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Synthesis of Heterocycles via Multicomponent Reactions I

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Aims and Scope

The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences etc. Metabolism is also included which provides information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic ring are also dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.

Overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which suits a larger heterocyclic community.

The individual volumes of *Topics in Heterocyclic Chemistry* are thematic. Review articles are generally invited by the volume editors.

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Preface

Synthetic sophistication has increased to an impressive level in the past two centuries. Ongoing development of novel synthetic concepts and methodologies has opened up the way to the construction of many complex and challenging synthetic targets. However, in spite of its scientific merits and its profound influence on the progress of organic chemistry, it has become clear that much of the present synthetic methodology does not meet the conditions set to future purposes. Increasingly, severe economic and environmental constraints force the synthetic community to think about novel procedures and synthetic concepts to optimize efficiency.

Robotics and combinatorial techniques allow chemists to synthesize single libraries that contain more compounds than ever before. Especially, medicinal chemists but also chemists active in the catalysis area have embraced this efficient new synthesis tool. Moreover, advances in molecular biology and genomics continue to improve our understanding of biological processes and to suggest new approaches to deal with inadequately or untreated diseases that afflict mankind. Despite all the progress in both molecular biology/genomics and combinatorial chemistry methods, it is generally recognized that the number of pharmaceutically relevant hits is not directly proportional to the number of compounds screened. Both structural diversity and complexity in a collection of molecules are essential to address.

Ideally, a synthesis starts from readily available building blocks and proceeds fast and in one simple, safe, environmentally acceptable, and resource-effective operation in quantitative yield. Inspired by Nature, the construction of complex molecules by performing multiple steps in a single operation is receiving considerable attention. Such processes, in which several bonds are formed in one sequence without isolating the intermediates, are commonly referred to as *tandem reactions*. An important subclass of tandem reactions is the multicomponent reactions (MCRs). These are defined as one-pot processes that combine at least three easily accessible components to form a single product, which incorporates essentially all the atoms of the starting materials. MCRs are highly flexible, (chemo)

selective, convergent, and atom-efficient processes of high exploratory power (EN) that minimize solvent consumption and maximize atom efficiency. Many MCRs are well suited for the construction of heterocyclic cores. MCR-based processes therefore contribute to a sustainable use of resources and form the perfect basis for modular reaction sequences comprised of simple reactions that achieve in a minimal number of steps a high degree of both complexity and diversity for a targeted set of scaffolds. As a consequence, the design of novel MCRs and their exploration as tools in especially heterocyclic chemistry receives growing international attention. Novel MCRs are applied in combinatorial and medicinal chemistry but also in catalysis and more traditional natural product syntheses.

These and other topics are at the heart of this volume of *Topics in Heterocyclic Chemistry*, which is entirely devoted to MCRs in the synthesis of heterocycles. This collection of major contributions from established scientists will certainly stimulate discussions and further development in this field of chemistry. I hope that you enjoy it.

VU University, Amsterdam

Romano V.A. Orru & Eelco Ruijter
Guest Editors

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Synthesis of Heterocycles Through Classical Ugi and Passerini Reactions Followed by Secondary Transformations Involving One or Two Additional Functional Groups

Luca Banfi, Andrea Basso, and Renata Riva

Abstract The combination of classical isocyanide-based multicomponent reactions (Ugi and Passerini) with a variety of post-condensation transformations, which take advantage of suitably positioned additional functional groups, allows the straightforward synthesis, often in 1–2 synthetic steps, of many diverse nitrogen-containing heterocycles. This review will cover all the applications of this strategy reported to date (September 2009).

Keywords Combinatorial chemistry · Diversity-oriented synthesis · Isocyanides · Multicomponent reactions · Passerini reaction · Ugi reaction

Contents

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1 Introduction

The classical isocyanide-based multicomponent reactions (IMCRs), named after Passerini [1, 2] and Ugi [3–5] (Fig. 1), are particularly well suited for combinatorial chemistry, allowing the introduction of 3 or 4 diversity inputs in just one synthetic step. The usefulness of these processes is demonstrated by their extensive applications in the synthesis of potential drug candidate libraries [6–8]. The classical versions of the Passerini and Ugi reactions are perfectly suited for exploring substituent diversity, but neither for generating different scaffolds, nor for producing heterocyclic systems. The latter drawback is quite important in view of the paramount importance of heterocycles in medicinal chemistry, and many efforts have been recently carried out to overcome it [9]. Intramolecular variants offer a useful chance to gain access to heterocyclic systems, although at the expense of one diversity input. However, the most potent strategy involves the coupling of the Ugi and Passerini reactions with post-condensation transformations [10–12].

Towards that goal, one or two additional functionalities are introduced into the initial MCR components (Fig. 2). In the case of two additional functionalities, they may interact, after the Ugi or Passerini reaction, in a post-condensation process, forming, in most cases, a heterocyclic system. In theory, any compatible function may be used and any known organic reaction can be exploited to join them, allowing an enormous number of possibilities. Moreover, proper positioning of the two additional functions into any two of the components leads, in the case of the Ugi 4-CR, to 12 different possibilities. However, looking at the many examples described below, the reader will notice that only seldom an additional group is inserted in the isocyanide component. The main reason is the well known preference of secondary amides for *s-trans* conformation. If the appendage bound to the NH group is involved in cyclization, only the *s-cis* conformer is able to undergo the process, unless large rings (>8) are to be produced, and the unfavourable rotameric equilibrium makes the heterocycle formation difficult. Even with this limitation, for each given transformation, six different combinations are possible. Finally, the

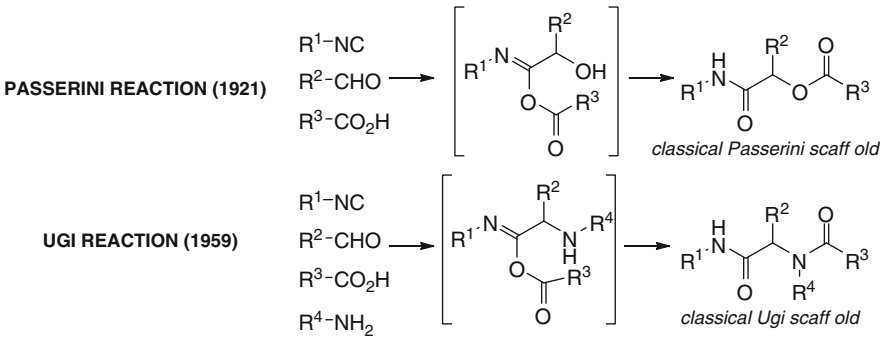

Fig. 1 Classical Passerini and Ugi reactions

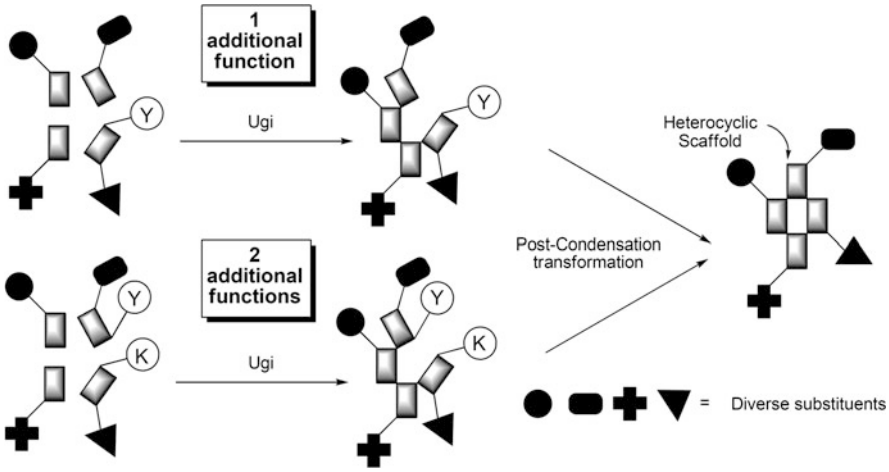

Fig. 2 General sketch of Ugi reaction followed by a post-condensation transformation

length and the structure of the spacers that connect the additional groups may be varied at will, affording heterocycles of different size and nature.

When only one additional function is introduced, it must interact with one of the moieties present in the classical scaffolds, which are in most cases the isocyanide-derived secondary amide and the acid-derived tertiary amide (Ugi) or ester (Passerini), while in fewer instances also the aldehyde-derived, central CH or CH_2 group has been exploited.

We propose here a compact classification of these diverse options. To each particular post-condensation transformation a code is given:

X-WWW[*n*][$Y_N k_E$] (for one additional function)
X-WWW[*n*][$Y_N K_E$] (for two additional functions)

where X is U or P for the respective Ugi and Passerini reaction, WWW is an abbreviation of the specific reaction (e.g. S_N2, S_NAr, RCM, Heck and so on), *n* is the ring size, Y and K indicate the specific components containing the additional groups (I = isocyanide, C = carbonyl compound, A = carboxylic acid, M = amine), k is the group of the classical scaffold involved in the post-condensation reaction (i = isocyanide derived amide, c = aldehyde derived CH or CH_2 group, a = carboxylic acid derived amide), N and E shows the role of the additional functional group in the given post-condensation transformation (N = nucleophile, E = electrophile); in those cases where nucleophilic or electrophilic reactivity cannot be clearly established (e.g. in radical reactions or olefin metathesis), these subscripts are not present.

For example, U-S_N2[7][$M_N A_E$] indicates a nucleophilic aliphatic substitution following an Ugi reaction to give a 7-membered ring, where the additional nucleophile is embedded in the amine component and the leaving group (electrophile) is introduced in the carboxylic component. When more than one new ring is formed,

two or more digits are used inside the square brackets, putting first the ring whose size depends on the spacer's length.

In this chapter we focus only on post-condensation transformations that follow "classical" Ugi or Passerini reactions (including the intramolecular ones) and that lead to heterocycles. Therefore, we will not report the many examples of post-condensation reactions applied to non-conventional Ugi or Passerini scaffolds generated by variants of these venerable reactions. Also post-IMCR transformations that involve the inclusion, in the final cyclic system, of sub-structures not initially present in the starting component will be overlooked.

In the discussion of the various examples, we will concentrate more on the secondary transformations than on the Ugi or Passerini reaction themselves, which are in most cases carried out under standard conditions (alcoholic solvents for the Ugi and apolar solvents for the Passerini). Classical IMCRs are well known to be, in most cases, poorly diastereoselective and thus the stereochemical aspect, already described in a previous review [13], will be mostly ignored in this chapter.

2 One Additional Functional Group

2.1 Isocyanide-Derived Amide Acting as Electrophile

Post-Ugi intramolecular acylations can be performed on substances that contain a single additional functionality, represented by an amine or an alcohol introduced in either the carbonyl, carboxylic or amine component. These nucleophiles can interact with the secondary amide derived from the isocyanide to give lactams or lactones. These transformations reduce the number of diversity inputs of the overall sequence to three, owing to loss of the isocyanide R^1 group. Analogous post-Passerini acylations are difficult to achieve because of competitive reaction of the more reactive ester group. Even in the case of Ugi reaction, the main problem is the poor reactivity of the secondary amide towards S_NAc reactions. To facilitate these cyclizations, a series of special isocyanides, called "convertible", have been developed during the years [14–28]. Figure 3 shows the most important ones. After the Ugi condensation, the secondary amide is converted, under suitable conditions (typically under acid catalysis, with the exception of isocyanides **2** and **6**), into intermediates **7–12**, where the acyl group is activated towards intramolecular S_NAc.

This general strategy has been employed for the synthesis of several types of heterocycles, including diketopiperazines [29–32], ketopiperazines [29, 33], pyrrolidinones [34], 1,4-benzodiazepines [29, 32, 35–37], dihydroquinoxalinones [29], hexahydropyrrolodiazepines [38], and oxetanones [27]. Figure 4 shows some selected examples.

Benzodiazepinediones **15** have been synthesized starting from anthranilic derivatives **13** and Armstrong convertible isocyanides **1**. When the amino group of **13** is secondary, it does not interfere too much with the Ugi reaction, and the acid

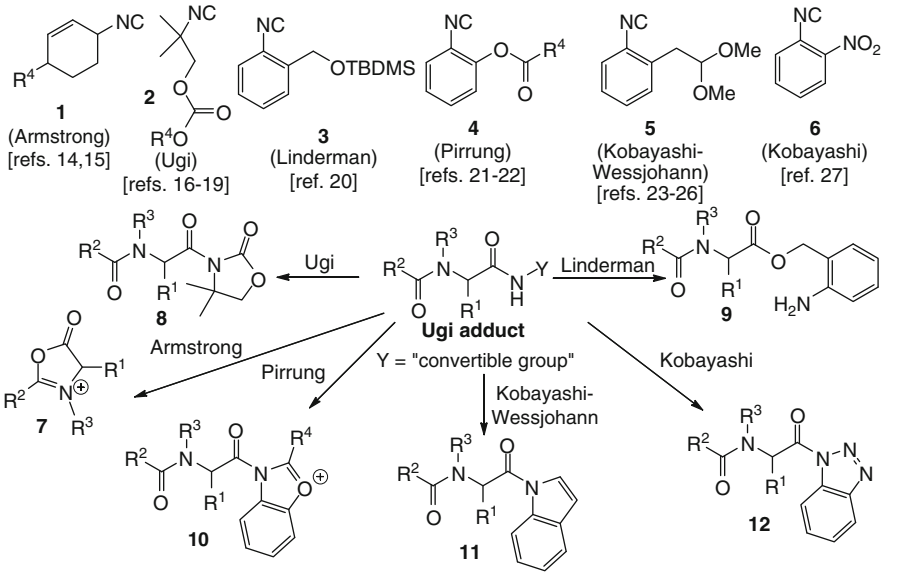

Fig. 3 Convertible isocyanides

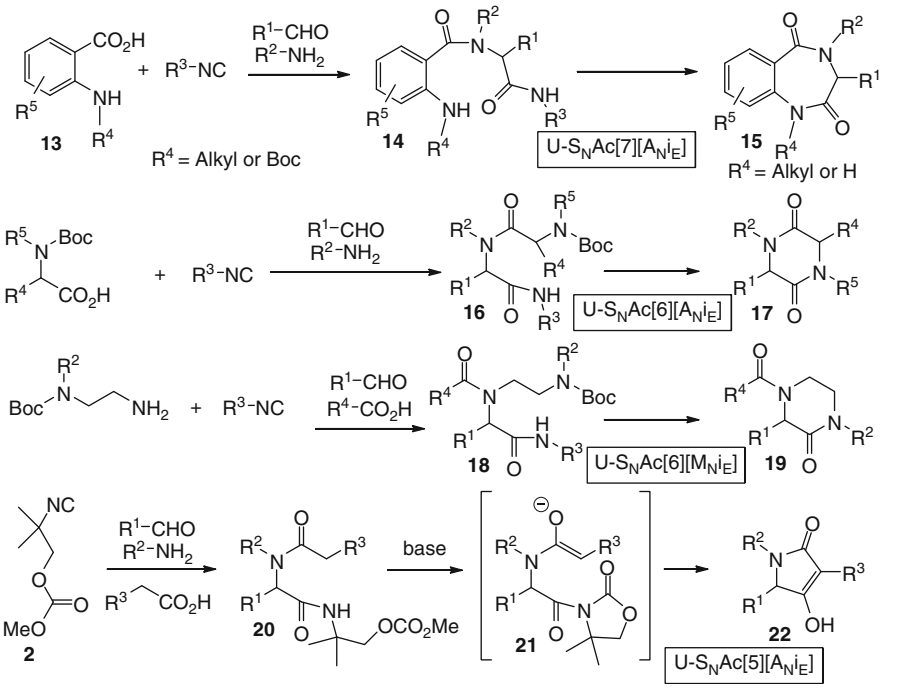

Fig. 4 Synthesis of heterocycles through intramolecular nucleophilic displacement of the isocyanide derived group

treatment leads to the desired heterocycle **15** through a münchnone intermediate such as **7** [35]. On the contrary, primary amines can themselves take part in the Ugi reaction and are therefore better used in masked form [37]. A particular useful protection is the *tert*-butyl urethane, which can be cleaved under the same conditions used for the activation of the secondary amide [37]. This strategy has been named "Ugi-de-Boc-cyclization" (UDC).

