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Multicomponent reactions of isocyanides in the synthesis of heterocycles

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Abstract. The latest achievements in the field of isocyanide-based multicomponent reactions for the synthesis of heterocycles are generalized. The attention is focused on the intramolecular Ugi reactions of oxocarboxylic acids and the reactions of diaza nucleophiles developed in recent years. The data on the biological activities of the products are presented and the advantages of this method as a convenient and effective tool of medicinal chemistry are demonstrated. The bibliography includes 162 references.

I. Introduction

The history of multicomponent reactions (MCR) in which three or more components react to give a single product extends to nearly a century and a half. The Strecker's[1] discovery in 1850 of α-aminonitrile synthesis by the reaction of ammonia and hydrocyanic acid with carbonyl compounds signified the birth of a three-component synthesis. Since then, organic chemists have invented numerous MCR and their number is still growing.

In the last two decades, MCR have drawn special attention due to the advent of high-throughput screening techniques that enabled rapid identification of potential new medicines among large collections of organic compounds. This required the development of new approaches to the synthesis of organic compounds. The methods that would provide rapid access to high-quality compound libraries came to be in high demand. The libraries were characterized by significant diversity with regard to both the core and the peripheral structure and were designed so as to contain a maximum number of so-called points of diversity. Multicomponent reactions ideally suited the new demand, and this, in turn, fueled more interest in the earlier developed reactions and in the invention of similar or even fundamentally new ones.

The modern society also sets stringent environmental requirements for any industrial production process including the production of chemicals and pharmaceuticals. Multistage syntheses are generally associated with the loss of matter during isolation and purification of intermediates and usually requires considerable amounts of solvents, which entails the waste disposal issues. Conversely, multicomponent reactions, which give rise to numerous chemical bonds in a one-pot procedure, appear to be much more ecologically sound.

Reactions involving isocyanides represent the centrepiece of the rapidly developing multicomponent chemistry. In addition to the usual efficiency of multicomponent processes, those of isocyanides have more benefits. Isocyanides are quite reactive species. As a functional group, isocyanides are quite unique in their ability (similarly to carbenes and carbon monoxide) to react with nucleophiles and electrophiles at the same carbon atom, resulting in so-called α-adduct.[2]

The multicomponent reactions of isocyanides produce stable C–C bonds; in many cases, they are chemo-, regio-, and stereoselective, highly effective and versatile. Using these reactions, it is possible to obtain a wide variety of organic compounds with high degree of easily variable structural diversity.

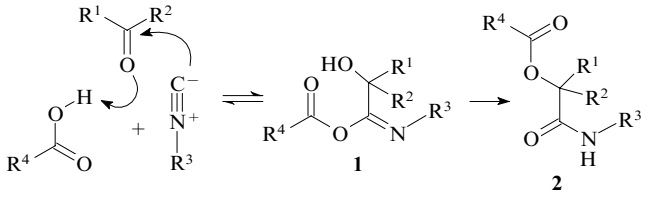
Historically, the reaction invented by Passerini in 1921[3,4] is regarded as the first isocyanide-based MCR. The starting materials for this reaction were carbonyl compounds, isocyanides and carboxylic acids, which reacted to give intermediate **1**. This underwent irreversible Mumm rearrangement to be converted to carbamoylmethyl ester (compound **2**) (Scheme 1).†

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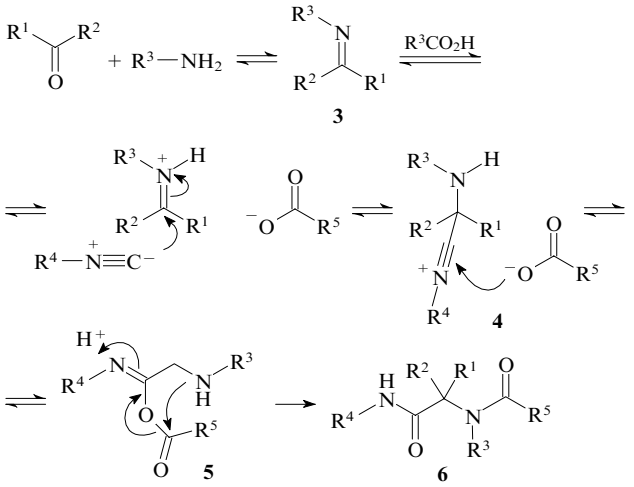
† Here and below, unless stated otherwise, R represents an alkyl, cycloalkyl, aryl or hetaryl substituent.

Scheme 1



It is noteworthy that over the next 40 years, this reaction, as well as the isocyanide chemistry as a whole, received very little attention from synthetic organic chemists. This could be related to the lack of reliable methods for preparation of isocyanides and certain difficulties associated with their application. For instante, the first synthetic isocyanide, allyl isocyanide, had a very unpleasant odour, which could be the main deterrent for the development of isocyanide-based chemistry. Further interest in isocyanides and isocyanide-based MCR was fueled by the works of Ugi ‡ (see Refs 5–8). He discovered a reaction that can be viewed as an aza version of the Passerini reaction, the only difference being the amine that Ugi added to the components of the Passerini reaction. The amine reacts with the carbonyl compound to give imine **3**, which is protonated by carboxylic acid being thus activated for an attack by isocyanide. This leads to the formation of a reactive nitrilium species **4**, which reacts with the carboxylate anion to give adduct **5**. This undergoes the irreversible Mumm rearrangement ending in the formation of bisamide **6** (Scheme 2).

Scheme 2



These two reactions can be used to obtain α-acyloxy and α-acylaminocarboxamides from readily accessible starting compounds. Structural fragments of these acids are parts of a broad range of pharmacologically active natural products and analogues thereof. Nevertheless, these unique reactions still received only marginal attention until the 1990s when the rapidly developing medicinal chemistry forced the search for new synthetic approaches to organic compounds. This initiated a new area of synthetic organic chemistry known as combinatorial chemistry. Ugi and his followers not only caught this trend but also realized quite well the potential of the newly discovered MCR in this context. Indeed, the relatively simple and practically convenient Ugi reaction may produce five new chemical bonds in a peptide-like structural motif containing at least four diversity points.

Considering the universal scope of the Ugi reaction with regard to the reaction components, which can also contain various functional groups, the synthetic potential of this reaction appears enormous. This reaction is operational both on a large preparative scale and on microscale, for preparation of combinatorial libraries in parallel format. Notably, the reaction proceeds both in solution and in the solid phase (*i.e.*, using polymer-bound reactants). The Ugi reaction is widely applied today in medicinal and combinatorial chemistry as witnessed by the ever increasing number of publications on the subject over the years (Fig. 1).

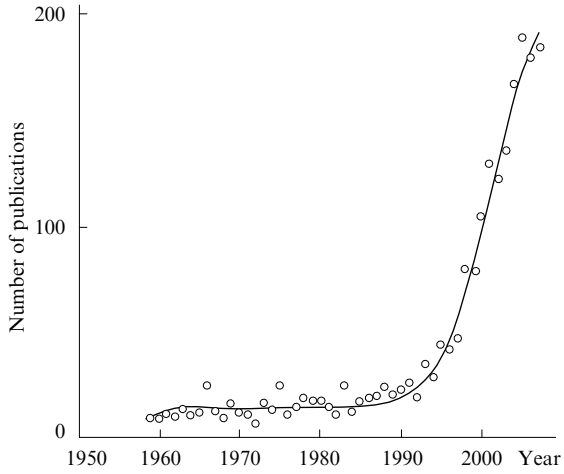


Figure 1. Number of publications devoted to the Ugi reaction (from the SciFinder database, 2008).

From the standpoint of medicinal chemistry, the Ugi reaction suffers from a considerable drawback: in the traditional linear design, the reaction lead to essentially one chemotype, namely, the bisamide backbone-containing compound. However, when it was discovered that the reaction can be applied to heterocycle synthesis as well, it exposed the potential of the Ugi reaction as a tool to construct a wide varierty of chemitypes. Initially, these new chemotypes contained the same peptide-like moiety but now it occured in the cyclic, lactam form. This obviously made such compounds much more appealing for medicinal chemistry.

The rapid development of the isocyanide-based MCR is reflected in many scientific reviews devoted to applied synthetic aspects of these processes. Most of these reviews were published in the last decade.[2,9–22] Among these publications, comprehensive studies,[2,17] which cover the original publications on isocyanide-based MCR up to 2005, deserve special note. Several reviews also pay attention to the use of isocyanide-based MCR in the heterocycle chemistry but after the publication of a review in 2003,[9] the knowledge on this subject matter has not been surveyed.§

‡ In 2010, the chemistry community celebrated the 50th anniversary of the remarkable Ugi reaction.

§ During the manuscript preparation, the review by Hulme[21] was published considering heterocycle syntheses based on the intramolecular Ugi reaction in terms of the concept of iterative efficiency in medicinal chemistry.

Two main approaches to the heterocycle chemistry using the Ugi MCR can be distinguished. The first one comprises the synthesis of bisamides using the four-component Ugi reaction and their subsequent cyclization — 'post-Ugi' reaction. The second approach is to perform intramolecular Ugi reactions and their analogues based on bifunctional reagents, directly giving rise to heterocycles. These approaches are considered in Section II of this review. In addition, two special cases of using the second approach are presented, in particular, isocyanide-based MCR with keto and aldehydo acids and with diaza nucleophiles. These transformations are the subjects of two separate Sections of the review due to the huge amount of published information on this topic.

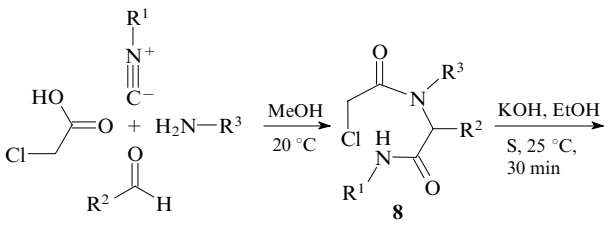
II. Key strategies of heterocycle synthesis using isocyanide-based multicomponent reactions

1. Heterocycle syntheses based on 'post-Ugi' transformations

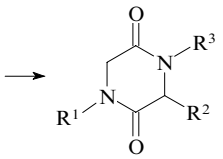
As noted above, in the four-component Ugi reaction (U-4CR), it is possible to use reagents containing different functional groups in explicit, protected or latent form. These functionalized 'tails' at the periphery of the bisamide skeleton (the initial Ugi condensation product) finally ensure its heterocyclization. Two types of such cyclizations can be noted, 'tail – skeleton' and 'tail – tail' types. In most cases, the bisamide skeleton has properties typical of carbamoyl derivatives: moderate reactivity with respect to electrophiles (for example, alkylating, arylating, and acylating reagents) and reduced reactivity with respect to nucleophiles (for example, amines, C – H acids, alcohols, phenols, and so on). Therefore, the potential reaction sites in the skeleton need to be activated by selecting the appropriate reaction conditions or by introducing activating groups into the reactant molecules. Since these strategies were reflected in a recent review,[22] we will consider only a few recent papers demonstrating the unique nature of this method for the synthesis of various heterocyclic compounds.

a. Tail – skeleton type heterocyclization

In the heterocyclizations occurring according to the tail – skeleton pattern, the starting reactants are selected in such a way that the primary U-4CR product contains an additional functional group (for example, a carbonyl or alkoxycarbonyl group, halogen atom, *etc.*) in a position suitable for the attack at a reaction site of the bisamide skeleton. An example of this type of MCR is the synthesis of substituted piperazine-2,5-diones where halogenated carboxylic acid, in the simplest case, chloroacetic acid, serves as a starting reactant.[23] This reaction has been successfully developed in the parallel synthesis of a combinatorial library of compounds containing 524 piperazine-2,5-diones with general structure **7**.[24] The yield of the primary U-4CR adducts, compounds **8**, was 50% – 80%.



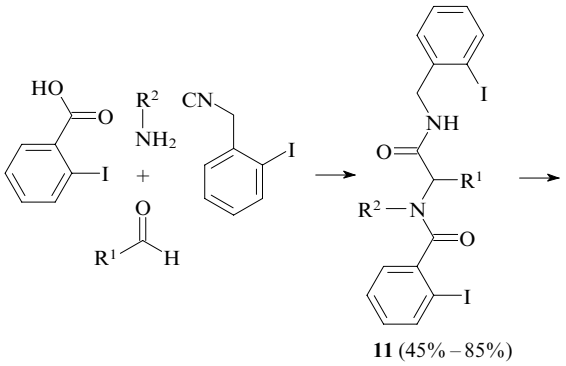
8



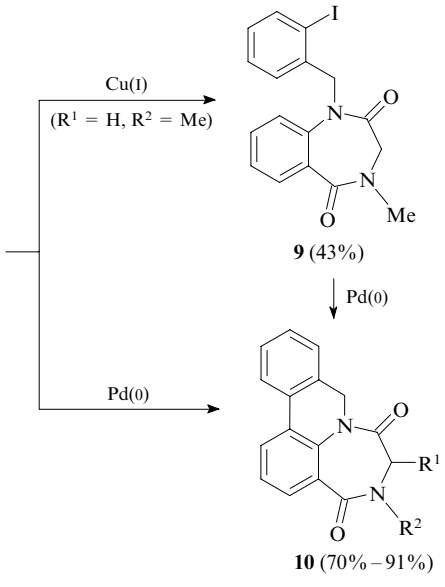
7 (40 – 95%)

R^1 = Bn, R^2 = 4-ClC_6H_4, R^3 = cyclo-C_6H_{11};
R^1 = 4-$ClC_6H_4CH_2$, R^2 = 2-Naph (Naph is naphthyl), R^3 = cyclo-C_6H_{11};
R^1 = cyclo-C_6H_{11}, R^2 = 4-BrC_6H_4, R^3 = Bn; S is sonication.

A similar approach has also been used to obtain benzoannelated lactams **9** and **10**. The intramolecular N-arylation of U-4CR products **11** (R^1 = H, R^2 = Me) containing two reactive iodine atoms in the presence of Cu(I) salts affords 1,4-benzodiazepine-2,5-dione **9**. Using Pd(0) catalyst, it is possible to carry out two cascade heterocyclizations, one following the tail – skeleton pattern and the other following the tail – tail pattern; this gives [1,4]diazepino-[6,7,1-*de*]phenanthridine-4,7-diones **10**.[25]



11 (45% – 85%)



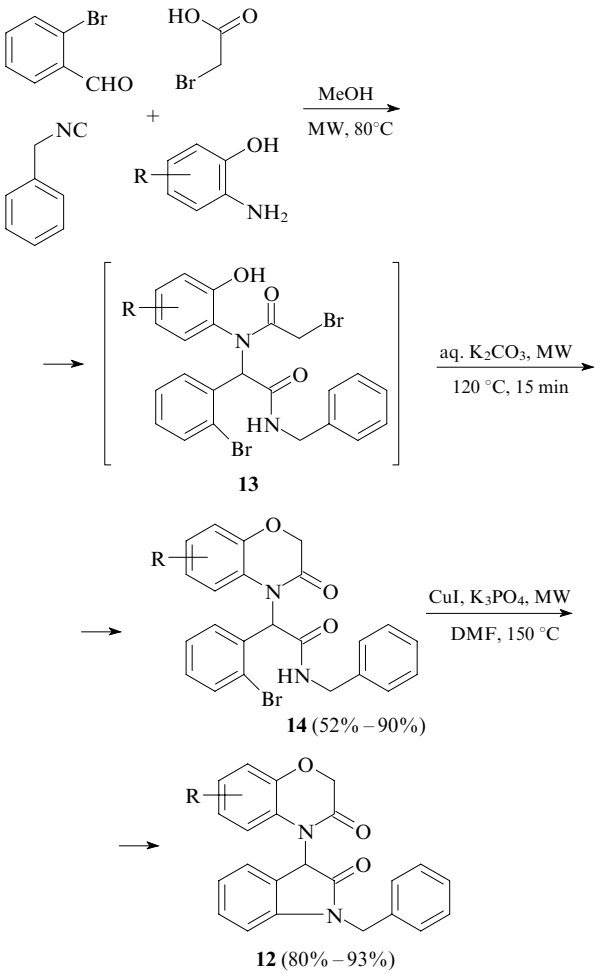
9 (43%)

10 (70% – 91%)

R^1 = H, R^2 = Me; R^1 = Pr^i, n-C_6H_{13}; R^2 = Bu^t, Bn.

The synthesis of oxoindolyl-1,4-benzoxazines **12** can serve as U-4CR involving three bifunctional reagents, namely, 2-bromobenzaldehyde, α-bromocarboxylic acid derivatives and 2-aminophenol.[26] This reaction furnishes product **13**, which undergoes two subsequent heterocyclizations giving rise to 1,4-benzoxazine (compound **14**) and then indoline rings (**12**). The first heterocyclization is induced by microwave radiation (MW) in the presence of K_2CO_3 in methanol and follows the tail – tail pattern. The subsequent

heating of the reaction mixture under MW irradiation in the presence of Cu(I) induces the tail–skeleton cyclization.



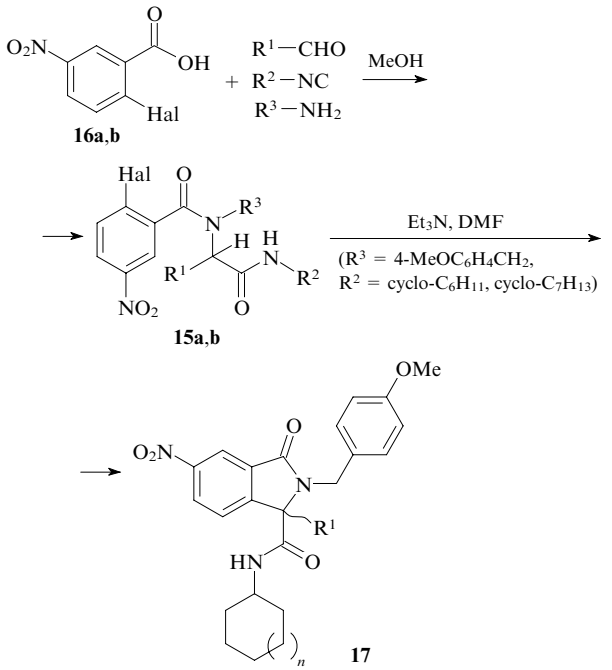
13

14 (52%–90%)

12 (80%–93%)

R = 4-Me, 5-Me, 5-Cl (for the starting aminophenol).

The formation of benzodiazepinediones like **9** might also be expected for intramolecular N-arylation of U-4CR products **15**; in this case, 2-fluoro- (**16a**) and 2-chloro-5-nitrobenzoic (**16b**) acids were used as bifunctional reagents.[27] It was assumed that, owing to halogen atom activation by the nitro group, cyclization of intermediates **15** can be performed without metal catalysts. However, it was found that in this case, the predominant reaction pathway is intramolecular C-arylation giving isoindolinones **17**, the structure of which was confirmed by NMR spectroscopy and X-ray diffraction data. It was also shown that cyclization of chloro derivatives **15b** occurs at a lower rate than cyclization of the fluorinated analogues **15a**. The yields were comparable being 45%–85% in both cases. The authors found that the reaction is fairly sensitive to the nature of the initial (hetero)aromatic aldehyde. Indeed, in the presence of electron-withdrawing substituents (R^1 = 2-, 3- and 4-pyridyl), intermediates **15** partly spontaneously cyclized during the U-4CR, whereas in the presence of other substituents, for example, for R^1 = 4-bromophenyl, 2-naphthyl, 1-methylpyrrol-2-yl, 1,3-dimethylpyrazol-4-yl, the reaction yielded only traces of the target products **17** even on heating in DMF in the presence of Et_3N. Evidently, side reactions predominate when the C–H acidity of the acetamide fragment is too low.



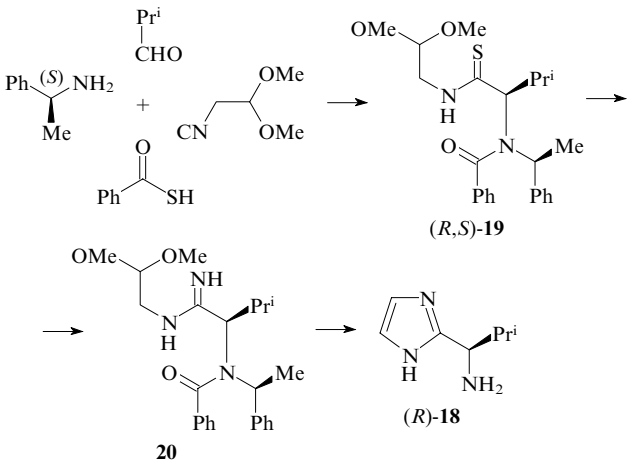
16a,**b**

15a,**b**

17

Hal = F (**a**), Cl (**b**); R^1 = Ar, Het; R^2 = Alk; R^3 = Alk, cyclo-Alk; n = 1, 2.

In some cases, the proper linear skeleton is modified in order to increase the nucleophilicity of particular atoms to perform heterocyclization. The elegant synthesis of aminoalkylimidazoles **18** proposed by Nenajdenko's group[28] can serve as an example. The fist stage gives thioamide **19**. In this case, thiobenzoic acid acts as the acid component and isocyanide contains an aldehyde function with acetal protection. Thioamide **19** is then converted to amidine **20**, which undergoes acid-catalyzed cyclization with simultaneous removal of the benzyl and benzoyl groups to give imidazole **18**. Note that the reaction is highly stereoselective: when chiral (*S*)-α-phenylethylamine is used, the condensation mainly produces the *R*-stereoisomer, which can be readily isolated from the reaction mixture. The process thus affords optically active α-aminoalkylimidazoles, which are of interest as key intermediates in the synthesis of SB203386, a HIV-1 protease inhibitor.



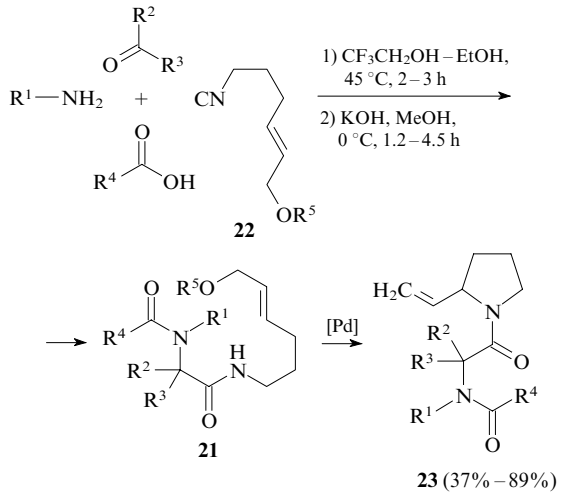
(*R*,*S*)-**19**

20

(*R*)-**18**

In some cases, cyclization involves the nitrogen atom of the amide group formed from isocyanide upon U-4CR. For example, Ugi adduct **21** obtained from isocyanide **22** cyclizes in the presence of Pd catalysts according to the

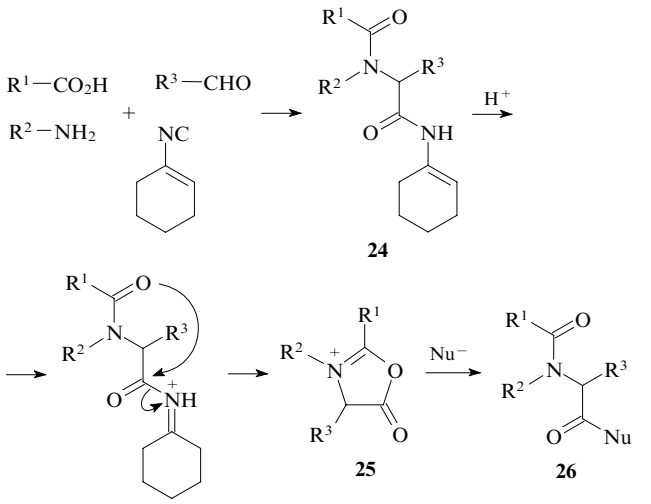
S_N2' mechanism to give vinylpyrrolidines **23**.[29] The choice of the catalyst is determined by the nature of the substituent at the oxygen atom in the unsaturated tail. When an alcohol hydroxyl group is present in compounds **22** (R^5 = H), Pd(II) is efficient, while the methoxycarbonylated analogues **22** (R^5 = CO_2Me) better cyclize in the presence of Pd(0).



