile molecule is more specific for



Scheme 20 Formation of position isomers in MCRs of aminotriazole

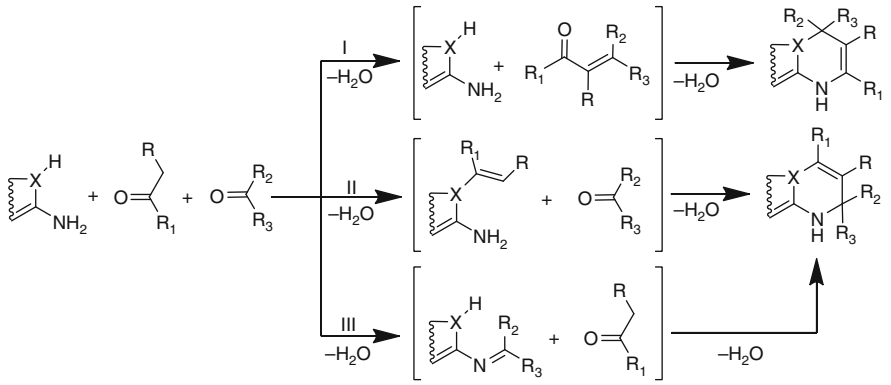
reactions of cyclic CH-acids and will be discussed in Sect. 2.1.2. However, there are several examples for noncyclic active methylene compounds.

For example, the formation of mixtures of 4,5- and 4,7-dihydroisomers **45** and **46** was observed by Werman and Hartman [79] in the reaction of 3-amino-1,2,4-triazole with two equivalents of methylarylketone in the presence of $ZnCl_2$ as a catalyst (Scheme 20). The ratios between two position isomers were from 50:50 to 74:26. However, Desenko et al. [80] established that treatment of the same starting compounds under acidic catalysis (acetic or mineral acids) yielded only 4,5-dihydroderivatives **46** and heterocycles **47** [81]. In the latter case, the third component of the multicomponent condensation was the solvent – DMF. It is worth noting that heterocyclic compounds **46** were also the products of the reaction between 3-amino-1,2,4-triazole with α,β-unsaturated ketones **48** (Scheme 20).

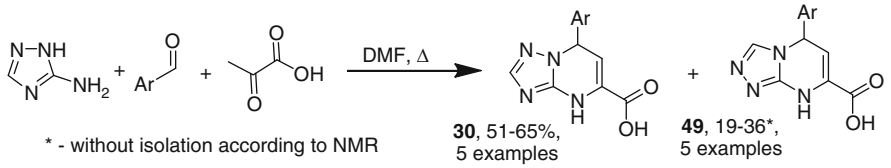
It is possible to suggest at least three mechanisms to explain different directions of the abovementioned MCRs (Scheme 21) [1, 79, 80]. It should be noted that the reaction passing according to pathway **I** is not an independent method for the formation of the dihydroazine system and corresponds to the normal treatment of α,β-unsaturated carbonyls, because the generation of the latter occurs in situ. On the contrary, reaction pathways **II** and **III** follow different mechanisms leading to compounds like **45**, which are hard to synthesize by other methods.

The results describing formation of regioisomers in the case of MCR involving 3-amino-1,2,4-triazole, aldehydes, and pyruvic acid were also published [62]. The treatment was carried out in boiling DMF and a mixture of two regioisomeric compounds **30** and **49** (Scheme 22) were isolated and characterized (**49** without separation).

It is important to note that the formation of heterocycles with participation of endocyclic nitrogen in position 4 of 3-amino1,2,4-triazole (azolopyrimidines **49**) is quite unusual, and there are only several references in literature concerning similar reaction products [1, 2]. It should be also mentioned again that the same reaction in acetic acid yielded solely carboxylic acid **30** [62] (Scheme 13).



Scheme 21 Mechanisms of position isomers formation



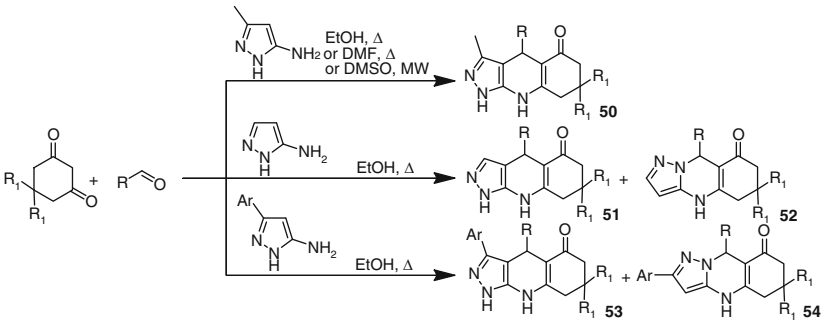
Scheme 22 Formation of regio-isomers in MCRs of 3-amino-1,2,4-triazole, pyruvic acid and aldehydes

2.1.2 Cyclic CH-Acids

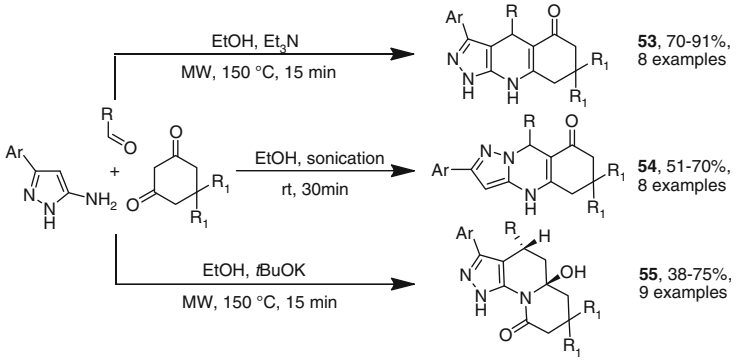
MCRs of Hantzsch and Biginelli-types with participation of aldehydes, aminoazoles, and cyclic CH-acids, first of all 1,3-diketones and Meldrum acid, as well as the treatments discussed in the previous sub-chapter, are in the focus of interest due to high biological activity of their products. However, on the other hand, in many cases these processes can give several final heterocycles with different position or regiodirection. Moreover, sometimes for the same reactions carried out under similar conditions contradictory facts were published with high level of credibility.

For example, it was reported in several independent articles that multicomponent treatment of 5-amino-3-methylpyrazles with 1,3-cyclohexandiones and aldehydes under refluxing in EtOH [82, 83], in DMF with methanol [84], or with application of continuous-flow microwave-assisted procedure in DMSO [85] yielded exclusively pyrazoloquinolinones **50** (Scheme 23). On the other hand, the treatment of 3-unsubstituted 5-aminopyrazoles with cyclic β-diketones or ketosulfones gave mixtures of Hantzsch dihydropyridines **51** and Biginelly dihydropyrimidines **52** in different ratios [86].

The data about MCRs involving 5-amino-3-arylpyrazoles are more discrepant. Quiroga et al. [82] reported three-component treatment of this pyrazole with dimedone and aromatic aldehydes in boiling ethanol, yielding only pyrazoloquinolinones



Scheme 23 Formation of regio-isomers in MCRs involving cyclic 1,3-diketones



Scheme 24 Selectivity tuning of MCRs involving cyclic 1,3-diketones

53. In another article, however, [59] it was shown that in the most case this reaction gave mixtures of two heterocycles **53** and **54**. To develop procedures allowing regioselective synthesis of both heterocyclic systems, the authors of [59] studied an influence of temperature regime and catalyst type on the direction of this MCR. With application of ultrasonication and microwave irradiation it was established that the reaction studied can pass under kinetic and thermodynamic control.

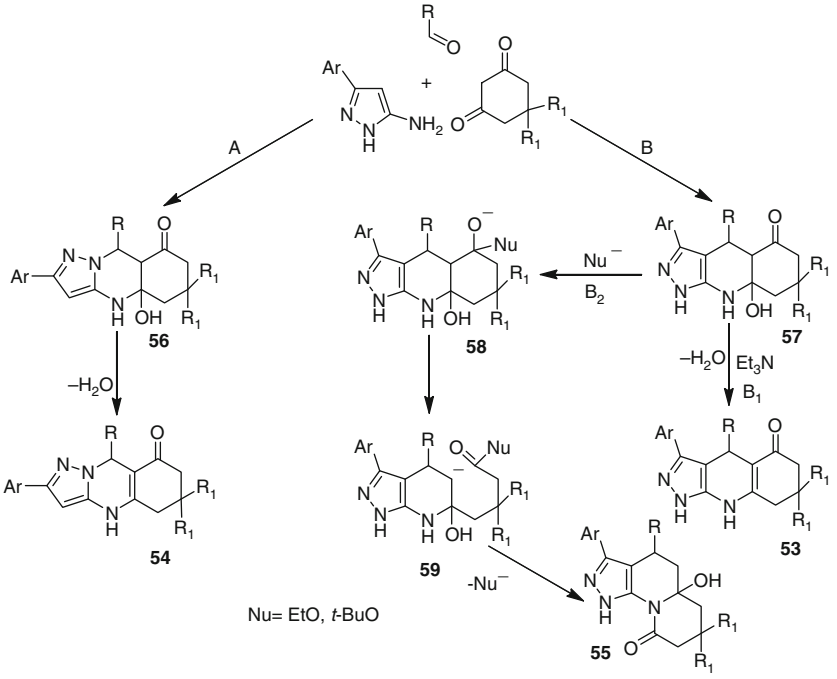
It was reported [59] that temperature in combination with the choice of catalyst is, indeed, the main factor in controlling the direction of this MCR. Under ambient and neutral conditions, the reaction between 5-amino-3-phenylpyrazole, cyclic diketones, and aromatic aldehydes yielded Biginelli-type dihydropyrimidines **54** (Scheme 24). Increase in the reaction temperature with simultaneous addition of triethylamine allowed the reaction to proceed along the thermodynamically controlled pathway with formation of dihydropyrazolopyridines **53**.