Diketopiperazines **17** and ketopiperazines **19**, which are important "privileged" structures, have been obtained by using various convertible isocyanides and by introducing the additional amino function, respectively, on the carboxylic [39] or amine component [33].

The use of "convertible" isocyanides is not always necessary: in particular cases, also normal alkyl [32, 40] or aryl [30] isocyanides have been employed for this task. For example, microwave irradiation of the Ugi adduct **16** (R^3 = *n*Bu) at 120°C in the presence of 10% CF_3CO_2H gave the desired diketopiperazines **17** in good yield, without the need to use more complex convertible isocyanides. However, for the synthesis of ketopiperazines **19**, butyl isocyanide was found to be unsuitable.

Alternatively, starting this time from aryl isocyanides, the secondary amide can be activated by conversion into an imide by the treatment with Boc_2O [29, 38, 41]. This strategy was employed in the synthesis of compounds **15**, **17** and **19** [29], and is particularly appropriate for solid-phase library synthesis.

While in most reported cases the nucleophiles were amines, there were few examples involving heterocyclic nitrogens [40], alcoholic oxygens [27] or carbon nucleophiles [42, 43] too. Figure 4 shows a recent example of tandem Ugi–Dieckmann protocol [42]. Ugi convertible isocyanide **2**, which requires a basic activation, was used, allowing a domino activation-cyclization of the intermediate **20** to give pyrrolidinediones (tetramic acids) **22**.

2.2 *Isocyanide-Derived Amide Acting as Nucleophile*

Intramolecular cyclization can be driven by an alkyl nucleophilic substitution of a leaving group incorporated into one of the Ugi components, with the secondary amide derived from the isocyanide serving as the nucleophile. This strategy overcomes a limitation of the Ugi MCR arising from the fact that only secondary amides can be obtained from the isocyanide component. For example, diketopiperazines **24** can be obtained by using α-haloacids as input and by performing cyclization of chloroamides **23** under basic conditions and with the aid of ultrasounds [44, 45] (Fig. 5). Alternatively, the same privileged structures can be synthesized from **25** by an aza-Michael reaction [46].

Introduction of a halogen atom into the amine component is not possible, but an alternative solution is represented by the use of ethanolamines **26**, performing the cyclization under Mitsunobu or Mitsunobu-like conditions to give ketopiperazines. These compounds have been observed as side products in reactions promoted by

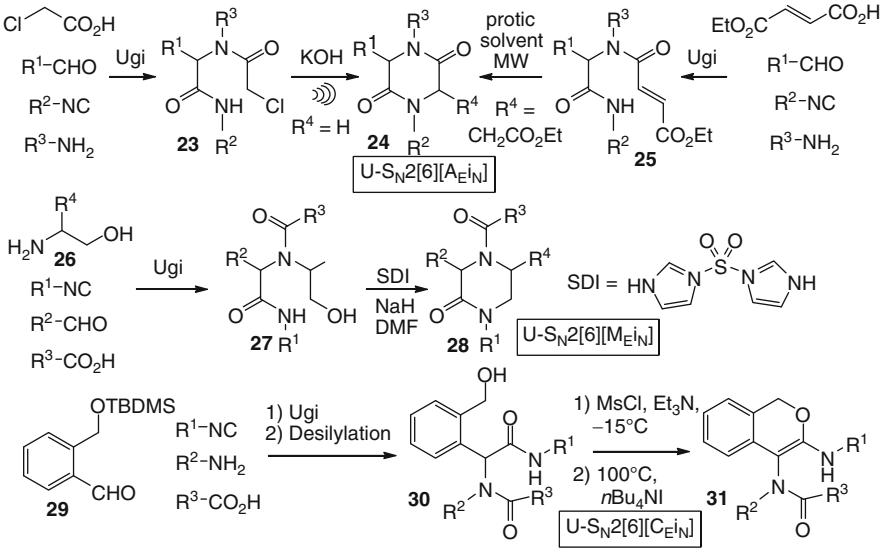

Fig. 5 Post-Ugi cyclization driven by nucleophilic alkyl substitutions where the isocyanide-derived amide serves as nucleophile

sulfuryl diimidazole (SDI) and NaH, which were intended to lead to other heterocyclic scaffolds [47]. Preliminary results have demonstrated that this ketopiperazine synthesis may be quite general.

Although diketo- and ketopiperazines can be formed by coupling the Ugi reaction with an intramolecular acylation using "convertible" isocyanides, as described earlier, the approach that involves S_N2 reactions enables the introduction of an additional substituent R^1, avoiding the loss of the diversity carried by the isocyanide.

When the alcoholic function was embedded in the carbonyl component instead, as in **29**, cyclization under Mitsunobu conditions or with SDI was unsuccessful, but warming of the methanesulfonate of **30** gave unexpectedly the novel isochromenes **31** through an *O*-cyclization process [48].

The Ugi or Passerini adducts **33** and **35** derived from α-halo- [49–51], α-sulfonyloxy- [49], α-acyloxy- [49, 52], α-alkoxy- [52] or α-hydroxycarbonyl compounds **32** [53] in principle can be manipulated to produce the respective β-lactams **34** and **36** through cyclization reactions involving the isocyanide-derived NH group (Fig. 6). However, when R^5 is not hydrogen, the β-lactam synthetic plan depicted in Fig. 6 has been reported only in the context of the Passerini reaction [49–51]. The problem with these processes is not associated with the Ugi reaction itself, but with the propensity of highly encumbered tertiary amides to undergo $N \rightarrow O$ acyl migration [54] when X = OH. On the other hand, starting from glycolaldehyde dimer and aromatic isocyanides, β-lactams can be generated via the Ugi–Mitsunobu reaction sequence [53]. When the SDI procedure is used, aliphatic isocyanides can also be employed as substrates [55].

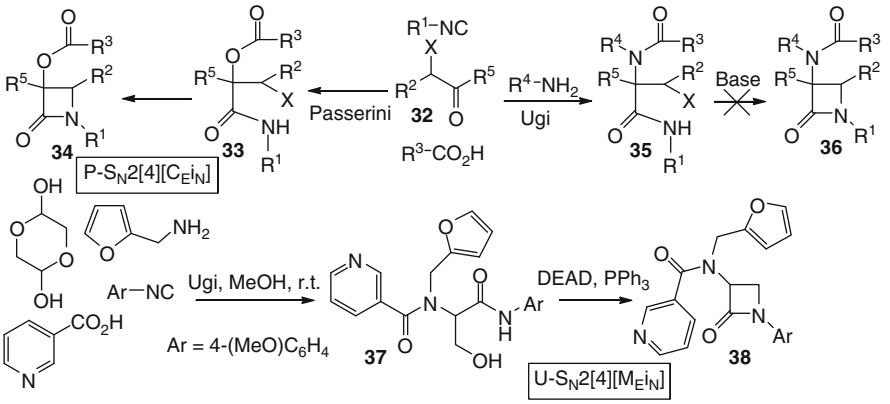

Fig. 6 Post-Ugi or post-Passerini cyclizations to β-lactams

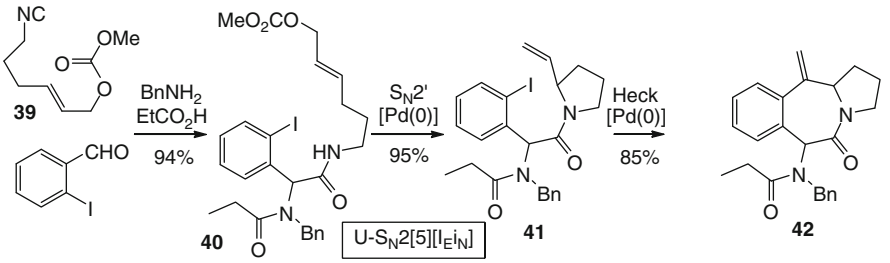

Fig. 7 Sequential Ugi-S_N2'-Heck

Finally, the leaving group can be inserted into the isocyanide component. This concept is outlined in Fig. 7, where the starting isocyanide is embodied with the functionality needed to carry out two successive cyclizations. Following the Ugi reaction of isocyanide **39**, containing an allylic carbonate, a Pd(0) catalysed S_N2' process takes place to produce simultaneously the first ring (pyrrolidine) and an exocyclic vinyl group [56]. The vinyl moiety can be employed for a second cyclization step through an intramolecular Heck reaction to give the tricyclic systems **42**, resembling alkaloids of the cephalotaxine family. Since both the S_N2' and the Heck reactions are catalysed by Pd(0), optimal conditions have been uncovered for carrying out the two steps in a "one-pot" manner in good yields [57].

A variety of benzo-fused heterocycles have been obtained through arylation of the isocyanide-derived nitrogen. The general strategy is depicted in Fig. 8. *N*-Arylation has been realized in all cases through transition-metal catalysis (Buchwald–Hartwig reaction), which has the great advantage of not requiring the strongly electron-withdrawing R^1 substituents as in traditional S_NAr. Different systems can be obtained by introducing the aryl halide into different components. For example, indol-2-ones **43** [58–60], quinoxalin-2-ones **44** [58, 61] and 1,4-benzodiazepin-2,5-diones **45** [58, 62, 63] have all been obtained with Pd(0) catalysis, also under MW irradiation

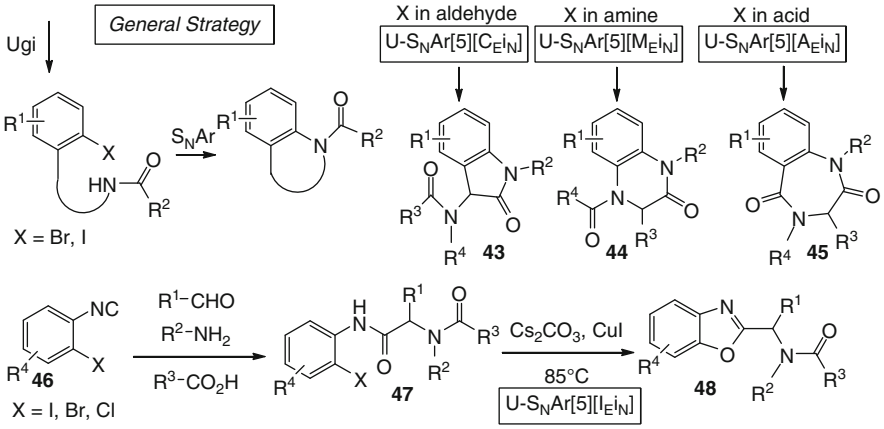

Fig. 8 Sequential Ugi-metal catalysed S_NAr (Buchwald–Hartwig)

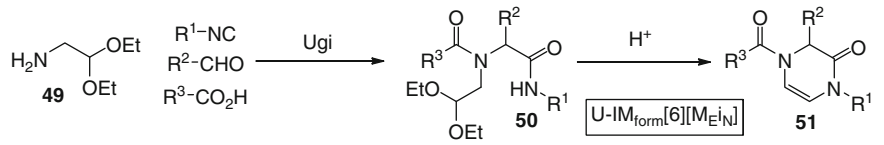

Fig. 9 Synthesis of 2-oxopiperazines

[59, 61]. Also in this case the leaving group can be placed on the isocyanide. When steric reasons prevent *N*-cyclization, *O*-cyclization can take place, as in the case of **47**, which generates, under Cu(I) catalysis, benzoxazoles **48** [64, 65].

Another electrophile that can interact with the isocyanide-derived amide is an aldehyde. However, an additional carbonyl function cannot be introduced as such into one of the components without interfering with the Ugi process. Thus it is better used in masked form as an acetal (Fig. 9). Starting from amine **49** a series of oxopiperazines **51** has been prepared, also on solid phase [66].

The secondary amide can also attack intramolecularly an additional ester function to form a cyclic imide, although only in moderate yields [67]. Finally, the palladium-catalysed intramolecular reaction with an alkyne, resulting in a hydroamination of the latter, will be described later (Fig. 17) [68].

2.3 Post-Condensation Transformations Involving the Acid-Derived Carbonyl

The amide (typically a tertiary one) or the ester derived from the carboxylic acid component in classical Ugi and Passerini reactions can undergo nucleophilic S_NAc by various nucleophiles [54]. These post-condensation reactions, however, do not

lead to cyclization, being merely acyl transfer processes. On the contrary, condensation reactions of suitable nucleophiles with the C=O group lead to various heterocycles. For example, starting from (Boc) protected α-aminoaldehydes, a convenient synthesis of imidazolines **53** is accomplished (Fig. 10). Boc removal and cyclization with loss of water proceeds as a domino process via acid and heat treatment [69]. On the other hand, benzimidazoles **55** can be obtained starting from *ortho*-phenylendiamine derivatives [32, 70]. Fluorous Boc analogues and MW irradiation have been employed to facilitate parallel synthesis [71]. Interestingly, the analogous synthesis of imidazolines starting from mono-Boc-protected ethylenediamines seems unfeasible [72].

Aromatic 5-membered heterocycles can be obtained by a Paal–Knorr cyclization, which involves the carboxylic derived C=O and an additional carbonyl suitably placed in one of the Passerini or Ugi component (Fig. 11). In this way

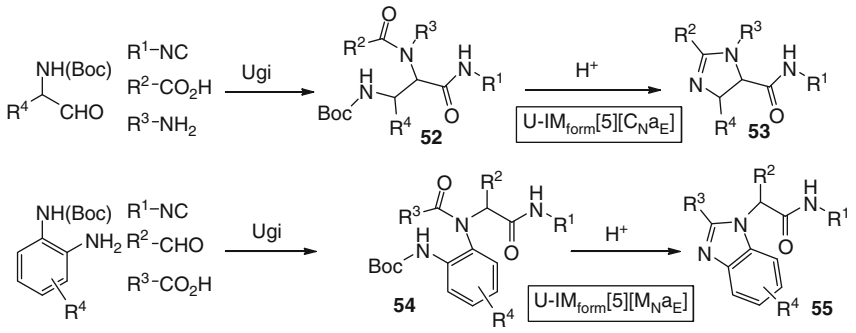

Fig. 10 Synthesis of imidazolines or benzimidazoles by condensation of an additional amine with the carboxylic acid-derived carbonyl

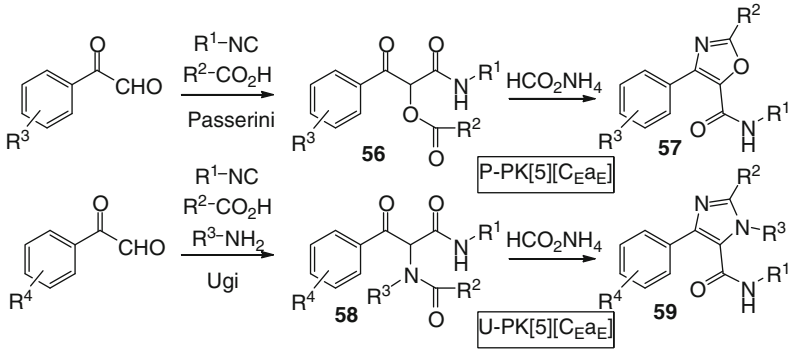

Fig. 11 Synthesis of various heterocycles by IMCR followed by Paal–Knorr cyclizations

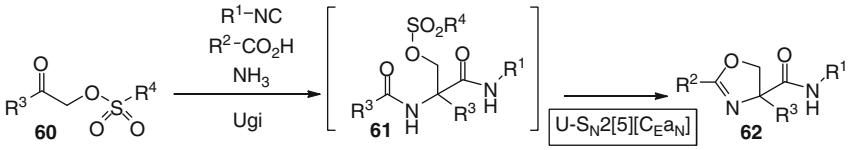

Fig. 12 Oxazoline synthesis with the acid-derived amide acting as nucleophile

arylglyoxals have been converted, via Passerini reaction, into oxazoles **57** [73–75] or, via Ugi reaction, into imidazoles **59** [76, 77].