22 **21** **23** (37%–89%)

R^1 = Bu^n, Bn, Ph; R^2 = H, Me, Pr^i, Ph, 2-$MeOC_6H_4$;
R^3 = H, Me; R^4 = Et, $Ph(CH_2)_3$, $BocNHCH_2$, Ph;
R^5 = H, CO_2Me; Boc is *tert*-butoxycarbonyl.

Since the carbonyl groups of the bisamide skeleton of the Ugi adducts cannot be classified as strong electrophiles, 'nucleophilic tail – electrophilic skeleton' type heterocyclizations are little studied. However, in the late 1990s – early 2000s, a significant progress was achieved, first of all, due to the convertible isocyanide concept put forward by Armstrong[30,31] in 1995. As a universal isocyanide, Armstrong used cyclohexen-1-yl isocyanide. During the Ugi reaction, this isocyanide is converted to adducts **24** containing a labile *N*-cyclohexenylcarbamoyl group whose enamide nature accounts for their transformation to oxazolinium intermediates **25** in acid medium. The latter products are readily cleaved by various nucleophiles to give stable products **26**.

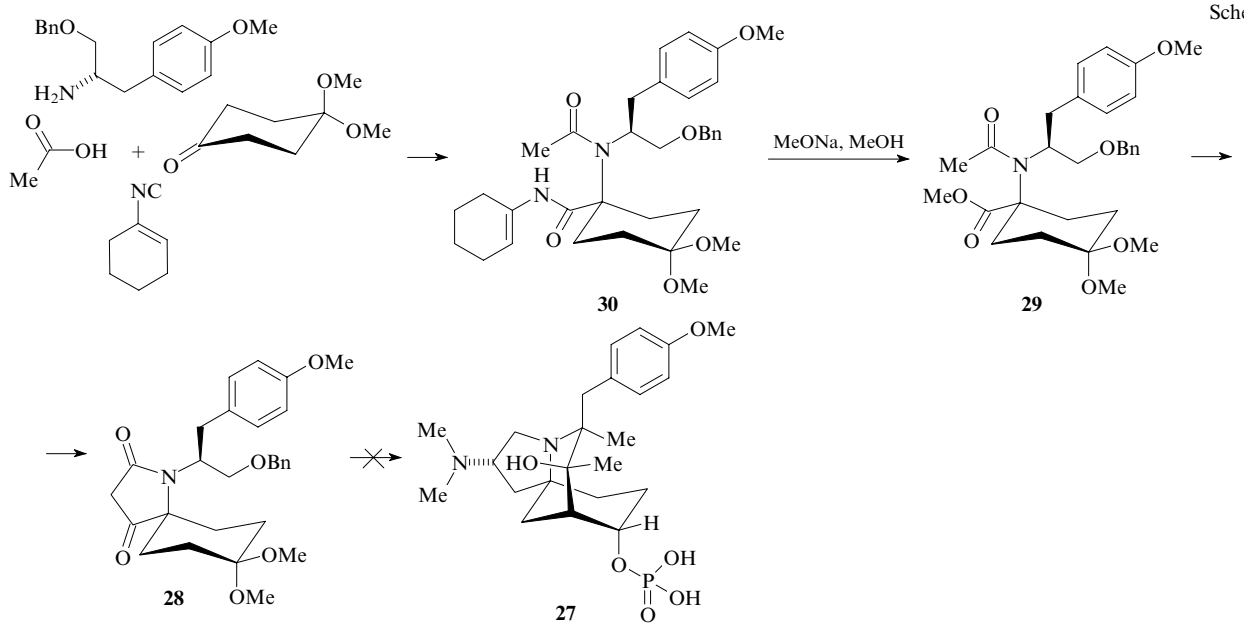


24 **25** **26**

If amine serves as the nucleophile, the reaction should produce amides. It is clear that amides with a primary amino group could be synthesized directly by U-4CR from the corresponding isocyanides. However, the use of one convertible isocyanide eliminates the need to prepare a number of isocyanides for the variation of substituents, *i.e.*, for attaining the structural diversity at the given amide group. This solution becomes more obvious in view of the organoleptic properties of isocyanides and of the fact that their synthesis is highly labour-consuming and in some cases absolutely impossible. In addition, the use of the universal isocyanide concept opens up the way for the synthesis of bisamides with the terminal secondary amino group, which cannot be prepared directly by the Ugi reaction.

This concept has found most interesting applications in the synthesis of heterocycles.[32] Within 10 years after the publication of Armstrong's works,[30,31] cyclohexen-1-yl isocyanide was strongly present in the synthetic practice, so that it was called Armstrong's isocyanide, although it was first synthesized and characterized in an early Ugi's work.[33] Examples of successful use of Armstrong's isocyanide were considered in detail.[2,11,14,15] Among the recent works, noteworthy is the publication by Seike and Sorensen,[34] who made an attempt to construct the tricyclic structure of

Scheme 3

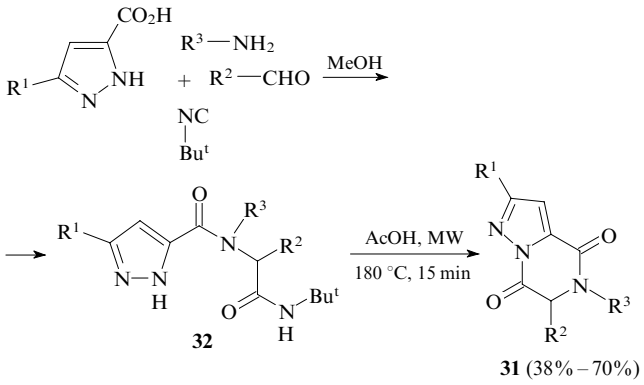


30 **29** **28** **27**

the FR901483 (**27**) immunosuppressant. Although the goal was not attained, the authors still developed a method for the synthesis of spirocyclic structure **28** by cyclization of methyl carboxylate **29** obtained by alcoholysis of U-4CR adduct **30** (Scheme 3).

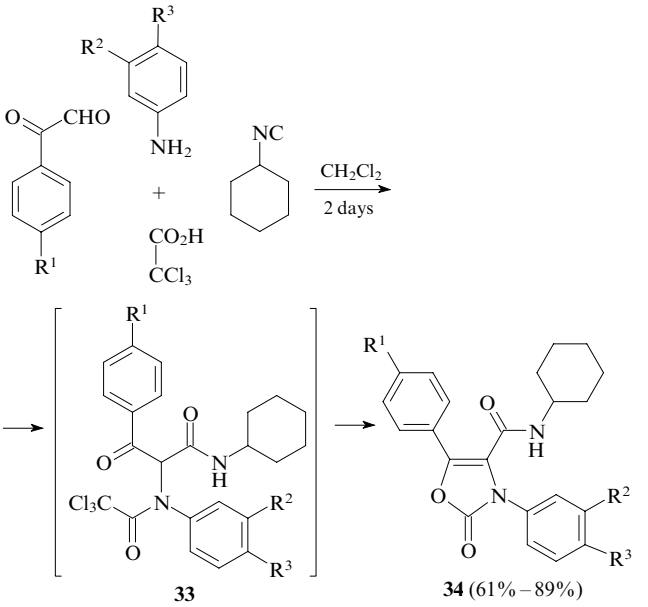
Despite its high synthetic potential, Armstrong's isocyanide has serious drawbacks such as difficulty of the syntheses, which is non-scalable, instability on long-term storage even with special precautions (−30 °C, inert atmosphere) and, as a consequence, lack of commercial availability. This circumstance stimulated many researchers to look for alternative convertible isocyanides obtained by modifying the Armstrong's isocyanide structure (see, for example, studies [35, 36]) or by other methods (see, for example, study [37]). However, the synthesis of these isocyanides requires a lot of effort and they are fairly expensive. In some cases, the search for alternative solutions based on the use of simple and commercially available isocyanides is much more reasonable.

Thus, recently a one-pot version of the synthesis of new pyrazolo[1,5-*a*]pyrazines **31** from pyrazole-5-carboxylic acids using *tert*-butyl isocyanide as the convertible isocyanide was developed and described.[38–42] The key reaction stage is MW-induced cyclization of Ugi adducts **32** in AcOH with elimination of *tert*-butylamine.



R^1 = 2-MeC_6H_4, 4-FC_6H_4; R^2 = Ph, 4-$MeOC_6H_4$, iso-C_5H_{11};
R^3 = cyclo-C_3H_5, 4-$EtOC_6H_4$, 3-$MeOC_6H_4$, 2-Th (Th is thienyl).

Unlike cyclizations with participation of the isocyanide amide group, analogous intramolecular transformations in which an amide group formed from carboxylic acid serves as the electrophile are represented by only few examples. As one example, consider the procedure reported by Ignacio *et al.*[43] A multicomponent reaction with two bifunctional reagents — trichloroacetic acid and phenylglyoxal — affords ketones **33**. These cyclize spontaneously in the enolate form to oxazolones **34**.[44] It is noteworthy that trichloroacetic acid acts in these processes as a synthetic equivalent of carbonic acid.

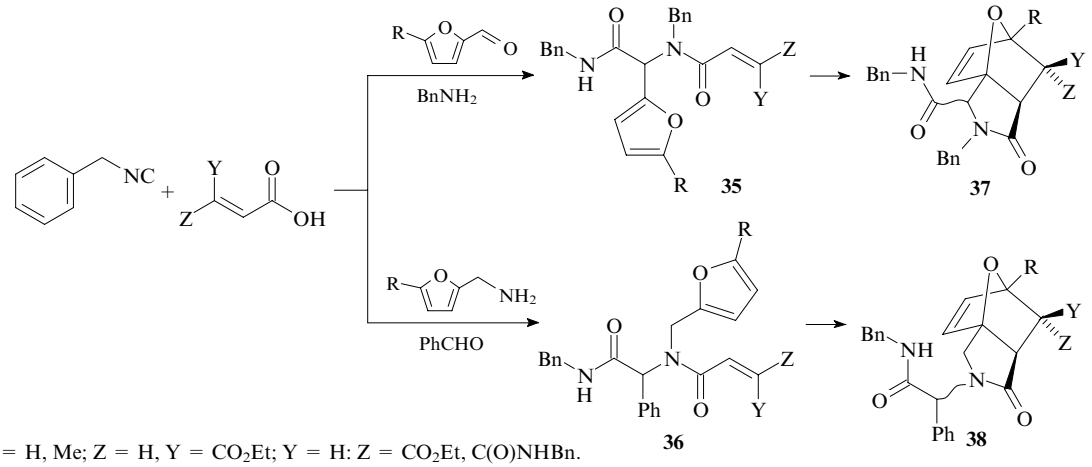


R^1 = H, Me, Cl, MeO; R^2 = H, Me, MeO, Cl; R^3 = H, Cl.

b. Tail – tail type heterocyclizations

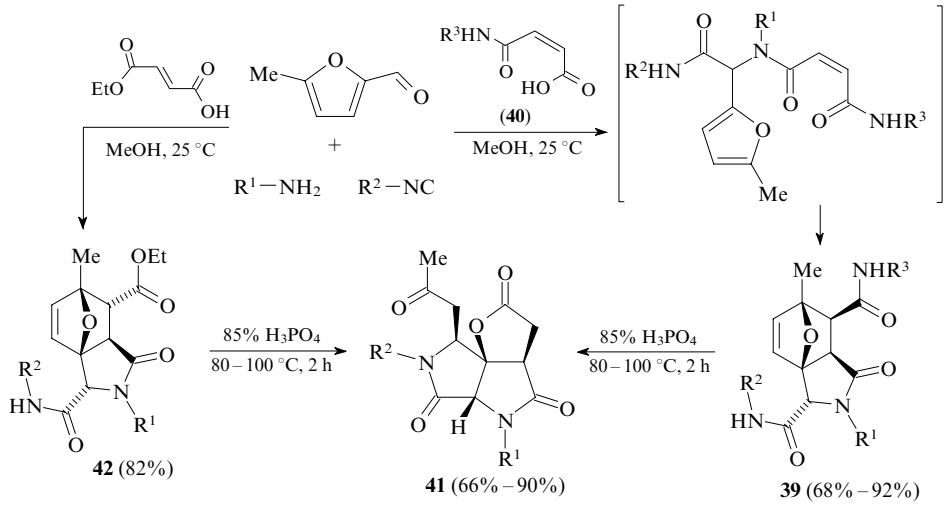
In heterocyclizations that follow the tail – tail pattern, the post-Ugi cyclization is provided by the reaction between two and more functional groups that are located at the periphery of the bisamide skeleton. This strategy underlay a number of interesting synthetic solutions; the combination of Ugi and Diels – Alder reactions first proposed by Paulvannan [45] in 1999 can serve as an example. The diene for the subsequent Diels – Alder reaction is introduced into the carbonyl (furan-2-carbaldehyde) or amine (furfurylamine) component of U-4CR and the dienophile fragment is present in the acid component (monoesters or amides of maleic or fumaric acids). The Ugi intermediates **35** and **36** cyclize spontaneously to give heterocyclic systems **37** and **38**. In the former case, the reaction has a high degree of diastereoselectivity [diastereomer ratio (*dr*) varies from 83 : 17 to 98 : 2 depending on the diene and dienophile structures], and in the latter case, it was somewhat lower (*dr* from 56 : 44 to 64 : 36) (Scheme 4).

Scheme 4



R = H, Me; Z = H, Y = CO_2Et; Y = H: Z = CO_2Et, C(O)NHBn.

Scheme 5

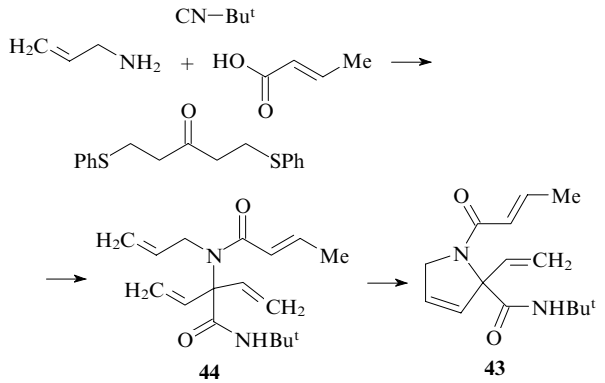


$R^1 = C_6H_{5-n}X_n$ [X_n = H, 4-Me, 2,4-Me_2, 2,3-Me_2, 3,6-$(MeO)_2$, 3-Cl-6-Me]; R^2 = Ph, cyclo-C_5H_9, cyclo-C_7H_{13}; R^3 = Ph, 2,6-$F_2C_6H_3$.

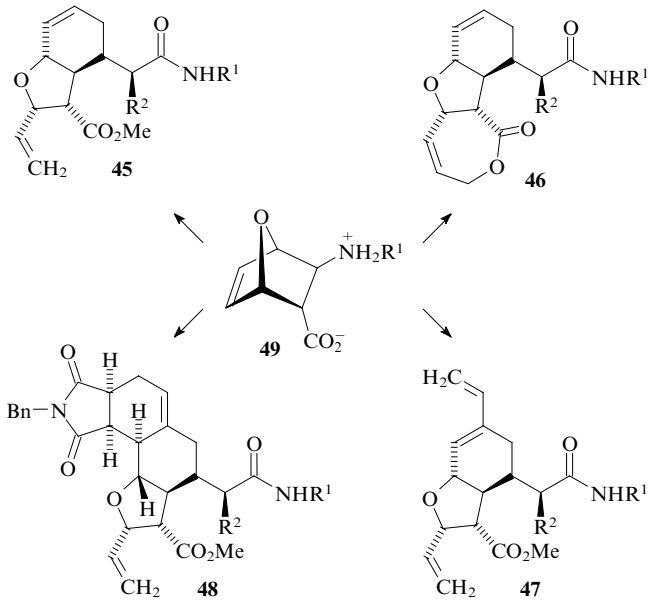
Recently Ilyin *et al.*[46] showed that lactams **39** formed as a result of Ugi and Diels–Alder tandem reactions from maleic monoamides **40** are able to undergo a unique skeletal rearrangement to 5,7-disubstituted hexahydro-1-oxa-5,7-diazacyclopenta[*c*]pentalene-2,4,6-triones **41**. The reaction takes place in phosphoric acid on heating and is accompanied by the loss of one asymmetric centre and considerable redistribution of the environment around the four remaining centres but, finally, this yields only one diastereomer. The mechanism of this rearrangement proposed by the authors provides a simple and rational explanation to the structural and stereochemical features of this transformation. This was confirmed by alternative synthesis of compounds **41** starting from monoethyl fumarate *via* the formation of lactams **42** whose stereochemical structure differs from the stereochemistry of lactams **39** obtained from maleimides (Scheme 5).

Ring-closing metathesis (RCM) as a tandem with U-4CR remains at the focus of researchers' attention as a method for the synthesis of original carbo- and heterocycles. The Ugi reaction provides unique opportunities for the synthesis of precursors for this transformations, *viz.*, dienes or even polyenes. Thus substituted pyrrolidines **43** were obtained recently by metathesis of azapolyenes **44** formed on the basis of bis(2-phenylthioethyl) ketone functioning as a synthetic equivalent of divinyl ketone (Scheme 6).[47]

Scheme 6

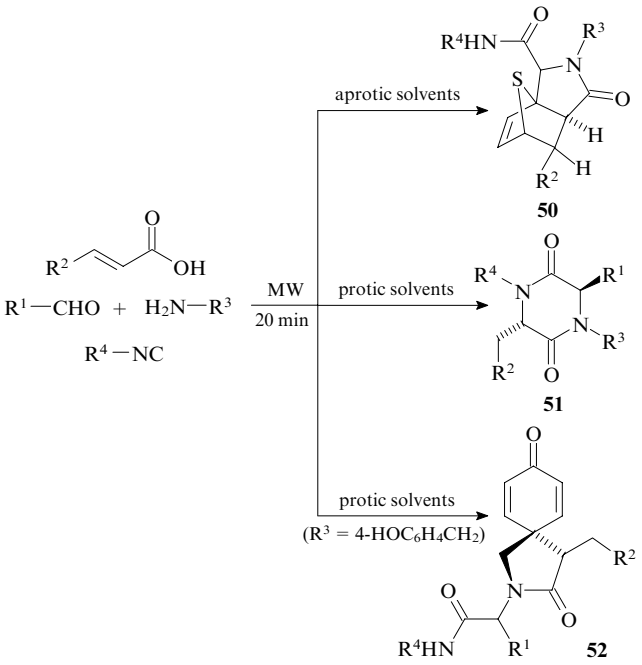


The use of a combination of the Ugi–metathesis–Diels–Alder reactions described by Guanri and co-workers[48] provided a unique set of heterocyclic structures **45**–**48**. The process has high stereoselectivity: the described reaction sequences result in the formation of up to 8 stereogenic centres and the final products were isolated in the enantiomerically pure state. The role of internal stereoinducing factor was played by 7-oxabicyclo[2.2.1]amino acid **49**.



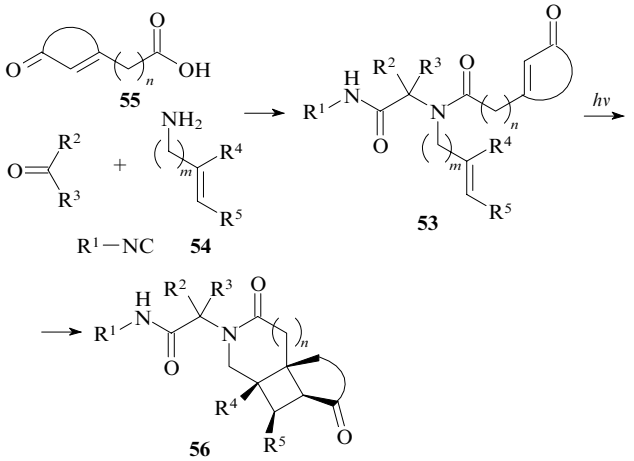
R^1, R^2 = Alk, Ar, Het.

Depending on the reaction conditions and the structure of the starting reactants, a variety of heterocyclic compounds can be prepared by U-4CR from unsaturated carboxylic acids.[49] Thus when 4-methoxybenzylamine is used in a MW-induced reaction in aprotic media, U-4CR is accompanied by the Diels–Alder reaction to give tricyclic structure **50**, while in protic solvents, aza-Michael reaction resulting in piperazinediones **51** predominates. However, the process using 4-hydroxybenzylamines occurs as a C-Michael reaction to give spirocyclic lactam **52**.

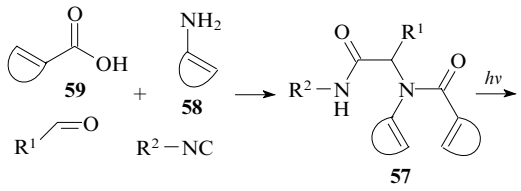


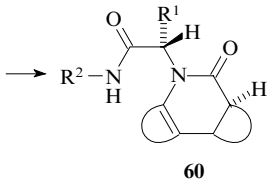
R^1 = Pr^i, Bu^t, 2-Th, 2-Naph; R^2 = Bz, EtO_2C; R^3 = 4-$MeOC_6H_4CH_2$, 4-$HOC_6H_4CH_2$, 4-HO-3-$MeOC_6H_3CH_2$; R^4 = Pr^i, Bu^n, Bu^t, cyclo-C_5H_9, cyclo-C_6H_{11}, Bn, 4-$MeOC_6H_4$.

A group of researchers from the Abbott company described [50] examples of intramolecular photocyclization involving olefinic fragments incorporated in the bisamide skeleton of compound **53**. The latter is formed upon the U-4CR of unsaturated reactants, for example, enamines **54** and acids **55**, with ketones and isocyanides. The photochemical intramolecular [2 + 2]-cycloaddition in the Ugi adduct **53** gives rise to four asymmetric centres but in most cases, only two diastereomers of **56** are formed



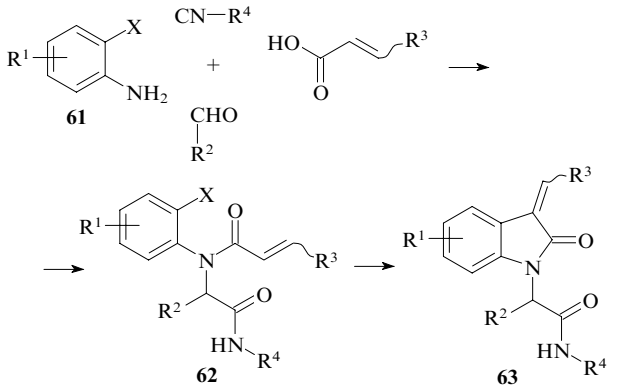
Meanwhile, photocyclization of U-4CR adducts **57** obtained from α,β-unsaturated amines **58** and carboxylic acids **59** produces dihydropyridine ring with predominant





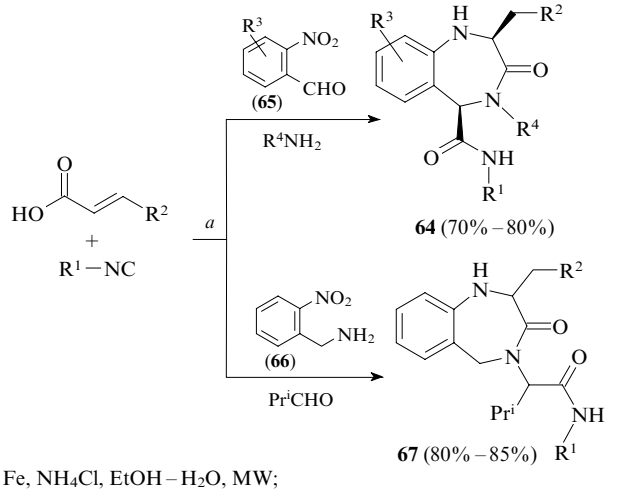
formation of products **60** with *trans*-orientation of hydrogen atoms.[51]

The Ugi and Heck reaction tandem is widely used for the synthesis of heterocycles. Thus researchers from the Preaton company showed [52] that the U-4CR of *o*-bromoanilines **61** (X = Br) with α,β-unsaturated carboxylic acids yields unsaturated anilides **62** (X = Br), which cyclize under Heck reaction conditions to give functionalized indolones **63**. Recently a modification of this approach was proposed in which *o*-aminophenols **61** (X = OH) were used as the amine component in the U-4CR and the subsequent Heck reaction was successfully implemented with triflates **62** (X = OTf) obtained from the corresponding phenols.[53]



R^1 = H, NO_2; R^2 = H, Pr^i, Ph; R^3 = Me, Ph, 4-$O_2NC_6H_4$, 3-$F_3CC_6H_4$, 3,4-$(MeO)_2C_6H_3$; R^4 = Pr^i, Bn, MeO_2CCH_2.