It is worth to be noted that Biginelli-like compounds **54** were also obtained by using trimethylsilylchloride as a reaction mediator in combination with acetonitrile as solvent under microwave irradiation [59].

The optimization of regioselective synthesis of quinolinones **53** and the search for the most favorable catalyst for this transformation resulted also in the discovery of a novel MCR involving the ring-opening and recyclization of diketone fragment with subsequent formation of unusual pyrazoloquinolizinone **55** [59] (Scheme 24). It was established that microwave-assisted condensation of the starting materials in ethanol or tert-butanol at 150°C in the presence of an equimolar amount of sodium ethoxide or potassium tert-butoxide led to novel heterocycles **55**, being similar to some natural alkaloids. The preliminary report about this new MCR was made in [60].

Chebanov et al. in [59] offered the key stages of all these three MCRs. According to their hypothesis at room temperature under ultrasonication, the reaction passed via kinetically controlled intermediate **56** with the formation of quinazolinones **54** (Scheme 25). The high-temperature protocol allowed the reaction following via thermodynamically preferable tricyclic intermediate **57**.

The transformation of intermediate **57** was recognized as one of the critical steps defining passing of the reaction either in sub-direction B_1 or in sub-direction B_2 [59]. The nature of the base and its strength plays an important role at this bifurcation. Tertiary bases like triethylamine are not capable to promote C–C bond cleavage and therefore cannot lead to an opening of the cyclic diketone ring and its recyclization. In the presence of such strong bases as sodium ethoxide and



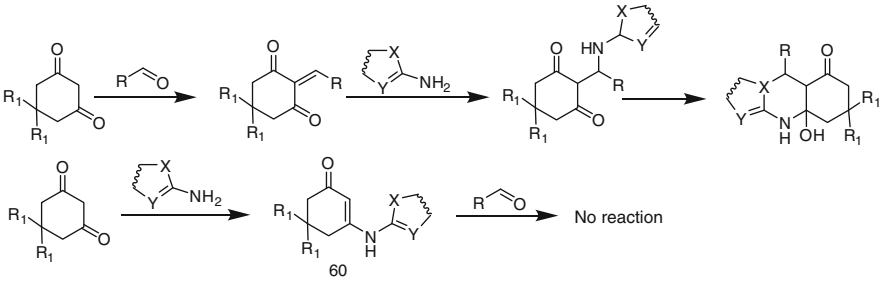
Scheme 25 Key stages for MCRs between 5-aminopyrazoles, aldehydes and cyclic 1,3-diketones

potassium tert-butoxide, the cyclic 1,3-dicarbonyl fragment in **57**, after nucleophilic attack of the base to the carbonyl group, undergoes ring-opening in accordance with the known mechanisms for the cleavage of β-diketones [87, 88].

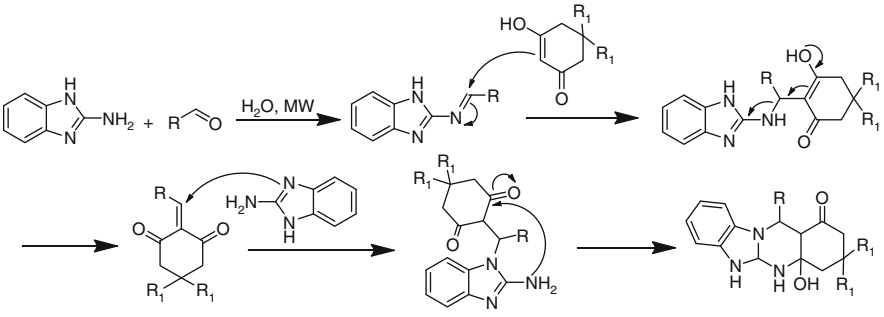
The mechanism of the formation of tricyclic intermediates **56** and **57** is also the important and conflicting matter. For example, Quiroga et al. [83] showed that these MCRs, the most probable, proceed via preliminary Knoevenagel condensation and Michael addition (Scheme 26). At the same time they rejected another pathway including the generation of enamine **60**, because no reaction was observed between it and aromatic aldehyde when their mixture was refluxed in ethanol.

Similar conclusions about mechanism, though without experimental evidences, were made by Shao et al. [89] when they studied microwave-assisted MCR of 2-aminobenzimidazole, aldehydes, and some cyclic 1,3-diketones in water medium (Scheme 27).

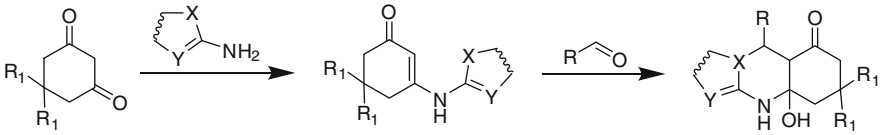
On the other hand, Lipson and co-authors in their publications described numerous MCRs of cyclic β-dicarbonyl compounds and aldehydes with 5-amino-3-methylpyrazole [84], 3-amino-1,2,4-triazole [90], 3-amino-5-methyltio-1,2,4-triazole [91], 2-aminobenimidazole [92], and 2,5-diamino-1,2,4-triazole [93]. It was shown that multicomponent treatments studied in the case of these aminoazoles should proceed via preliminary formation of corresponding enamines, which were isolated and subsequently transformed into target heterocycles (Scheme 28). Intermediates



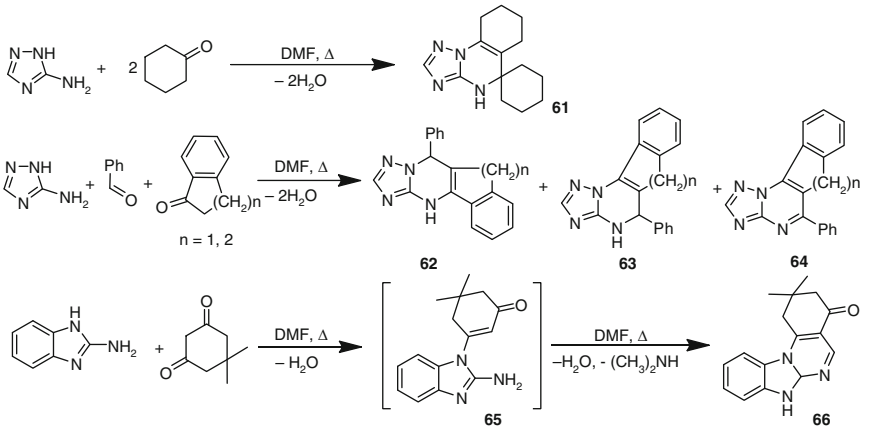
Scheme 26 Possible mechanism of tricyclic intermediate formation



Scheme 27 Microwave-assisted Knoevenagel condensation and Michael addition cascade



Scheme 28 Alternative mechanism of tricyclic intermediate formation



Scheme 29 Formation of angular heterocycles in MCRs

derived from Knoevenagel condensation were not isolated or even observed in these articles.

Besides the different regiodirections described earlier for the MCRs involving amizoazoles and cyclic CH-acids, a problem of positional selectivity in some cases also arises. In the most reactions analyzed, the formation of fused heterocycles with linear polycyclic structure is described, while angular products (such as compound **45** at Scheme 20) were not observed. In some publications an absence of such heterocycles was noted especially [84, 90–93].

One of the first mentions about reaction products with angular structure was published by Desenko and co-authors in [94]. It was shown that multicomponent treatment of 3-amino-1,2,4-triazole with two equivalents of cyclohexanone yielded spiroheterocycles **61** (Scheme 29).

Further, in [95] it was shown that, in the MCR of aminotriazole with benzaldehyde and benzocycloalkanones, in addition to the major product – 4,7-dihydro-l,2,4-triazolo[l,5-a]pyrimidines **62** in yields of 15–25% – isomeric compounds **63** and products of their dehydrogenation **64** were also isolated (Scheme 29).

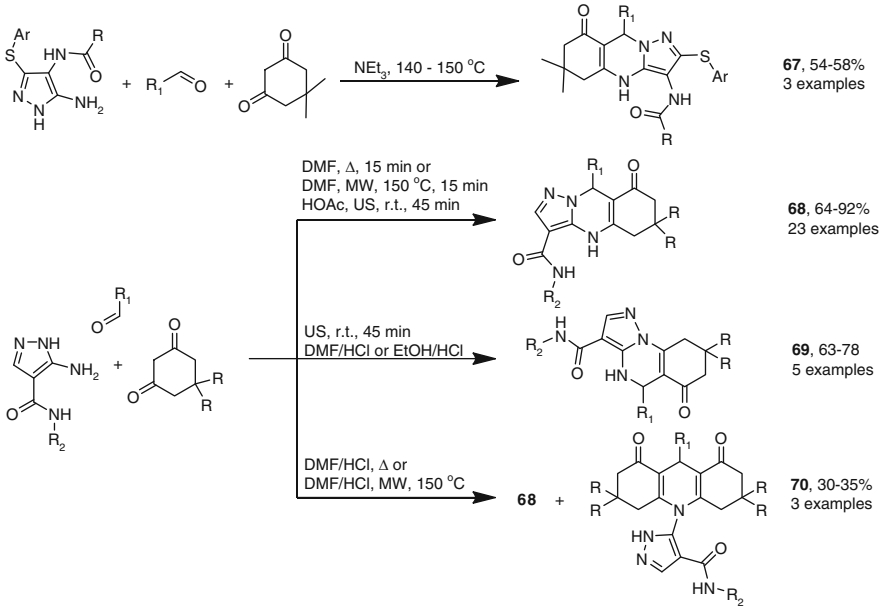
Lipson et al. in several publications [91–93] in the reactions of dimedone and aromatic aldehydes with 2-aminobenzimidazole, 3,5-diamino-1,2,4-triazole, and 3-amino-5-methyltio-1,2,4-triazole described a formation of angular tri- and four-cyclic heterocycles as minor reaction products. However, aldehydes did not participate in these MCRs and the solvent (DMF) acted as a carbonyl component

(see, e.g., compound **66**, Scheme 29). In the opinion of the authors of [91–93], these multicomponent treatments proceeded via enamines of type **65**.