The amide derived from the carboxylic acid in Ugi adducts is in most cases tertiary, and therefore it cannot serve as nucleophilic partner in post-condensation transformations, unless a post-Ugi rearrangement converts it into a free amine [52, 54]. An exception is represented by Ugi adducts derived from ammonia, which give rise to two secondary amides, each of them potentially involved, as nucleophile, in nucleophilic substitution processes. Four competitive pathways are in principle possible (*N*- or *O*-alkylations of the two amides), and the reaction is mainly driven by the stability of the formed rings. In the example shown in Fig. 12, *O*-alkylation of the carboxylic-derived amide is favoured as it generates a 5-membered ring (oxazoline **62**), while the alternative cyclization modes would have formed 3- or 4-membered rings [49]. When R^2CO_2H is phthalic acid, however, acylaziridines are formed instead via *N*-alkylation [49]. In both cases, the intramolecular S_N2 reactions takes place directly under the Ugi conditions.

2.4 *Cyclization Exploiting the Aldehyde-Derived Carbon as Nucleophile*

Post-MCR cyclizations can be also driven by interaction between the additional function and the central carbon atom of the classical peptidomimetic Ugi scaffold, derived from the aldehyde carbonyl. This CH group is characterized by relative acidity when the R^2 group is an aryl or heteroaryl substituent. In the example shown in Fig. 13, the aryl fluoride of **64** undergoes an S_NAr process, being displaced not by the isocyanide-derived NH group, as expected, but by the aldehyde-derived CH group, generating isoindolones **65** instead of benzodiazepinediones [78]. This transformation was carried out in a "one-pot" manner.

Alternatively, the acidity of the aldehyde-derived CH or CH_2 group can be enhanced by converting the isocyanide derived amide into an ester. According to this principle, tandem Ugi–Dieckmann was exploited in the context of carbapenem synthesis, where the first 4-membered ring was built through an intramolecular Ugi reaction of β-amino acid **66**. Then, after a three-step manipulation of the carboxylic appendages, a Dieckmann cyclization afforded, stereoselectively, the desired carbapenem skeleton **67** [79].

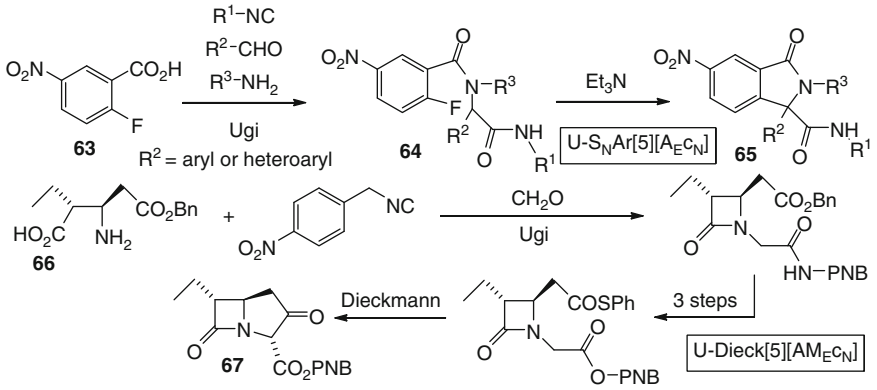

Fig. 13 Cyclization exploiting the aldehyde derived carbon as nucleophile

3 Two Additional Functional Groups

3.1 Nucleophilic Alkyl Substitutions

Cyclization through S_N2 reactions requires the introduction of a leaving group in one of the components and of a suitable nucleophile in another one. Of course, halogens are good leaving groups, and they have been indeed employed for the synthesis of ketopiperazines **68** [80], benzoxazinones **69** [81], macrocyclic ansapeptoids **70** [82] and β-lactams **71** [83] (Fig. 14), exploiting, respectively, *N*-, *O*- or *C*-nucleophiles. It should be noted that the synthesis of **69** has been carried out as a "one-pot" process.

In all the processes reported to date, halides were always incorporated into the carboxylic component. Probably the use of alkyl halides as electrophilic components in this strategy is not fully general: for example, the preparation and use of haloamines is expected to be problematic, whereas chiral α-haloaldehydes are difficult to prepare in optically pure form and are configurationally poorly stable. A more general approach is to use an alcohol as leaving group and Mitsunobu ($PPh_3 + RO_2C–N=N–CO_2R$) or Mitsunobu-like conditions for cyclization. Figure 15 shows the various heterocyclic systems obtained through this strategy. Protection of the alcoholic hydroxyl is not usually necessary, although in one case improved yields have been obtained by using benzyl ethers and by performing a hydrogenolytic deblocking just before cyclization [84].

Starting from ethanolamines **72**, benzoxazepinones **73** [84–86], benzodiazepinones **74** [47, 86] and diazepanones **75** [47] have been produced depending on the starting carboxylic components. In the last case, classical Mitsunobu conditions gave unsatisfactory yields, and the conditions developed by Hanessian (SDI and NaH) were used instead. Using α-hydroxyacids **76**, both benzoxazinones **69** [55] and benzoxazepinones **77** [55] have been accessed. The same compounds can also

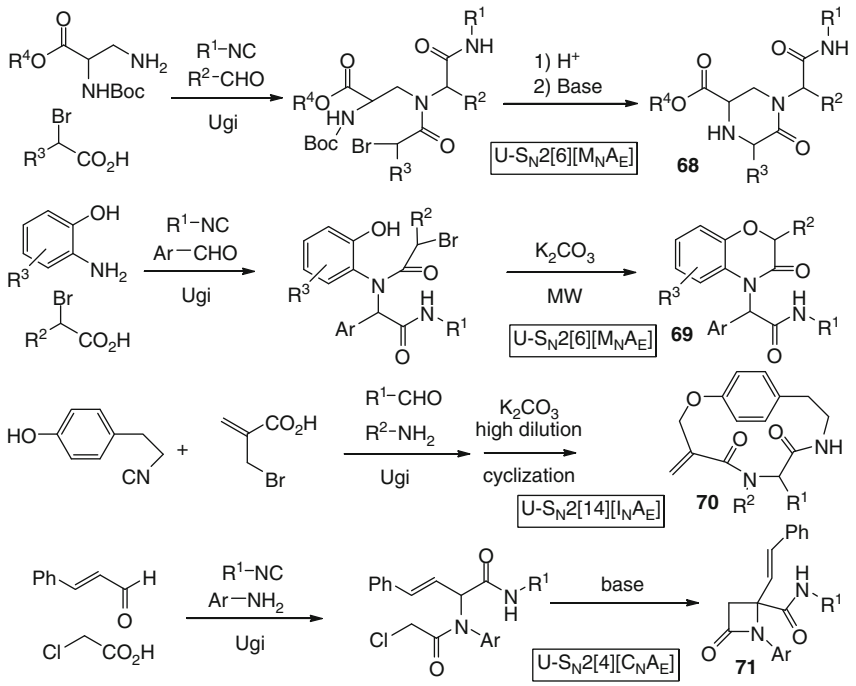

Fig. 14 Tandem Ugi-S_N2 starting from α-halo acids

be generated using α-haloacids, but α-hydroxyacids are more easily generated in enantiomerically pure form, and the Mitsunobu reaction was demonstrated to be stereospecific. Finally, the alcoholic function was also introduced into the aldehyde input, using glycolaldehyde dimer. In this case, an unexpected outcome was observed during the cyclization reaction: benzoxazinones **78** resulting from a formal *cine* substitution were obtained using modified Mitsunobu conditions [53].

3.2 Nucleophilic Aryl Substitutions

Several biologically useful medium-sized benzo-fused heterocycles have been efficiently constructed by combining the efficiency of the Ugi condensation with a post-condensation S_NAr cyclization, using an internal amino or hydroxyl nucleophile, and a nitrohalobenzoic acid **63** (Fig. 16). By introducing the additional nucleophile into the amine component, benzodiazepinones **79** [72], benzodiazocinones **80** [72], their benzo-fused counterparts **81** [72], benzoxazepinones **82** [72] and their fused counterparts **84** [60] and finally benzoxazocinones **83** [72] have been obtained. For the first two systems, the already described UDC strategy was exploited, whereas for the oxa heterocycles, the alcoholic or phenolic hydroxyl did

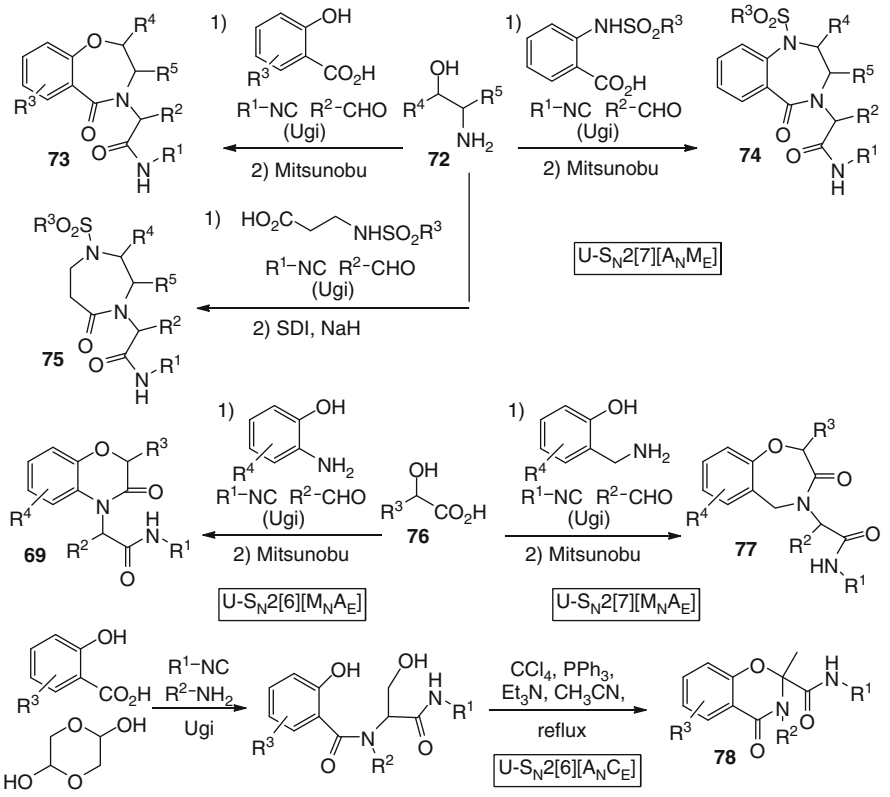

Fig. 15 Synthesis of various heterocyclic systems through tandem Ugi–Mitsunobu processes

not need to be protected. Benzodiazepinones **85** have been generated by the UDC strategy as well, this time positioning the protected additional amino nucleophile into the aldehyde component [87].

Special dibenzoxazepinones **86**, obtained through the general method described in Fig. 16 and containing, as a third additional functionality, a triple bond, have been further cyclized via a palladium-catalysed hydroamination reaction (Fig. 17) [68]. In this way complex polycyclic systems **87** have been assembled in three steps, taking advantage of the three additional functions embedded in the starting component: the aryl fluoride, the phenol and the triple bond.

Many other possibilities can be conceived by positioning the aryl halide into another component. Figure 18 shows the synthesis of dibenzoxazepines **90** starting from *o*-aminophenols and from *o*-chloro-*p*-nitrobenzaldehyde **88** [60].

On the other hand, imidazoquinoxalines **94** or pyrazoloquinoxalines **95** have been built starting from *ortho*-fluoroanilines **91** and imidazol- or pyrazol-carboxylic acids **92** and **93**. Interestingly, the presence of an electron-withdrawing group as the R^3 substituent is not needed: in most entries R^3 was just hydrogen. Cyclization by

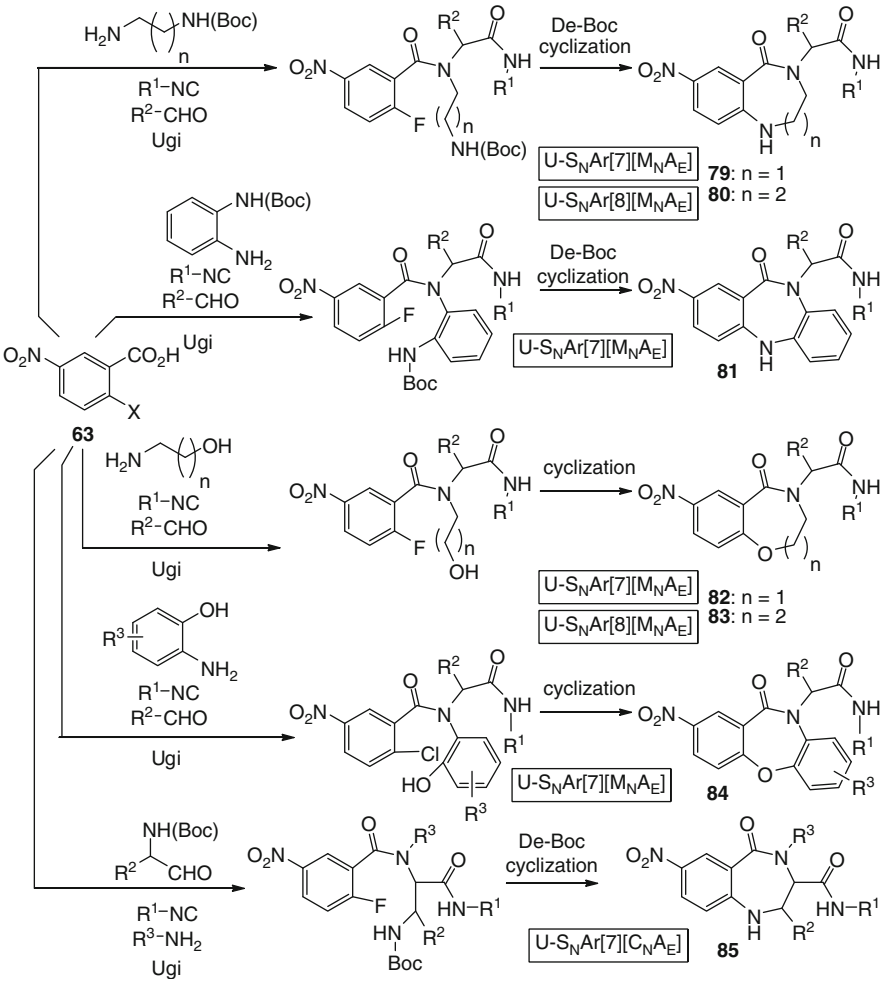

Fig. 16 Synthesis of medium-sized benzo-fused heterocycles through tandem Ugi-S_NAr processes

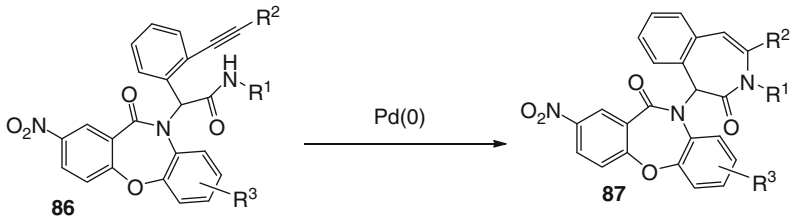

Fig. 17 Alkyne hydroamidation as a second post-Ugi transformation

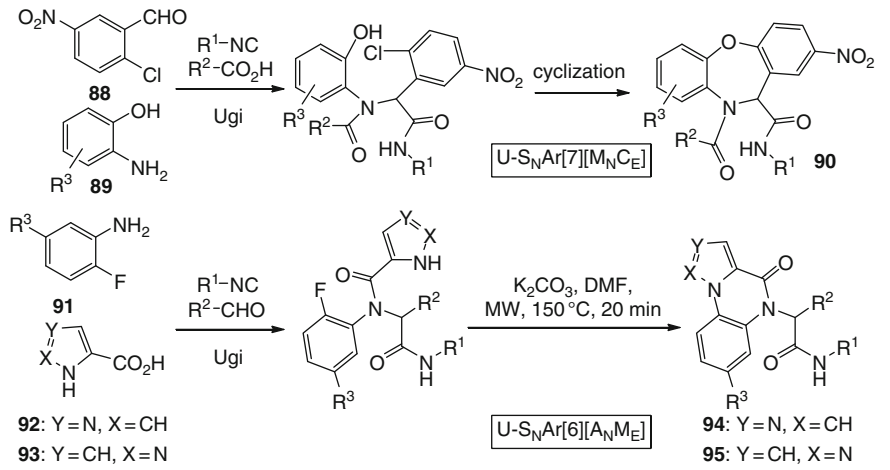

Fig. 18 Synthesis of medium-sized benzo-fused heterocycles through tandem Ugi-S_NAr processes

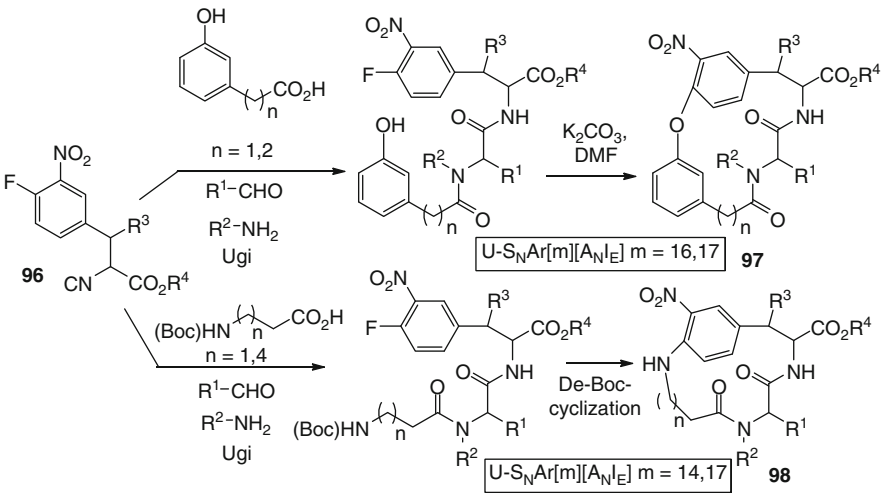

Fig. 19 Synthesis of *para*-cyclophanes through tandem Ugi-S_NAr processes

means of the pyrrole-type nitrogen which serves as the nucleophile requires, however, high temperature. The use of microwave activation allowed for high yields in short reaction times [88].