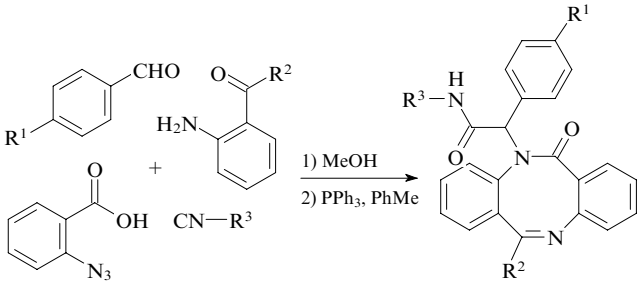
Some other *ortho*-functionalized aromatic derivatives have found wide use in the synthesis of heterocycles. For instance, De Silva *et al.*[54] proposed a convenient two-stage one-pot synthesis of benzodiazepinones **64** from isocyanides, unsaturated carboxylic acids, amines and *o*-nitrobenzaldehydes **65**. The whole process carried out under MW



(*a*) Fe, NH_4Cl, EtOH – H_2O, MW;
R^1 = Bu^t, cyclo-C_5H_9, cyclo-C_6H_{11}; R^2 = EtO_2C, Bz, 4-$MeC_6H_4C(O)$; R^3 = H, 4-F_3C, 4,5-$(MeO)_2$; R^4 = All, Bn, 4-$BrC_6H_4CH_2$, 4-AcC_6H_4, 3,4-$(OCH_2O)C_6H_3CH_2$.

radiation includes the following reaction sequence: U-4CR, reduction of the nitro group and lactam ring formation through the aza-Michael reaction. The use of *o*-nitrobenzylamine (**66**) in the reaction with isobutyraldehyde under analogous conditions leads to the formation of benzodiazepines **67** as a mixture of diastereomers ($dr = >1.5:1$), whereas the former condensation was more stereoselective resulting in the predominant formation of *cis*-diastereomers ($dr = >20:1$).

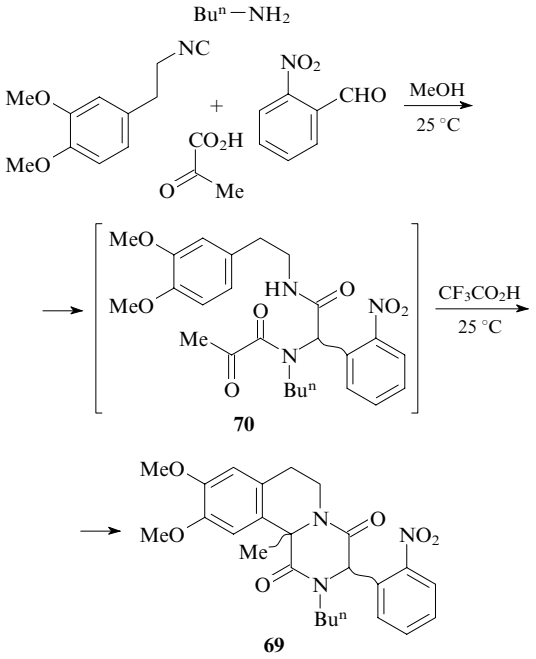
In a recent publication,[55] it was demonstrated that the introduction of the azide group in the *ortho*-position of aromatic acids (*e.g.*, *o*-azidobenzoic acid) and introduction of the amino group in the *ortho*-position of ketones (*o*-aminophenyl ketones) for the U-4CR creates conditions for the subsequent combined Staudinger – aza-Wittig reaction. This gives dibenzodiazocine lactams **68**.



68

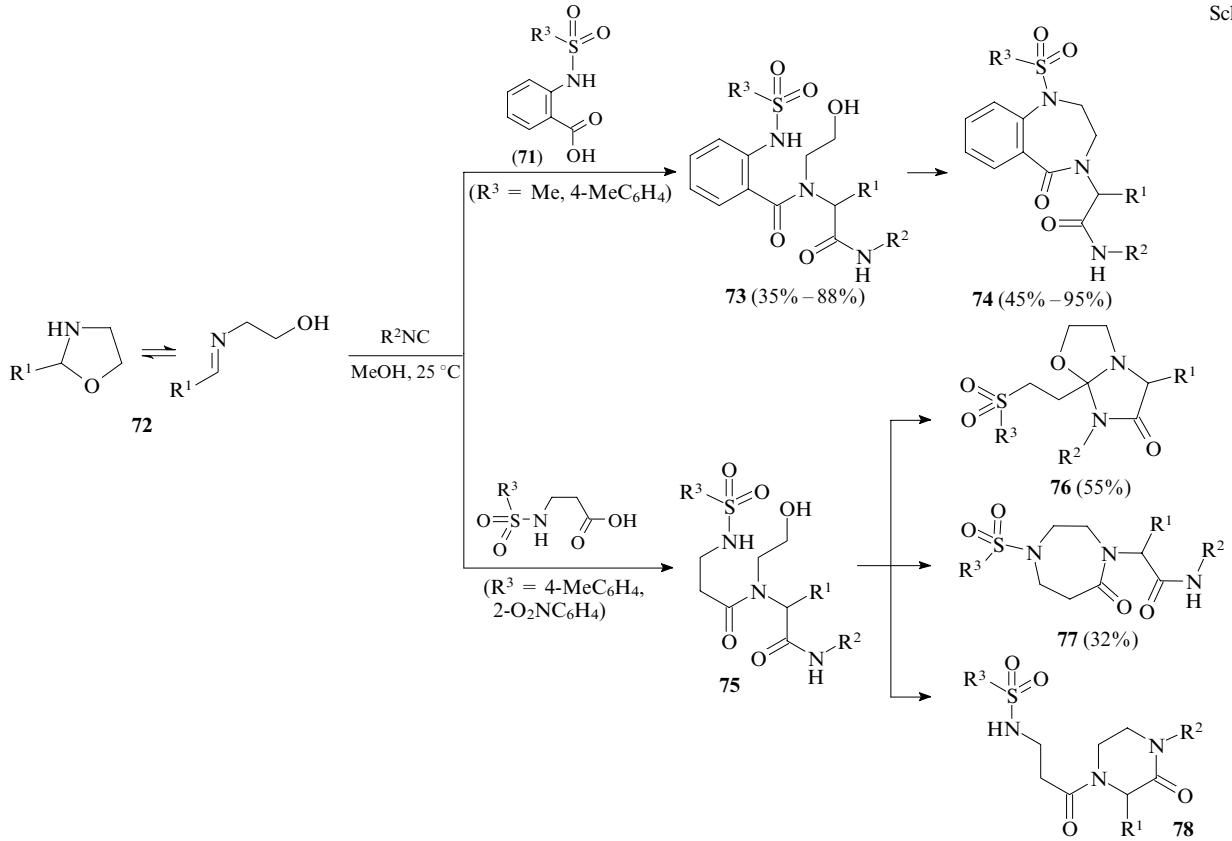
R^1 = Cl, Br, MeO; R^2 = Me, Ph; R^3 = cyclo-C_6H_{11}, Bn.

Electron-donating substituents present in the starting isocyanide favour the formation of isoquinoline ring **69** by the Pictet – Spengler reaction from Ugi adducts **70** obtained with participation of α-ketocarboxylic acid.[56] It is noteworthy that azomethine formation from *o*-nitrobenzaldehyde at an early reaction stage is the decisive factor for the success of the reaction, because this substantially reduces the competition with the keto group of the acid component (this reaction was also performed using cyclopentanone).



For the Ugi and Mitsunobu reaction tandem, Banfi *et al.*[57] used *o*-sulfonylaminobenzoic acids **71**, isocyanides (R^2NC) and imines **72** as the starting compounds. Owing to

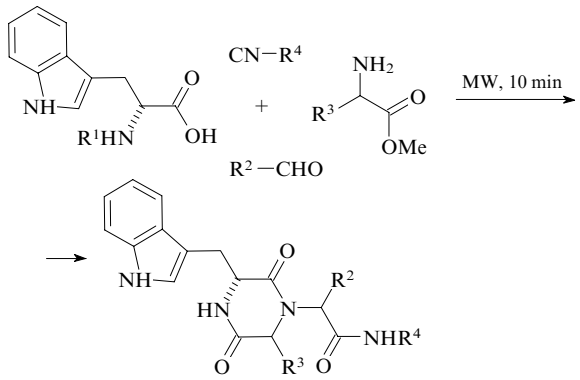
Scheme 7



R^1 = Pr^i, Bu^t, cyclo-C_6H_{11}, Ph, 3-BrC_6H_4, 3-$MeOC_6H_4$, 4-ClC_6H_4, 2-Fu (Fu is furyl); R^2 = Bu^n, Bu^t, Bn; R^3 = Me, 4-MeC_6H_4, 2-$O_2NC_6H_4$.

the high NH-acidity of the sulfamide fragment of Ugi adduct **73**, the subsequent Mitsunobu alkylation proceeded efficiently to give sulfonyl-substituted benzodiazepinones **74** in high yields. It was also shown that the use of *N*-sulfonyl-β-alanines as the starting components resulted in the formation of intermediates **75**. Under the reaction conditions, the latter were converted to bicyclic products **76**, while the yields of the target diazepinones **77** did not exceed 32%. However, the researchers succeeded in partially solving this problem by using sulfuryldiimidazole as the condensing agent. In some cases, a side piperazinone **78** was formed as the by-product (Scheme 7).

The post-Ugi cyclizations based on α-amino acid derivatives are widely used in the synthesis of piperazinediones.



79 (51% – 55%)

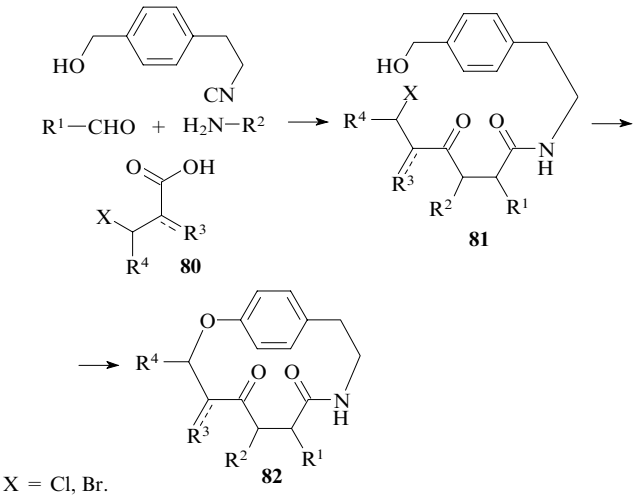
R^1 = Boc, Fmoc (Fmoc is 9-fluorenylmethoxycarbonyl);
$R^2 - R^4$ = Alk, Ar.

A recent communication [58] describes the synthesis of indolyl-substituted piperazinediones **79** using *N*-Boc- and *N*-Fmoc-protected tryptophane as the acid component and α-amino acid esters as the amine component. Deprotection and the subsequent cyclization were accomplished by heating in the presence of trifluoroacetic acid (for Boc protection) under MW radiation or in the presence of piperidine (for Fmoc protection).

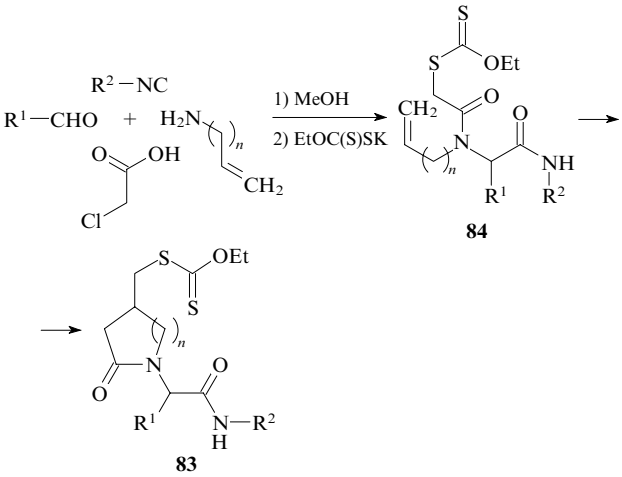
An interesting application of post-Ugi condensations was found in the macrocycle chemistry.[59] For example, the use of 2-(4-hydroxyphenyl)ethyl isocyanide and halo-substituted acids **80** as bifunctional reagents in the U-4CR gives adducts **81**. The adducts cyclize upon intramolecular alkylation on heating in acetone in the presence of K_2CO_3 as the base and 18-crown-6 ether as the phase transfer catalyst. In some cases, high (up to 87%) yields of target macrocycles **82**, which are analogues of 14-membered cyclopeptide alkaloids, were attained.

A number of unique approaches to the synthesis of various macrocycles by means of Ugi and Passerini reactions were reported in recent publications.[60 – 62]

A combination of U-4CR and the 'xanthate' radical cyclization was proposed for the synthesis of substituted lactams **83**.[63] First, two bifunctional reagents, chloroacetic acid and unsaturated amine, are made to react with aldehydes and isocyanides. The adducts thus formed are used subsequently as alkylating agents in the reaction with potassium ethyl xanthate, giving rise to xanthates **84**. These readily cyclize to target heterocycles **83** in the presence of dilauroyl peroxide as the initiator. Thus, the researchers were able to synthesize five- to eight-membered lactams **83**, their yields being dependent on the ring size.

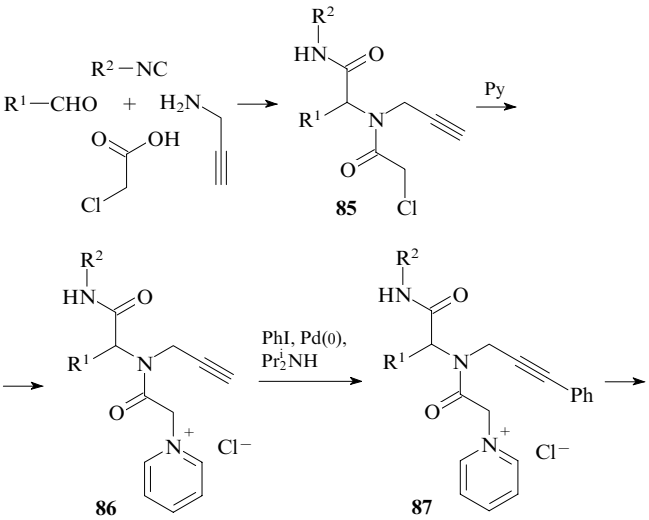


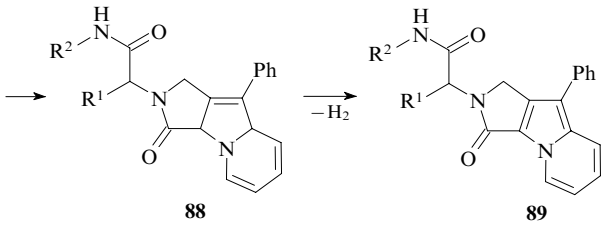
X = Cl, Br.



R^1 = Bu^t, 4-$MeOC_6H_4$, R^2 = Bu^t, 4-$ClC_6H_4CH_2$; n = 1 – 4.

The reaction involving chloroacetic acid and propargylamine may serve as another example of isocyanide-based MCR using two bifunctional reagents.[64] Pyridine quaternization of Ugi adducts **85** results in quaternary salts **86**, which add iodobenzene at the terminal acetylene group according to the Sonogashira reaction pattern to give substituted alkynes **87**. The subsequent heterocyclization through [3 + 2]-cycloaddition of product **88** followed by oxidation affords pyrroloindolizinones **89**.





88 **89**

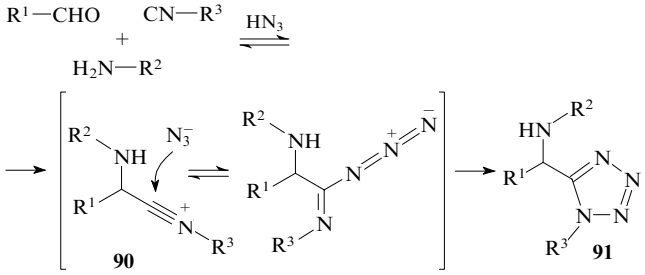
R^1 = H, Et, 4-$MeOC_6H_4$; R^2 = Bu^t, cyclo-C_6H_{11}, 3,4-$(MeO)_2C_6H_3$.

Some authors state that the above-considered examples that include post-Ugi cyclization are the most flexible applications of the Ugi MCR in the heterocycle chemistry. Nevertheless, recent years have witnessed an increase in the fraction of publications in which the strategy of heterocyclic synthesis is based on the intramolecular Ugi reaction. This approach considerably extends the scope of applicability of the Ugi reaction and provides synthetic routes to diverse heterocyclic structures with conformationally fixed peptide-like fragment, which are promising for medicinal chemistry. A considerable contribution to these works was made by the Chemical Diversity Research Institute (CDRI, Khimki, Russia, www.iihr.ru) in cooperation with ChemDiv company (CDI, San Diego, USA, www.chemdiv.com).

2. Intramolecular Ugi reactions in the synthesis of heterocycles

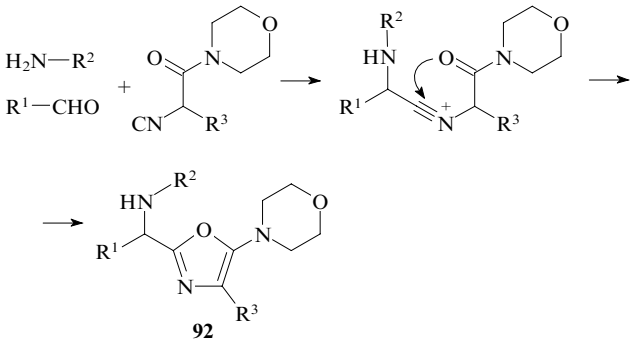
The heterocyclic synthetic strategies comprising intramolecular isocyanide-based MCR are based on the use of bifunctional reagents containing two of the functions of the Ugi ensemble. Obviously, these functions must be located in the positions suitable for heterocyclization. Examples of such reagents are amino acids, functionalized isocyanides, isocyanocarbonyl compounds, aldehydo and keto acids. Since the reagents have each two functions, their heterocyclizations are classified as three-component Ugi reactions (U-3CR). Sometimes, in order to emphasize the participation of two functions, these reactions are called in the literature four-centre three-component reactions (4C-3CR).

Unique properties of isocyanides initiated the search for new MCR differing from the Ugi reaction. For example, one can assume that the nitrilium cation **90** (α-adduct) formed in the Ugi reaction can be attacked by a nucleophile other than the carboxylate anion. A classical example is the MCR proposed by Ugi himself in his early work.[65] The reaction of aldehydes, amines, isocyanides and hydrazoic acid is accompanied by spontaneous cyclization of intermediates, finally resulting in tetrazoles **91**.



90 **91**

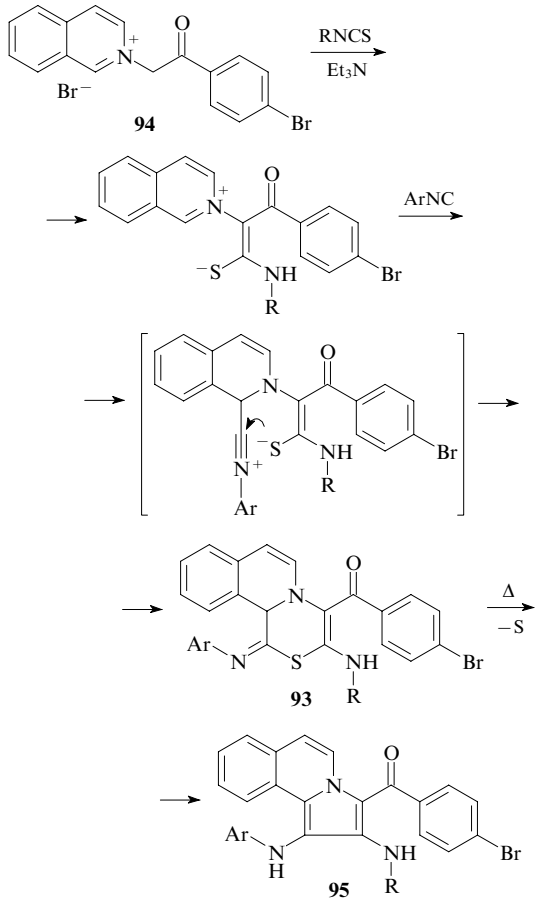
Good prospects for the heterocyclic synthesis are provided by the reactions in which this type of capture of the nitrilium cation by a nucleophile is intramolecular. For example, in the case of readily enolyzing isocyanoacetamides, O-capture takes place and oxazoles **92** are produced.[66]



92

R^1 = Pr^n, n-C_6H_{13}, cyclo-C_8H_{15}, Ph, 4-$MeOC_6H_4$; R^2 = $MeO_2C(CH_2)_5$, 3-$MeC_6H_4CH_2$, 4-$FC_6H_4CH_2$, 4-$MeOC_6H_4CH_2$, *etc.*; R^3 = Pr^i, Bn, Ph.

The intramolecular S-capture to give pyridothiazines **93** is also involved in the MCR of 2-phenacylisoquinolinium bromide **94** (a similar reaction was described for 1-phenacylquinolinium bromide) with isothiocyanates and isocyanides.[67] At elevated temperatures (> 80 °C), the reaction is accompanied by sulfur extrusion to give substituted pyrrolo[2,1-*a*]isoquinolines **95**.



94 **93** **95**

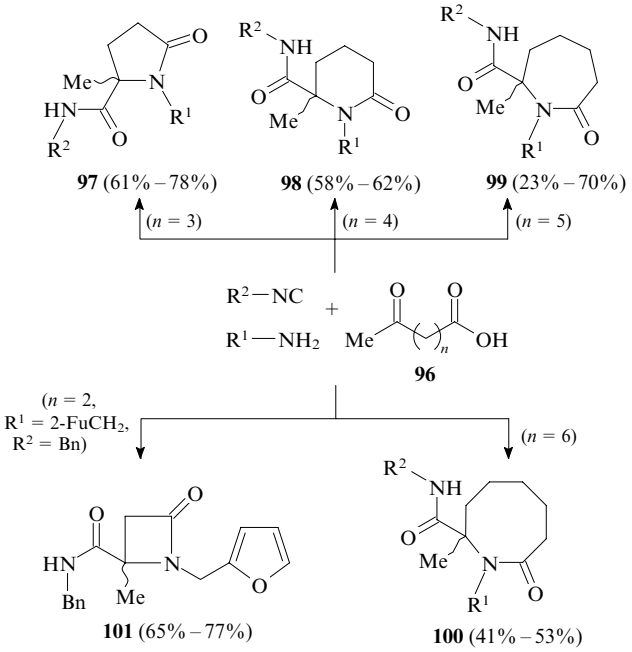
The mechanism and synthetic aspects of these reactions occurring through capture of the nitrilium cation by various N-, C-, O- and S-nucleophiles and accompanied by the subsequent cyclization of the resulting adducts were described in detail in a review.[18]

III. Intramolecular Ugi reactions based on aldehydo and keto acids in the synthesis of carbamoyl-lactams

1. Synthesis of monocyclic and annelated carbamoyl-lactams

Multicomponent reactions of isocyanides with keto and aldehydo acids as bifunctional reagents have now been studied for more than 10 years. They opened up the way to numerous heterocyclic systems incorporating a central lactam fragment.

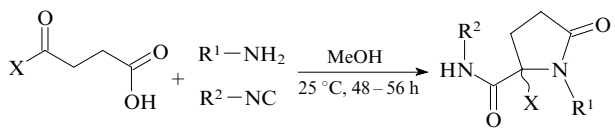
In 1997 two research groups reported a new version of isocyanide-based MCR with keto acids **96** used for the first time as bifunctional reagents.[68,69] The use of these compounds in reactions with amines and isocyanides resulted in the synthesis of carbamoyl derivatives of five-, six-, seven- and eight-membered lactams **97**–**100**,[68]; in 2004, a similar four-membered lactam **101** was prepared.[70]



R^1 = Bn, $HO_2C(CH_2)_m$ (m = 1, 2), $O(CH_2CH_2)_2N(CH_2)_2$, *etc.*; R^2 = Pr^n, Bn, *etc.*; n = 2–6.