Interesting reagents for such MCRs from the viewpoint of selectivity tuning are 5-aminopyrazoles containing carboxamide substituent. In the first article concerning the behavior of these aminozoles in the reactions with cyclic 1,3-diketone and aldehydes, it was found that only one direction of the treatment leads to tricyclic Biginelli-like heterocycles **67** (Scheme 30) [96].

However, further a possibility of the formation of several different reaction products in similar processes was reported [97–99]. With the help of microwave irradiation and ultrasonication, the problem of selectivity was also touched in these communications. It was found that three-component reaction of equimolar mixture of 5-amino-*N*-arylpyrazole-4-carboxamides, aldehydes, and cyclic β-diketones in DMF under conventional thermal heating or under microwave irradiation at 150°C yielded pyrazoloquinazolines **68**. The treatment at room temperature under ultrasonication gave the same reaction products, although addition of catalytic amounts of hydrochloric acid changed direction and positional isomeric quinazolines **69** were only isolated in this case.

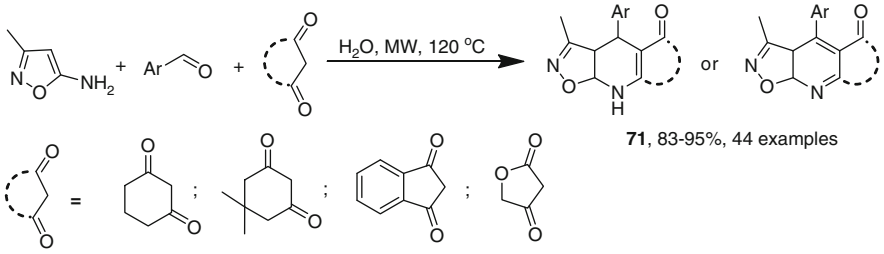
It is very important that this preparative procedure allowed selective synthesis of Biginelli-like fused dihydropyrimidines of type **69** having angular structure. As everyone can see from the other publications cited above in other cases, these heterocycles were usually minor reaction by-products. The third direction discovered in [97–99] led to acridinediones **70** (Scheme 30).



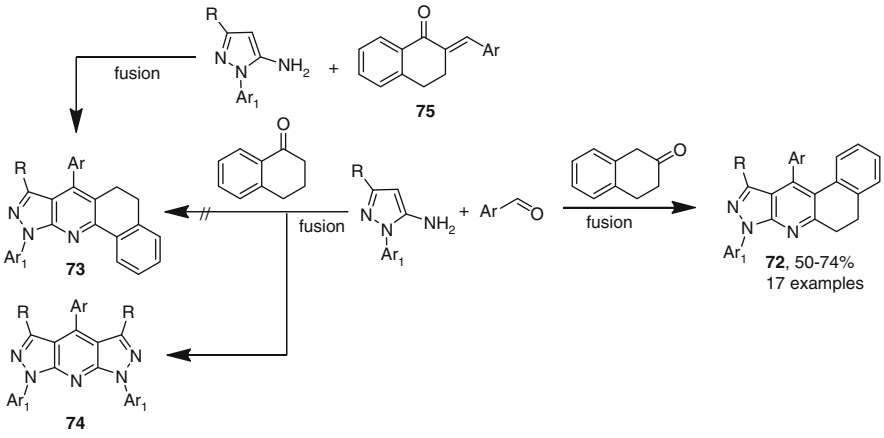
Scheme 30 Tuning of selectivity of MCRs involving carboxamide containing 5-aminopyrazoles

To carry out MCRs of aminoazoles with aldehydes and cyclic CH-acids, the methods of "green chemistry" were also applied. For example, treatments of 3-methylisoxazol-5-amine and aromatic aldehydes with 1,3-cyclohexanedione, dimedone, 1,3-indanedione, or titronic acid were proceeded in water under microwave irradiation at 120°C [100] (Scheme 31). As a result, clean, efficient, and convenient procedures for the generation of polycyclic-fused isoxazolo[5,4-b] pyridines **71** were developed. An interesting fact is that, in the case of 1,3-cyclohexanedione, dihydropyridines were obtained while in all other cases only heteroaromatized derivatives were isolated. No reason for this experimental fact was discussed in the article.

Quiroga and co-authors [101] also reported eco-friendly solvent-free approach to the synthesis of fused benzo[f]pyrazolo[3,4-b]quinolines **72** by three-component reaction of 5-aminopyrazoles, aldehydes, and β-tetralone accomplished by fusion procedure (Scheme 32). However, this method was found inapplicable for the similar reaction of α-tetralone – multicomponent procedure allowed obtaining only bispyrazolopyridines **74** instead of benzo[h]pyrazolo[3,4-b]quinolines **73**. According to these experimental results, the latter were generated via preliminary synthesis of arylidentetralones **75**.



Scheme 31 MCRs based on "green chemistry" methods



Scheme 32 Tetralones in MCRs with aminoazoles

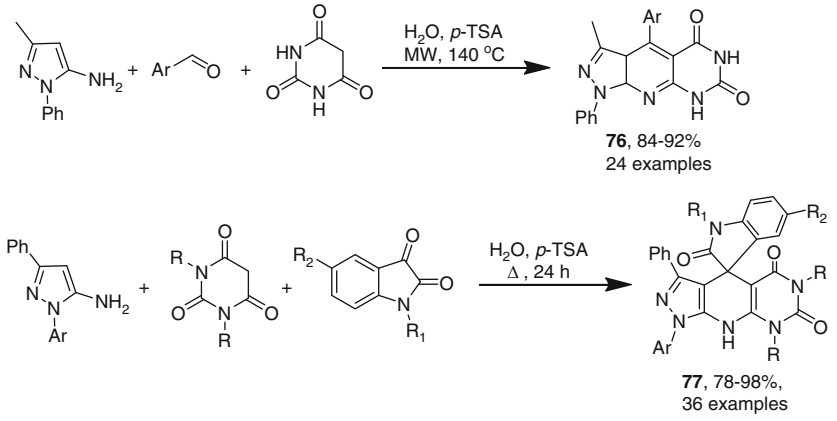
Barbituric acid and its derivatives are other cyclic 1,3-dicarbonyl reagents playing significant role in medicinal-oriented chemistry as well as in material science. Fused heterocyclic compounds having pyrazole, pyridine and pyrimidine moieties simultaneously showed wide spectrum of application such as antimycobacterial, fungicidal, anticancer, antihistamic and anticonvulsant agents [102–106], colorants [107, 108], and photographic couplers [109]. Some derivatives of pyrazolopyridopyridines have also been found to be useful in agriculture [110].

The first positive results in the synthesis of these heterocyclic compounds by MCR of aminoazoles, aldehydes, and barbituric acids were published in 2008 by Shi et al. [111]. They also used "green chemistry" methodology and carried out treatment of the starting materials in water under microwave irradiation. The temperature optimization procedure and search for the best catalytic system allowed selecting one equivalent of *p*-TSA and 140°C as optimum conditions for the synthesis. With application of the procedure elaborated 24 novel pyrazolopyridopyrimidines **76** were generated (Scheme 33).

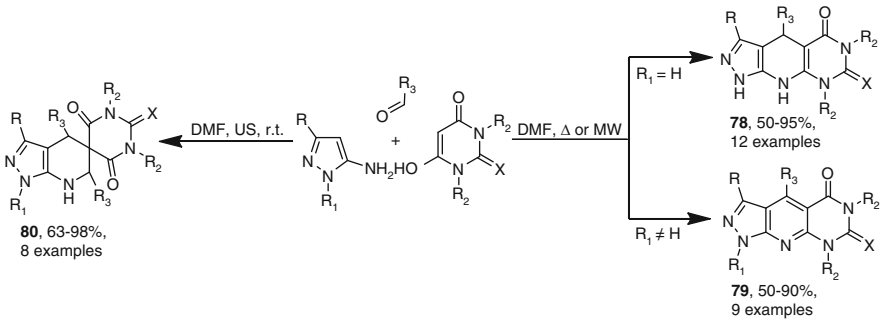
Water-based "green" protocol under conventional heating was used in another publication [112] to carry out three-component treatment between 3-substituted 5-aminopyrazoles, barbituric acids, and several isatines. The reaction gave up required spiroheterocycles **77** in excellent yields and purity (Scheme 33).

The detailed study of the MCRs involving barbituric acids and 5-aminopyrazoles was published by Muravyova et al. [58]. The article describes the development of chemoselective cyclocondensations with help of microwave and ultrasonic irradiation. It was established that the temperature was the main factor in controlling the direction of the MCRs studied.