Finally, by introducing the aryl halide into the isocyanide component, as in **96**, various macrocyclic peptidomimetics containing a nonsymmetrical endo biaryl ether bridge have been synthesized [89–91]. Aryl nucleophilic substitution also takes place in this case under standard base-promoted conditions. The synthesis was also carried out on solid phase. Selected examples are shown in Fig. 19, but also a

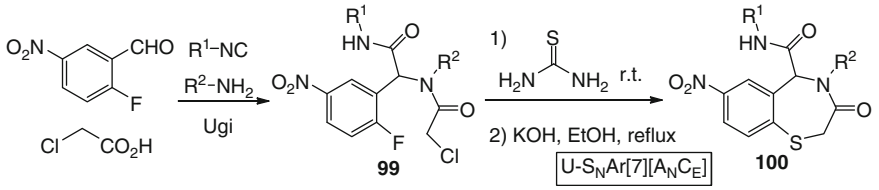

Fig. 20 Synthesis of benzothiazinones by a sequence of Ugi-S_N2-S_NAr

U-S_NAr[15][C_NI_E] process was implemented. These *para*-cyclophanes **97** and **98** are interesting from the stereochemical point of view because they generate atropisomerism. Moreover, the stereogenic centres of the peptide backbone are configurationally unstable under the cyclization conditions, affording, under thermodynamic control, only two diastereoisomers (atropisomers) instead of the expected four.

A special case of S_NAr is shown in Fig. 20. It actually involves a tandem S_N2-S_NAr process on an Ugi adduct containing both an alkyl and an aryl halide. In **99**, the acid-derived alkyl halide behaves therefore as a masked nucleophile. Treatment with thiourea (S_N2) forms an intermediate thiouronium salt which, upon basic hydrolysis, releases the required thiolate that undergoes the S_NAr process. A library of benzothiazepinones **100** was produced in this way [92].

As already seen in the first section, S_NAr processes may also be metal-catalysed. This reaction involves milder reaction conditions and is not strongly dependent on the electron-withdrawing properties of the substituents. Starting from an *orto*-iodoaniline **101**, the Ugi reaction gives intermediate **102** that can undergo two different modes of cyclization. If the nucleophile is the isocyanide derived NH group, the S_NAr process (Buchwald–Hartwig reaction) affords quinoxalinones [45] as already described in Fig. 8. On the contrary, if the nucleophile is the enolate stemming from deprotonation of the carboxylic-derived amide, then indolones **103** are generated (Fig. 21). The choice of ligand diverges the two reaction pathways: with BINAP, good yields of the indolones are obtained, whereas with Xphos, quinoxalinones are exclusively obtained [61].

3.3 Nucleophilic Acyl Substitution

We have previously seen how cyclic lactams can be synthesized by installing a protected amine in one of the Ugi or Passerini components, followed by cyclization onto the isocyanide-derived amide, taking advantage of the particular reactivity of "convertible" isocyanides. The same type of compounds can be accessed through nucleophilic attack of the amine onto an ester moiety, suitably installed as additional function into another component. This strategy has been widely used for the preparation of diketopiperazines **104** (Fig. 22), a typical privileged structure, starting with

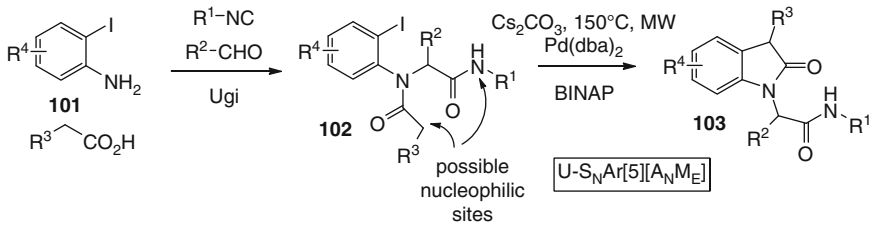

Fig. 21 Synthesis of indolones via *C*-arylation

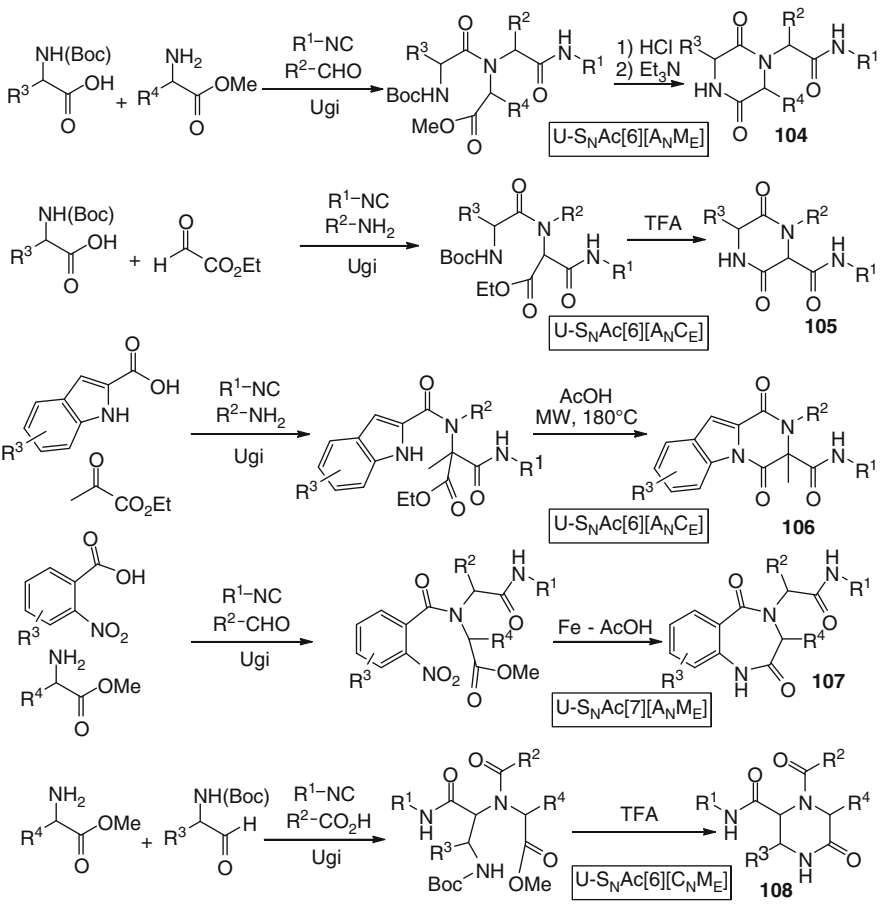

Fig. 22 Lactams formed by cyclization of an additional nitrogen into an additional ester

α-aminoesters (amine component) and protected α-aminoacids (carboxylic components) as inputs [93–97]. This is another example of the so-called UDC strategy (Ugi-DeBoc-Cyclize), although Fmoc protection has been employed too.

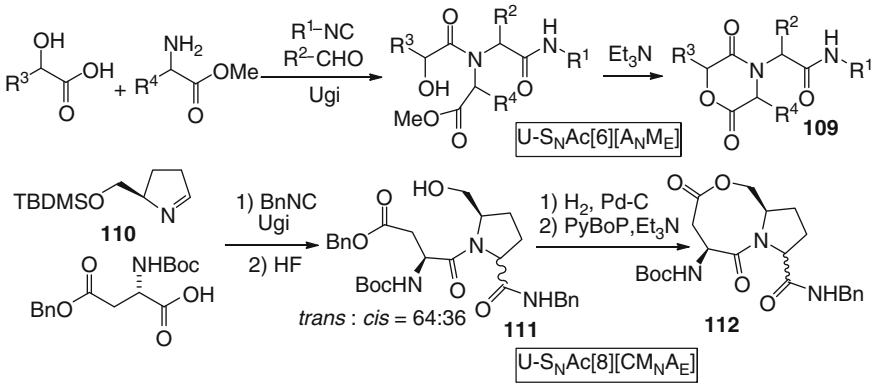

Fig. 23 Lactones formed by cyclization of an additional hydroxyl into an additional ester or acid

Other types of diketopiperazines **105** and **106** were prepared by incorporating the additional ester moiety into the carbonyl component (ethyl glyoxalate or pyruvate) [98, 99]. By using similar routes, 1,4-benzodiazepine-2,5-diones, such as **107**, have been synthesized by inserting the additional primary amine group into the carbonyl or carboxylic inputs either in a protected form [38, 98, 100] or masked as a nitro group [101]. Finally, ketopiperazines **108** have been prepared by installing the Boc-protected amines into the carbonyl component [100]. Benzodiazepine and ketopiperazine libraries have been generated on solid phase too [100].

Similarly, various types of lactones have been synthesized by incorporating an additional alcohol (as such or in protected form) into one of the components (Fig. 23). For example, diketomorpholines **109** were prepared in two steps starting with α-hydroxy acids [94]. On the other hand, enantiomerically pure chiral pyrroline **110** was coupled with benzyl isocyanide and with an aspartic derivative in an intramolecular Ugi variant. After removal of the two protecting groups, cyclization took place in a remarkably high yield (81%) to give the unprecedented pyrroloxazocinediones **112** [38].

3.4 Condensations Leading to C=N Bond Formation

Cyclic imines or enamines are generated starting from Ugi adducts containing an additional primary amine and an additional carbonyl group (Fig. 24). In this way quinaxolinones **113** [71, 102], benzodiazepines **115** [103] and **117** [104] and finally dibenzodiazocines **118** [105] have been prepared. The additional primary amine needs to be protected or masked during the Ugi condensation. Three strategies have been implemented: the amine was protected as Boc urethane (a further example of UDC strategy) or replaced by two synthetic equivalents

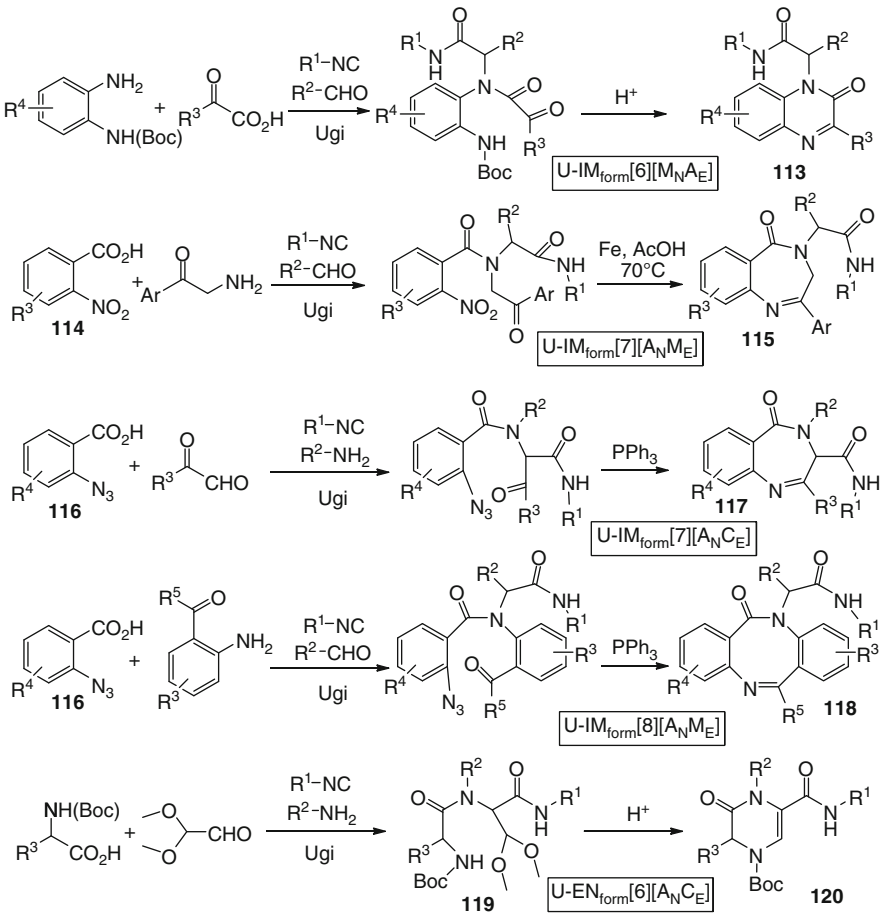

Fig. 24 Cyclic imines/enamines from post-Ugi cyclization of amino ketones or amino aldehydes

(a nitro group for **115** or an azide for **117** and **118**). The latter case is particularly convenient, since cyclization can be carried out under neutral conditions with triphenylphosphine (aza-Staudinger reaction). As far as it concerns the additional oxo group, in most cases it is a ketone and does not need protection, thanks to the lower reactivity in the Ugi condensation. In one case, an acetal-protected form of glyoxal was used to give intermediate **119**. Interestingly, under acid conditions the acetal was cleaved first, leading to dihydropyrazinones **120**, having an enamine-like structure [106].

C=N bond formation has also been achieved starting from two additional carbonyl functions properly installed in an Ugi component. Cyclization has been accomplished in this case through a Paal–Knorr reaction of the dicarbonyl compound generated by the Ugi condensation, leading to pyrazinones [107].

3.5 *Base-Promoted Condensations*

Several interesting heterocyclic compounds have been obtained starting from arylglyoxals **121** or other α-keto aldehydes or α-diketones, in conjuction with carboxylic acids containing an electron-withdrawing group [108–111]. For example, the tandem Passerini–Knoevenagel process depicted in Fig. 25 affords a series of furanones (butenolides) **122**. These products have also been easily converted into the more stable methoxyfurans **123**. Pyrroles **124** and **125** (EWG = CN) have been obtained similarly this time by performing an Ugi reaction [112].

The required carbonyl group can also be introduced in other MCR components. Amino ketones **126** and **128** have been used for the synthesis of another type of pyrrolones **127** [113], as well as of quinolones **129** [114].