The yields of the target lactams usually decrease with an increase in the size of the ring formed.[68,69] A study of this transformation exemplified by 4-oxopentanoic acid **96** (n = 2) has shown that the reaction occurs with a high yield in aqueous and methanol solutions. However, the procedure of choice envisages the use of aqueous solution as the products are poorly soluble in water and can be readily isolated.[71]

This reaction was used[72] to prepare a combinatorial library of 2-carbamoyl-5-oxopyrrolidines described by structure **97** using parallel liquid-phase synthesis. The reaction was carried out in methanol at room temperature. 4-Oxobutanoic acid **102** (X = H) was also used as the bifunctional reagent. The yield of products **97** (X = Me) and **103** (X = H) was in the range of 35%–68% and depended little on the nature of the keto acid used.

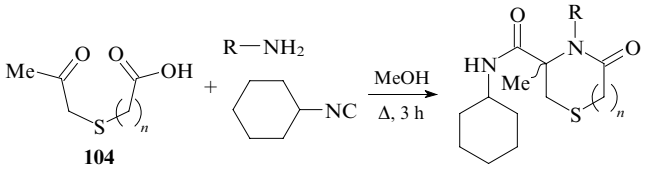


96: X = Me; **102**: X = H

97: X = Me; **103**: X = H

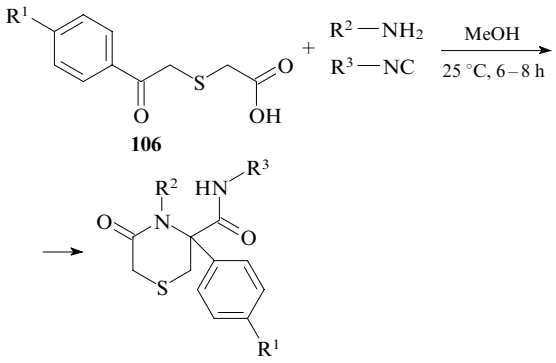
R^1 = cyclo-C_mH_{2m-1} (m = 5, 7), Ph, 3,4-$(OCH_2O)_2C_6H_3$, 2-$FuCH_2$, *etc.*; R^2 = Bu^s, cyclo-C_5H_9, CH_2=CH, $EtO(CH_2)_2$, Ph, 2-ClC_6H_4, 2-$MeOC_6H_4$, 2-Py, *etc.*

The introduction of heteroatoms into the polymethylene chain of the starting keto acids opens up the route to complication of the heterocycles obtained by intramolecular U-3CR.[73,74] For example, the reaction of (acetonylsulfanyl)acetic (**104**, n = 1) or -propionic (**104**, n = 2) acid with primary amines and cyclohexyl isocyanide in boiling methanol gives 3-carbamoyl-3-methyl-5-oxothiomorpholines (**105**, n = 1)[73] or -1,4-thiazepanes (**105**, n = 2), respectively, in high yields.[74]



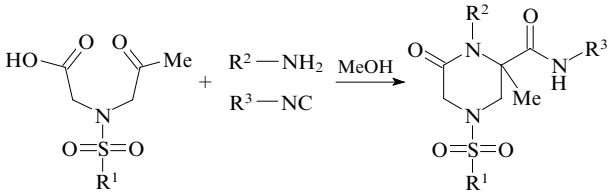
n = 1, 2; R = Bn, 4-$ClC_6H_4CH_2$, 3,4-$(OCH_2O)_2C_6H_3CH_2$, (*S*)-PhCHMe.

Subsequently, (phenacylsulfanyl)acetic acids **106** were used as the bifunctional reagents to form a library comprising sixty (3-carbamoyl-5-oxo-3-phenyl)thiomorpholines of the general formula **107**.[72]



R^1 = H, Cl, *etc.*; R^2 = $X_nC_6H_{5-n}$ (X_n = 4-Pr^i, 4-OMe, 3,5-Me_2), 2-$FC_6H_4CH_2$, *etc.*; R^3 = cyclo-C_6H_{11}, 3-Me-cyclo-C_6H_{10}, *etc.*

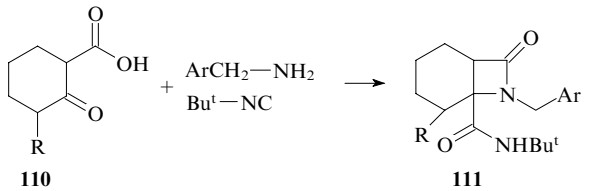
A similar strategy was employed for the synthesis of 2-carbamoyl-2-methyl-4-sulfonyl-6-oxopiperazines **108**.[75] In this case, substituted [sulfonyl(2-oxopropyl)amino]acetic acids **109** served as the starting compounds.



R^1 = Me, Et, Pr^n, Ph, 4-MeC_6H_4; R^2 = Alk, Ar; R^3 = cyclo-Alk.

Carbocyclic bifunctional reagents are suitable for preparing carbocycle-annelated 2-carbamoyl-lactams. For example, the reaction of 2-oxocyclohexanecarboxylic acid **110** with aralkylamines and *tert*-butyl isocyanide furnished *N*-*tert*-butyl-6-carbamoyl-7-furfuryl- and

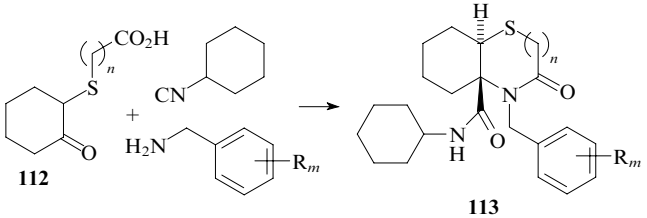
N-tert-butyl-6-carbamoyl-7-(2,4-dimethoxybenzyl)-8-oxo-7-azabicyclo[4.2.0]-octanes **111**.[76]



110 **111**

R = H, Me; Ar = 2-Fu, 2,4-$(MeO)_2C_6H_3$.

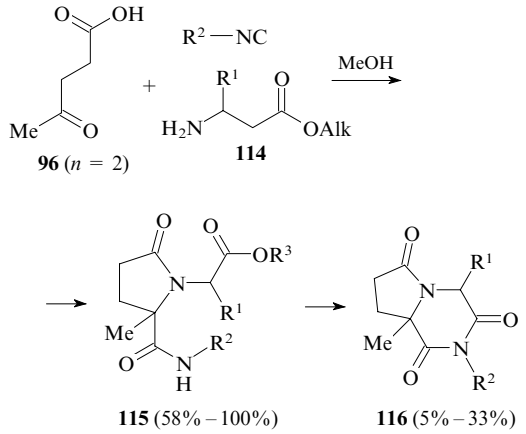
(2-Oxocyclohexylsulfanyl)acetic (**112**, $n = 1$) and -propionic acids (**112**, $n = 2$) were proposed as keto acids in a similar reaction.[73,74] They react with benzylamines and cyclohexyl isocyanide to give 4*a*-carbamoyl-3-oxoperhydrobenzo[*b*][1,4]thiazines (**113**, $n = 1$) and 5*a*-carbamoyl-4-oxoperhydrobenzo[*b*][1,4]thiazepines (**113**, $n = 2$) in high yields (> 80%).



112 **113**

$n = 1, 2$; R_m = H, 4-Cl, 3,4-OCH_2O.

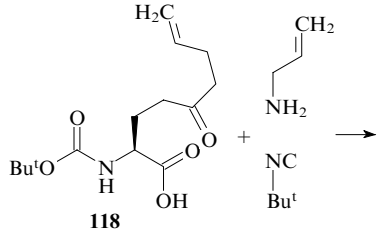
Tandem procedures for the synthesis of annelated systems comprising intramolecular U-3CR followed by cyclocondensation were described. Thus Hanusch-Kompa and Ugi[77] demonstrated the possibility of using two bifunctional reagents, levulinic acid **96** ($n = 2$) and amino acid ester **114**, in the reaction with isocyanides. Lactams **115** formed in high yields are converted to substituted dihydropyrrolo[1,2-*a*]pyrazine-1,3,6-triones **116** *via* subsequent condensation.



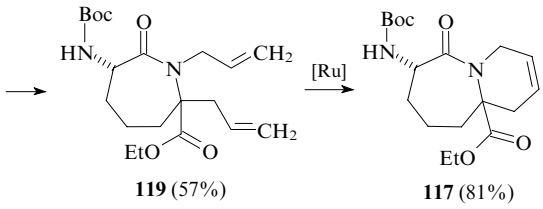
96 ($n = 2$) **114**

115 (58% – 100%) **116** (5% – 33%)

Bicyclic lactam **117** was synthesized by two consecutive transformations: intramolecular U-4CR with trifunctional keto acid **118** to give 2-piperidone **119** and ring closure by



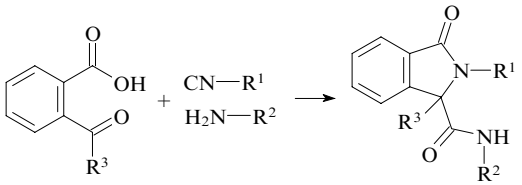
118



119 (57%) **117** (81%)

olefin metathesis. The target product **117** was thus obtained in high yield.[78]

Hanusch-Kompa and Ugi[77] demonstrated the use of aromatic aldehydo and keto acids in isocyanide-based MCR to obtain lactams annelated to benzene rings. Thus 2-formyl- (**120**, R^3 = H) and 2-acetylbenzoic acid (**120**, R^3 = Me) was converted to carbamoyl 3-oxoisoindoline derivatives **121**.

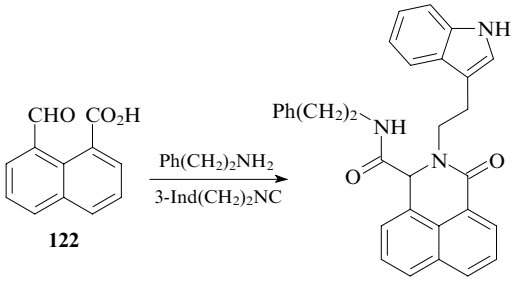


120 **121** (30% – 70%)

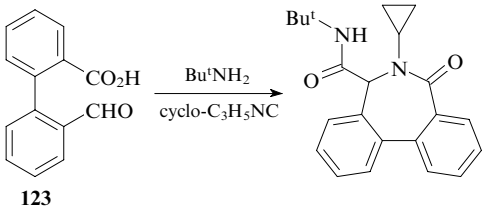
R^1 = Pr^n, Bu^s, 2-MeO-5-$BrC_6H_3CH_2$, 3,4-$(OCH_2O)C_6H_3CH_2$, *etc.*;
R^2 = Bu^s, cyclo-C_nH_{2n-1} ($n = 5-7$), EtO_2CCH_2, 2,3-$Me_2C_6H_3$;
R^3 = H, Me.

Later, reactions of 2-formylbenzoic acid (**120**, R^3 = H) with various amines and isocyanides were utilized for parallel synthesis of a combinatorial library of 1-carbamoyl-3-oxo-2,3-dihydro-1*H*-isoindoles.[79] The process was carried out in methanol in the presence of $HClO_4$ as a catalyst at room temperature for 48 – 56 h.

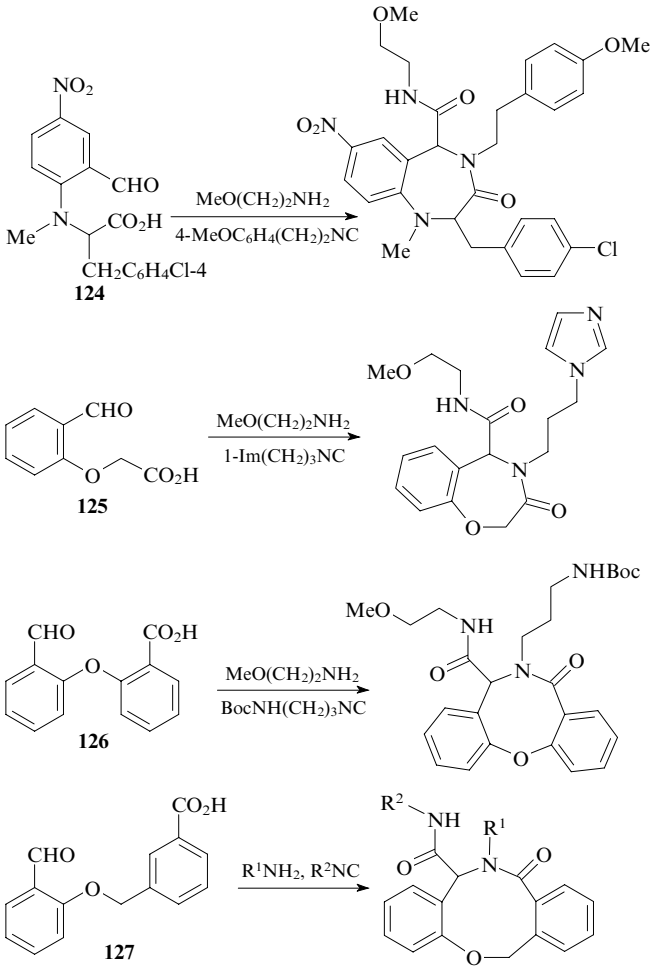
8-Formylnaphthalene-1-carboxylic (**122**),[80] 2′-formylbiphenyl-2-carboxylic (**123**),[81] 2-[(2-formyl-4-nitrophenyl)methylamino]-3-(4-chlorophenyl)propionic (**124**),[40,41] (2-formylphenoxy)acetic (**125**),[82] 2-(2-formylphenoxy)benzoic (**126**)[82] and 2-(2-formylphenoxymethyl)benzoic acid (**127**) were also introduced in the MCR as aldehydo acids.[40,41,83] The reactions of these bifunctional reagents with primary amines and isocyanides provided benzoannalated lactams.



122

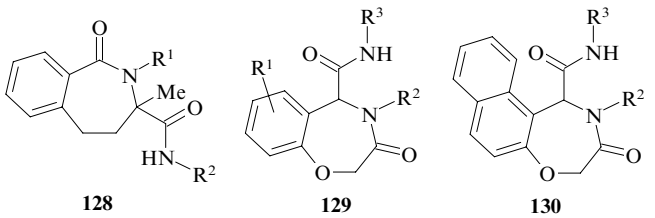


123



Ind is indolyl, Im is imidazolyl.

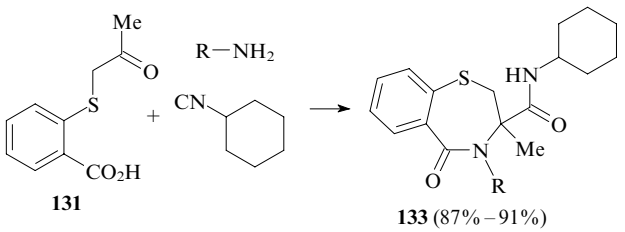
As a continuation of these studies, three aldehydo acid-based combinatorial libraries were synthesized at the CDRI. 2-(3-Oxobutyl)benzoic acid,[40, 41, 84, 85] substituted (2-formylphenoxy)acetic acids[86] and (1-formyl-2-naphthyloxy)acetic acid[79, 87] were subjected to U-3CR with amines (R^1NH_2) and isocyanides (R^2NC) to produce 3-carbamoyl-3-methyl-1-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepines **128**, 5-carbamoyl-3-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines **129** and 5-carbamoyl-3-oxo-1,2,3,4-tetrahydronaphtho[1,2-*f*][1,4]-oxazepine **130**.[79, 87] All reactions were carried out in boiling methanol for 18 h, the product yield were 40% to 75%.



128 **129** **130**

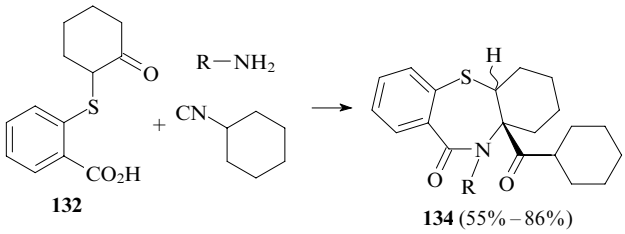
(R^1 = 4-Br, 6-OMe)

The MCR using 2-(acetonylsulfanyl)- (**131**) and 2-(2-oxocyclohexylsulfanyl)benzoic acids (**132**) as keto acids led to the synthesis of the corresponding 5-oxotetrahydrobenzothiazepines **133**, **134** in high yields (> 80%).[73, 74]



131 **133** (87% – 91%)

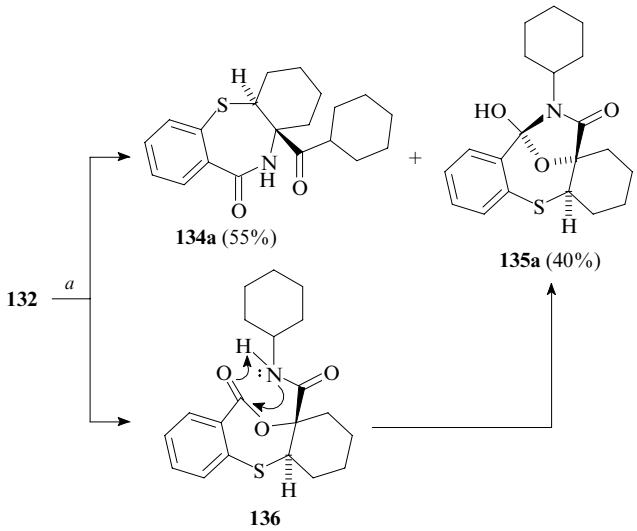
R = Bn, 4-$ClC_6H_4CH_2$, 3,4-$(OCH_2O)C_6H_3CH_2$.



132 **134** (55% – 86%)

R = H, Bn, 4-$ClC_6H_4CH_2$, 3,4-$(OCH_2O)C_6H_3CH_2$, $HO(CH_2)_3$.

The reaction of keto acid **132** and cyclohexyl isocyanide with ammonia (as the amine component) produced a mixture of two products: the expected 9*a*-carbamoyl-11-oxo-5*a*,6,7,8,9,9*a*,10,11-octahydrodibenzo[*b*,*f*][1,4]thiazepine **134a** (R = H) and orthoamide **135a**.[74] The formation of the latter was attributed to the simultaneous Passerini reaction followed by cyclization of intermediate **136**.

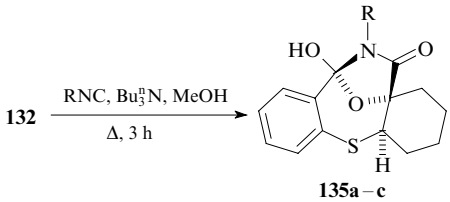


134a (55%) **135a** (40%)

132 —(*a*)→ **136**

(*a*) NH_3, cyclo-$C_6H_{11}NC$, MeOH, Δ, 3 h.

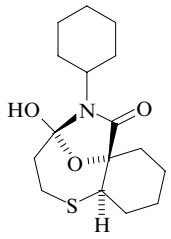
The presumptive mechanism was confirmed by the reaction of the keto acid **132** with isocyanides in methanol in the presence of tributylamine, which gave cyclic orthoamides **135a** – **c** in high yields.



132 —(RNC, Bu^n_3N, MeOH, Δ, 3 h)→ **135a** – **c**

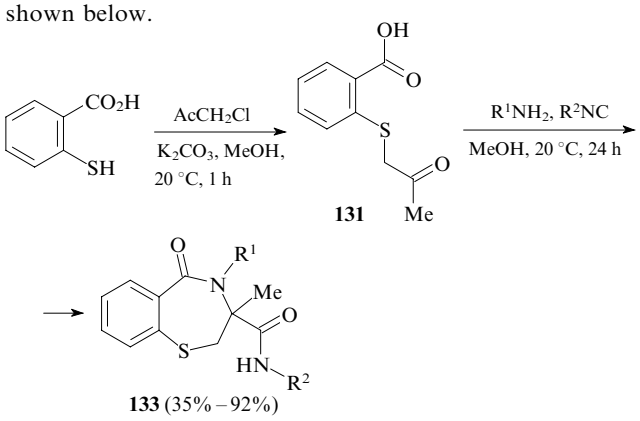
R = cyclo-C_6H_{11} (**a**, 91%), Bu^n (**b**, 87%), 4-$O_2NC_6H_4CH_2$ (**c**, 73%).

The reaction of keto acid **112** ($n = 2$) with cyclohexyl isocyanide follows a similar route; however, the yield of the final product **137** is rather low.



137 (17%)

Mironov *et al.*[88] described the synthesis of an extended series of 3-carbamoyl-3-methyl-5-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepines **133** by the reaction of 2-(2-oxopropylsulfanyl)benzoic acid (**131**) with amines and isocyanides in methanol. Keto acid **131** was synthesized by alkylation of 2-mercaptobenzoic acid by chloroacetone in the presence of potassium carbonate in aqueous methanol. Examples of 1,4-benzothiazepin-5-ones **133** prepared by the authors are shown below.

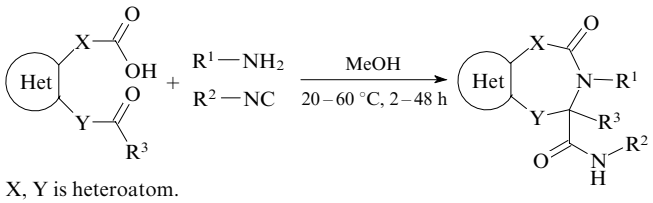


133 (35%–92%)

R^1 = cyclo-C_3H_5, Ph, 4-$MeOC_6H_4$, 4-$F_3CC_6H_4$, *etc.*; R^2 = 1-Ad, 4-$Me_2NC_6H_4$, 4-[$O(CH_2CH_2)_2N$]C_6H_4, 2,4-$(MeO)_2C_6H_3$, *etc.*; Ad is adamantyl.

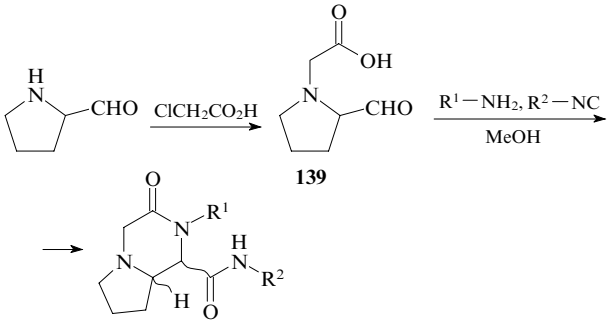
2. Synthesis of carbamoyl-lactams annelated by hetarenes

The diversity of approaches to the synthesis of heterocyclic keto and aldehydo acids, which accounts for their synthetic accessibility, considerably extends the scope of applicability of the intramolecular Ugi reaction. These bifunctional reagents were employed to synthesize six- to nine-membered carbamoyl-lactams annelated by various heterocycles.[89–95] The process is usually carried out in methanol at room temperature or on gentle heating.



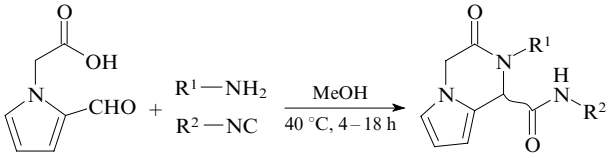
X, Y is heteroatom.

1-Carbamoyl-3-oxooctahydropyrrolo[1,2-*a*]pyrazines **138** can serve as an example of heteroannelated 2-carbamoyl-6-oxopiperazines.[95] These compounds are formed (with different diastereoselectivity) upon the MCR between (2-formylpyrrolidin-1-yl)acetic acid (**139**) obtained by alkylation of pyrrolidine-2-carbaldehyde with monochloroacetic acid and amines and isocyanides.