At high temperatures (170–190°C) the starting materials reacted in two different ways. Surprisingly, it was found that substituent in the position 1 of aminopyrazoles sufficiently influenced the structure of the reaction products. In the case of N-substituted aminopyrazoles (both with electron-withdrawing and with electron-releasing R_1-groups), the reaction yielded pyrazolopyridopyrimidines **79**



Scheme 33 MCRs involving barbituric acids



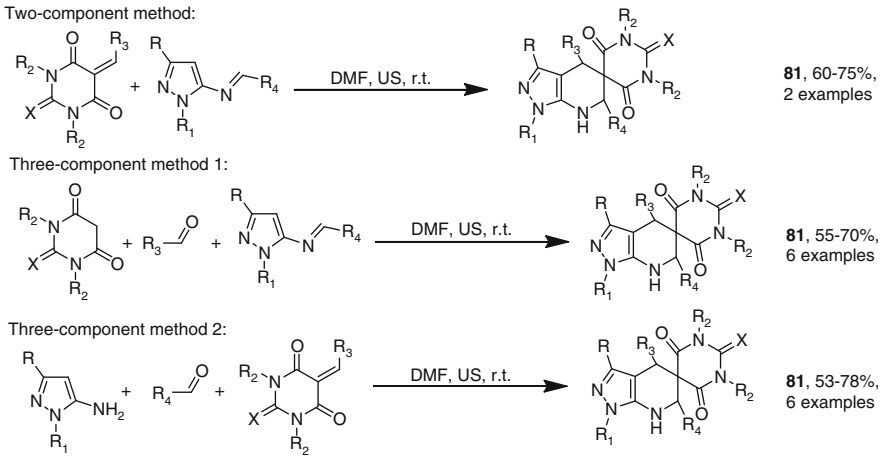
Scheme 34 Selectivity tuning for MCRs involving barbituric acids

(Scheme 34). When $R_1 = H$, MCRs under high temperature in DMF always gave dihydroderivatives **78**. Another interesting facts concerned microwave-assisted treatment. Application of controlled MW irradiation (temperatures from 150 to 190°C) to carry out MCR involving N-unsubstituted pyrazoles did not give any positive result and led to complicated mixture of several inseparable products. However, using microwave field to promote the reaction when $R_1 \neq H$ was successful. The most preferable microwave-assisted procedure for the synthesis of compound **79** from the viewpoint of their yields and purity consisted in the treatment of the starting building-blocks in DMF under microwave irradiation at 190°C for 3 min.

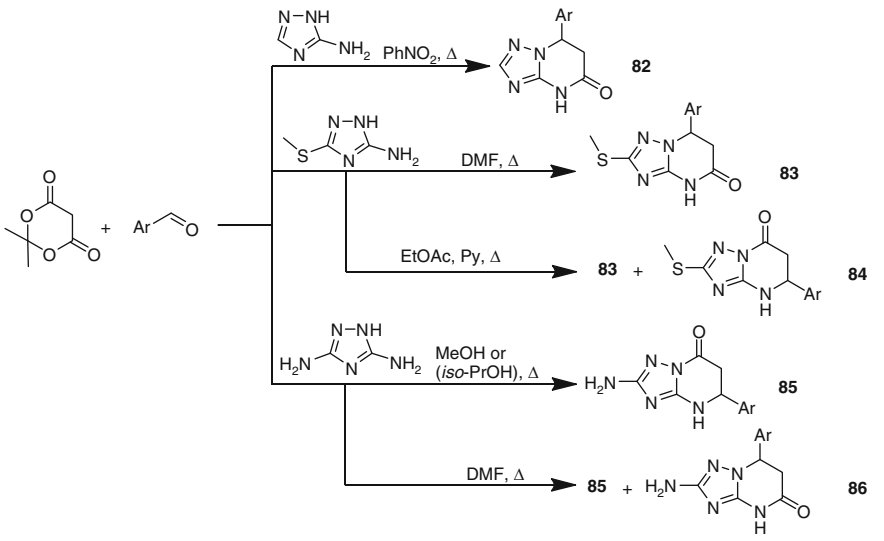
On the other hand, unexpectedly it was additionally established that the same MCR at room temperature under ultrasonication or with the help of simple stirring yielded novel type of spirocompounds **80** in 63–98% yields (Scheme 34). Biginelli-type dihydropyrimidines observed in similar processes involving cyclic 1,3-diketones [59] (Scheme 24) were not isolated.

To avoid the main limitation of the new four-component reaction – the impossibility to introduce two different substituents R_3 in positions 4 and 6 of heterocycle – additional two-component procedure consisted in the reaction of corresponding arylidenbarbituric acids and azomethines was developed (two-component method, Scheme 35) [58]. However, this method requested a preliminary synthesis of two starting compounds, making the procedure less efficient and facile. For reasons given, two three-component approaches to target compounds **81** were additionally offered and optimized. The spiroheterocycles were obtained by the treatment of azomethines with barbituric acids and corresponding aromatic aldehydes (three-component method 1, Scheme 35) or by the reaction of arylidenbarbituric acids, 5-aminopyrazoles, and aldehydes (three-component method 2, Scheme 35).

In MCRs involving aminoazoles and carbonyl compounds, Meldrum's acid can also be used as reagent. The comprehensive review of the application of Meldrum's acid in the synthesis of pyridine and pyrimidine derivatives including reactions with aminoazoles was recently published [113]. In this connection, further we give only few selected facts concerning positional selectivity of such reactions.



Scheme 35 Alernative procedures for the sysnthesis of spiroheterocycles



Scheme 36 MCRs of Meldrum's acid

Significant contribution in the studying of the MCRs based on aminoazoles, aldehydes, and Meldrum's acid was made by Lipson and co-authors in their publications [114–119]. It was established that in some cases these multicomponent treatments can yield positional isomers. For example, refluxing of 3-amino-1,2,4-triazole with aldehydes and Meldrum's acid gave only triazolopyrimidinones **82** [114] (Scheme 36). On the other hand, MCRs involving 3-amino-5-methylthio-1,2,4-triazoles in boiling DMF yielded solely 5-pyrimidinones **83**, while the

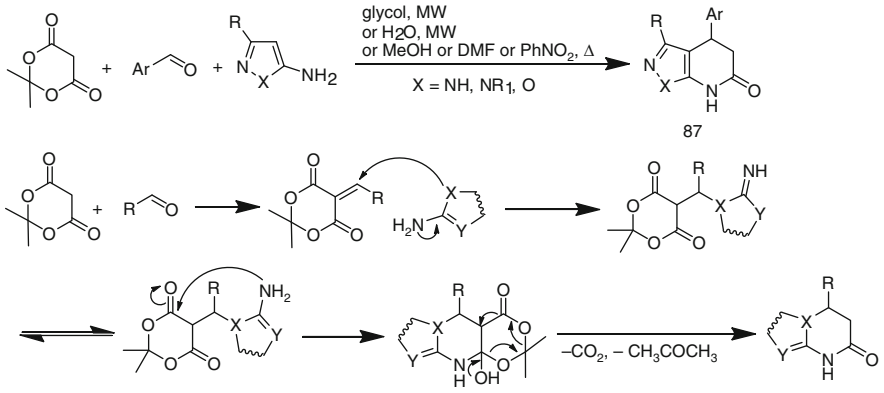
treatment in ethylacetate with catalytic amounts of pyridine led to positional isomeric 7-pyrimidineos **84** in mixture with **83** [116].

In the case of 3,5-diamino-1,2,4-triazole, the situation was different: refluxing in DMF gave two isomers **85** and **86** while application of methanol or iso-propanol as reaction medium allowed obtaining only one reaction product – heterocycles **85** (Scheme 36) [115]. Selective MCR with the formation of corresponding 7-pyrimidinenone was also observed when 3-amino-1,2,4-riazoles and Meldrum's acid reacted with ketones instead of aldehydes.

5-Aminopyrazoles and other aminoazoles having CH-nucleophilic center in MCRs with Meldrum's acids and aldehydes in boiling primary alcohols, DMF, or nitrobenezene [119, 120] as well as in glycol [121] or in water [100] under microwave irradiation yielded exclusively azolopyrimidineones of type **87** (Scheme 37).

The mechanism of these MCRs involving Meldrum's acid should include Knoevenagel condensation and Michael addition cascade process [100, 113] (Scheme 37). To form positional isomeric reaction product, arylliden derivatives of Meldrum's acid are attacked by exocyclic NH_2-group instead of endocyclic nucleophilic center.

Some other publications and patents are also devoted to the MCRs of aminoazoles and carbonyl compounds with cyclic CH-acids and concern particular matters of this chemistry. For example, Drizin and co-authors dealt with medicinal-oriented synthesis based on three-component reactions of cyclic 1,3-diketones, aminopirazoles, and aldehydes [86, 122, 123]. To study anticancer activity of indenopyridines, Manpadi et al. [124] carried out numerous three-component reactions of indane-1,3-dione with aldehydes and different aminozoles in diverse solvents. Among other significant synthetic and biological results, they described the formation of target heterocycles with participation of nitrogen atom in position 4 of 3-amino-1,2,4-triazole. However, no strong evidence of this unusual direction was given in the article.



Scheme 37 Possible mechanism of MCRs involving Meldrum's acid

2.2 *Groebke-Type Heterocyclizations*

In the 1998, Groebke [125], Blackburn [126], and Bienayme [127] independently reported an efficient method for the synthesis of imidazo[1,2-a]annulated heterobicyclic compounds.

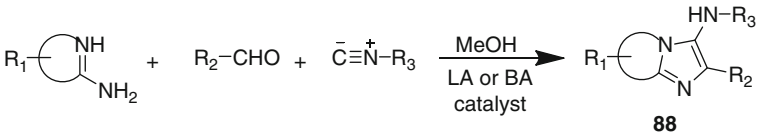
By carrying out the Ugi-reaction with a large number of isonitrils, aldehydes, carboxylic acids, and amines, it was found that formation of different products of the reaction occurred depending on the structure of the amines used. Thus, 3-aminoimidazoles **88** were isolated when aldehyde reacted with isocyanide and heterocyclic aromatic 2-aminoazine as primary amine (Scheme 38).