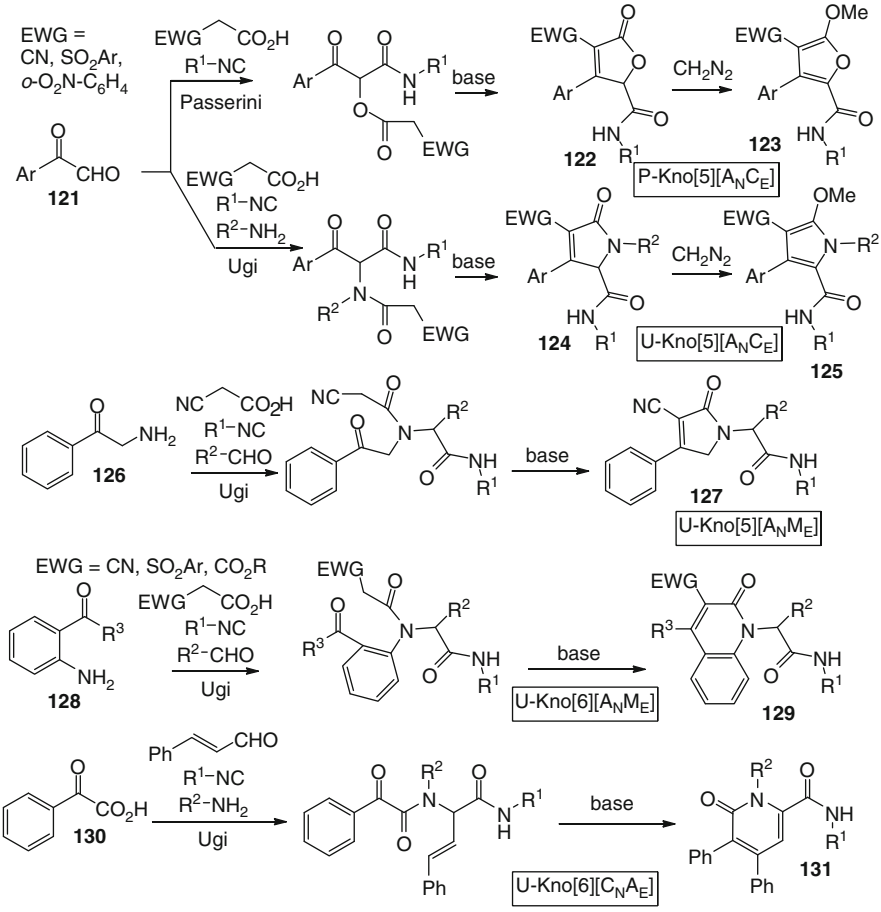

Fig. 25 Five- and six-membered heterocycles from tandem IMCR-Knoevenagel

Finally, by placing the additional carbonyl in the carboxylic component, a synthesis of pyridinones **131** has been realized [115]. In this case, the nucleophilic carbon is not the one derived from the acid, but the one initially embedded in the starting aldehyde. Moreover, here a vinylogous Knoevenagel is operating, which is clearly favoured over the reaction involving the carbon α to the amide, thanks to the formation of a stable aromatic 6-membered ring.

Furanones **133** and pyrrolones **134** can be obtained, starting from arylglyoxals, through tandem Passerini [116] or Ugi [117]/Horner–Wadsworth–Emmons (HWE) (Fig. 26), using α-phosphonoacids **132**. Using β-ketoaldehydes instead of glyoxals, pyridones can be obtained as well. This method has the advantage, compared to tandem IMCR/Knoevenagel, to be able to introduce any type of R^3 group in the final heterocycles (they do not need to be electron-withdrawing). By using β-ketoaldehydes, pyridones also have been synthesized [117].

Furandiones **136** have been prepared by using this time an ester as additional electrophile in a tandem Passerini–Dieckmann process [118] (Fig. 27). It is interesting to note that in this case it was unnecessary to have an electron-withdrawing group in the carboxylic acid component.

Heterocyclic systems similar to those obtained by tandem Ugi-S_N2 may be accessed also through tandem Ugi-Michael, provided that a component containing an electron-poor double bond is used and a suitable nucleophile is introduced into

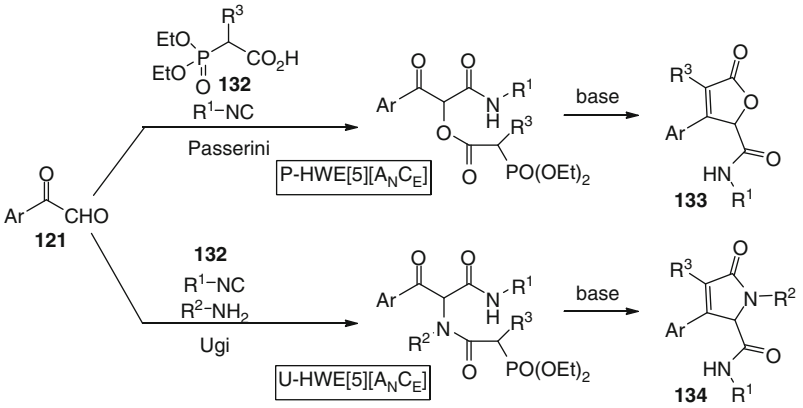

Fig. 26 Tandem IMCR-HWE

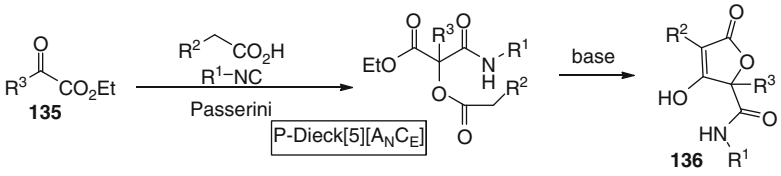

Fig. 27 Tandem IMCR-Dieckmann

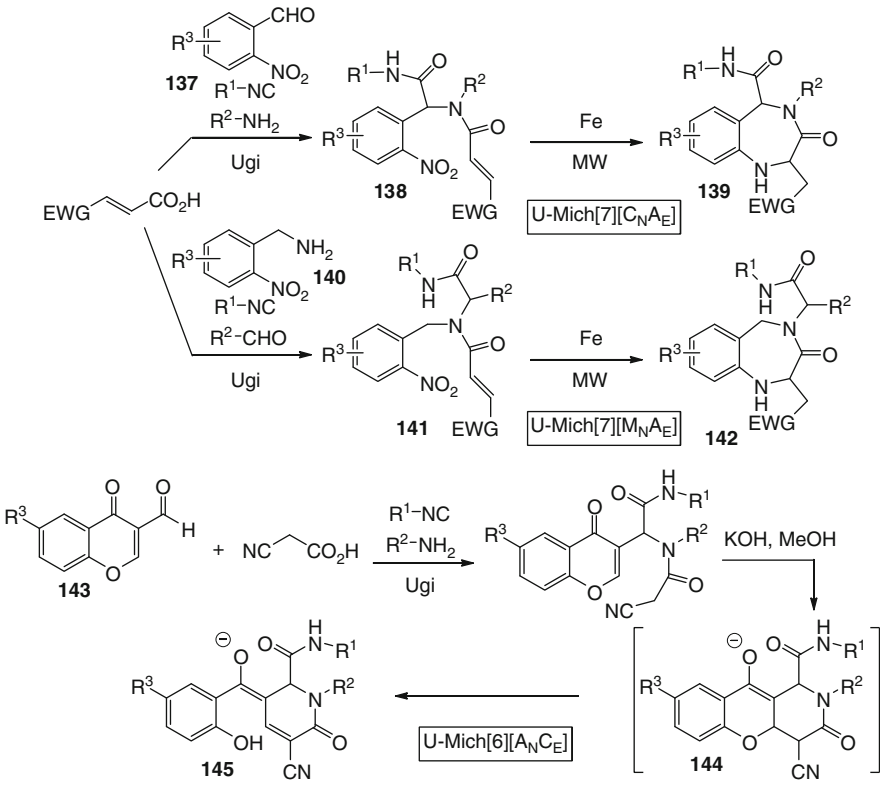

Fig. 28 Tandem Ugi-Michael processes

another component. Masked amines **137** and **140** are perfectly suited for this task (Fig. 28). Reduction of the nitro group in the intermediate Ugi adducts **138** and **141** and heating under microwave irradiation brings about cyclization through an aza-Michael, leading to benzodiazepinones **139** and **142** [119].

Another interesting example of Ugi-Michael process is represented by the synthesis of pyridones **145** (Fig. 28), which originate from an intramolecular domino addition–elimination reaction of the active methylene group proceeding through intermediate **144** [120].

3.6 Cycloadditions

Intramolecular Diels–Alder (IMDA) is a very powerful reaction, which converts an acyclic system into a bicyclic one, often with high stereocontrol. By positioning a good dienophile (typically in the carboxylic component) and a highly

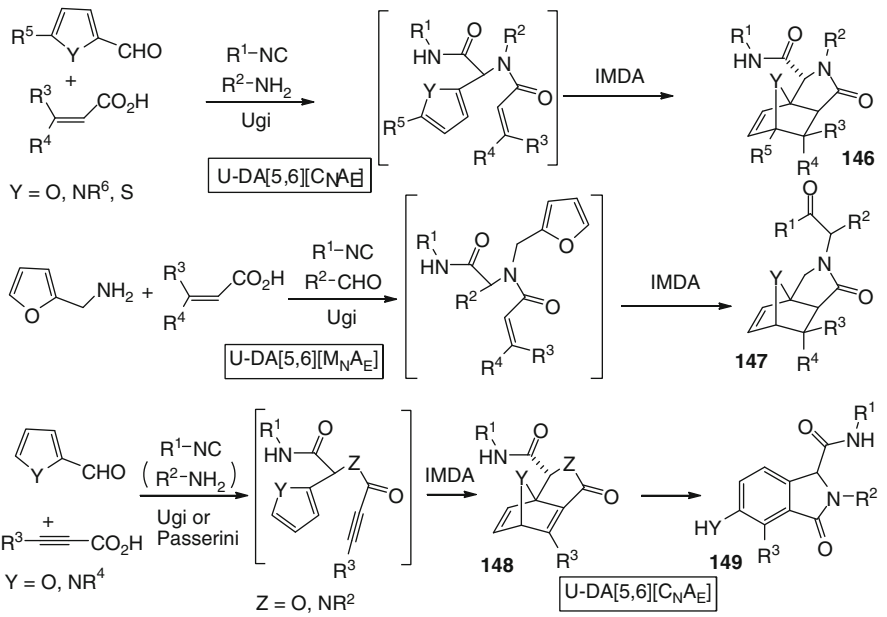

Fig. 29 Tandem Ugi-IMDA processes that exploit heterocyclic dienes

reactive diene in another substrate of the IMCR, the intramolecular cycloaddition leads to architecturally complex systems (Fig. 29). The most widely used activated dienes are furan [121–126], pyrrole [127] and tiophene [46]. With the former the reaction takes place spontaneously at room temperature under the MCR conditions, while with the other two heating is required. This strategy was applied to the Ugi reaction, introducing the diene in the carbonyl [46, 121–127] or in the amine [121] component.

The reactions that lead to **146** are usually highly stereoselective, giving only two diastereoisomers in high diastereomeric ratio. In particular, the stereogenic centre formed during the Ugi step seems to direct the attack of the diene onto one of the two diastereotopic faces of the dienophile (the preferred stereoisomer is shown in the figure). On the contrary, the synthesis of **147** was much less stereoselective.

Bicyclic systems **146** have been further elaborated into other natural product-like structures by acid-promoted rearrangement, which affords fused tricyclic systems [125], or by ring-opening/ring-closing metathesis processes [123, 126], after installing allyl groups into the structure.

Also acetylenic dienophiles have been used, this time both in the Ugi [127, 128] and in the Passerini MCRs [128]. The bicyclic compounds **148** (Z = NR^2), stemming from an Ugi reaction on furaldehyde, are somewhat unstable and can be converted, under Lewis acid catalysis, into isoindolinones **149** [127, 128]. On the contrary, compounds **148** (Z = O), coming from a Passerini reaction, are stable under the same conditions and therefore are not converted into isobenzofuranones.

Acetylenic dienophiles have also been used in conjunction with a different type of diene (**150**) for the combinatorial synthesis of isoindolones **151** fused with furan, pyrrole or thiophene rings (Fig. 30) [129]. In this case, the diene involved in IMDA is not the 5-membered heterocycle itself, but the one including the exocyclic double bond. The resulting dihydrobenzene is easily aromatized by oxidation with DDQ or C/O_2. The synthetic protocol is accomplished in a one-pot process.

Intramolecular [3+2] dipolar cycloadditions have also been employed as a post-Ugi transformation to generate heterobicyclic structures, namely fused isoxazolines [130], isoxazoles [130] and triazoles [131] (Fig. 31). Isoxazoles were obtained through intramolecular nitrile oxide cycloaddition. The precursor of the nitrile oxide (a nitro group) was introduced into the carboxylic component, while a triple bond was positioned in the starting amine. Treatment of **152** with $POCl_3/Et_3N$ gave the intermediate nitrile oxide, which spontaneously cyclized to isoxazoles **153**.

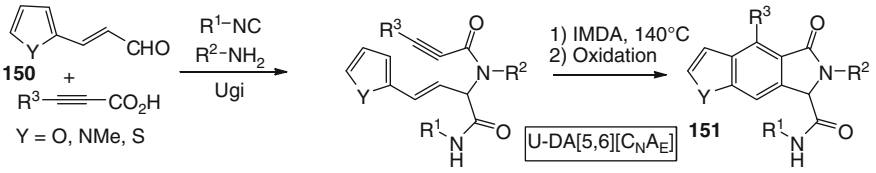

Fig. 30 Tandem Ugi-IMDA processes that exploit exocyclic dienes

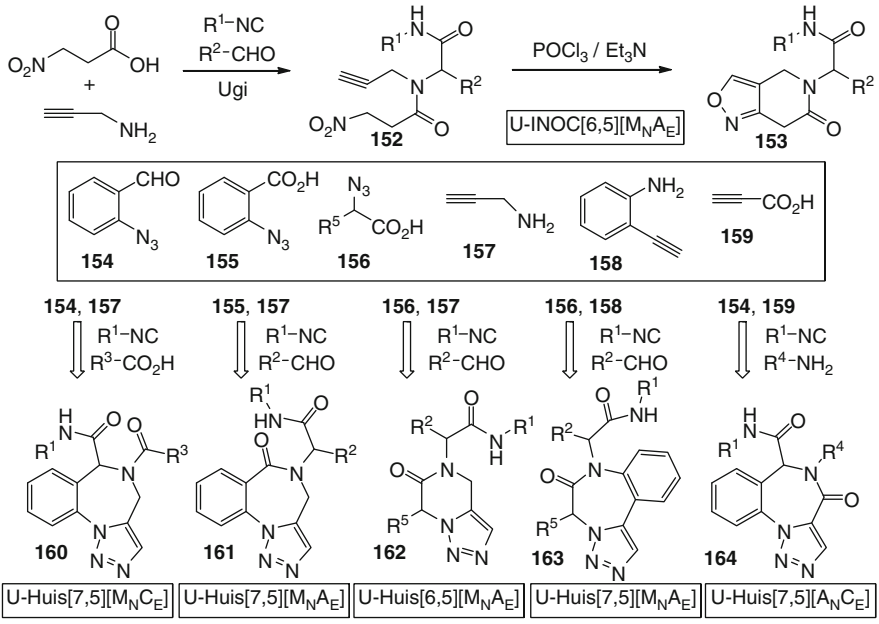

Fig. 31 Tandem Ugi-1,3-Dipolar cycloaddition processes

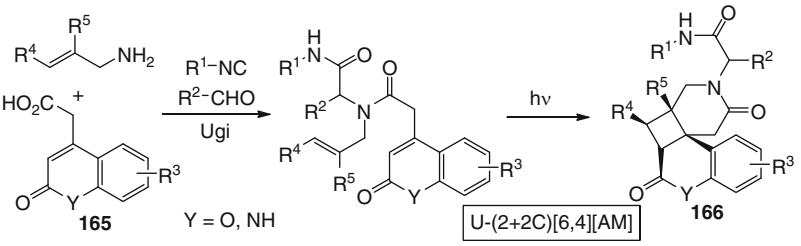

Fig. 32 Tandem Ugi-2+2 cycloaddition processes

The use of allylamine led to isoxazolines instead, whereas starting with γ-nitrobutanoic acid, the ring that fused to the isoxazole was 7-membered.