138

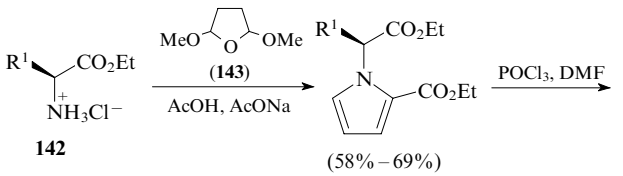
Under similar conditions, pyrrole-2-carbaldehyde and bromoacetic acid were made to react to give (2-formylpyrrol-1-yl)acetic acid (**140a**). This reacts with amines and isocyanides giving rise to 1-carbamoyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **141**.[89,90,96,97]



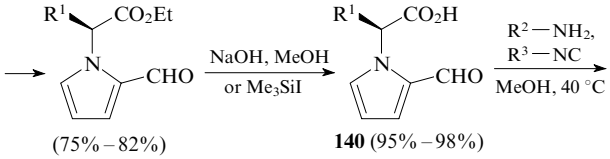
140a **141** (40%–81%)

R^1 = cyclo-C_3H_5, $MeO(CH_2)_3$, 4-FC_6H_4, 3,4-$(MeO)_2C_6H_3CH_2$, 4-$ClC_6H_4(CH_2)_2$; R^2 = iso-C_5H_{11}, cyclo-C_nH_{2n-1} (n = 5, 6, 8), 4-Me-cyclo-C_6H_{10}.

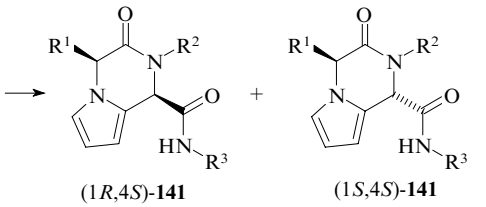
The synthesis of a number of 2-substituted 2-(2-formylpyrrol-1-yl)acetic acids starting from natural amino acids **142** and 2,5-dimethoxytetrahydrofuran (**143**) was reported.[97] The authors studied the stereochemical behaviour of these compounds in reactions with primary amines and isocyanides, resulting in the mixtures of 1-carbamoyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine **141** diastereomers (overall yield 58%–74%, isomer ratio from 1.6 : 1 to 4 : 1). These products were successfully separated by column chromatography on silica gel to single stereoisomers (1*S*,4*S*)-**141** and (1*R*,4*S*)-**141**. It was shown that the use of chiral amines in this MCR, as in the linear Ugi reaction,[98] does not increase the stereoselectivity, which is apparently determined by the bulk of the R^1 substituent.



(58%–69%)



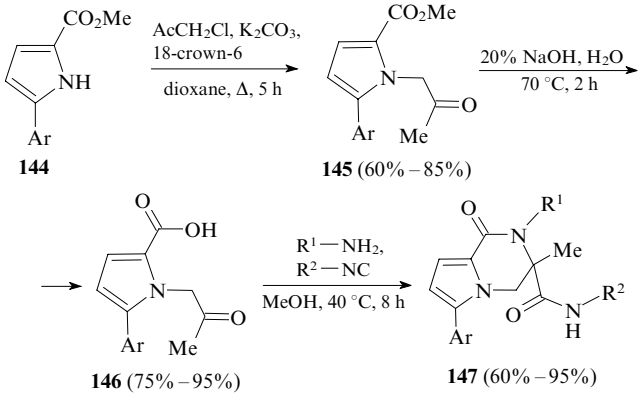
(75%–82%) **140** (95%–98%)



(1*R*,4*S*)-**141** (1*S*,4*S*)-**141**

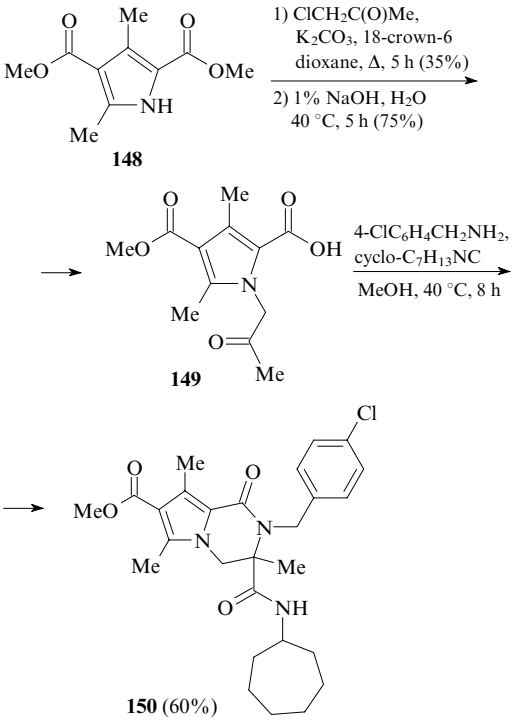
R^1 = H, Me, Pr^i, Bu^i, Bu^n, Bn.

Alkylation of methyl 5-arylpyrrol-2-carboxylates **144** with chloroacetone in dioxane in the presence of K_2CO_3 and 18-crown-6 ether produced compounds **145**, which were converted upon alkaline hydrolysis to 5-aryl-1-acetonyl-1*H*-pyrrole-2-carboxylic acids **146**. The use of keto acids **146** as the bifunctional reagents in the MCR involving primary amines and isocyanides resulted in the formation of a combinatorial library of 3-carbamoyl-3-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **147**.[89, 90, 94, 96]

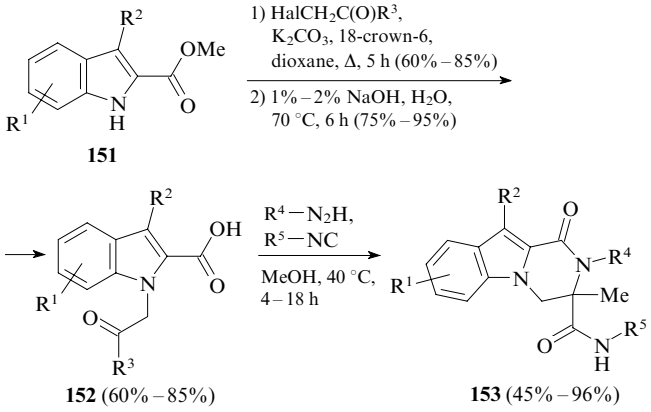


R^1 = $Me_2N(CH_2)_2$, $O(CH_2CH_2)_2N(CH_2)_2$, 4-$MeOC_6H_4CH_2$, 2-$FC_6H_4CH_2$, 2-$FuCH_2$, $Cy(CH_2)_2$ (Cy is cyclohex-1-yl); R^2 = cyclo-C_nH_{2n-1} (n = 5–8).

Under conditions similar to those described above, dimethyl 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**148**) was converted to the corresponding alkylated pyrrole, which was subjected to mild alkaline hydrolysis to be selectively transformed to monomethyl ester **149**. This product was introduced into the MCR with benzylamine and cycloheptyl isocyanide, which afforded methyl-2-(4-chlorobenzyl)-3-cycloheptylcarbamoyl-3,6,8-trimethyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-7-carboxylate (**150**) (Refs 89, 90, 94, 96).

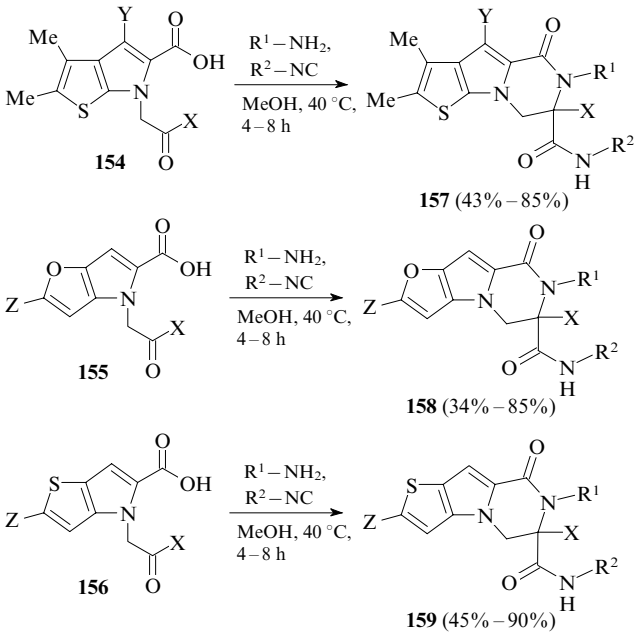


This approach was successfully used to annelate lactams by indole and pyrazine rings. For this purpose, *N*-unsubstituted methyl indole-2-carboxylates **151** were alkylated, and compounds **152** formed upon hydrolysis of the ester group were used to prepare 3-carbamoyl-3-methyl-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **153**.[89, 90, 94, 96]



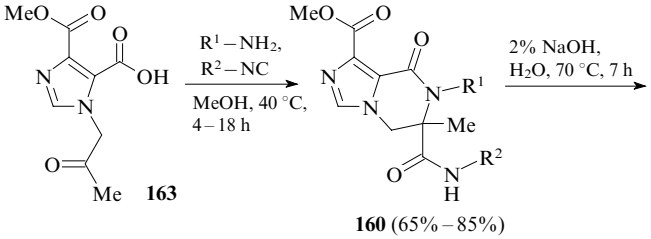
Hal = Cl, Br; R^1 = H, Me, F, MeO; R^2 = H, AcNH, 1-Pyr (Pyr is pyrrolyl); R^3 = H, Me; R^4 = Pr^i, $Me_2N(CH_2)_2$, 3-$MeOC_6H_4CH_2$, 2-Cl-3-$MeC_6H_3CH_2$, 3-$PyCH_2$, 2-$ThCH_2$; R^5 = iso-C_5H_{11}, neo-C_5H_{11}, cyclo-C_nH_{2n-1} (n = 5, 6, 8), 4-Me-cyclo-C_6H_{10}.

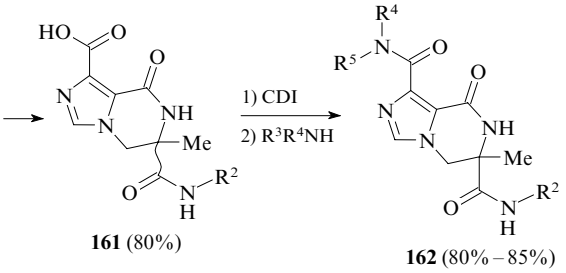
By analogy with the bifunctional reagents **152**, 2,3-dimethyl-6-(2-oxopropyl)-6*H*-thieno[2,3-*b*]- (**154**), 4-(2-acylmethyl)-4*H*-furo[3,2-*b*]- (**155**) and 4-(2-acylmethyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acids (**156**) were synthesized. These were employed in the Ugi reaction to synthesize combinatorial libraries of 6-carbamoyl-2,3,7-trimethyl-5-oxo-7,8-dihydro-6*H*-thieno[3′,2′:4,5]- (**157**),[89, 90, 99] 6-methyl-8-oxo-6,7-dihydro-5*H*-furo[2′,3′:4,5]- (**158**) and 6-methyl-8-oxo-6,7-dihydro-5*H*-thieno[2′,3′:4,5]pyrrolo[1,2-*a*]pyrazines (**159**), respectively.[89, 90, 96]



X = Me, Ph; Y = H, AcNH; Z = H, Me; R^1 = Pr^n, 3-FC_6H_4, 4-$ClC_6H_4CH_2$, cyclo-$C_6H_{11}N(Me)CH_2$, 2-H_4FuCH_2 (H_4Fu is tetrahydrofuryl); R^2 = cyclo-C_nH_{2n-1} (n = 6–8), 2,3-Me_2-cyclo-C_6H_9.

Relatively recently, an extensive series of 8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazines **160**–**162** was obtained.[89,90,94,100] Initially, methyl 6-carbamoyl-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylates **160** were formed as a result of MCR of monomethyl ester of 1-acetonyl-1*H*-imidazole-4,5-dicarboxylic acid (**163**) with various primary amines and isocyanides.

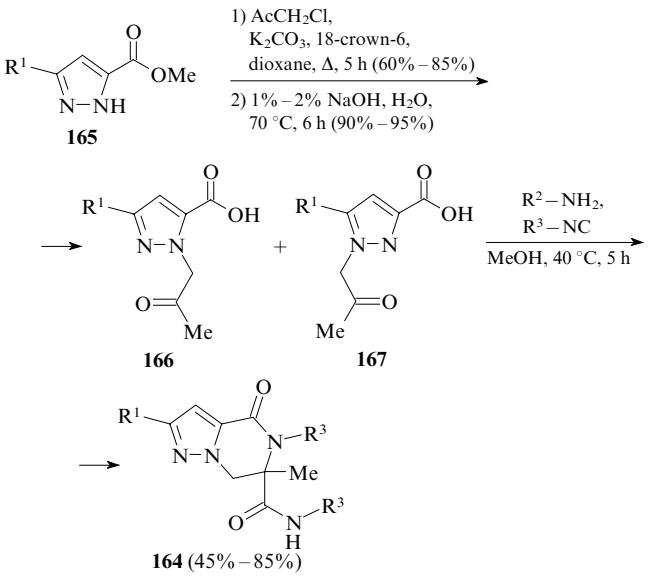




R^1 = cyclo-C_3H_5, 4-$FC_6H_4CH_2$, 2-$ClC_6H_4CH_2$, 2-Th$(CH_2)_2$;
R^2 = cyclo-C_nH_{2n-1} (n = 5–7), R^3 = H, R^4 = 4-$MeOC_6H_4(CH_2)_2$;
R^4–R^5 = $(CH_2)_2N(Ph)(CH_2)_2$.

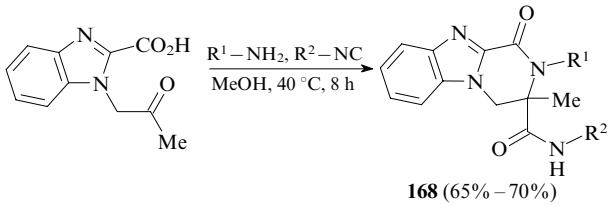
It is noteworthy that the possibility of performing the Ugi reaction with compounds containing an ester group was successfully utilized to introduce one more functional group into the molecule. For this purpose, esters **160** were subjected to alkaline hydrolysis to give acids **161**, and these were made to react with amines in the presence of 1,1′-carbonyldiimidazole (CDI).

A multicomponent synthesis of 6-carbamoyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazines **164** was described.[93] Alkylation of pyrazole **165** with chloroacetone in the presence of potassium carbonate and 18-crown-6 ether affords an equimolar mixture of two isomeric esters converted on saponification to a mixture of acetonyl-substituted pyrazolecarboxylic acids **166** and **167**. This mixture was introduced without separation into the MCR with primary amines and isocyanides. It is noteworthy that the predominance of the intramolecular Ugi reaction involving keto acid **166** over the intermolecular processes involving keto acid **167** allowed direct isolation of the target 6-carbamoyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazines **164** from the reaction mixtures without resorting to special purification techniques.



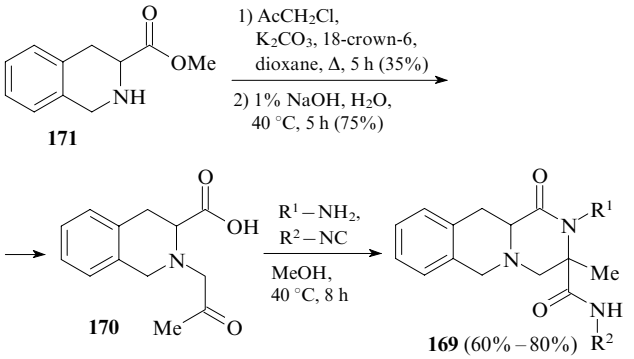
R^1 = cyclo-C_3H_5, Bu^t, EtO_2C, 4-$MeOC_6H_4$, 2-Fu, 2-Th;
R^2 = 3(4)-$MeOC_6H_4$, 2-ClC_6H_4, 2-ThCH_2;
R^3 = cyclo-C_nH_{2n-1} (n = 6–8).

The synthesis of 3-carbamoyl-3-methyl-1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazoles **168** can serve as yet another example of successful implementation of the Ugi reaction with participation of heterocyclic bifunctional reagents and isocyanides.[89,90] The target heterocyclic structures were obtained from 1-acetonyl-1*H*-benzimidazole-2-carboxylic acid, primary amines and isocyanides.

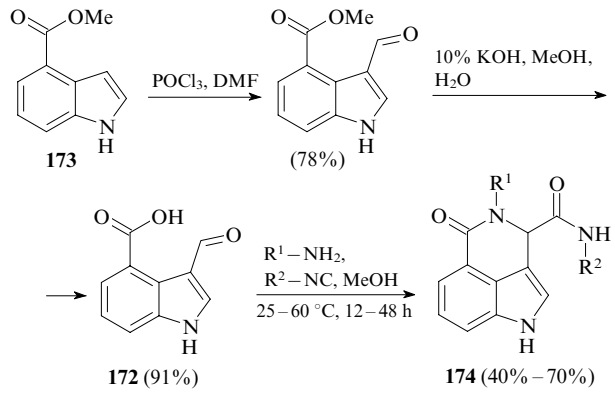


R^1 = cyclo-C_3H_5, $MeO(CH_2)_2$, $Pr^nS(CH_2)_3$, 4-FC_6H_4, 3-$ClC_6H_4CH_2$, 3-PyCH_2; R^2 = iso-C_5H_{11}, 4-$ClC_6H_4CH_2$, cyclo-C_nH_{2n-1} (n = 5–8).

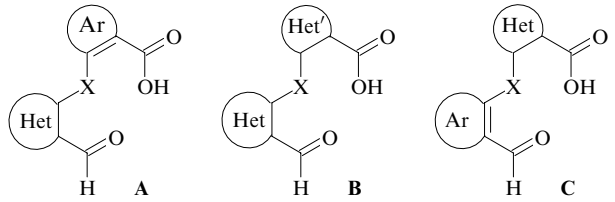
A single example of MCR resulting in heterocyclic systems **169**, which incorporate a 3-carbamoyl-1-oxo-1,2,3,4,11,11*a*-hexahydro-6*H*-pyrazino[1,2-*b*]isoquinoline fragment, was reported.[101] Compounds **169** were synthesized from 2-acetonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**170**), primary amines and isocyanides. As in the above reaction schemes, the key bifunctional reagent **170** was obtained by alkylation of methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**171**) by chloroacetone and subsequent alkaline hydrolysis.



In some reagents, the aldehyde and carboxyl functions occur in different rings of the fused aromatic system. For example, 3-formyl-1*H*-indole-4-carboxylic acid (**172**) obtained from methyl indole-4-carboxylate (**173**) reacts with amines and isocyanides to give *N*-substituted 3-carbamoyl-5-oxo-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]isoquinolines **174**.[40,41,102,103]



Great potential for the construction of azaheteroannelated systems is opened by using aldehydo acids **A**–**C** as bifunctional reagents. These compounds contain heteroaromatic and aromatic rings in various combinations (structures **A**, **C**) or two heterocycles (structure **B**).

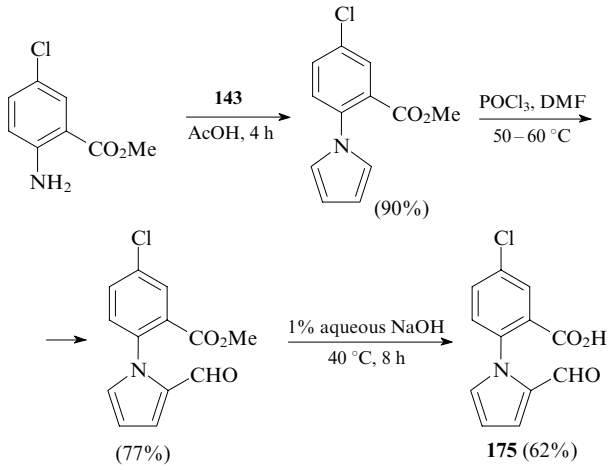


X = $(CH_2)_n$ (n = 0, 1, 2, *etc.*) or heteroatom.

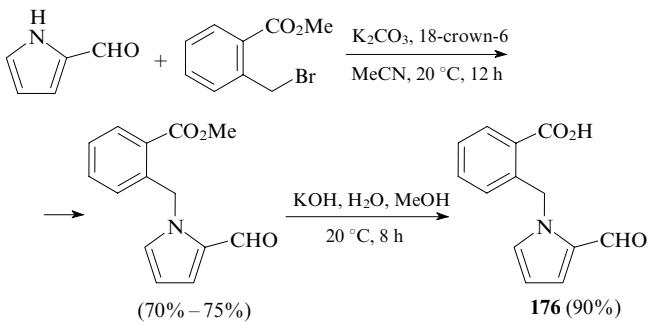
Bifunctional reagents of this type are rather convenient for the use in MCR owing to the ease of their synthesis and high degree of structural diversity, which can be created before the multicomponent reaction.

Examples of bifunctional reagents with structure **A** include 5-chloro-2-(2-formylpyrrol-1-yl)- (**175**)[91] and 2-(2-formylpyrrol-1-ylmethyl)benzoic acids (**176**).[104] Acid **175** is obtained from methyl 2-amino-5-chlorobenzoate, which reacts with 2,5-dimethoxytetrahydrofuran (**143**) in acetic acid to give 5-chloro-2-(pyrrol-1-yl)benzoic acid. This is followed by Vilsmeier formylation and alkaline hydrolysis (Scheme 8).[91]

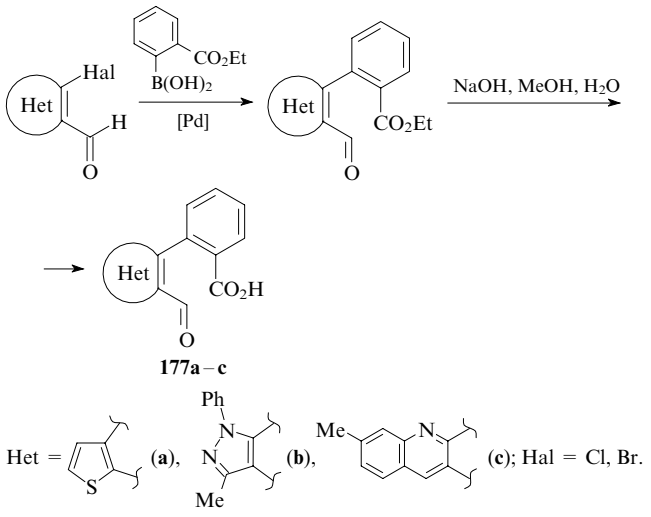
Scheme 8



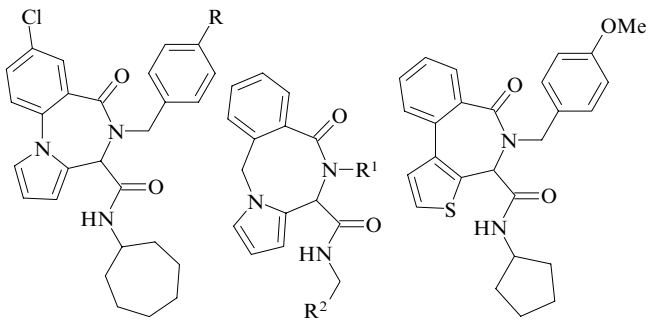
Aldehydo acid **176** was obtained by alkylation of pyrrole-2-carbaldehyde by methyl 2-bromomethylbenzoate and subsequent alkaline hydrolysis of the aldehydo ester.[103]



Other bifunctional reagents that can be assigned to structures **A** are also known. These include 2-(2-formylthiophen-3-yl)- (**177a**), 2-(4-formyl-5-methyl-2-phenyl-2*H*-pyrazol-3-yl)- (**177b**) and 2-(3-formyl-7-methylquinolin-2-yl)benzoic acids (**177c**) obtained by the Suzuki reaction from the corresponding halo-substituted heterocyclic aldehydes and 2-carbethoxyphenylboronic acid followed by hydrolysis.[105]

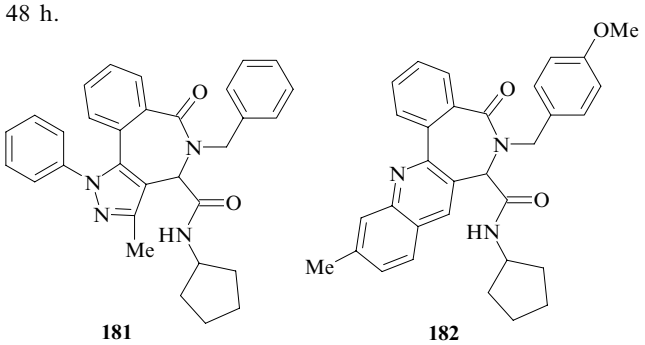


The use of bifunctional reagents **175**–**177** in the MCR with amines and isocyanides provided an extended series of carbamoyl-lactam derivatives annelated to (hetero)aromatic rings, in particular, *N*-cycloheptyl-5-benzyl-4-carbamoyl-8-chloro-6-oxo-5,6-dihydro-4*H*-benzo[*f*]pyrrolo[1,2-*a*][1,4]-diazepines **178**,[40,41,91] 4-carbamoyl-6-oxo-4,5,6,11-tetrahydrobenzo[*f*]pyrrolo[1,2-*a*][1,4]diazocines **179**,[40,41,103] *N*-cyclopentyl-4-carbamoyl-5-(4-methoxybenzyl)-6-oxo-5,6-dihydro-4*H*-thieno-[2,3-*d*][2]benzazepine **180**, *N*-cyclopentyl-5-benzyl-4-carbamoyl-6-oxo-1-phenyl-1,4,5,6-tetrahydropyr-



178 (R = H, Me) **179** [R^1 = Ar, PhCH(Me), $XC_6H_4CH_2$; R^2 = Bu^i, 4-MeC_6H_4] **180**

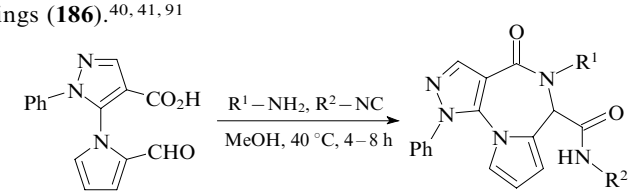
azolo[4,3-*d*][2]-benzazepine **181** and *N*-cyclopentyl-7-carbamoyl-6-(4-methoxybenzyl)-11-methyl-5-oxo-6,7-dihydro-5*H*-quino[3,2-*d*][2]benzazepine **182**.[40,41,104] All processes take place in methanol at 50 °C, the reaction time being 24 to 48 h.