This new three-component condensation was performed in the presence of either Brønsted (e.g., perchloric [127] or glacial acetic acid [125]) or Lewis acids [126] in methanol at room temperature giving the desired fused imidazoles in good yields and was defined as Ugi-type 3-CR or Groebke reaction [128].

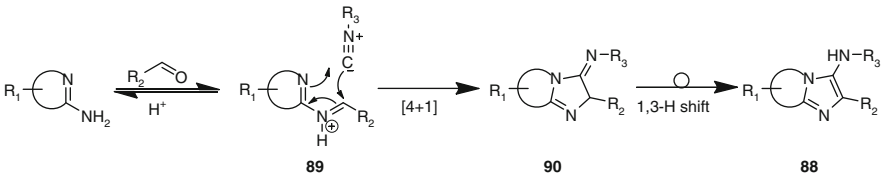
The formation of bicycles **88** occurred through the iminium intermediate 89, in the similar manner as Ugi-reaction. But in contrast to the four-component classical Ugi-reaction, the protonated Schiff base **89**, containing both nucleophilic and electrophilic centers, undergoes [4+1] cycloaddition with isonitrile to the bicyclic adduct **90** followed by rearomatization via 1,3-H shift (Scheme 39).

However, this method possesses several disadvantages such as long reaction time and complicated work-up procedure. For example, in the case of $Sc(OTf)_3$-catalyzed reaction, the treatment required 72 h to get completed at the ambient temperature. After that a pure product was isolated from the reaction mixture by the capture of the solid phase by using strongly acidic cation exchange resin, followed by washing of the solvent and final treatment of resin with 2 M methanolic ammonia.

Later, to improve this powerful MCR synthetic methodology on the way to the combinatorial arrays of therapeutic important moieties, nonclassical approaches were applied. The reactions were carried out under microwave irradiation in the



Scheme 38 Geoebke-type heterocyclizations



Scheme 39 Mechanism of Groebke-type heterocyclizations

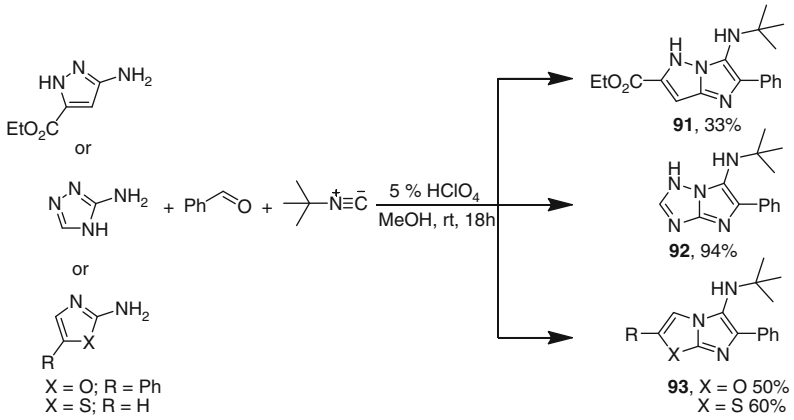
presence of $Sc(OTf)_3$ [129]. Solvent-free microwave facilitated version on the clay (Montmorillonite K10) was also reported [130]. In addition, to disfavor the formation of unwanted side-products, Groebke reaction has been performed using non-polar solvent [131, 132] and involving environment-friendly reagents such as water [133] and ionic liquids [134]. Interesting results were achieved in the field of solid-supported synthesis of fused imidazoles by the application of resin linker, anchored with any of the three components [135–137].

Among the Groebke reaction products, the diversity imidazo[1,2-a]annelated azoles were synthesized. An interest on these bicycles is closely related due to their known pharmacological properties. For instance, it has been reported that compounds containing imidazo[2,1-b][1,3]thiazole moiety possess anthelmintic, fungicidal, herbicidal, antitumor, antihypertensive activities [133 and references therein] while imidazo[1,2,4]triazole derivates have been used as antiflammatories, antifungicides, antimicrobial agents and analgesics [138 and references therein].

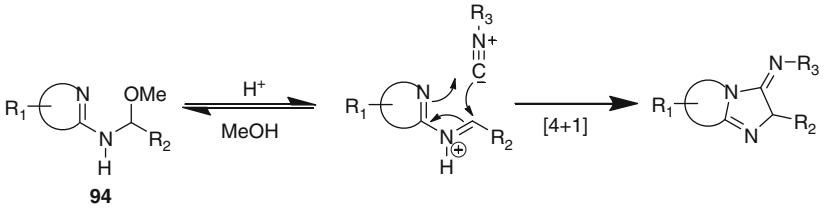
Several imidazo[2,1-b][1,3]thiazoles based on 2-aminothiazoles were successfully prepared by stirring in methanol at ambient temperature in the presence of $HClO_4$ as a catalyst [127]. Additionally, it was shown that Groebke reaction involving 2-aminopyrazoles, 2-aminooxazoles, and 3-amino-5-unsubstituted-1,2,4-triazoles also led to the desired products **91**–**93** (Scheme 40).

The authors noted about the influence of electronic nature of 2-aminoazoles on the reaction efficiency. By the treatment of electron-deficient aminoazoles such as 2-aminothiadiazoles or 2-aminooxazoles, the low conversion of the reaction was observed. As an explanation of this outcome they supposed that the reactions in these cases occurred very slowly and the competing reaction processes did not take place. As a result the formation of side-products is favored, one of which might be the compound **94** (Scheme 41).

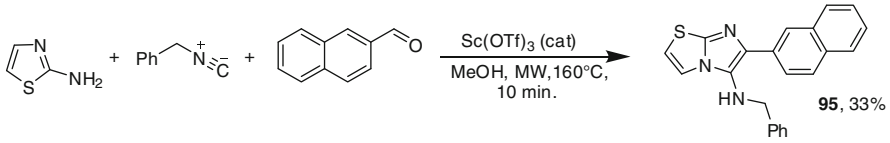
Indeed, the application of less nucleophilic solvent than methanol (e.g., trifluoroethanol) was found to be successful for the improvement of the reaction conversion level and helped to prevent the side-reactions.



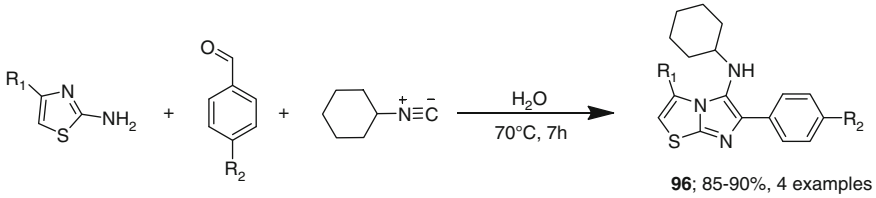
Scheme 40 Synthesis of imidazoazoles



Scheme 41 Side-products in Groebke-type heterocyclization



Scheme 42 MCR of 2-aminothiazole with benzylisocyanide and naphthaldehyde



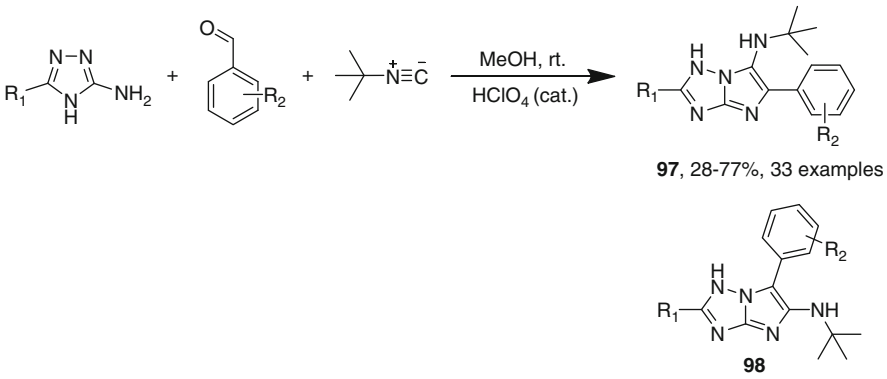
Scheme 43 Water-based procedure for the synthesis of imidazothiazole

However, attempts from the authors of [125] to synthesize fused imidazoles involving isoxazols, pyrazols, or 1,3,5-triazols as primary amines in the presence of catalytic amounts of glacial acetic acid were unsuccessful and led either to the formation of complex product mixtures or even to the formation of Ugi-type four-component condensation compounds in low yields.

The problem of the reduced reaction conversion was discussed in [129] when the attempts to promote the reaction of 2-aminothiazole with benzylisocyanide and naphthaldehyde by microwave irradiation coupled with catalyst were undertaken. But the desired imidazothiazole **95** was obtained only in 33% within 10 min at 160°C (200 W MW power) in methanol (Scheme 42).

Another example of imidazo[2,1-b][1,3]thiazole formation was reported by Adib et al. in their publication concerning eco-friendly catalyst-free MCR in the water [133]. Reaction of cyclohexyl isocyanide with diverse aromatic aldehydes and 2-aminothiazoles in water at 70°C allowed the isolation of heterocycles **96** in good-to-excellent yields (Scheme 43). According to the spectral data, compounds **96** were determined as single products of the MCR.