Fused triazoles were synthesized in a similar manner through the Huisgen azide–alkyne cycloaddition, which was carried out by simple heating the Ugi adducts at 100°C. Five different fused triazole scaffolds **160–164** were obtained by placing the additional functions in different components or changing the distance between them and the Ugi-reacting group [131].

A new methodology for the construction of novel and uniquely shaped 3-azabicyclo[4.2.0]octan-4-one derivatives **166** by combining the Ugi multicomponent reaction with [2 + 2] enone-olefin photochemical transformations was recently reported [132] (Fig. 32). The additional functional groups are in this case an enone (**165**) and a C=C double bond. Although the overall sequence is capable of creating up to five stereocentres, in most cases only two diastereomers are observed, which are epimeric at the exocyclic stereogenic centre.

3.7 Ring-Closing Metathesis and Other Transition Metal-Catalysed Processes

Ring-closing metathesis seems particularly well suited to be combined with Passerini and Ugi reactions, due to the low reactivity of the needed additional olefin functions, which avoid any interference with the MCR reaction. However, some limitations are present. First of all, it is not easy to embed diversity into the two olefinic components, because this leads in most cases to chiral substrates whose obtainment in enantiomerically pure form may not be trivial. Second, some unsaturated substrates, such as enamines, acrolein and β,γ-unsaturated aldehydes cannot be used as component for the IMCR, whereas α,β-unsaturated amides are not ideal for RCM processes. Finally, the introduction of the double bond into the isocyanide component is possible only if 9-membered or larger rings are to be synthesized (see below). The smallest ring that has been synthesized to date is the 6-membered one represented by dihydropyridones **167**, obtained starting with allylamine and butenoic acid [133] (Fig. 33). Note that, for the reasons explained earlier, compounds

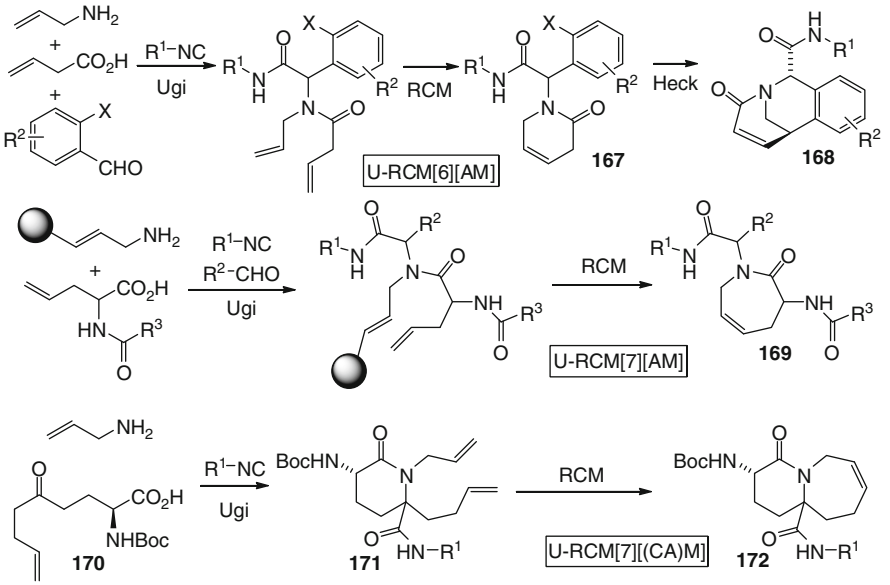

Fig. 33 Six- and seven-membered rings by tandem IMCR-RCM processes

167 entail only two diversity points. When *ortho*-halobenzaldehydes were used, a three-step sequence of Ugi, RCM and Heck reactions produced bridged bicyclic lactams **168**.

Using again unsaturated amines and unsaturated carboxylic acids, 7-membered lactams **169** (unsaturated Freidinger lactams) have been prepared on solid phase [134]. Here a third diversity input was placed in the carboxylic acid as well, but this brought about the presence of a stereogenic centre in the starting component and hence the formation of a diastereomeric mixture of the products.

Bicyclic lactams **172** have been obtained by combining an intramolecular Ugi reaction of ketoacid **170**, which generates the first ring, and a post-condensation RCM [135].

Introduction of one of the required double bonds into the isocyanide component leads to efficient RCM only when the secondary amide prefers the *s-trans* rotamer in the formed ring. This happens with ring size >8, as in the case of tetrahydroazoninones **173** [136] (Fig. 34). **169**, **172** and **173** can be considered conformationally biased peptidomimetics. Tetrahydroazoninones **173** have been used as "external reverse turn mimetics" [80] in cyclic peptides in the context of integrin antagonists [137, 138]. Tandem Ugi-RCM was also used for embedding tripeptides into a large ring [139, 140]. Compounds **174** are shown as an example, but other aminoacids have been incorporated as well. The protocol leads to just one diastereomer, thanks to the induction given by the chiral amine and to the fact that only the major, all (*S*), diastereoisomer undergoes cyclization. Finally, macrocycles **175** have been prepared by combining RCM with the Passerini reaction [75].

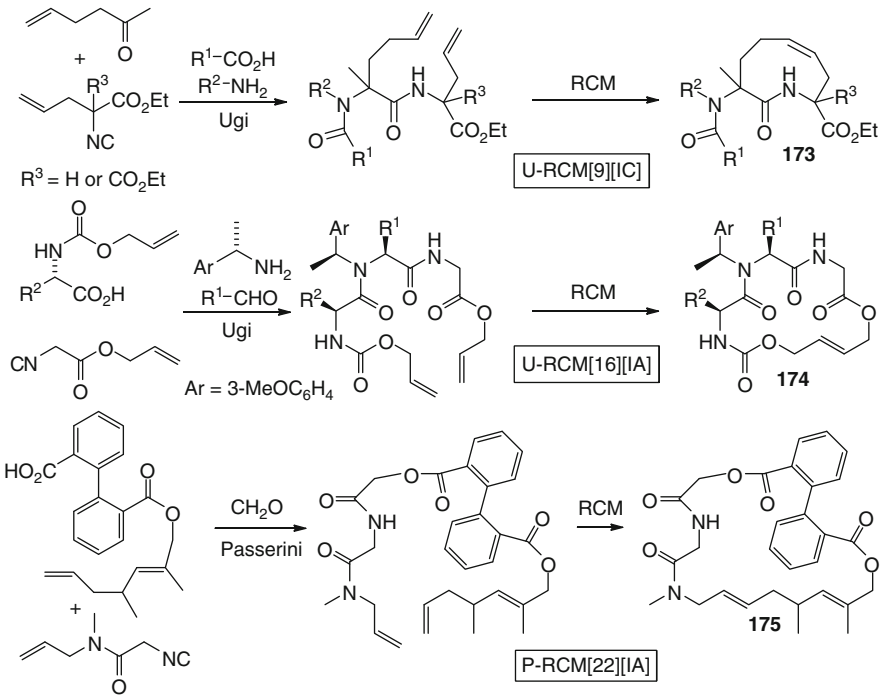

Fig. 34 Medium and large rings by tandem IMCR-RCM processes

As far as it concerns the geometry of the double bond, all the above quoted compounds have been obtained with complete stereoselectivity (*Z* for **168**, **169**, **172** and **173** and *E* for **174** and **175**).

Another powerful transition metal-catalysed process that has been combined with the Ugi reaction to produce bicyclic systems is the Heck reaction. For example, the synthesis of dihydroindoles through this approach has been reported (Fig. 35). Compounds **176** were obtained starting with α,β-unsaturated aldehydes. When using formic acid as the carboxylic input, cleavage of the tertiary amide and isomerization to the corresponding indoles took place under the Heck conditions [141]. By introducing the double bond into the carboxylic component, a different class of dihydroindoles **177** was synthesized [142]. The same compounds were also obtained starting from *ortho*-aminophenols by converting the phenolic hydroxyl into a triflate after the Ugi step and then submitting it to Heck cyclization [143].

Six- and seven-membered rings (dihydroisoquinolines **178**, isoquinolinones **179**, **180** and benzazepines **181**) were obtained starting from *ortho*-halobenzaldehydes or *ortho*-halobenzoic acids [144, 145]. In all the cases, the *exo-trig* cyclization mode was strongly favoured. However, for **178** and **180**, isomerization of the double bond from exocyclic to endocyclic occurred spontaneously under the Heck conditions.

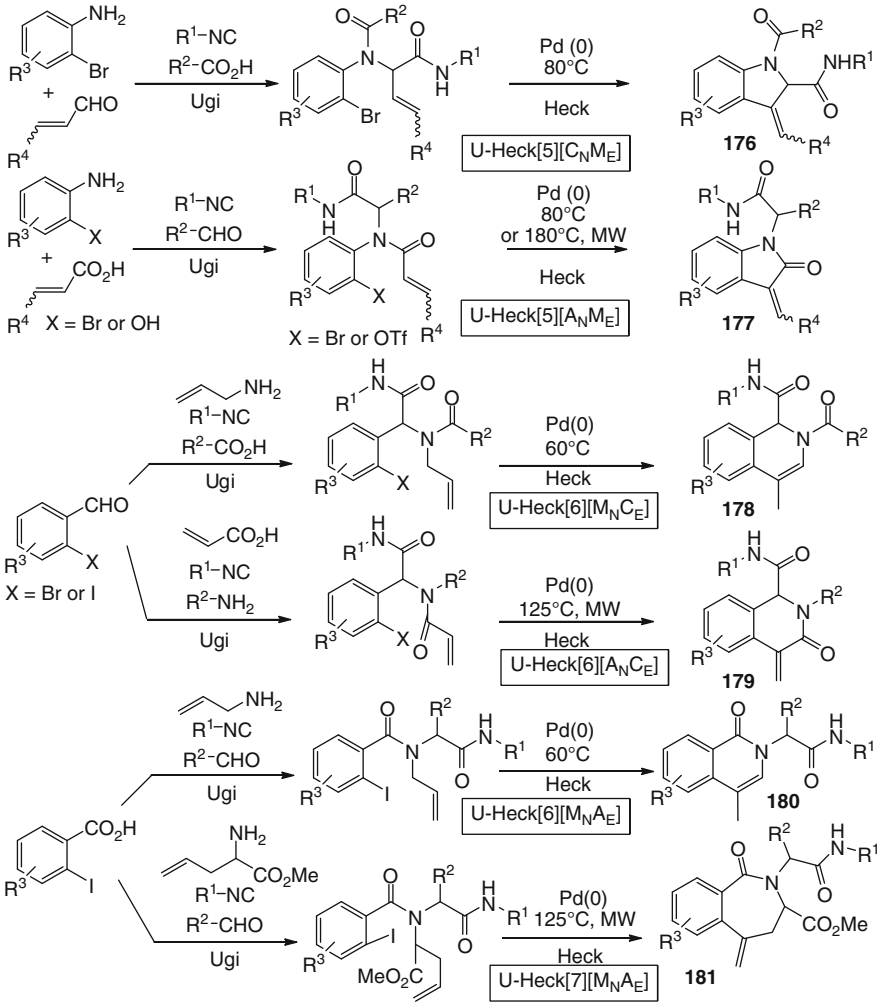

Fig. 35 Tandem Ugi–Heck processes

Benzodiazocines **182** and **183** were obtained through a sequence of Ugi-deprotection–carbonylation/intramolecular amidation using *ortho*-iodobenzaldehyde and a bifunctional acid or amine [146] (Fig. 36). This cyclocarbonylation was carefully optimized and succeeded in affording 8-membered lactams, which are typically difficult to obtain, in good yields.

Starting with iodobenzoic acids or iodobenzaldehydes and anilines, also a tandem Ugi-direct arylation (DAR) process is conceivable. In this manner, isoquinolines **184** and **185** have been prepared [147, 148] (Fig. 37). DAR has been exploited also as a tertiary transformation following an Ugi and a Buchwald–Hartwig *N*-arylation [62, 65].

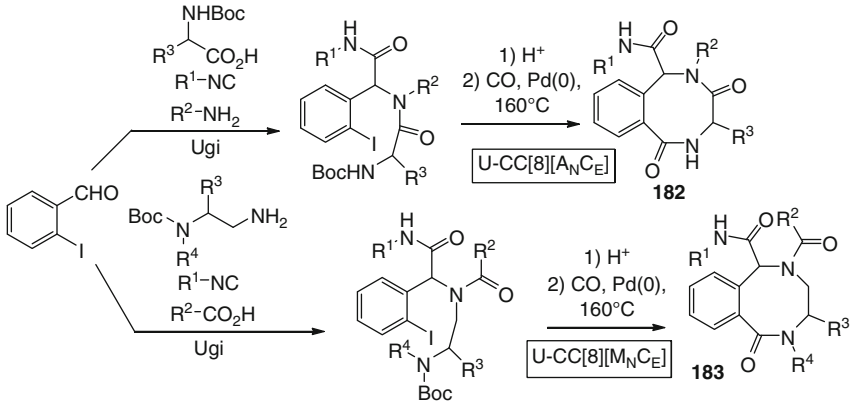

Fig. 36 Tandem Ugi-cyclocarbonylation processes

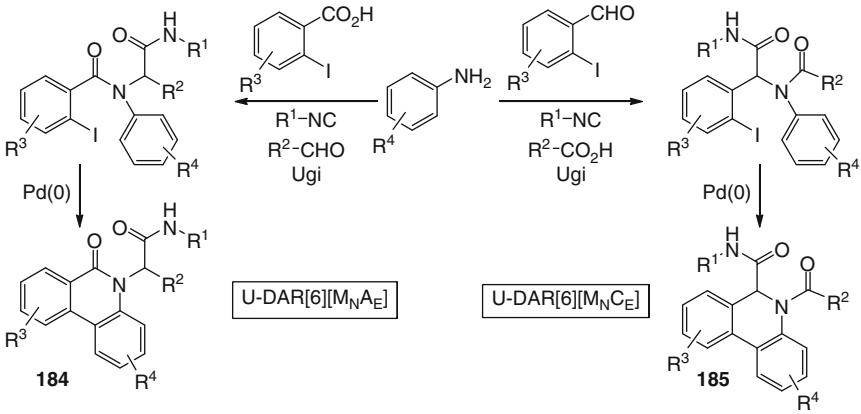

Fig. 37 Tandem Ugi-direct arylation processes

3.8 Others

The Pictet–Spengler reaction, involving the cyclization of electron rich aryl or heteroaryl groups with iminium electrophiles, is a key step in the synthesis of many alkaloids. If one of the Ugi component encompasses an additional carbonyl, this can form an iminium species by interaction with the isocyanide-derived NH group, which in turn can react with an electron-rich arene, suitably positioned into the isocyanide structure. The result is the formation of a tricyclic system stemming from the interaction of two additional groups plus the isocyanide-derived secondary amide. Figure 38 shows the synthesis of alkaloid-type systems **186** [149], **187** [150] and **188** [150]. It is worth noting that, while an additional keto group can be

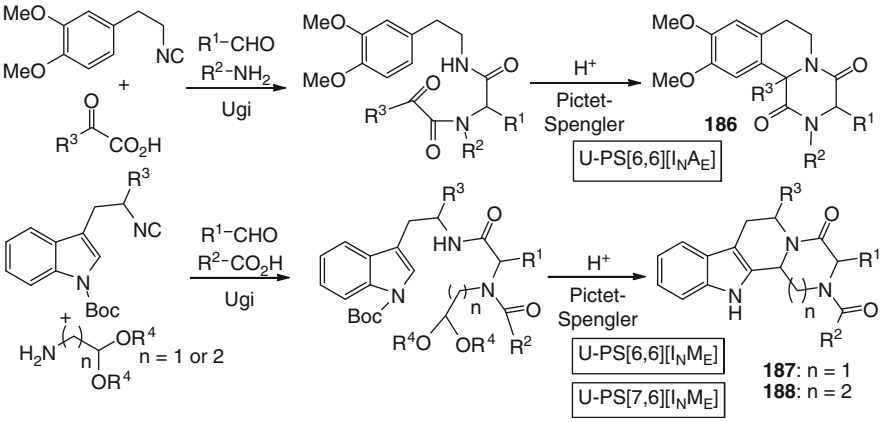

Fig. 38 Tandem Ugi/Pictet–Spengler

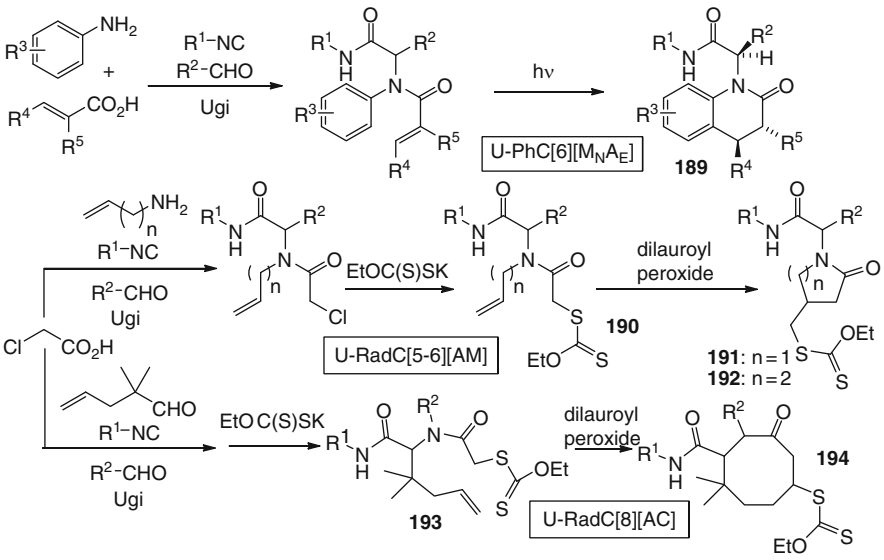

Fig. 39 Tandem Ugi-photochemical or radical cyclizations

employed without protection in the Ugi reaction, thanks to its lower reactivity, an additional aldehyde must be blocked. Also protection of the indole nitrogen was beneficial. However, both acetal and Boc protections are cleaved under the same acidic conditions required for Pictet–Spengler cyclization. Cyclization was poorly stereoselective in both cases.