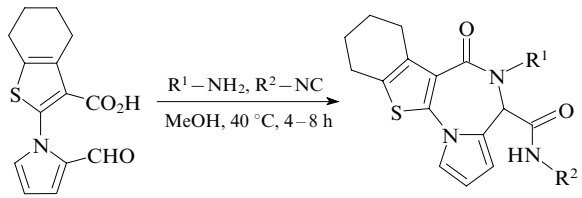
181 **182**

Examples of bifunctional reagents of type **B** are provided by 5-(2-formylpyrrol-1-yl)-1-phenyl-1*H*-pyrazol-(**183**) and 2-(2-formylpyrrol-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acids (**184**).[40,41,91] For the synthesis of **183** and **184**, the authors proceeded from heterocyclic compounds containing a methyl 3-aminoacrylate fragment. The sequence of transformations was similar to that shown in Scheme 8. Note that the proposed procedure is general and is suitable for the synthesis of a broad range of bifunctional reagents.

Two combinatorial libraries were formed by MCR from aldehydo acids **183** and **184**, namely, 1-carbamoyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepines annelated by pyrazole (**185**) and 4,5,6,7-tetrahydrobenzo[*b*]thiophene rings (**186**).[40,41,91]



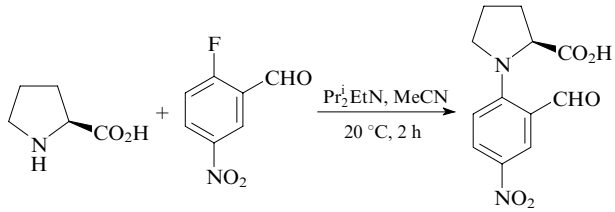
183 **185** (60%–78%)



184 **186** (67%–85%)

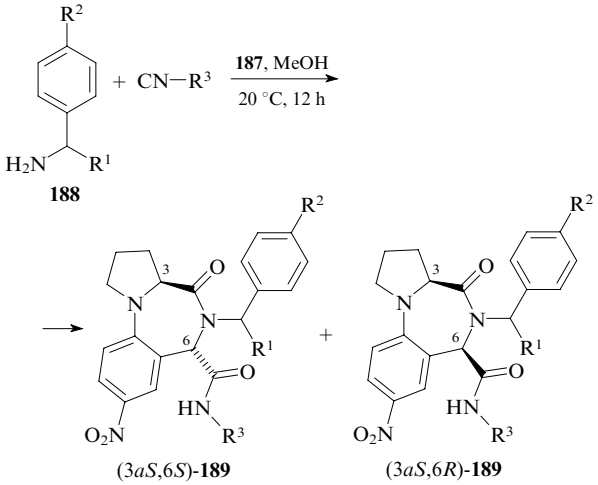
R^1 = $MeO(CH_2)_n$ (n = 2, 3), $O(CH_2CH_2)_2N(CH_2)_2$, 4-ClC_6H_4, 2-$ClC_6H_4CH_2$, 2-$FuCH_2$, *etc.*; R^2 = cyclo-C_mH_{2m-1} (m = 6, 7).

Apart from (het)aromatic aldehydo acids, bifunctional reagents containing a fully saturated heterocycle together with the aromatic ring, were introduced in the Ugi reaction. An example is (*S*)-1-(4-nitro-2-formylphenyl)pyrrolidine-2-carboxylic acid (**187**) prepared by the reaction of L-proline with 2-fluoro-5-nitrobenzaldehyde.[100,106,107]



(*S*)-**187** (80%)

The MCR of compound (*S*)-**187** with benzylamines **188** and isocyanides afforded diastereomer mixture of 6-carbamoyl-8-nitro-4-oxo-2,3,3*a*,4,5,6-hexahydro-1*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines **189**, which was separated by chromatography on silica gel. The structure of each diastereomer was determined by X-ray diffraction. The reaction was characterized by rather low stereoselectivity, the diastereomer ratio (3*aS*,6*S*):(3*aS*,6*R*) varirf from 1:1.4 to 1:2.2. The introduction of chiral (*S*)- and (*R*)-α-methylbenzylamines **188** did not affect noticeably the isomer ratio of the products.

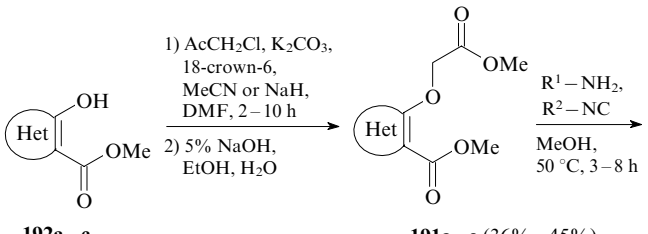


188

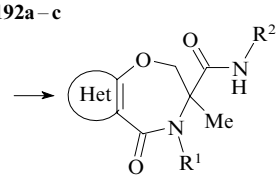
(3*aS*,6*S*)-**189** (3*aS*,6*R*)-**189**

R^1 = H, (*S*)-Me, (*R*)-Me; R^2 = H, OMe; R^3 = Bu^n, Bu^t.

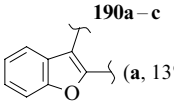
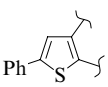
A convenient method for the synthesis of heteroannelated 3-carbamoyl-5-oxo-1,4-oxazepines **190a**–**c** was proposed.[87] Keto acids **191a**–**c** obtained by alkylation of esters of hydroxy-substituted hetarylcarboxylic acids **192a**–**c** with chloroacetone with subsequent alkaline hydrolysis were used as the key reagents. The U-3CR was carried out to convert keto acids **191a**–**c** to the annelation products of the oxazepine ring by benzofuran (**a**), thiophene (**b**) and thiazole (**c**) rings.

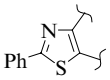


192a–**c** **191a**–**c** (36%–45%)



190a–**c**

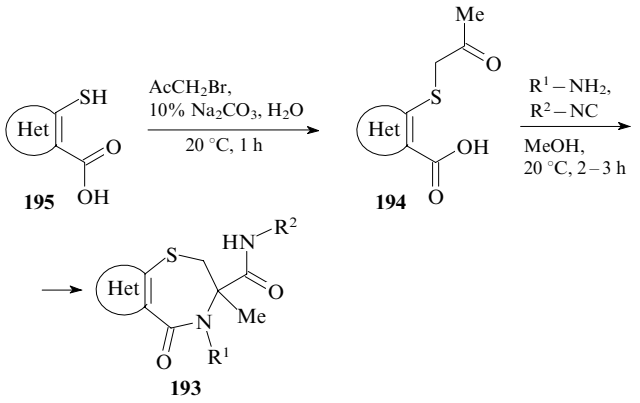
Het =  (**a**, 13%–66%),  (**b**, 89%–94%),

 (**c**, 52%–55%);

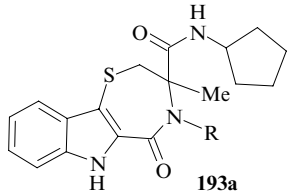
R^1 = $MeO(CH_2)_2$, 4-$MeC_6H_4CH_2$, 3-$FC_6H_4CH_2$, $Ph(CH_2)_2$;
R^2 = 2-$MeOC_6H_4CH_2$, cyclo-C_nH_{2n-1} (n = 5, 6, 8).

It should be specially noted that this reaction is applicable to a broad range of cycloaliphatic and aromatic primary amines without any substantial limitations and the proposed scheme is general and can be used successfully for the preparation of both various heterocyclic bifunctional reagents with a 3-(acetonyloxy)acrylic acid and the corresponding MCR products.[100]

A similar approach was used [108] to prepare heteroannelated 2-carbamoyl-5-oxo[1,4]thiazepines **193**. The synthesis was based on 3-(acetonylsulfanyl)acrylic acids **194** containing heteroaromatic fragments. Keto acids **194** are formed upon alkylation of readily accessible heterocyclic 2-sulfanylcarboxylic acids **195** with bromoacetones.

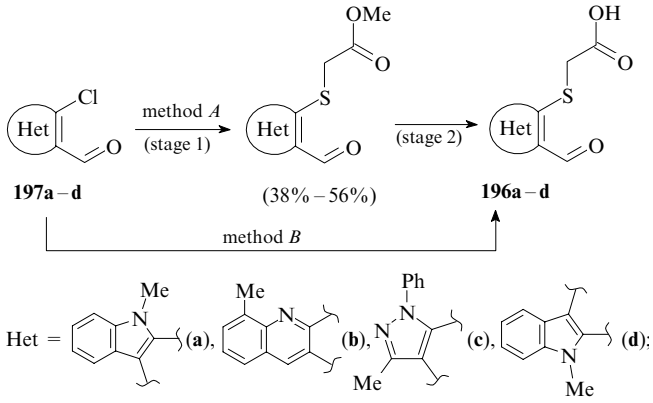


The synthesis of thiazepino[6,7-*b*]indoles **193a** by the reaction of 3-mercaptoindole-2-carboxylic acid with various benzylamines and cyclopentyl isocyanide (yields 64%–75%) can serve as an example of successful implementation of this approach.



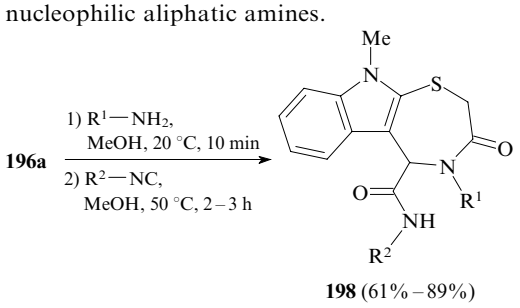
R = $X_nC_6H_{5-n}CH_2$ (X_n = H, 4-Me, 4-Cl, 4-F, 3,4-CH_2OCH_2).

In the same publication,[108] an alternative way of annelation of the thiazepine nucleus by heterocycles based on the use of (2-formylhetaryl)thioacetic acids **196a–d** is proposed. Two methods, *A* and *B*, were developed for the transformation of the starting chlorocarbaldehydes **197a–d** to aldehydo acids. For compounds **197c**,**d**, method *B* was more efficient as it gave the products in considerably higher yields.

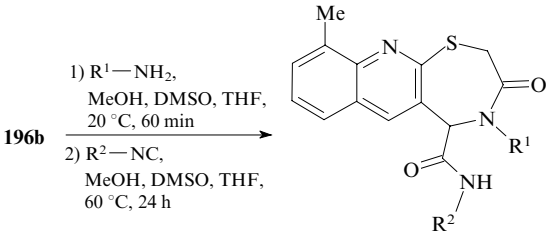


Method *A*: stage 1 — $HSCH_2CO_2Me$, DMF, K_2CO_3, 35 °C, 3 h; stage 2 — KOH, EtOH, 30 °C, 1.5 h (yields 33%–48%); method *B*: $NaSCH_2CO_2Na$, MeOH, Δ, 4 h (yields 45%–70%).

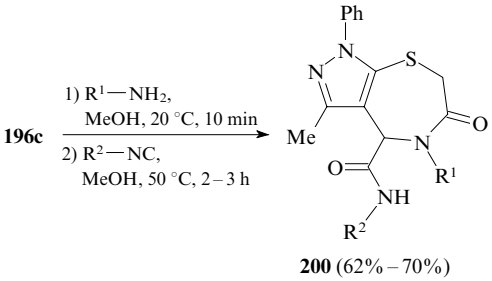
The multicomponent reaction of aldehydo acids **196a–d** with various amines and isocyanides in methanol affords 5-carbamoyl-3-oxo-1,4-thiazepines **198–201**, their yields being dependent on the order in which the components are introduced in the reaction. The best results were attained by keeping equimolar amounts of bifunctional reagent **196** and primary amine in an appropriate solvent for 10–60 min (up to complete conversion of the starting aldehydo acid) followed by the addition of equimolar amount of isocyanide and heating the resulting mixture for 1–24 h. The nature of the amine component was found to have almost no effect on the process, which can take place with cycloaliphatic, aromatic, linear and branched primary aliphatic amines. It is noteworthy that even aromatic amines with electron-withdrawing groups such as 3-$CF_3C_6H_4NH_2$ easily undergo this condensation, although they react slower than more nucleophilic aliphatic amines.



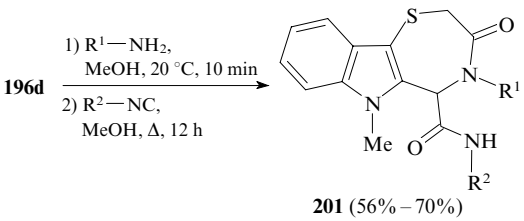
198 (61%–89%)



199 (60%–68%)



200 (62%–70%)



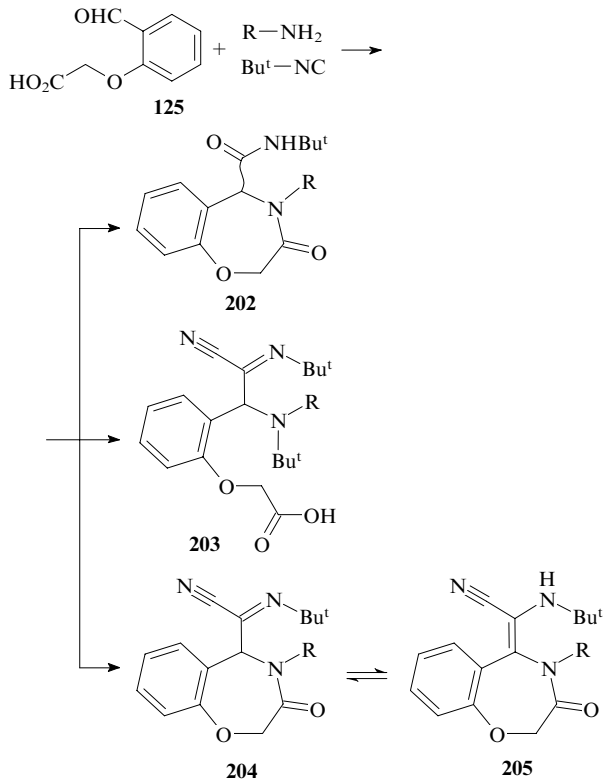
201 (56%–70%)

R^1 = cyclo-C_6H_{11}, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4CH_2$, 3,4-[$O(CH_2)_2O$]C_6H_3; R^2 = iso-C_5H_{11}, cyclo-C_7H_{13}, Bn, EtO_2CCH_2.

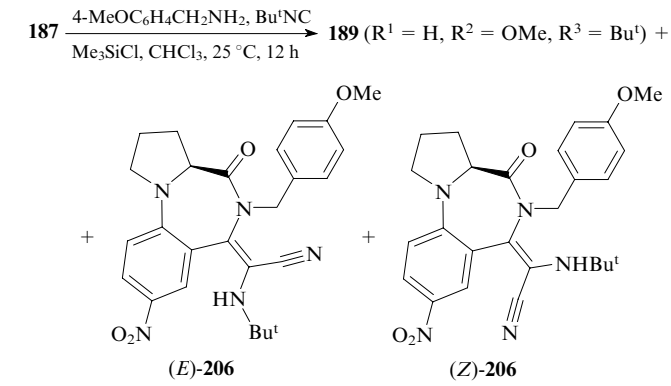
Recently, a new MCR involving aldehydo acid, amines and *tert*-butyl isocyanide taking place in the presence of Lewis acids was proposed.[109] According to HPLC, in

addition to expected *N*-*tert*-butyl-5-carbamoyl-3-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines **202**, the reaction of (2-formylphenoxy)acetic acid (**125**) gave compounds **203**–**205**. When 2 equiv. of *tert*-butyl isocyanide were used, only benzo[*f*][1,4]oxazepines **205** were obtained (Scheme 9).

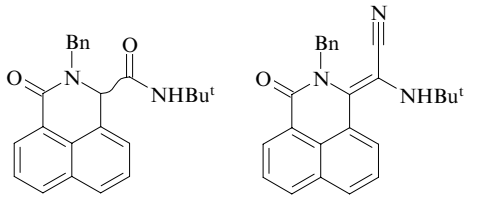
Scheme 9



The MCR of aldehydo acid **187** with 4-methoxybenzylamine and *tert*-butyl isocyanide in the presence of trimethylchlorosilane occurs in a similar way. Apart from diastereomers **189** (R^1 = H, R^2 = OMe, R^3 = Bu^t), diazepines **206** are formed. When the reaction is carried out in chloroform at room temperature and the **187** : 4-methoxybenzylamine : *tert*-butyl isocyanide : Me_3SiCl reactant ratio is 1 : 1 : 2 : 1, products **206** predominate (yield 36% *versus* 9% for **189**).[40, 41, 109]



It was shown [109] that the reaction of aldehydo acid **120**, **122** or **125** with benzylamine and *tert*-butyl isocyanide in the presence of Me_3SiCl (reactant ratio 1 : 1 : 2 : 1) in chloroform at room temperature can follow different routes. Thus in the case of 2-formylbenzoic acid (**120**), *N*-*tert*-butyl-2-benzyl-1-carbamoyl-3-oxo-2,3-dihydro-1*H*-isoindole (**121**, R^1 = Bn, R^2 = Bu^t, R^3 = H) is the only reaction product, 8-formylnaphthalene-1-carboxylic acid (**122**) is converted to *N*-*tert*-butyl-2-benzyl-1-carbamoyl-3-oxo-2,3-dihydro-1*H*-benzo[*de*]isoquinoline (**207**) and [2-benzyl-3-oxo-2,3-dihydrobenzo[*de*]-isoquinolin-(1*E*)-ylidene]-*tert*-butylaminoacetonitrile (**208**), and (2-formylphenoxy)acetic acid (**125**) is converted to [4-benzyl-3-oxo-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-(5*Z*)-ylidene]-*tert*-butylaminoacetonitrile (**205**) (R = Bn). Studies into the mechanism and possible applications of this reaction are currently in progress.

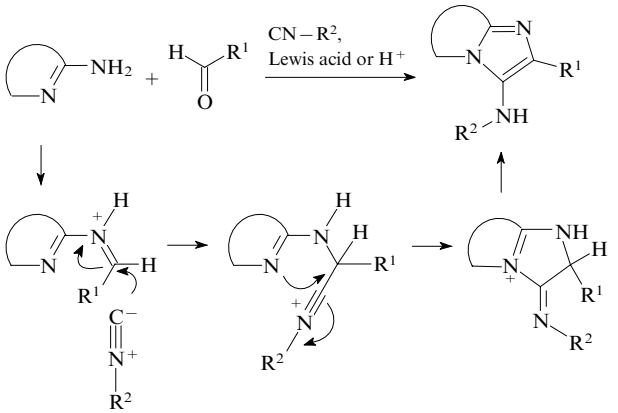


IV. Intramolecular multicomponent reactions of isocyanides and diazanucleophiles

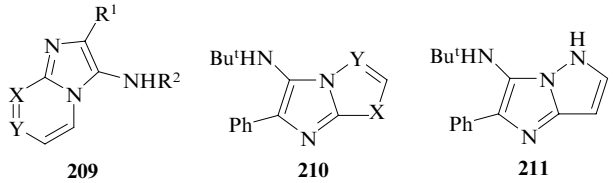
1. Reactions of α-aminoazaheterocycles

Three research groups headed by Blackburn,[110, 111] Groebke [112] (at the same time) and Bienayme [113] (somewhat later) described, independently of one another, a new version of MCR of α-aminoazaheterocycles, aldehydes and isocyanides, giving rise to aminoimidazoles annelated by various azaheterocycles. This process called the Groebke–Blackburn–Bienayme reaction (Scheme 10) requires acid catalysis and can be performed in the presence of Lewis acids, in particular, rare earth metal triflates,[110, 111] or protic acids, either perchloric [113] or acetic acid.[112]

Scheme 10



The reaction is applicable to a broad range of 2-aminoazines and 2-aminoazoles in which the amino group is usually the first of reaction sites, while the nitrogen atom of the heterocyclic nucleus functions as the nucleophile that traps the nitrilium cation (*i.e.*, plays the role of carboxylate anion in terms of the classical Ugi reaction). Thus, this process can be classified as a four-centre three-component reaction (4C-3CR), giving rise to a new imidazole ring. Heterocyclic compounds **209**–**211** shown below were prepared in this way.[110–113]

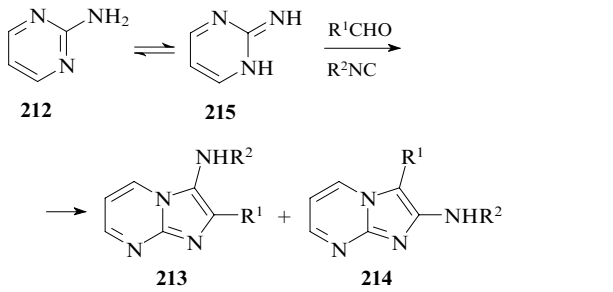


209 (X, Y = CH, N)

210 (Y = CH: X = S, O, NH; Y = N, X = S)

211

It was believed for some time that this reaction is regioselective; however, subsequently a research group headed by Bradley [114] found that the reaction of 2-aminopyrimidine (**212**) with aldehydes and isocyanides gives not only 3-aminoimidazo[1,2-*a*]pyrimidines **213** but also 2-regioisomers **214**. Depending on the reaction conditions, the nature of reactants and the acid catalyst used [0.05 equiv. $Sc(OTf)_3$ in a $MeOH-CH_2Cl_2$ mixture (1 : 4), or 2 equiv. of glacial AcOH in MeOH, or 1 equiv. of $HClO_4$ in MeOH], the ratio of the end products varied.

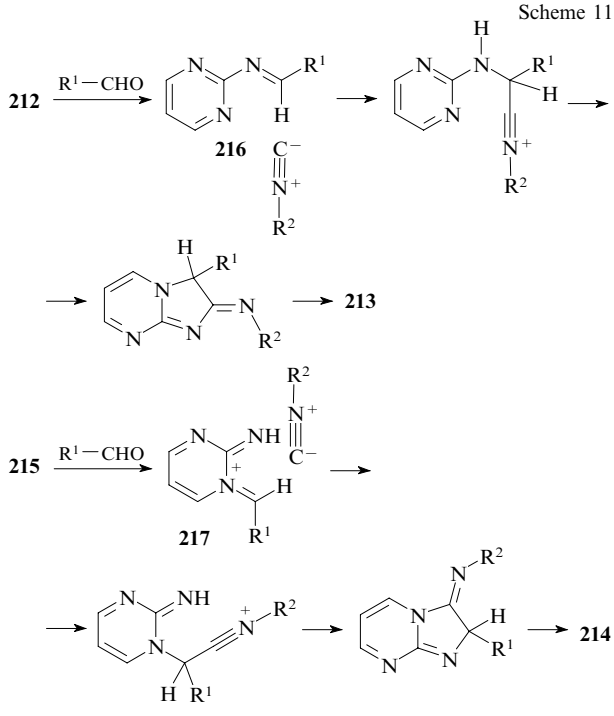


212 **215** **213** **214**

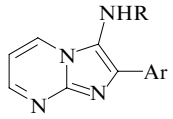
R^1 = Ph, 4-$MeO_2CC_6H_4$, 2-Th, $Ph(CH_2)_2$; R^2 = Bu^t, $Bu^tCH_2CMe_2$.