On the way to the investigation of the structure–activity relationship Huang et al. [138] performed the MCRs involving diverse-substituted 3-amino-1,2,4-triazoles,



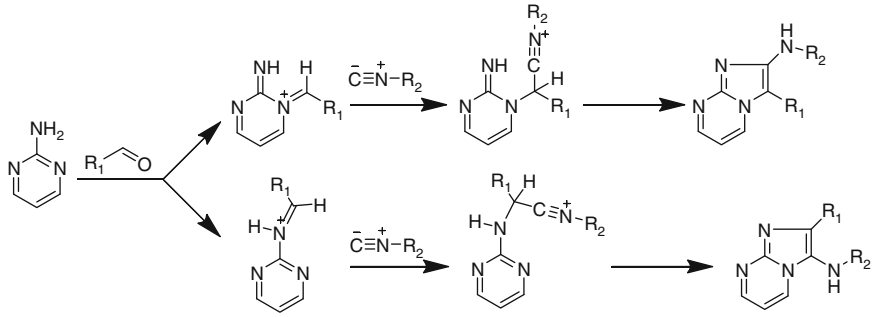
Scheme 44 Synthesis of highly substituted imidazotriazoles

aromatic aldehydes, and tertbutylisonitrile. The desired imidazo[1,2-b]-1,2,4-triazol-6-amines **97** were synthesized according to the known procedure [127] with moderate-to-good yields (Scheme 44).

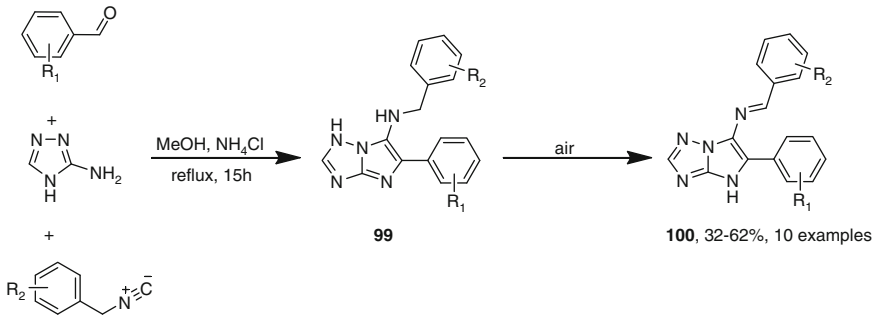
The results obtained showed that both the electron nature of the substituents in 3-amino-1,2,4-triazoles and a space effect of substituents in the aldehyde had an influence on the MCRs' yields. Thus, the presence of electron-donating groups in imidazoles (e.g., R = CH_3 compared to the R = H) led to a slight increase in the reaction conversion level. At the same time the electron-deficient groups (e.g., C_6H_5, 4-HalC_6H_5) accumulate the reactivity of aminotriazoles. On the other hand, the higher yields of heterocycles **97** in the case of o-substituted aryl aldehydes compared to the m- and p-substituted were explained only through the bulky effect disregarding the electron effects. However, moving out of the published results, it is not so obvious.

In addition, we should note that data of ^{1}H, ^{13}C NMR spectroscopy, mass-spectra, and elemental analysis given in [138] did not contradict the structure of compound **98**, being regioisomer of **97**. The similar situation had already been shown in the synthesis of 3-aminoimidazo[1,2-a]pyrimidines [139]. Mandair et al. carried out the model MCRs of 2-aminopyrimidine with several aldehydes and isonitrile components in the methanol under the ambient temperature with the various catalysts. As a result, 3-aminoimidazo[1,2-a]pyrimidine and position isomeric 2-aminoimidazo[1,2-a]pyrimidines were isolated from the reaction mixture in different ratio (Scheme 45). The structures of the isomers obtained in this case were confirmed by the X-ray diffraction analysis, as well as the structures of the side-products isolated.

Later Parchinsky et al. [131] showed that Groebke reaction promoted by ammonium chloride as mild catalyst, often employing the Ugi-reaction, in the non-nucleophilic aprotic solvent (e.g., toluene) led to the formation of exclusively one product of the reaction – 3-alkylamino-substituted imidazo[1,2-a]pyrimidines, while the formation of unwanted side-products was excepted in this method.



Scheme 45 Formation of position isomers in Groebke-type reactions



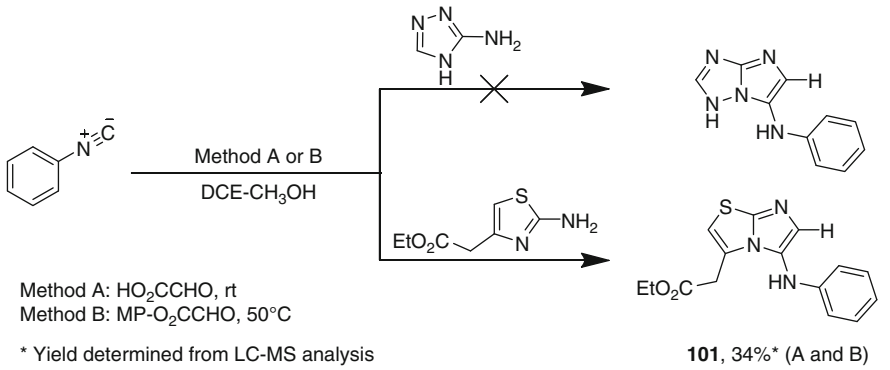
Scheme 46 MCRs involving aliphatic nitriles

In continuation, the same authors published the similar efficient method for the synthesis of imidazo[1,2-b][1,2,4]triazoles, an example of which had already been known and discussed before [140]. A number of aliphatic nitriles were reacted with 3-amino-1,2,4-triazole and diverse benzaldehydes in methanol under refluxing for 15 h in the presence of ammonium chloride (Scheme 46).

Additional dilution with water followed by the simple filtration of the resulting precipitate and recrystallization yielded the oxidized product of Groebke reaction *N*-alkylideneimidazotriazoles **100**, whose structure was confirmed with the help of X-ray diffraction analysis. The authors supposed that removal of two hydrogen atoms at the N–H and C–H bonds occurred due to the air-oxidation of the benzylic group of the initial MCR's product **99**.

However, when simple aliphatic isonitriles (e.g., isobutyl- or 2-(methoxy)ethyl-isonitriles) were introduced in the reaction, the complex mixtures of several products were obtained without the possibility of individual compound isolation.

On the way to the 2-unsubstituted 3-aminoimidazo[1,2-a]heterocycles, Lyon and Kercher [141] suggested interesting approach involving glyoxylic acid as formaldehyde equivalent in the three-component reaction. According to the standard protocol, glyoxylic acid was introduced either in solution or captured on the macroporous



Scheme 47 Limitation of Groebke-type MCR

polysterene carbonate resin and left in both cases the similar yields of the reaction, which allowed for the versatile experimental application of this method.

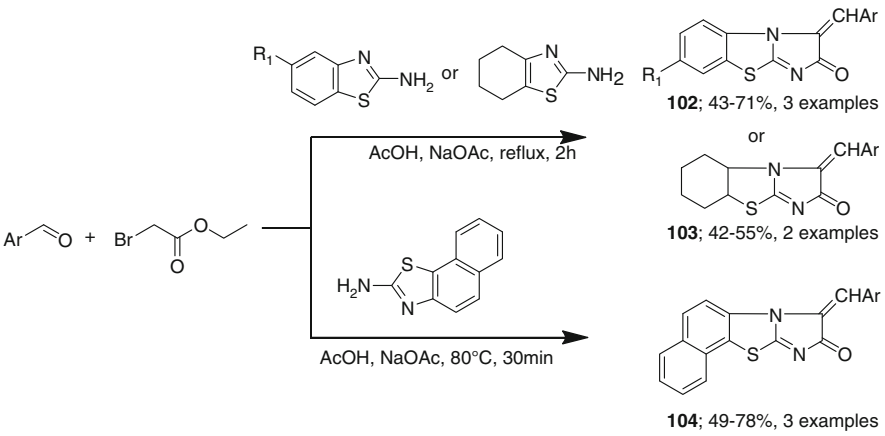
Among binucleophiles used in this reaction 3-amino-1,2,4-triazole and 2-aminothiazole were also selected. However, in the reaction of the latter with phenyl isonitrile and formaldehyde, only the moderate yields of the target product **101** were observed by the LC-MS analysis of the crude reaction mixture. In case of aminotriazole, any product of the reaction was failed to be detected (Scheme 47).

2.3 Other Types of Heterocyclizations

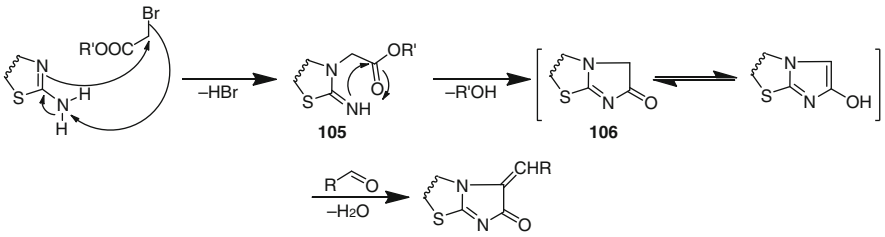
Here we discuss several examples of the multicomponent processes involving aminoazoles, aldehydes, and other organic components such as mercaptoacids, haloacetic acids and their ester, α,β-unsaturated imines, etc., which were not incorporated into the previous two sections of the review.

The previously published results [142, 143] devoted to the synthesis of thiazolo [3,2-a]imidazol-2-ones attracted attention of Krasovskii et al. [144] to synthesize corresponding ylidene derivates and to investigate biological activities, promising to be interesting for the medicinal chemistry. By heating 2-aminothiazoles with ethyl bromacetate and a variety of aromatic aldehydes at the appropriate temperature (either 80°C or reflux) in the glacial acetic acid with anhydrous sodium acetate, ylidene derivates of structures **102–104** were isolated (Scheme 48).