Highly functionalized 3,4-dihydroquinolin-2(1*H*)-ones **189** have been prepared via sequential Ugi/acrylamide [6 π] photocyclization (PhC) reaction with a preferential *trans* relationship between the substituents R^4 and R^5 (Fig. 39) [151].

Finally, a radical cyclization was accomplished taking advantage of the capability of xanthates to stabilize a radical at the α-carbon atom. However, the xanthates **190** and **193**, required for the ring forming step, could not be obtained directly by an Ugi reaction. Therefore, the MCR was carried out with chloroacetic acid and the xanthate moiety was introduced later through an S_N2 reaction. Final cyclization gave pyrrolidinones **191**, piperidinones **192** or tetrahydroazepinones **194** depending on the nature of the component that carries the C=C double bond. The reaction is regioselective, forming only the products **191**,**192** derived from *exo-trig* attack starting from **190**, whereas unusual *endo-trig* product **194** was the only isolated species starting from **193**. The process was, however, poorly stereoselective [152].

In conclusion, the general strategy of combining IMCRs with post-condensation transformations has produced so far several types of heterocyclic systems, in most cases non-aromatic, including medium of large-sized ones. They have been prepared efficiently in few steps and with the typical introduction of three or more diversity inputs. However, the authors' feeling is that we are only at the beginning of a long story and that many other ring types and reaction types are still waiting to be explored.

References

1. Banfi L, Riva R (2005) The passerini reaction. In: Overman LE (ed) Organic reactions. Wiley, Hoboken, pp 1–140
2. Passerini M (1921) Sopra gli isonitrili (I). Composto del p-isonitril-azobenzolo con acetone ed acido acetico. Gazz Chim Ital 51(II):126–129
3. Dömling A, Ugi I (2000) Multicomponent reactions with isocyanides. Angew Chem Int Ed Engl 39:3169–3210
4. Ugi I, Steinbrückner C (1960) Über ein neues kondensations-prinzip. Angew Chem 72:267–268
5. Marcaccini S, Torroba T (2007) The use of the Ugi four-component condensation. Nat Protoc 2:632–639
6. Dömling A (2006) Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev 106:17–89
7. Akritopoulou-Zanze I (2008) Isocyanide-based multicomponent reactions in drug discovery. Curr Opin Chem Biol 12:324–331
8. Hulme C, Gore V (2003) Multi-component reactions: emerging chemistry in drug discover. From xylocain to crixivan. Curr Med Chem 10:51–80
9. Orru RVA, de Greef M (2003) Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. Synthesis 10:1471–1499
10. Akritopoulou-Zanze I, Djuric SW (2007) Recent advances in the development and applications of post-Ugi transformations. Heterocycles 73:125–147
11. Hulme C, Nixey T, Bienaymé H, Chenera B, Jones W, Tempest P, Smith AL (2003) Library generation via postcondensation modifications of isocyanide-based multicomponent reactions. Meth Enzymol 369:469–496
12. Marcaccini S, Torroba T (2005) Post-condensation transformations of the Passerini and Ugi reactions. In: Zhu J, Bienaymé H (eds) Multicomponent reactions. Wiley-VCH, Weinheim, pp 33–75
13. Banfi L, Basso A, Guanti G, Riva R (2005) Asymmetric isocyanide-based MCRs. In: Zhu J, Bienaymé H (eds) Multicomponent reactions. Wiley-VCH, Weinheim, pp 1–32

14. Keating TA, Armstrong RW (1995) Molecular diversity via a convertible isocyanide in the Ugi four-component condensation. J Am Chem Soc 117:7842–7843
15. Maison W, Schlemminger I, Westerhoff O, Martens J (2000) Multicomponent synthesis of novel amino acid-nucleobase chimeras: a versatile approach to PNA-monomers. Bioorg Med Chem 8:1343–1360
16. Lindhorst T, Bock H, Ugi I (1999) A new class of convertible isocyanides in the Ugi four-component reaction. Tetrahedron 55:7411–7420
17. Kennedy AL, Fryer AM, Josey JA (2002) A new resin-bound universal isonitrile for the ugi 4CC reaction: preparation and applications to the synthesis of 2, 5-diketopiperazines and 1, 4-benzodiazepine-2, 5-diones. Org Lett 4:1167–1170
18. Rikimaru K, Yanagisawa A, Kan T, Fukuyama T (2004) A versatile synthesis of α-amino acid derivatives via the ugi four-component condensation with a novel convertible isonitrile. Synlett 1:41–44
19. Rikimaru K, Yanagisawa A, Kan T, Fukuyama T (2007) A versatile synthesis of α-amino acid derivatives via the Ugi four-component condensation with a novel convertible isonitrile. Heterocycles 73:403–417
20. Linderman RJ, Binet S, Petrich SR (1999) Enhanced diastereoselectivity in the asymmetric Ugi reaction using a new "convertible" isonitrile. J Org Chem 64:336–337
21. Pirrung MC, Ghorai S (2006) Versatile, fragrant, convertible isonitriles. J Am Chem Soc 128:11772–11773
22. Pirrung MC, Ghorai S, Ibarra-Rivera TR (2009) Multicomponent reactions of convertible isonitriles. J Org Chem 74:4110–4117
23. Gilley CB, Buller MJ, Kobayashi Y (2007) New entry to convertible isocyanides for the ugi reaction and its application to the stereocontrolled formal total synthesis of the proteasome inhibitor Omuralide. Org Lett 9:3631–3634
24. Isaacson J, Gilley CB, Kobayashi Y (2007) Expeditious access to unprotected racemic pyroglutamic acids. J Org Chem 72:3913–3916
25. Vamos M, Ozboya K, Kobayashi Y (2007) Synthesis of bicyclic pyroglutamic acid featuring the Ugi reaction and a unique stereoisomerization at the angular position by Grob fragmentation followed by a transannular ketene [2+2] cycloaddition reaction. Synlett 1595–1599.
26. Kreye O, Westermann B, Wessjohann LA (2007) A stable, convertible isonitrile as a formic acid carbanion [-COOH] equivalent and its application in multicomponent reactions. Synlett 20:3188–3192
27. Gilley CB, Kobayashi Y (2008) 2-nitrophenyl isocyanide as a versatile convertible isocyanide: rapid access to a fused γ-lactam β-lactone bicycle. J Org Chem 73:4198–4204
28. Chen JJ, Golebiowski A, Klopfenstein SR, West L (2002) The universal Rink-isonitrile resin: applications in Ugi reactions. Tetrahedron Lett 43:4083–4085
29. Hulme C, Peng J, Morton G, Salvino JM, Herpin T, Labaudiniere R (1998) Novel safety-catch linker and its application with a Ugi/De-BOC/Cyclization (UDC) strategy to access carboxylic acids, 1, 4-benzodiazepines, diketopiperazines, ketopiperazines and dihydroquinoxalinones. Tetrahedron Lett 39:7227–7230
30. Mori K, Rikimaru K, Kan T, Fukuyama T (2004) Synthetic studies on (+)-naphthyridinomycin: stereoselective synthesis of the tetracyclic core framework. Org Lett 6:3095–3097
31. Lin Q, Blackwell HE (2006) Rapid synthesis of diketopiperazine macroarrays via Ugi four-component reactions on planar solid supports. Chem Commun:2884–2886
32. Hulme C, Chappeta S, Dietrich J (2009) A simple, cheap alternative to 'designer convertible isonitriles' expedited with microwaves. Tetrahedron Lett 50:4054–4057
33. Hulme C, Peng J, Louridas B, Menard P, Krolikowski P, Kumar NV (1998) Applications of N-BOC-diamines for the solution phase synthesis of ketopiperazine libraries utilizing a Ugi/De-BOC/Cyclization (UDC) strategy. Tetrahedron Lett 39:8047–8050
34. Hulme C, Ma L, Cherrier MP, Romano JJ, Morton G, Duquenne C, Salvino J, Labaudiniere R (2000) Novel applications of convertible isonitriles for the synthesis of mono and bicyclic γ-lactams via a UDC strategy. Tetrahedron Lett 41:1883–1887

35. Keating TA, Armstrong RW (1996) A remarkable two-step synthesis of diverse 1, 4-benzodiazepine-2, 5-diones using the Ugi four-component condensation. J Org Chem 61:8935–8939
36. Hulme C, Chappeta S, Griffith C, Lee YS, Dietrich J (2009) An efficient solution phase synthesis of triazadibenzoazulenones: 'designer isonitrile free' methodology enabled by microwaves. Tetrahedron Lett 50:1939–1942
37. Hulme C, Peng J, Tang S-Y, Burns CJ, Morize I, Labaudiniere R (1998) Improved procedure for the solution phase preparation of 1, 4-benzodiazepine-2, 5-dione libraries via Armstrong's convertible isonitrile and the Ugi reaction. J Org Chem 63:8021–8023
38. Banfi L, Basso A, Guanti G, Merlo S, Repetto C, Riva R (2008) A convergent synthesis of enantiopure bicyclic scaffolds through multicomponent Ugi reaction. Tetrahedron 64:1114–1134
39. Habashita H, Kokubo M, Hamano S, Hamanaka N, Toda M, Shibayama S, Tada H, Sagawa K, Fukushima D, Maeda K et al (2006) Design, synthesis, and biological evaluation of the combinatorial library with a new spirodiketopiperazine scaffold. Discovery of novel potent and selective low-molecular-weight CCR5 antagonists. J Med Chem 49:4140–4152
40. Nikulnikov M, Tsirulnikov S, Kysil V, Ivachtchenko A, K-Rasavin M (2009) tert-Butyl isocyanide as a convertible reagent in Ugi reaction: microwave-assisted preparation of 5,6-dihydropyrazolo[1,5-a]pyrazine-4,7-diones. Synlett:260–262
41. Mjalli AMM, Sarshar S, Baiga TJ (1996) Solid phase synthesis of pyrroles derived from a four component condensation. Tetrahedron Lett 37:2943–2946
42. Spatz JH, Welsch SJ, Duhaut DE, Jager N, Boursier T, Fredrich M, Allmendinger L, Ross G, Kolb J, Burdack C et al (2009) Tetramic acid derivatives via Ugi-Dieckmann-reaction. Tetrahedron Lett 50:1705–1707
43. Seike H, Sorensen EJ (2008) A synthesis of the tricyclic core structure of FR901483 featuring an Ugi four-component coupling and a remarkably selective elimination reaction. Synlett 5:695–701
44. Marcaccini S, Pepino R, Cruz Pozo M (2001) A facile synthesis of 2, 5-diketopiperazines based on isocyanide chemistry. Tetrahedron Lett 42:2727–2728
45. Bruttomesso AC, Eiras J, Ramirez JA, Galagovsky LR (2009) Highly stereoselective synthesis of steroidal 2, 5-diketopiperazines based on isocyanide chemistry. Tetrahedron Lett 50:4022–4024
46. Santra S, Andreana PR (2007) A one-pot, microwave-influenced synthesis of diverse small molecules by multicomponent reaction cascades. Org Lett 9:5035–5038
47. Banfi L, Basso A, Guanti G, Kielland N, Repetto C, Riva R (2007) Ugi multicomponent reaction followed by an intramolecular nucleophilic substitution: convergent multicomponent synthesis of 1-sulfonyl 1, 4-diazepan-5-ones and of their benzo-fused derivatives. J Org Chem 72:2151–2160
48. Banfi L, Basso A, Casuscelli F, Guanti G, Naz F, Riva R, Zito P (2010) Synthesis of novel isochromene derivatives by tandem Ugi Reaction/nucleophilic substitution. Synlett 85–88
49. Fan L, Adams AM, Polisar JG, Ganem B (2008) Studies on the chemistry and reactivity of α-substituted ketones in isonitrile-based multicomponent reactions. J Org Chem 73:9720–9726
50. Sebti S, Foucaud A (1983) A convenient conversion of 2-acyloxy-3-chlorocarboxamides to 3-acyloxy-2-azetidinones in heterogeneous media. Synthesis:546–549
51. Sebti S, Foucaud A (1984) Reaction des acyloxy-2 chloro-3 chloromethyl-2 propanamides avec l'hydroxyde de potassium ou le fluorure de cesium en milieu heterogene synthese de spiro β-lactames. Tetrahedron 40:3223–3228
52. Banfi L, Basso A, Guanti G, Paravidino M, Riva R (2006) A new highly convergent entry to densely functionalized aziridines based on the Ugi reaction. Qsar Comb Sci 25:457–460
53. Banfi L, Basso A, Guanti G, Lecinska P, Riva R (2008) Multicomponent synthesis of benzoxazinones via tandem Ugi/Mitsunobu reactions: an unexpected cine-substitution. Mol Div 12:187–190