The authors attributed this result to tautomeric transformation of the starting 2-aminopyrimidine (**212**) to 2-imino-1,2-dihydropyrimidine (**215**). In this case, aldehyde reacts both at the exocyclic amino group of compound **212** and at the endocyclic nitrogen atom of compound **215** to yield intermediates **216** and **217**, respectively. The subsequent reaction with isocyanide and intramolecular cyclization furnish products **213** and **214** (Scheme 11).

Scheme 11



The problem of regioselective synthesis of 3-amino isomers has been solved in another work.[115] It was shown that performing this MCR in two stages where a mixture of 2-aminopyrimidine (**212**) and aromatic aldehyde (ArCHO) is first heated in toluene for 30 min at 50 °C and then isocyanide (RNC) is added in the presence of ammonium chloride (toluene, 25 °C) produces only 3-aminoimidazo[1,2-*a*]pyrimidines **218a–c** in satisfactory yields. The reaction time is 30 h.



218a–c

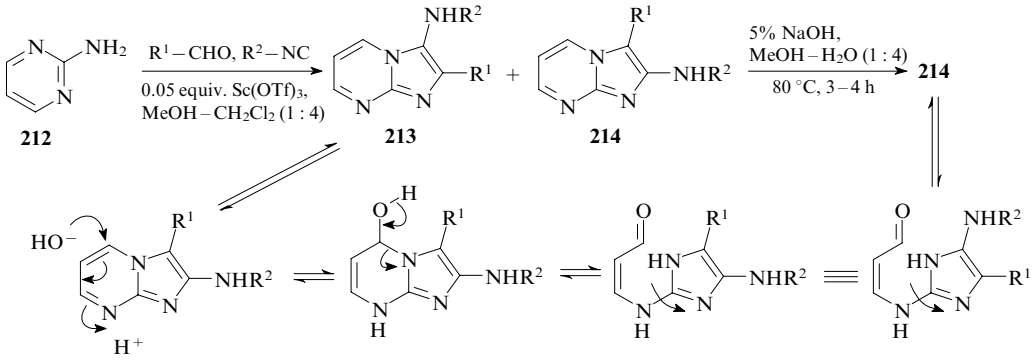
Ar = 4-$Me_2NC_6H_4$, R = Bn (**a**, 60%);
Ar = 4-Cl-3-FC_6H_3, R = 2-$MeOC_6H_4CH_2$ (**b**, 58%);
Ar = 3-$BnOC_6H_4$, R = 4-Me-cyclo-C_6H_{10} (**c**, 52%).

Meanwhile, attention is attracted by the fact that isomers **213** and **214** are interrelated as the Dimroth rearrangement products. Apparently, this prompted the authors [116] an elegant solution of the problem of regioselective synthesis of 2-aminoimidazo[1,2-*a*]pyrimidines of type **214**. In control experiments, they demonstrated that 3-aminoisomers **213** obtained regiospecifically according to a reported procedure [115] undergo ring transformation in alkaline media to give 2-amino isomers **214**. The isomerization occurs quantitatively in 3–4 h on heating the reactants in a 5% solution of NaOH in aqueous methanol (1 : 4). In view of this observation, the authors proposed a convenient method for the synthesis of regioisomers **214**. The first stage, the MCR involving 2-aminopyrimidine (**212**), took place in the presence of $Sc(OTf)_3$ being non-selective but fast and gave isomeric products **213** and **214** in good yields, their ratio varying over a broad range from 95 : 5 to 1 : 1. Then the product mixtures were treated with alkali under above-described conditions, and as a result, 3-aminoimidazo[1,2-*a*]pyrimidine **213** underwent quantitative ring transformation to 2-isomer **214** (Scheme 12).

The ring transformation mechanism is based on the known mechanism of the Dimroth rearrangement. Being generally reversible, this rearrangement proceeds toward the formation of thermodynamically more stable products, in this particular case, 2-amino isomers **214**. Apparently, for this reason, in two cases, complete conversion was not achieved. Presumably, the Dimroth rearrangement, which can also be catalyzed by acids, rather than the formation of azomethine salts at the endocyclic nitrogen atom (see Scheme 11) is the source of 2-amino isomers **214** through the MCR of 2-aminopyrimidine (**212**). At least, we failed to find reliable published data indicating the formation of isomeric aminoimidazoles in the Groebke–Blackburn–Bienayme reaction with other 2-aminoazines and 2-aminoazoles, *i.e.*, the problem of low regioselectivity arises only in the case of 2-aminopyrimidines, which are most susceptible to the Dimroth rearrangement.

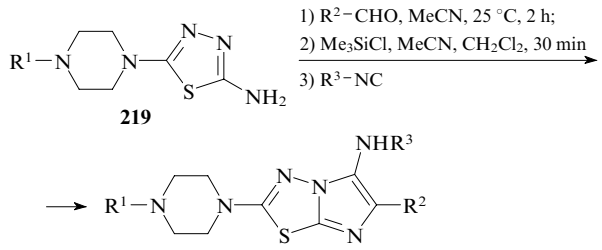
As noted above, the Groebke–Blackburn–Bienayme reaction is applicable to aminoazoles. However, the yields of annelation of imidazole by a five-membered ring are usually lower than those for a six-membered ring. In some cases, for example, for aminothiadiazole **219**, the above-listed catalysts are inefficient. Nevertheless, this problem was circumvented [117] by using trimethylchlorosilane as the promoter, and thus a series of 5-amino-2-piperazin-1-ylimi-

Scheme 12



R^1 = Pr^i, Bu^n, Ph, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-Py; R^2 = Bn, $Bu^tCH_2CMe_2$, Ph.

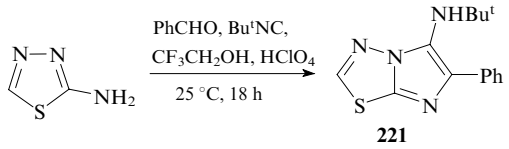
dazo[2,1-*b*][1,3,4]thiadiazoles **220** were synthesized in satisfactory or high yields.



220 (48% – 92%)

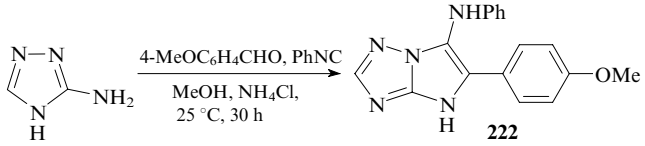
R^1 = $MeO(CH_2)_2NHC(O)$, cyclo-$C_6H_{11}CH_2C(O)$, 3-$MeOC_6H_4CH_2$, All;
R^2 = XC_6H_4 (X = 2-Me, 4-Me, 3-F, 4-F); R^3 = Bu^t, cyclo-C_5H_9.

Note that the simplest representative of this series of compounds, 3-*tert*-butylamino-2-phenylimidazo[2,1-*b*]-[1,3,4]thiadiazole (**221**), was prepared by the MCR of 2-amino-1,3,4-thiadiazole, benzaldehyde and *tert*-butyl isocyanide in trifluoromethylethanol in the presence of perchloric acid.[113]



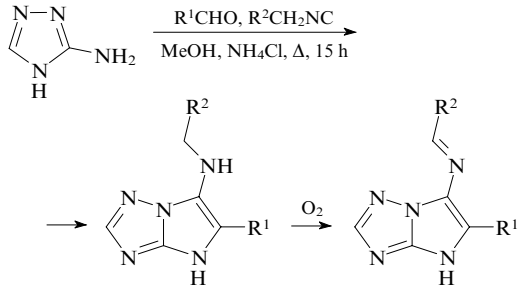
221

Krasavin and co-workers[118] studied a similar reaction with 3-amino-1,2,4-triazole as the starting bifunctional reagent. However, its reaction with 4-methoxybenzaldehyde and phenyl isocyanide in methanol gave compound **222** only in a low yield.



222

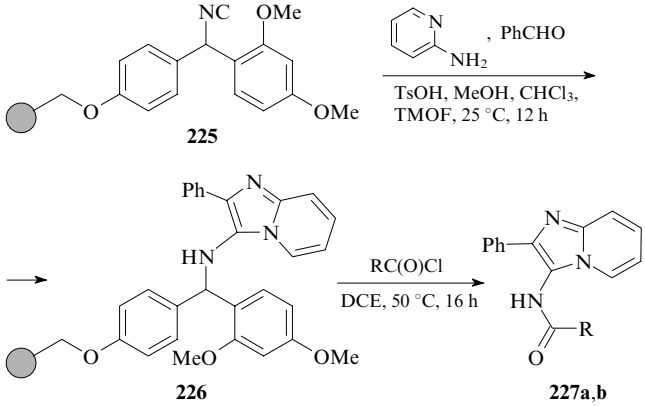
The use of various benzyl isocyanides instead of phenyl isocyanide gives rise to air-unstable 5-substituted 6-amino-4*H*-imidazo[1,2-*b*][1,2,4]thiazoles **223**, which are oxidized by atmospheric oxygen to the corresponding azomethines **224**.[118]



223 **224** (32% – 62%)

R^1 = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, *etc.*;
R^2 = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_4$, *etc.*

Chen *et al.*[119] demonstrated the possibility of using the solid-phase MCR version for the synthesis of imidazo[1,2-*a*]pyridines from immobilized isonitrile **225**, 2-aminopyridine and benzaldehyde. The imidazo[1,2-*a*]pyridine **226** formed on the polymeric support was then subjected to acylation with acyl chlorides in dichloroethane to give 3-acylamino-2-phenylimidazo[1,2-*a*]pyridines **227a**,**b**.

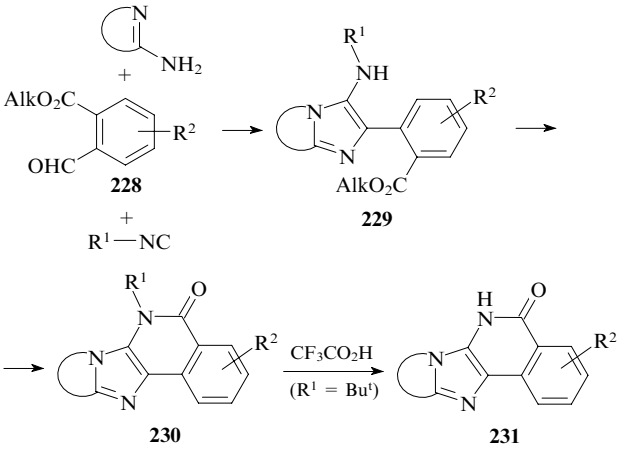


225 **226** **227a**,**b**

● is polymer; R = cyclo-C_6H_{11} (**a**), 4-ClC_6H_4 (**b**);
TMOF is trimethyl orthoformate, DCE is dichloroethane.

The Groebke – Blackburn – Bienayme reaction is successfully used in combinatorial synthesis of annelated aminoimidazoles.[14,120] Recently, Array BioPharma scientists[121] synthesized a number of heterocyclic systems annelated by an imidazole ring and containing amino groups in different positions at different distances from the heterocyclic skeleton, which may be useful for medicinal chemistry.

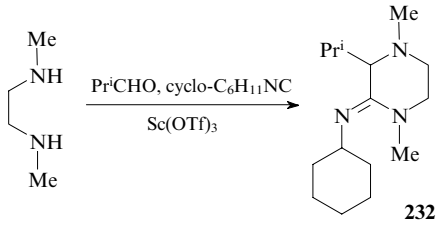
Unusual condensations that take place after the Groebke–Blackburn–Bienayme reaction were also described. For example, in the MCR of α-aminoazaheterocycles with *o*-formylbenzoic acid esters **228**, intramolecular amidation of the ester group in intermediates **229** leads to tetracyclic structures **230**.[122, 123] When *tert*-butyl isocyanide is used, the reaction products can be cleaved, without isolation, by trifluoroacetic acid to give *N*-unsubstituted annelated isoquinolones **231**.[123]



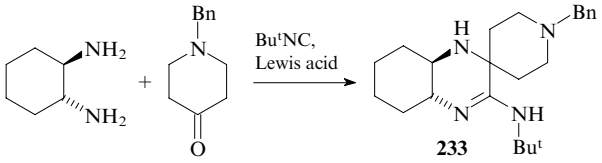
The currently available data on the Groebke–Blackburn–Bienayme reaction provide the conclusion that it can be performed only for compounds in which the amidine fragment is a part of a highly conjugated heterocyclic system, as is the case in aminoazines and aminoazoles. Moreover, the formation of conjugated aminoimidazoles is the decisive factor and the driving force of the reaction. In any case, we did not find any published data on the use of ketones instead of aldehydes as the carbonyl component in the reaction, which should give imidazolidinimines; moreover, direct evidence for unsuccessful attempts to introduce ketones into this process was reported.[112]

2. Reactions of vicinal diazanucleophiles

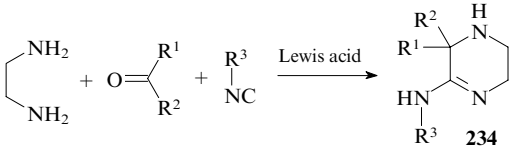
The stringent restrictions on the Groebke–Blackburn–Bienayme reaction components suggest that analogous reactions involving 1,2- and, the more so, 1,3-diazanucleophiles, if they are at all possible, should have much greater restrictions and/or require special conditions to be carried out. In 2004, Keung *et al.*[124] showed, using the reaction of *N*,*N*′-dimethylethylenediamine, isobutyraldehyde and cyclohexyl isocyanide as the only example, the possibility of preparing 2-iminopiperazine **232**. The reaction required the presence of 50 mol.% of $Sc(OTf)_3$ as the acid catalyst.



In 2007, this transformation was studied in detail[125] using the model reaction of *trans*-1,2-diaminocyclohexane with 1-benzyl-4-piperidone and *tert*-butyl isocyanide. Testing of as number of potential acid promoters of this reaction showed that the use of 1 equiv. of trimethylchlorosilane in polar aprotic (acetonitrile) or protic (methanol) solvents is the promoter of choice. The reaction was almost regioselective, and target 1-benzyl-3′-(*tert*-butylamino)octahydro-1′*H*-spiro[piperidine-4,2′-quinoxaline] (**233**) was isolated in a high yield without using chromatography.

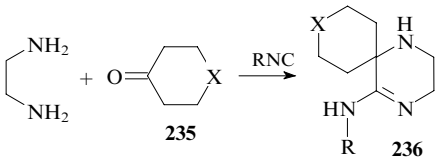


Reactions of unsubstituted ethylenediamine with carbonyl compounds and isocyanides under the above-indicated conditions were successfully carried out.[41, 125–130] 2-Amino-3,4,5,6-tetrahydropyrazines **234** were synthesized in this way.



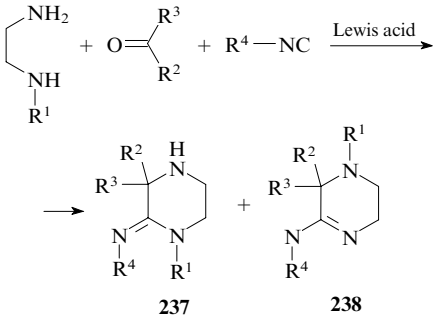
R^1 = Alk, Ar, Het; R^2 = H, Alk, R^3 = Alk, cyclo-Alk, $ArCH_2$.

This reaction was shown to be applicable to a broad range of isocyanides and, what is more important, to different carbonyl compounds including ketones, aliphatic, aromatic and heterocyclic aldehydes, both electron-rich and electron-deficient ones. It is noteworthy that the MCR of ethylenediamine with cyclic ketones **235** opens up the way for one-stage synthesis of unique functionalized spirocyclic tetrahydropyrazines **236**.[41, 125–130]

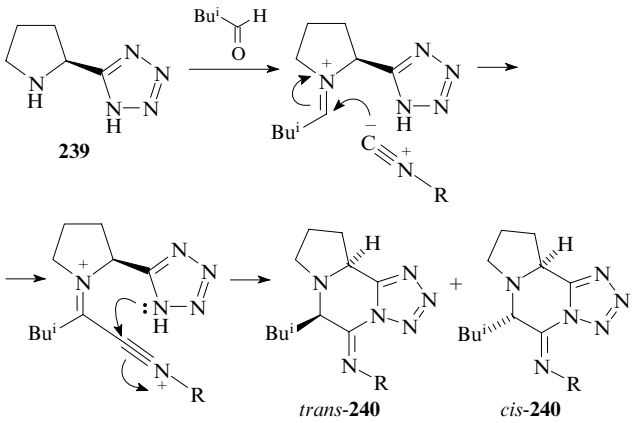


X = CH_2, O, S, NAlk.

The reactions involving *N*-monosubstituted ethylenediamines are not regioselective, resulting in mixtures of products **237** and **238** where the former predominates.[41, 128]



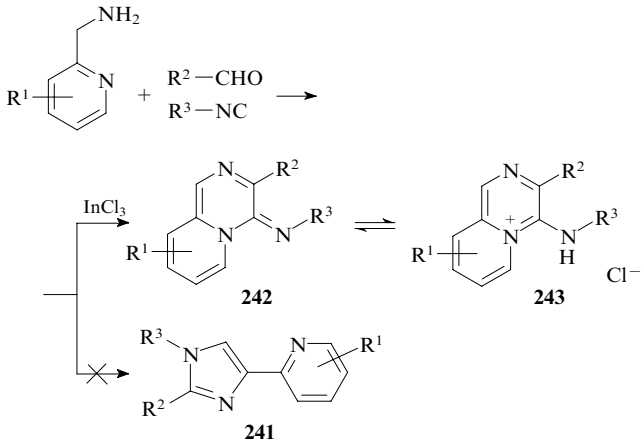
Recently a new MCR involving (*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**239**) as the bifunctional reagent was developed.[131] It was made to react with isopentanal and isocyanides to give a mixture of 8,9,10,10*a*-tetrahydropyrrolo[2,1-*c*]tetrazolo[5,1-*c*]pyrazine **240** epimers. The putative transformation mechanism is presented below.



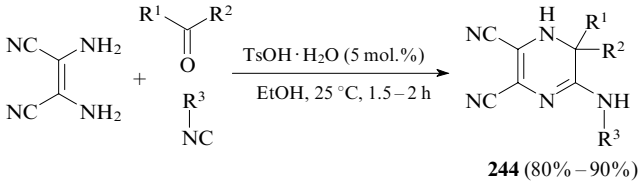
R = Bn, Bu^t, cyclo-C_6H_{11}, 4-$MeOC_6H_4$.

Depending on the reaction conditions and the reactant nature, the process has different degrees of stereoselectivity and, in some cases, the authors succeeded in isolating products as pure diastereomers.

It was shown [132–134] that aminomethylpyridines can be used as 1,2-diazanucleophiles in $InCl_3$-catalyzed MCR. This reaction is accompanied by spontaneous oxidation of intermediates and, instead of imidazolylpyridines **241**, gives the corresponding substituted pyrido[1,2-*a*]pyrazines **242** and **243**.

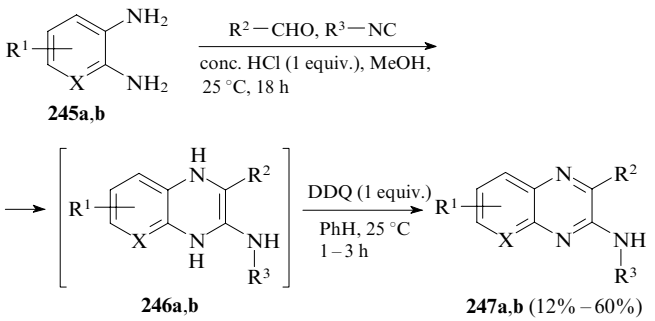


2,3-Diaminomaleonitrile was introduced into MCR.[135] It reacted with carbonyl compounds and isocyanides in ethanol in the presence of *p*-toluenesulfonic acid to give substituted 1,6-dihydropyrazine-2,3-dicarbonitriles **244** in high yield.



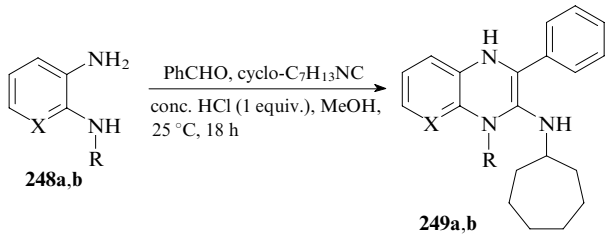
R^1, R^2 = Me, Ph; R^1–R^2 = $(CH_2)_n$ (n = 4, 5);
R^3 = Bu^t, Bu^tCH_2CMe_2, cyclo-C_6H_{11}.

A number of recent publications are devoted to MCR of aromatic and heterocyclic *ortho*-diamines. Examples of these reactions were reported.[41, 126–130, 136–138] In particular, it was shown [136] that *o*-phenylenediamine (**245a**, X = CH) and 2,3-diaminopyridine (**245b**, X = N) react with aldehydes and isocyanides in methanol in the presence of HCl to give unstable 1,4-dihydroquinoxalines **246a** (X = CH) and 1,4-dihydropyrido[2,3-*b*]pyrazines **246b** (X = N). Compounds **246a**,**b** are readily oxidized in air or in the presence of oxidants to quinoxalines **247a** (X = CH) and pyrido[2,3-*b*]pyrazines **247b** (X = N).



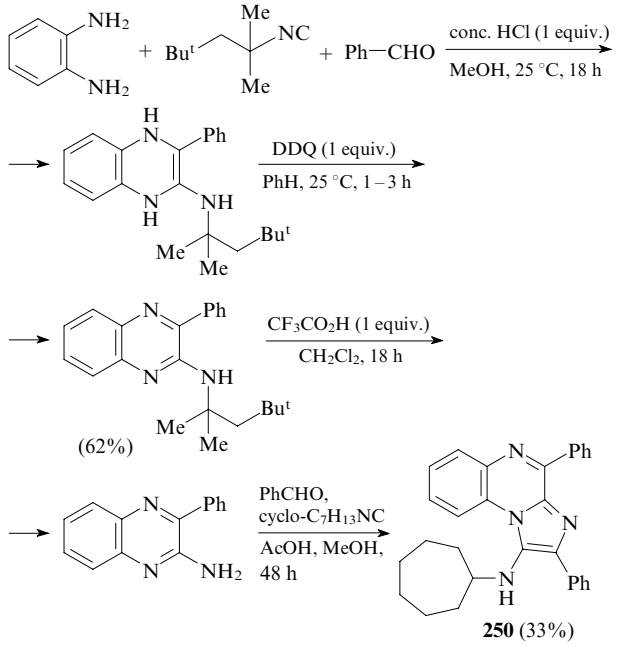
X = CH (**a**), N (**b**); R^1 = H, Me; R^2 = Ph, 2-Th, 1-methylpyrazol-5-yl;
R^3 = $MeO(CH_2)_2$, $BnCH_2$, cyclo-C_5H_9;
DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

The formation of unstable dihydrogenated heterocycles **246a**,**b** in this reaction was confirmed by reactions of *N*-methyl-*o*-phenylenediamine (**248a**) and 3-amino-2-(2-methoxyethylamino)pyridine (**248b**) with benzaldehyde and cycloheptyl isocyanide, giving rise to 2-cycloheptylamino-1-methyl-3-phenyl-1,4-dihydroquinoxaline (**249a**) and 3-cycloheptylamino-4-(2-methoxyethyl)-2-phenyl-1,4-dihydropyrido[2,3-*b*]pyrazine (**249b**).[136]



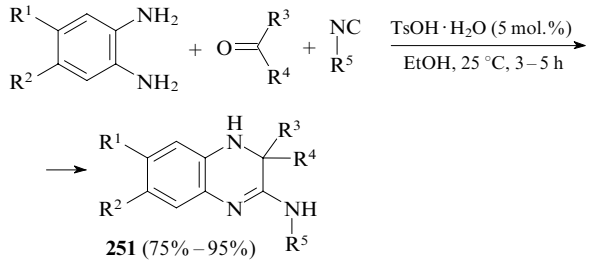
X = CH, R = Me (**a**, 44%); X = N, R = $MeO(CH_2)_2$ (**b**, 25%).