The key step of this MCR according to the opinion of the authors is an interaction of bromacetic ester with aminoazole via ring nitrogen atom to the 3-carboxymethyl-2-iminothiazoline **105**, also isolated as a product in the steps-sequence reaction (Scheme 49). Further cyclization of **105** leads to the formation of thiazolo[3,2-a] imidazol-6-one **106**, which then reacts with aldehyde affording the desired ylidene in moderate-to-good yields.



Scheme 48 MCRs involving bromacetic esters



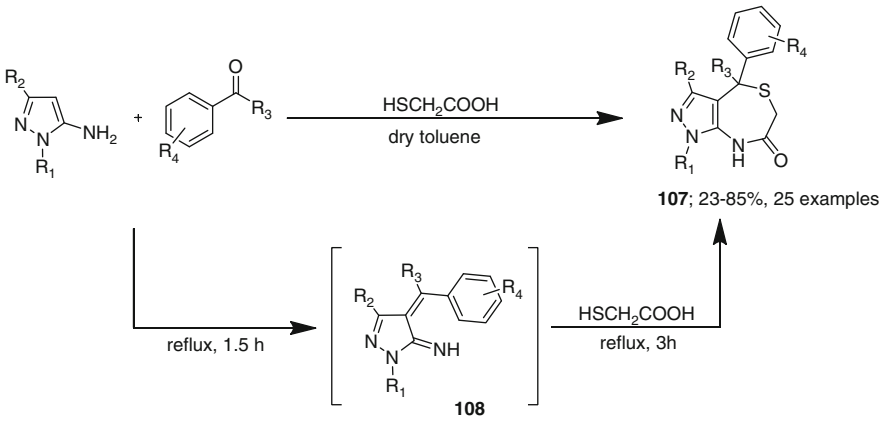
Scheme 49 Mechanism of MCRs involving bromacetic ester

In addition, the results of biological tests of the compounds synthesized showed that only one possessed the high antiviral activity against adenovirus type 23 and several of them had moderate-to-week activities towards Gram-positive bacteria and pathogenic fungi, whereas the rest of compounds were inactive.

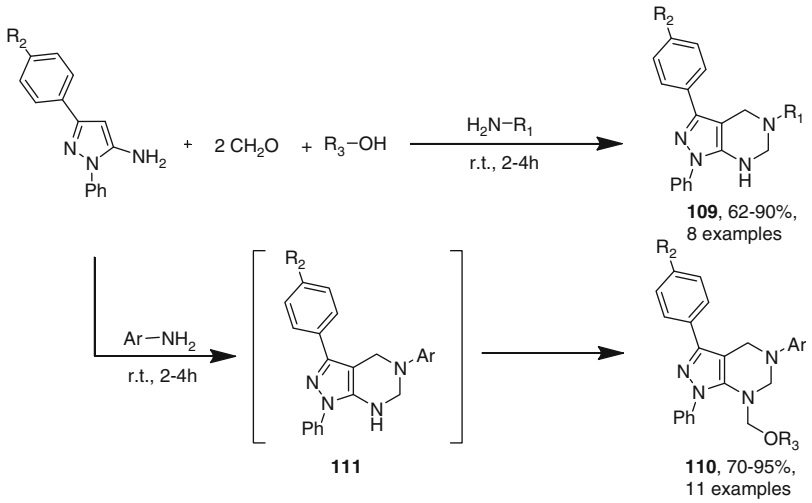
Mercaptoacids were successfully applied in the MRCs with aminozoles on the way to the novel sulfur containing seven-membered heterocycles [145–147]. Thus, condensation of 5-aminopyrazoles with mercaptoacetoacid and aromatic ketones or aldehydes resulted in the formation of pyrazolothiazepines **107** (Scheme 50).

Swett et al. [145] suggested the reaction that most likely occurred through the formation of intermediate **108** though they were unable to isolate it. However, the authors of [148] by the step-sequel performance of the same reaction obtained the imine **108** as a sole product of the treatment. Its rapid condensation with mercaptoacetoacid led to the desired 7-membered bicycle **107**.

Hozien et al. in their publication [149] studied the Mannich-type cyclization of 5-aminopyrazoles with formaldehyde and diverse amines. It was shown that treatment of 5-aminopyrazoles with primary aliphatic amines and formaldehyde in the ethanol under the ambient temperature gave 1,3,5-trisubstituted tetrahydropyrazolo



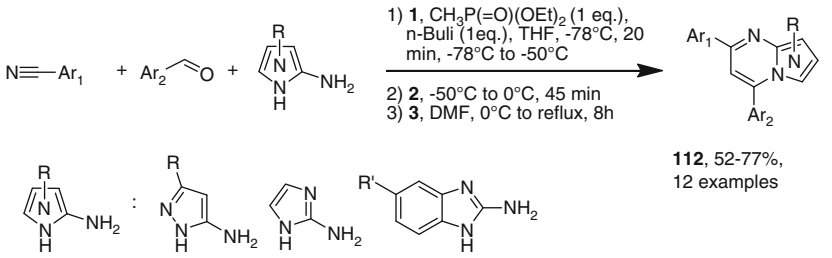
Scheme 50 Multicomponent synthesis of pyrazolothioazepinons



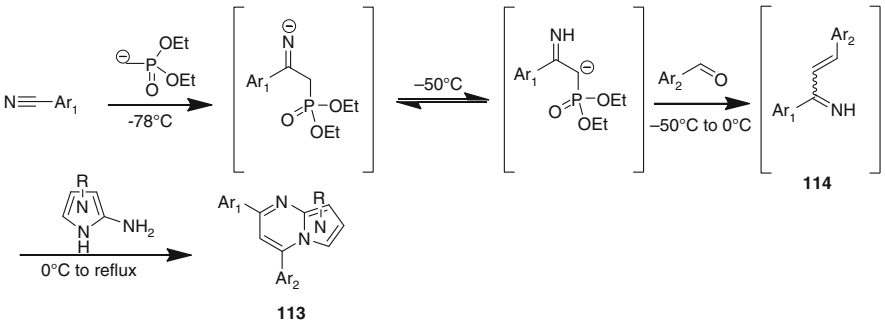
Scheme 51 Mannich reactions of aminopyrazoles

[3,4-d]pyrimidines **109** in good yields. However, when 5-aminopyrazoles were introduced in the Mannich reaction using aromatic primary amines, compounds of structure **110** were isolated (Scheme 51). The authors suggested the formation of **110** through the second condensation of intermediate **111** with formaldehyde and ethanol, methanol, or propanol, which were used as solvents for this reaction.

In addition, an interesting treatment of in situ-generated α,β-unsaturated imines with aminoazoles was described in [150]. This one-pot procedure yielded the anticipated pyrazolo[1,5-a]- and imidazo[1,2-a]pyrimidine derivates **112** (Scheme 52).



Scheme 52 MCRs proceeding via unsaturated imines formation



Scheme 53 Mechanism of the MCRs via formation of unsaturated imines

The authors noted the regeoselective character of this treatment – only one regioisomer was always isolated from the reaction mixture. Furthermore, a precise temperature control and solvent choice are decisive factors for the successful outcome of the reaction.

The abovementioned transformation proceeds via initial formation of α,β-unsaturated imines **114** from the starting aromatic nitriles, which then undergo the further nucleophilic attack at C_3 atom by the exocyclic amino group of aminoazole followed by the cyclization and aromatization and yielding the observed products **113** (Scheme 53).

3 Aminoazoles as 1,1-Binucleophiles

As it has been already mentioned in the Introduction, aminoazoles besides the role of 1,3-binucleophiles can take part in the MCRs as 1,1-binucleophiles with participation of exclusively exocyclic NH_2-group. Usual products of such multicomponent interaction are five-membered heterocycles having azole ring as a substituent.

Other reactants incorporated in this type of reactions are generally carboxylic acids or their derivates and aldehydes. There are also several publications concerning the MCRs involving aminoazoles as 1,1-binuclephiles, CH-acids, and carbonyl compounds passing in alternative to those previously discussed pathways [51, 52, 151].

One of the most studied and well described reactions involving 2-aminoazoles as 1,1-binucliophile lead to the 3-substituted thiazolidin-4-ones which are well known in medical chemistry as a fragment of natural products or as pharmaceutical substances having wide range of pharmacological activities [152–161]. On the other hand it is known that some aminoazoles also possess some types of activities, for example against tumors [162, 163]. Thus, idea to combine both biological active fragments in one novel drug-like scaffold has attracted attention of several chemical groups over the world.

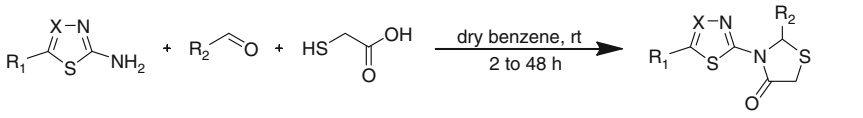
Attempts to perform synthesis of 3-substituted thiazolidinones by the MCR of 2-aminoazoles with mercaptoacetic acid and aldehydes were described by Grasso et al. [164–166].

For instance, the treatment of 2-aminothiazole or 2-amino-1,3,4-thiadiazole with a equimolar amounts of appropriate (hetero)aromatic or aliphatic aldehydes in the presence of an excess of mercaptoacetic acid under refluxing in anhydrous benzene gave diverse 2-substituted 3-(2-thiazolyl)- and 3-[2-(1,3,4-thiadiazolyl)]-4-thiazolidinones **115a** or **115b**, respectively (Scheme 54).