This transformation as a tandem with the Groebke–Blackburn–Bienayme reaction was used to prepare imidazoquinoxaline **250**.[138] The four-stage synthesis included the reaction of *o*-phenylenediamine with benzaldehyde and 1,1,3,3-tetramethylbutyl isocyanide, oxidation of the unsta-



ble 1,4-dihydroquinoxaline, acid-induced cleavage of 1,1,3,3-tetramethylbutyl group and, finally, one more MCR with benzaldehyde and cycloheptyl isocyanide. Ultimately, this gave 1-cycloheptylamino-2,5-diphenylimidazo[1,2-*a*]quinoxaline (**250**).

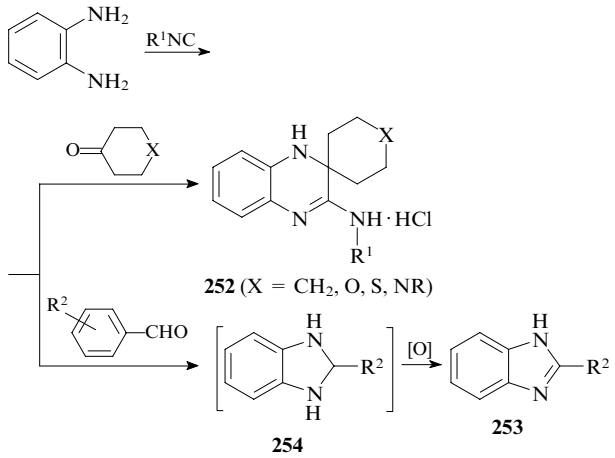
Somewhat later, independently of these works, the reaction of *o*-phenylenediamines with ketones and isocyanides in the presence of *p*-toluenesulfonic acid was successfully carried out to give 3,3-disubstituted 2-amino-3,4-dihydroquinoxalines **251**, which are not prone to imine–enamine tautomerism and/or oxidation.[139]



251 (75%–95%)

It was demonstrated that the use of aldehydes under the same conditions leads to 3-monosubstituted 2-amino-3,4-dihydroquinoxalines **251** (R^4 = H). However, in this case, only *o*-phenylenediamines containing strong electron-withdrawing substituents such as benzoyl or nitro group in the benzene ring were introduced in the reaction.

We found that the MCR conditions found previously for ethylenediamine (in the presence of 1 equiv. of trimethylchlorosilane) are applicable to the reaction of unsubstituted *o*-phenylenediamine with ketones, which gives spiro compounds **252** in high yields.[126] However, the attempts to use benzaldehydes in this reaction failed: benzimidazoles **253** resulting from oxidation of intermediate cyclic aminals **254** were the only products to be isolated and analytically identified.

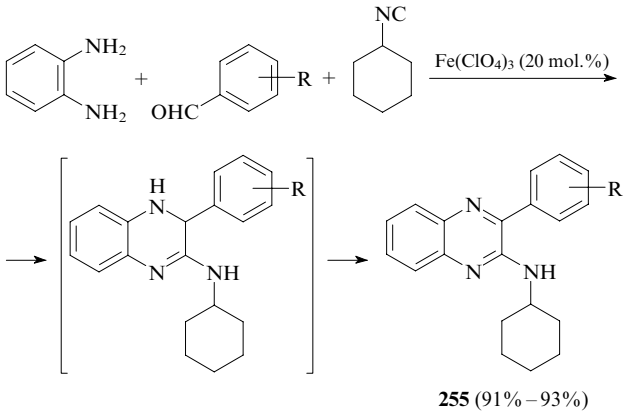


252 (X = CH_2, O, S, NR)

253

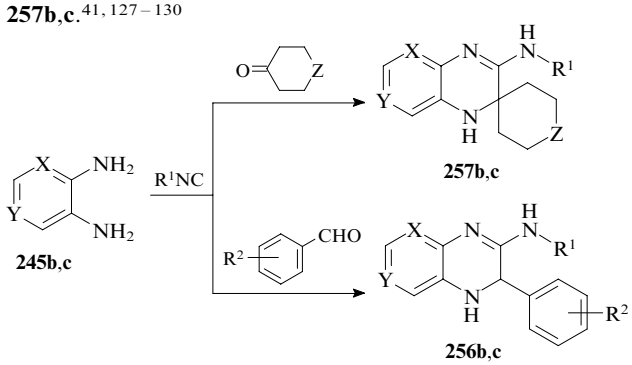
254

Note that all attempts to avoid oxidation under special conditions (inert atmosphere, special purity grade starting compounds and solvents, stabilizing additives, *etc.*) also failed. In view of these data, the reported[140] quantitative yields of compounds **255**, which result from reaction of *o*-phenylenediamine with benzaldehydes and cyclohexyl isocyanide, are surprising. In the authors' opinion, the reaction was accompanied by catalytic dehydrogenation of the intermediate dihydro derivatives in the presence of $Fe(ClO_4)_3$, which possesses clear-cut oxidative properties.



255 (91%–93%)

Whereas MCR of unsubstituted *o*-phenylenediamine with aldehydes are subject to the limitations indicated above, these limitations are eliminated when pyridine analogues are used. The reactions of 2,3-diaminopyridine (**245b**) and 3,4-diaminopyridine (**245c**) with aldehydes and isocyanides carried out in the presence of Me_3SiCl give dihydropyridopyrazines **256b**,**c**. The use of cyclic ketones as the carbonyl component affords spiro compounds **257b**,**c**.[41,127–130]



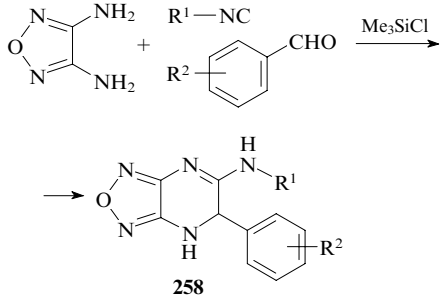
245b,**c**

257b,**c**

256b,**c**

X = N, Y = CH (**b**); X = CH, Y = N (**c**); Z = CH_2, O, S, NAlk.

1,2,5-Oxadiazole-3,4-diamine also readily reacts with aldehydes and isocyanides in the presence of Me_3SiCl; this gives 5-amino-6-aryl-6,7-dihydro[1,2,5]oxadiazolo[3,4-*b*]pyrazines **258** in high yields.[126]

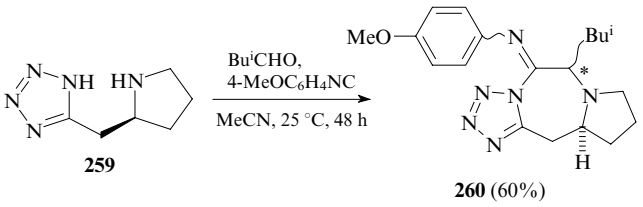


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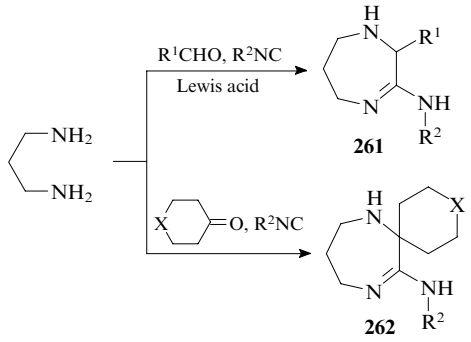
R^1 = Bu^t, Bn, 4-$ClC_6H_4CH_2$, cyclo-C_6H_{11}; R^2 = Pr^i, OH, Me.

3. Reactions of 1,3-diazanucleophiles

The historically first and the only one published in Ref. 131 example of using 1,3-diazanucleophiles is the reaction of 5-[(*S*)-1-pyrrolidin-2-ylmethyl]-1*H*-tetrazole (**259**), isovaleraldehyde and 4-methoxyphenyl isocyanide having low stereoselectivity. The transformation does not require acid catalysis and affords a mixture of diastereomeric pyrrolo[1,2-*d*]tetrazolo[5,1-*a*][1,4]-diazepine-5-imines **260** in a good yield (*dr* = 2.5 : 1; the structure of the major diastereomer was not determined).

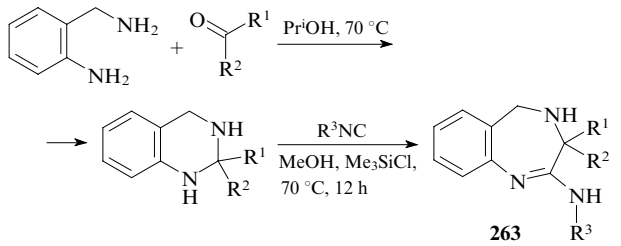


The MCR involving 1,3-diazanucleophiles as a convenient method for the synthesis of 1,4-diazepines has been described in more detail.[141] The authors demonstrated that 1,3-diaminopropane reacts with carbonyl compounds and isocyanides in the presence of 1 equiv. of Me_3SiCl to give the corresponding substituted 2-amino-4,5,6,7-tetrahydro-3*H*-[1,4]diazepines **261**, **262**. This reaction can be performed for various isocyanides and carbonyl compounds including substituted ketones and aldehydes, for example:



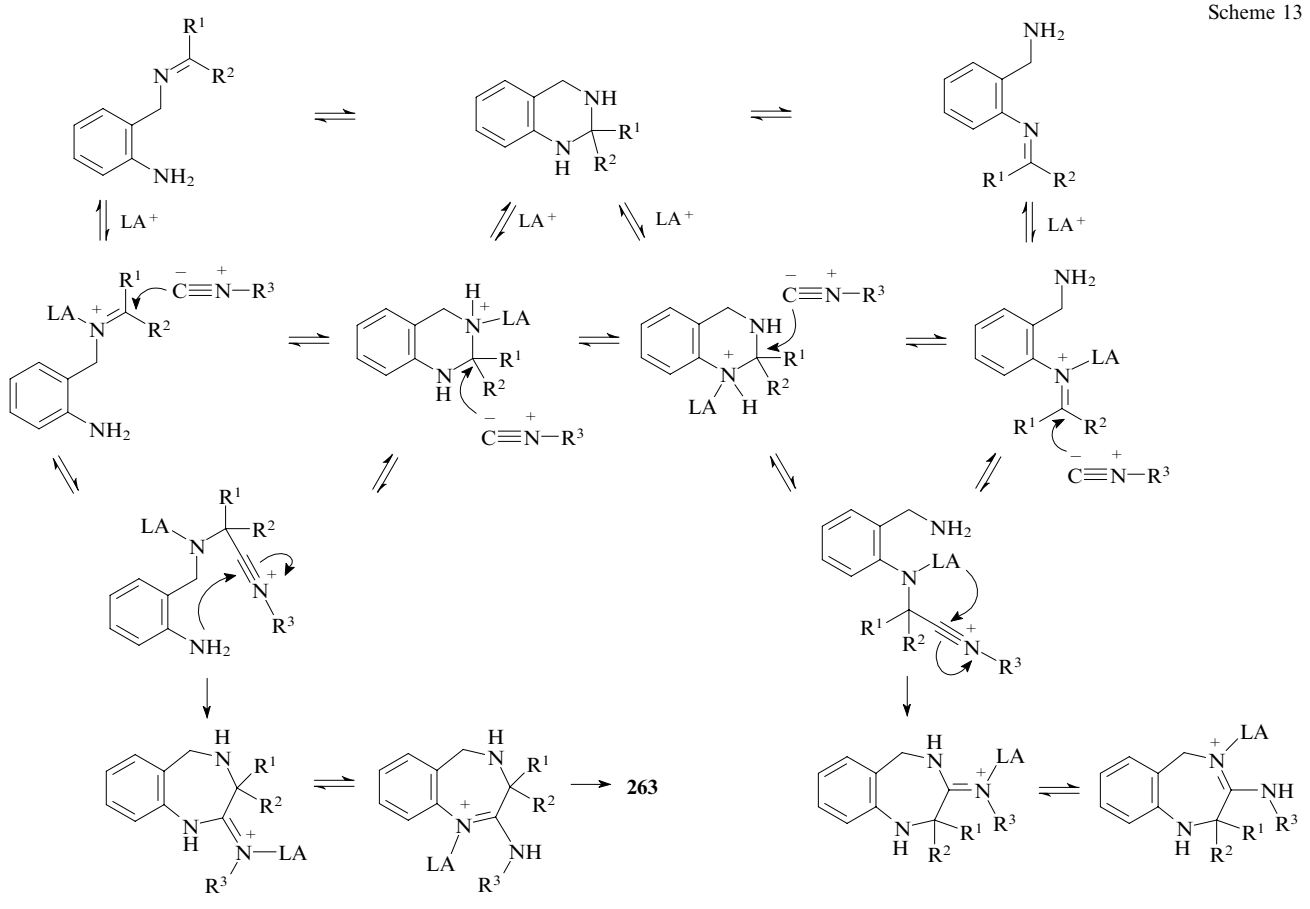
R^1 = 4-$MeOC_6H_4$, 1-methylpyrrol-2-yl; R^2 = Bu^t, cyclo-C_6H_{11}; X = CH_2, S, NY (Y = H, Boc).

Subsequently, the behaviour of 2-aminobenzylamine in this reaction as the 1,3-diazanucleophile was studied in detail; this opened up a unique approach to the synthesis of 2-amino-4,5-dihydro-3*H*-benzo[1,4]diazepines **263** (Refs 41, 128, 129 and 141) The process involves the intermediate formation of tetrahydroquinazolines, which react with isocyanides in the presence of Me_3SiCl. Although isolation of intermediate tetrahydroquinazolines is not necessary and the reaction can be carried out in the multicomponent version, the best target product yield and purity were achieved in the case where individual reactants were fed to the second stage. Note that this reaction can be regarded as formal insertion of the isocyanide into cyclic aminal, resulting in ring expansion. A broad range of isocyanides and carbonyl derivatives are suitable, in particular, cyclic and linear ketones, methyl(het)aryl ketones, aromatic and heterocyclic aldehydes containing a broad range of functional groups. This method was used to obtain diverse 4,5-dihydro-3*H*-benzo[1,4]diazepines **263**.



R^1 = H: R^2 = Ph, 4-HOC_6H_4, 4-$MeO_2CC_6H_4$, 2-$HO_3SC_6H_4$, 4-Py; R^1–R^2 = $CH_2X(CH_2)_2$, $(CH_2)_2X(CH_2)_2$ (X = CH_2, S, *N*-Boc); R^3 = $EtO(CH_2)_3$, Bu$^t CH_2CMe_2$, cyclo-C_6H_{11}.

Scheme 13



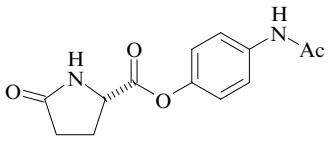
According to the probable reaction mechanism proposed by the authors and shown in Scheme 13, isocyanide insertion may follow two alternative pathways giving different regioisomers (LA is the Lewis acid).

However, the reaction is regiospecific and affords only one isomer, in particular, 2-amino isomer **263**, which is attributable to the higher basicity and, hence, reactivity of the benzyl amino group. The latter is preferred both for coordination to the Lewis acid in the cyclic aminal and for the formation of open-form azomethines.

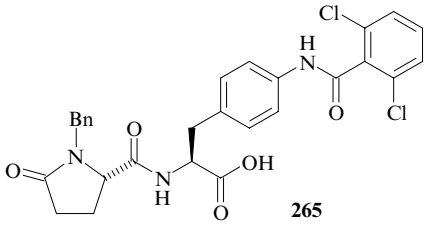
V. Biological activities of compounds obtained using multicomponent reactions

The isocyanide-based MCR considered above open up extensive prospects for the synthesis of heterocyclic compounds comprising carbamoyl-lactam and amidine fragments, which are typical of many natural and synthetic biologically active substances. These reactions afford new types of heterocyclic systems among which highly active products having different biological activity profiles have already been detected.

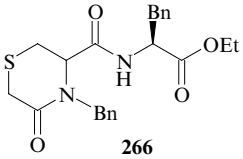
For instance, 5-oxo-L-proline **264** (Pidolacetamol) has antipyretic and analgesic action,[142] and *N*-benzyl-substituted pyrrolidine **265** is an L-phenylalanine and integrin (VLA-4) antagonist.[143] Thiomorpholines exert an inhibiting action on the serotonin receptors,[144] and, hence, they can be considered as promising drugs for treating mental depression, migraine, hypertension, Parkinson's disease and many other conditions. For example, 5-oxothiomorpholine **266** is integran inhibitor and has antiallergic and antiasthmatic activities,[145] and 5-oxothiomorpholine-*N*-(L-histidine-L-prolinamide) **267** (Montirelin analogue) is a CNS-active agent used to treat Parkinson's disease.[146–148]



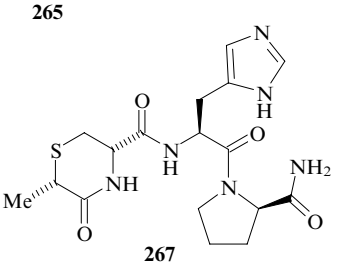
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265

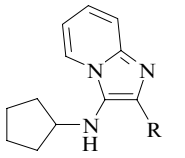


266



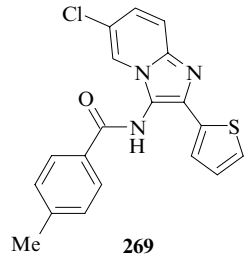
267

Among imidazo[1,2-*a*]pyridines obtained by the Groebke–Blackburn–Bienayme reaction, sodium channel modulators (compounds **268a**,**b**) promising for treating chronic pain syndrome,[149] GABA(A)-receptor agonists (GABA is γ-aminobutyric acid) (**269**, **270**),[150,151] and ubiquitin ligase inhibitor (**271**) were found.[152] The kinase inhibitor JNK1 (**272**) has an inhibition constant (IC_{50}) of 6–20 nmol litre^{-1} (Ref. 153). Compound **273** was patented as a sodium-dependent glucose transporter inhibitor (SGLT1) (IC_{50} = 10 nM) and is considered as an effective drug against diabetes.[154] Histone deacetylase inhibitors (HDACs) (**274**) (IC_{50} = 150 nM),[155] and skeletal muscle myosin regulator (**275**) were also found in this series.[156]

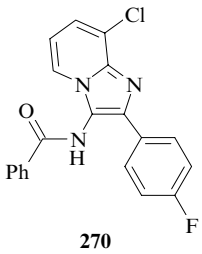


268a,**b**

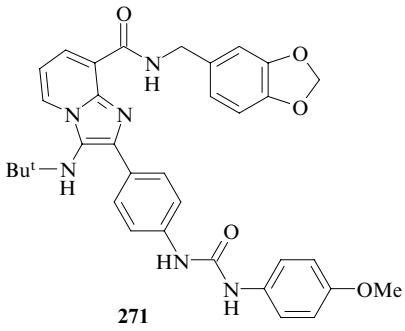
R = 3-Py (**a**),
2,5-$(MeO)_2C_6H_3$ (**b**).



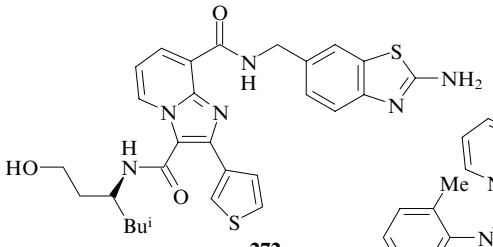
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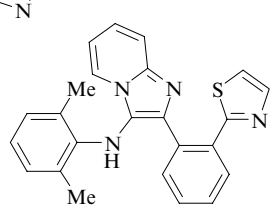
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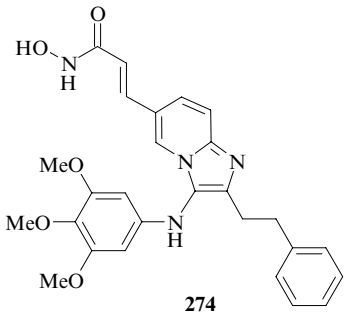
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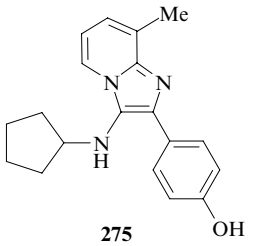
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273

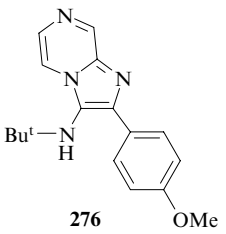


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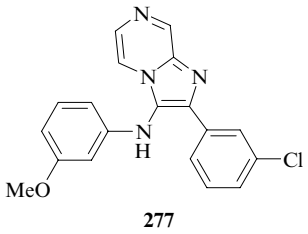


275

The series of imidazo[1,2-*a*]pyrazines, which are also prepared by the Groebke–Blackburn–Bienayme reaction, was found to include GPCR-receptor inhibitor (GPCR is the G-protein conjugated receptor) PAR2, which is a promising target in the drug therapy of tumour and inflammatory diseases. Examples are provided by the promising pathogenic angiogenesis inhibitors, compounds **276**[157] and **277**.[158] In addition, many imidazo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrimidines exhibit activities similar to that described for imidazo[1,2-*a*]pyridines.[153]

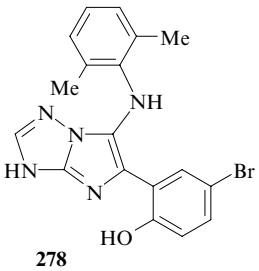


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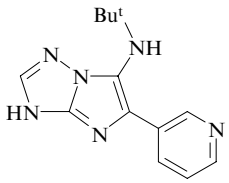


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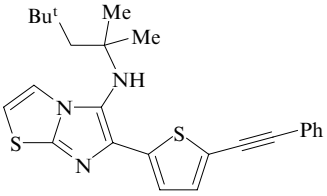
The Groebke – Blackburn – Bienayme synthesis of imidazo[2,1-*b*]azoles and the biological activities of these products have been much less studied. However, some examples of biologically active compounds of this class can be found in special literature. Among these, note intracellular toxin transport inhibitors (compound **278**),[159] α_2-adrenergic receptors blockers having analgesic activities (**279**),[160] and modulators of the metabotropic glutamate receptor 5 (mGluR5) (**280**).[161]



278

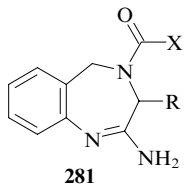


279



280

Heterocyclic systems with a benzodiazepine fragment synthesized *via* MCR are quite attractive for medicinal chemistry. Recently, 1,4-benzodiazepines **281** were patented as a new class of ligands for TLR8 receptors (a class of cell receptors with one transmembrane fragment), which makes them promising for the use as potential immunomodulators and medicinal agents for the therapy of cancer and viral diseases, including HIV, HCV, HBV and HSV.[162]



281

R = H, Me; X = OAlk, NAlk, OAr.

Thus, the broad range of biological activities of heterocyclic derivatives comprising carbamoyl-lactam and amidine fragments allows considering these compounds as potential valuable prodrugs. In this connection, the described MCR resulting in the formation of such azaheterocyclic systems may be useful for implementation of the current and future projects in medicinal chemistry and for the development of organic chemistry as a whole.

* * *

Isocyanide-based multicomponent reactions form a potent tool of synthetic organic chemistry, which provides economic and fast preparation of a broad diversity of unique heterocyclic structures on the basis of commercially or synthetically available starting compounds. The potential of these transformations is widely used by chemists in the studies aimed at the search and design of new pharmaceuticals. The growing interest in the isocyanide-based multicomponent chemistry led to the recent discoveries of new reactions providing derivatives of diverse heterocyclic systems that meet all requirements imposed on the candidate drugs. The scope of MCR is far from being fully utilized, as indicated by numerous relevant publications that appeared while the review was being prepared for publication.

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