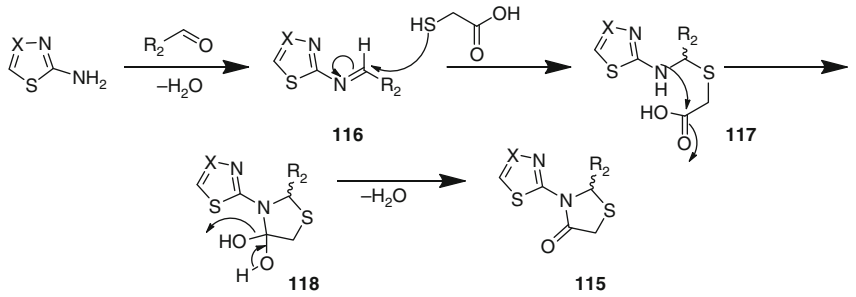
Formation of compounds like **115** seems to have occurred in the similar way as it was established for anilines and other primary amines [167]. The initial step of this reaction is treatment of aldehyde with aminozole giving Schiff base **116**. Further, nucleophilic attack of imine carbon by mercapto moiety of the acid leads to the intermediate **117** and its subsequent cyclization via gem-diol **118** yields target heterocycles **115** (Scheme 55).

This mechanism of heterocycles **115** formation is in good correlation with data of other publications [168–171].

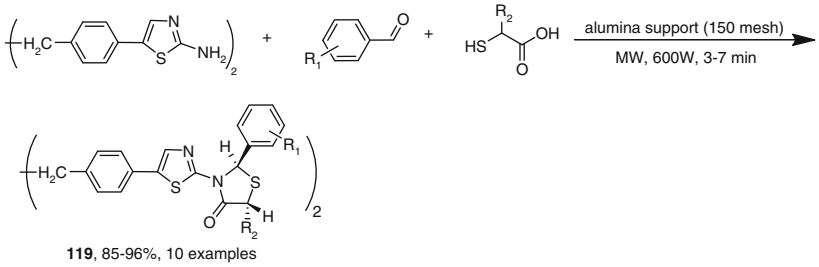
According to the results obtained from the biologic studies, several SAR tendencies were established [167]. By the evaluation of anticancer activities towards tumor cells, the authors found that thiazolyl derivates were generally less active in comparison with thiadiazolyl-containing compounds. The introduction of alkyl fragments in the position 2 of 4-thiazolidinone ring to increase the lipophilicity of the molecule seems to influence the activity negatively.



Scheme 54 Synthesis of azolyl-4-thiazolidinones



Scheme 55 Mechanism of the MCR leading to azolyl-4-thiazolidinones



119, 85-96%, 10 examples

Scheme 56 Microwave-assisted solid-supported of some analogs of fungitoxic dibenzyles

In addition, several 3-thiadiazolyl-4-thiazolidinones were prepared by refluxing of the corresponding starting compounds in dry toluene during 24 h and then evaluated for possessing anti-HIV-1 properties by the comparison of their ability to bind to the alosteric side of the reverse transcriptase (RT) and to inhibit enzyme activity [172, 173]. The results of in vitro tests showed that several compounds had higher HIV-1-RT activity with minimal toxicity as well as higher selectivity index compared to the reference molecule (thiobenzimidazole). It was associated with a flexible conformation of thiadiazolyl derivative, allowing the more efficient binding to the non-nucleoside TR inhibitory binding pocket [172].

To decrease the reaction time required for the conventional treatment (from 2 up to 48 h) and to improve the conversion level of the reaction, microwave irradiation was successfully applied for obtaining 4-thiazolidinones substituted with azole ring. Siddiqui et al. [174] reported the efficient microwave-assisted solid-supported approach for one-pot diastereoselective synthesis of some analogs of fungitoxic dibenzyles.

To reach this target, bis-aminothiazoles, aromatic aldehydes, and 2-mercapto-propionic acid or 2-mercaptosuccinic acid were adsorbed on the neutral alumina support and were microwave-irradiated under solvent-free conditions (Scheme 56). The authors reported the high level of the reaction conversion, which gave the desired products **119** in excellent yields for a rather short time (up to 7 min).

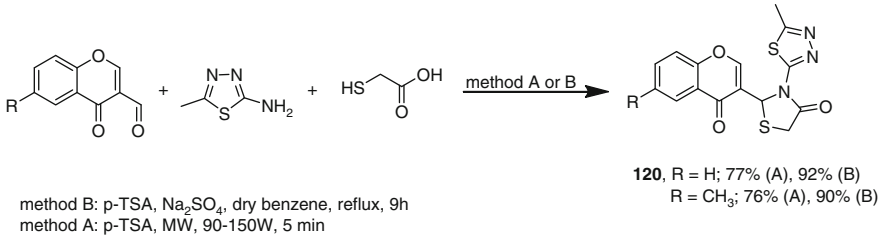
Additionally, it was noted that this MCR had diastereoselective character – only the one *trans*-diastereomer was isolated in all the experiments performed.

In another publication [81], the treatments of 3-formyl chromones with 2-amino-5-methyl-1,3,4-thiadiazoles and mercaptoacitic acids leading to compounds **120** were carried out both with the application of microwave techniques and by the conventional parallel synthesis.

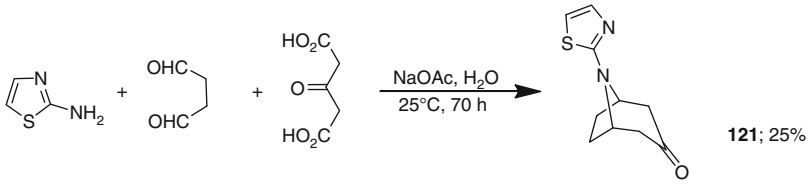
The liquid-phase microwave-assisted approach allowed the dramatic decrease in reaction time and enhancing level of the conversion. The reaction mixture of the starting building blocks in benzene in the presence of catalytic amounts of *p*-toluene sulfonic acid was exposed in microwave field for 5 min, which gave the target compounds in 90–92% yields (Scheme 57). The conventional thermal methods required 9 h of heating and allowed yields 76–77%. Additionally, the authors mentioned about the influence of electronic nature of 3-formyl chromone R substituent on the reaction efficiency – a presence of strong electron-withdrawing groups led to the decreasing of the MCR's yields.

Another interesting example is the synthesis of *N*-(2-thiazolyl)-nortropinon **121**. Stoll and co-authors [175] described the synthesis of this drug-like product via the legendary first total synthetic approach proposed by Robinson in 1917 [176] for the natural alkoloid tropinone, also well known as a good example of biomimetic reaction. In this tandem treatment, 2-aminothiazole was reacted with succinaldehyde and acetonedicarboxylic acid yielding *N*-(2-thiazolyl)-nortropinon **121** in moderate yields (Scheme 58).

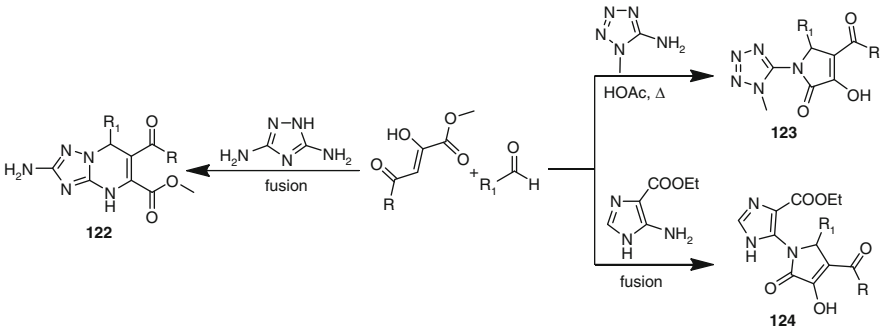
Along with the formation of dihydropyrimidine derivatives, an unusual directions of multicomponent treatment of 2,4-dioxobutanoates with aldehydes and several aminoazoles were described by Gein and co-authors [151]. Thus, fusion of carbonyl compounds with 3,5-diamino-1,2,4-triazole gave as usual for this type



Scheme 57 Optimization of MCRs using microwave-assisted synthesis



Scheme 58 Synthesis of nortropinon derivative



Scheme 59 Alternative directions of MCRs 2,4-dioxobutanoates

of interaction triazolopyrimidines **122**, while similar reaction with ethyl 5-amino-1H-imidazole-4-carboxylate yielded imidazolylpyrrolones **124** (Scheme 59).

Such direction with the formation of heterocyclic compounds **123** was also observed for the MCR of 2,4-dioxobutanoates and aldehydes with 5-amino-1-methyl-tetrazole. The authors did not discuss the reasons for different pathways of these MCRs.

Similar results were reported by Sakhno et al. in their recent publications [51, 52]. As it was already mentioned in this review (see Scheme 13) depending on reaction conditions, MCRs of arylpyruvic acids with 3-amino-1,2,4-triazoles or 5-amino-*N*-aryl-1H-pyrazole-4-carboxamides can yield different heterocyclic systems. For example, microwave-assisted treatment of the starting materials at 170°C gave corresponding azolylpyrrolones, that is, aminoazole played a role of 1,1-binucleophile, while ultrasonication at room temperature led to the formation tetrahydroazolopyrimidine fragment, that is, aminoazole acted as 1,3-binucleophile. These different directions at room and high temperatures were connected in [51, 52] with kinetic and thermodynamic controls of the reactions.

4 Concluding Remarks

Comprehensive review of the literature data dealing with the MCRs of aminoazols has been made, and cyclocondensations being important for combinatorial, medicinal, and biologically oriented chemistry yielding diverse five-, six-, and seven-membered heterocycles have been described. Such reactions can pass in two main directions, leading either to fused heterocyclic system, when aminoazoles act as 1,3-binuclephile, or to azolyl-substituted compounds, when aminoazole plays a role of 1,1-binucleophile. Selectivity of these multicomponent heterocyclizations can be effectively controlled with the help of several basic methods, including nonclassical approaches like microwave and ultrasonic irradiation.

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