54. Banfi L, Basso A, Riva R (2010) Coupling isocyanide-based multicomponent reactions with aliphatic or acyl nucleophilic substitution processes. Synlett 23–41
55. Banfi L, Basso A, Riva R unpublished results
56. Banfi L, Basso A, Cerulli V, Guanti G, Riva R (2008) Polyfunctionalized pyrrolidines by Ugi multicomponent reaction followed by palladium mediated S_N2' cyclizations. J Org Chem 73:1608–1611
57. Banfi L, Basso A, Cerulli V, Guanti G, Riva R (2009) IV international conference on "multicomponent reactions and related chemistry", 24–28/5. Ekaterinburg (Russia), p S16
58. Kalinski C, Umkehrer M, Ross G, Kolb J, Burdack C, Hiller W (2006) Highly substituted indol-2-ones, quinoxalin-2-ones and benzodiazepin-2, 5-diones via a new Ugi(4CR)-Pd assisted *N*-aryl amidation strategy. Tetrahedron Lett 47:3423–3426
59. Bonnaterre F, Bois-Choussy M, Zhu JP (2006) Rapid access to oxindoles by the combined use of an Ugi four-component reaction and a microwave-assisted intramolecular Buchwald-Hartwig amidation reaction. Org Lett 8:4351–4354
60. Xing XL, Wu JL, Luo JL, Dai WM (2006) C–N bond-linked conjugates of dibenz [b, f][1, 4] oxazepines with 2-oxindole. Synlett 13:2099–2103
61. Erb W, Neuville L, Zhu JP (2009) Ugi-post functionalization, from a single set of Ugi-adducts to two distinct heterocycles by microwave-assisted palladium-catalyzed cyclizations: tuning the reaction pathways by ligand switch. J Org Chem 74:3109–3115
62. Cuny G, Bois-Choussy M, Zhu JP (2004) Palladium- and copper-catalyzed synthesis of medium- and large-sized ring-fused dihydroazaphenanthrenes and 1, 4-benzodiazepine-2, 5-diones. Control of reaction pathway by metal-switching. J Am Chem Soc 126:14475–14484
63. Salcedo A, Neuville L, Rondot C, Retailleau P, Zhu J (2008) Palladium-catalyzed domino intramolecular *N*-arylation/intermolecular C–C bond formation for the synthesis of functionalized benzodiazepinediones. Org Lett 10:857–860
64. Spatz JH, Bach T, Umkehrer M, Bardin J, Ross G, Burdack C, Kolb J (2007) Diversity oriented synthesis of benzoxazoles and benzothiazoles. Tetrahedron Lett 48:9030–9034
65. Salcedo A, Neuville L, Zhu JP (2008) Palladium-catalyzed intramolecular C-arylation of benzylic carbon: synthesis of 3-benzoxazolylisoindolinones by a sequence of Ugi-4CR/postfunctionalization. J Org Chem 73:3600–3603
66. Cheng JF, Chen M, Arrhenius T, Nadzan A (2002) A convenient solution and solid-phase synthesis of Δ5-2-oxopiperazines via *N*-acyliminium ions cyclization. Tetrahedron Lett 43:6293–6295
67. Hanusch-Kompa C, Ugi I (1998) Multi-component reactions 13: synthesis of γ-lactams as part of a multi-ring system via Ugi-4-centre-3-component reaction. Tetrahedron Lett 39:2725–2728
68. Wu JL, Jiang Y, Dai WM (2009) Assembly of 1,3-dihydro-2H-3-benzazepin-2-one conjugates via Ugi four-component reaction and palladium-catalyzed hydroamidation. Synlett: 1162–1166
69. Hulme C, Ma L, Romano JJ, Morrissette MM (1999) Remarkable three-step-one-pot solution phase preparation of novel imidazolines utilizing a UDC (Ugi/de-Boc/cyclize) strategy. Tetrahedron Lett 40:7925–7928
70. Tempest P, Ma V, Thomas S, Hua Z, Kelly MG, Hulme C (2001) Two-step solution-phase synthesis of novel benzimidazoles utilizing a UDC (Ugi/de-Boc/cyclize) strategy. Tetrahedron Lett 42:4959–4962
71. Zhang W, Tempest P (2004) Highly efficient microwave-assisted fluorous Ugi and post-condensation reactions for benzimidazoles and quinoxalinones. Tetrahedron Lett 45:6757–6760
72. Tempest P, Ma V, Kelly MG, Jones W, Hulme C (2001) MCC/SNAr methodology. Part 1: Novel access to a range of heterocyclic cores. Tetrahedron Lett 42:4963–4968
73. Bossio R, Marcaccini S, Pepino R (1991) Synthesis of isocyanides and related compounds. Synthesis of oxazole derivatives via the Passerini reaction. Liebigs Ann Chem 1107–1108

74. Bossio R, Marcaccini S, Pepino R, Polo C, Torroba T (1992) Synthesis of *N*-substituted 2-alkyl-4-aryloxazole-5-carboxamides. Org Prep Proced Int 24:188–191
75. Beck B, Larbig G, Mejat B, Magnin Lachaux M, Picard A, Herdtweck E, Dömling A (2003) Short and diverse route toward complex natural product-like macrocycles. Org Lett 5: 1047–1050
76. Zhang C, Moran EJ, Woiwode TF, Short KM, Mjalli AMM (1996) Synthesis of tetrasubstituted imidazoles via α-(*N*-acyl-*N*-alkylamino)-β-ketoamides on Wang resin. Tetrahedron Lett 37:751–754
77. Sung KS, Wu SH, Chen PI (2002) Facile two-pot syntheses of novel alternating benzene/imidazole systems. Tetrahedron 58:5599–5602
78. Trifilenkov AS, Ilyin AP, Kysil VM, Sandulenko YB, Ivachtchenko AV (2007) One-pot tandem complexity-generating reaction based on Ugi four component condensation and intramolecular cyclization. Tetrahedron Lett 48:2563–2567
79. Hatanaka M, Nitta H, Ishimaru T (1984) The synthesis of the 1-carbopenem antibiotic (±)-ps-5 and its 6-epi analogue. Tetrahedron Lett 25:2387–2390
80. Golebiowski A, Jozwik J, Klopfenstein SR, Colson AO, Grieb AL, Russell AF, Rastogi VL, Diven CF, Portlock DE, Chen JJ (2002) Solid-supported synthesis of putative peptide β-turn mimetics via Ugi reaction for diketopiperazine formation. J Comb Chem 4:584–590
81. Xing XL, Wu JL, Feng GF, Dai WM (2006) Microwave-assisted one-pot U-4CR and intramolecular O-alkylation toward heterocyclic scaffolds. Tetrahedron 62:6774–6781
82. de Greef M, Abeln S, Belkasmi K, Doemling A, Orru RVA, Wessjohann LA (2006) Rapid combinatorial access to macrocyclic ansapeptoids and ansapeptides with natural-product-like core structures. Synthesis 23:3997–4004
83. Bossio R, Marcos CF, Marcaccini S, Pepino R (1997) A facile synthesis of β-lactams based on isocyanide chemistry. Tetrahedron Lett 38:2519–2520
84. Banfi L, Basso A, Cerulli V, Guanti G, Monfardini I, Riva R (2009) Mol Div. doi: 10.1007/s11030-009-9210-4 (in press)
85. Banfi L, Basso A, Guanti G, Lecinska P, Riva R (2006) Multicomponent synthesis of dihydrobenzoxazepinones by coupling Ugi and Mitsunobu reactions. Org Biomol Chem 4:4236–4240
86. Banfi L, Basso A, Guanti G, Lecinska P, Riva R, Rocca V (2007) Multicomponent synthesis of novel 2- and 3-substituted dihydrobenzo[1, 4]oxazepinones and tetrahydrobenzo[1, 4]diazepin-5-ones and their conformational analysis. Heterocycles 73:699–728
87. Tempest P, Pettus L, Gore V, Hulme C (2003) MCC/SNAr methodology. Part 2: Novel three-step solution phase access to libraries of benzodiazepines. Tetrahedron Lett 44:1947–1950
88. Spatz JH, Umkehrer M, Kalinski C, Ross G, Burdack C, Kolb J, Bach T (2007) Combinatorial synthesis of 4-oxo-4H-imidazo[1, 5-a]quinoxalines and 4-oxo-4H-pyrazolo[1, 5-a]quinoxalines. Tetrahedron Lett 48:8060–8064
89. Cristau P, Vors JP, Zhu JP (2001) A rapid access to biaryl ether containing macrocycles by pairwise use of Ugi 4CR and intramolecular SNAr-based cycloetherification. Org Lett 3:4079–4082
90. Cristau P, Vors JP, Zhu JP (2003) Rapid and diverse route to natural product-like biaryl ether containing macrocycles. Tetrahedron 59:7859–7870
91. Cristau P, Vors JP, Zhu JP (2006) Rapid synthesis of cyclopeptide alkaloid-like paracyclophanes by combined use of Ugi-4CR and intramolecular SNAr reaction. Qsar & Comb Sci 25:519–526
92. Neo AG, Marcos CF, Marcaccini S, Pepino R (2005) Studies on isocyanides. A facile synthesis of 4, 5-dihydro-1, 4-benzothiazepin-3(2H)-ones via post-condensation modifications of the Ugi reaction. Tetrahedron Lett 46:7977–7979
93. Wyatt PG, Allen MJ, Borthwick AD, Davies DE, Exall AM, Hatley RJD, Irving WR, Livermore DG, Miller ND, Nerozzi F et al (2005) 2, 5-diketopiperazines as potent and selective oxytocin antagonists-1: identification, stereochemistry and initial SAR. Bioorg Med Chem Lett 15:2579–2582

94. Szardenings AK, Burkoth TS, Lu HH, Tien DW, Campbell DA (1997) A simple procedure for the solid phase synthesis of diketopiperazine and diketomorpholine derivatives. Tetrahedron 53:6573–6593
95. Szardenings AK, Antonenko V, Campbell DA, DeFrancisco N, Ida S, Shi L, Sharkov N, Tien D, Wang Y, Navre M (1999) Identification of highly selective inhibitors of collagenase-1 from combinatorial libraries of diketopiperazines. J Med Chem 42:1348–1357
96. Sollis SL (2005) Short and novel stereospecific synthesis of trisubstituted 2, 5-diketopiperazines. J Org Chem 70:4735–4740
97. Bohn Rhoden CR, Westermann B, Wessjohann LA (2008) One-pot multicomponent synthesis of N-substituted tryptophan-derived diketopiperazines. Synthesis (Stuttg) 13: 2077–2082
98. Hulme C, Cherrier MP (1999) Novel applications of ethyl glyoxalate with the Ugi MCR. Tetrahedron Lett 40:5295–5299
99. Tsirulnikov S, Nikulnikov M, Kysil V, Ivachtchenko A, Krasavin M (2009) Streamlined access to 2, 3-dihydropyrazino[1, 2-a]indole-1, 4-diones via Ugi reaction followed by microwave-assisted cyclization. Tetrahedron Lett 50:5529–5531
100. Hulme C, Ma L, Kumar NV, Krolikowski PH, Allen AC, Labaudiniere R (2000) Novel applications of resin bound α-amino acids for the synthesis of benzodiazepines (via Wang resin) and ketopiperazines (via hydroxymethyl resin). Tetrahedron Lett 41:1509–1514
101. Faggi C, Marcaccini S, Pepino R, Pozo MC (2002) Studies on isocyanides and related compounds; synthesis of 1,4-benzodiazepine-2,5-diones via Ugi four-component condensation. Synthesis 18:2756–2760
102. Nixey T, Tempest P, Hulme C (2002) Two-step solution-phase synthesis of novel quinoxalinones utilizing a UDC (Ugi/de-Boc/cyclize) strategy. Tetrahedron Lett 43:1637–1639
103. Marcaccini S, Miliciani M, Pepino R (2005) A facile synthesis of 1, 4-benzodiazepine derivatives via Ugi four-component condensation. Tetrahedron Lett 46:711–713
104. Sanudo M, Garcia-Valverde M, Marcaccini S, Delgado JJ, Rojo J, Torroba T (2009) Synthesis of benzodiazepine β-turn mimetics by an Ugi 4CC/Staudinger/Aza-Wittig sequence. Solving the conformational behavior of the Ugi 4CC adducts. J Org Chem 74:2189–2192
105. Corres N, Delgado JJ, Garcia-Valverde M, Marcaccini S, Rodriguez T, Rojo J, Torroba T (2008) Synthesis of pseudopeptidic [(5H)-6-oxodibenzo[b, f][1, 5]diazocine-5-yf]arylglycinamides by an Ugi 4CC/Staudinger/aza-Wittig sequence. Tetrahedron 64:2225–2232
106. Rikimaru K, Mori K, Kan T, Fukuyama T (2005) Synthetic studies on (-)-lemonomycin: stereocontrolled construction of the 3,8-diazabicyclo[3.2.1] skeleton. Chem Commun (3): 394–396
107. Faggi C, Garcia Valverde M, Marcaccini S, Pepino R, Pozo MC (2003) Studies on Isocyanides and related compounds: a facile synthesis of 1,6-dihydro-6-oxopyrazine-2-carboxylic acid derivatives via ugi four-component condensation. Synthesis 10:1553–1558
108. Sebti S, Foucaud A (1986) Anionic activation by fluoride ion in solid-liquid systems: synthesis of 3(2H)-furanones and 2 (5H)-furanones. Tetrahedron 42:1361–1367
109. Bossio R, Marcaccini S, Pepino R, Torroba T (1993) Studies on isocyanides and related compounds: A novel synthetic route to furan derivatives. Synthesis 8:783–785
110. Bossio R, Marcaccini S, Pepino R (1994) Synthesis of isocyanides and related compounds. Synthesis of a novel class of furan derivatives. Liebigs Ann Chem 527–528
111. Marcaccini S, Pepino R, Marcos CF, Polo C, Torroba T (2000) Studies on isocyanides and related compounds. Synthesis of furan derivatives and their transformation into indole derivatives. J Heterocycl Chem 37:1501–1503
112. Bossio R, Marcaccini S, Pepino R (1994) Studies on isocyanides and related compounds: a novel synthesis of pyrroles via Ugi reaction. Synthesis 8:765–766
113. Bossio R, Marcaccini S, Pepino R, Torroba T (1999) Studies on isocyanides and related compounds. A facile synthesis of 1-substituted 3-cyano-2-methoxy-3-phenylpyrroles. Heterocycles 50(1):463–467

114. Marcaccini S, Pepino R, Cruz Pozo M, Basurto S, Garcia Valverde M, Torroba T (2004) One-pot synthesis of quinolin-2-(1H)-ones via tandem Ugi–Knoevenagel condensations. Tetrahedron Lett 45:3999–4001
115. Bossio R, Marcos CF, Marcaccini S, Pepino R (1997) Studies on isocyanides and related compounds. A novel synthetic route to 1, 6-dihydro-6-oxopyridine-2-carboxylic acid derivatives. Heterocycles 45:1589–1592
116. Beck B, Magnin-Lachaux M, Herdtweck E, Dömling A (2001) A novel three-component butenolide synthesis. Org Lett 3:2875–2787
117. Beck B, Picard A, Herdtweck E, Dömling A (2004) Highly substituted pyrrolidinones and pyridones by 4-CR/2-CR sequence. Org Lett 6:39–42
118. Yehia NAM, Antuch W, Beck B, Hess S, Schauer Vukasinovic V, Almstetter M, Furer P, Herdtweck E, Dömling A (2004) Novel nonpeptidic inhibitors of HIV-1 protease obtained via a new multicomponent chemistry strategy. Bioorg Med Chem Lett 14:3121–3125
119. De Silva RA, Santra S, Andreana PR (2008) A tandem one-pot, microwave-assisted synthesis of regiochemically differentiated 1, 2, 4, 5-tetrahydro-1, 4-benzodiazepin-3-ones. Org Lett 10:4541–4544
120. Neo AG, Carrillo RM, Barriga S, Moman E, Marcaccini S, Marcos CF (2007) Multicomponent synthesis of highly substituted 2-pyridones. Synlett 2:327–329
121. Paulvannan K (1999) Preparation of tricyclic nitrogen heterocycles via tandem four-component condensation/intramolecular Diels-Alder reaction. Tetrahedron Lett 40:1851–1854
122. Lee D, Sello JK, Schreiber SL (2000) Pairwise use of complexity-generating reactions in diversity-oriented organic synthesis. Org Lett 2:709–712
123. Sello JK, Andreana PR, Lee D, Schreiber SL (2003) Stereochemical control of skeletal diversity. Org Lett 5:4125–4127
124. Oikawa M, Ikoma M, Sasaki M (2005) Parallel synthesis of tandem Ugi/Diels-Alder reaction products on a soluble polymer support directed toward split-pool realization of a small molecule library. Tetrahedron Lett 46:415–418
125. Ilyin A, Kysil V, Krasavin M, Kurashvili I, Ivachtchenko AV (2006) Complexity-enhancing acid-promoted rearrangement of tricyclic products of tandem Ugi 4CC/intramolecular Diels-Alder reaction. J Org Chem 71:9544–9547
126. Ikoma M, Oikawa M, Sasaki M (2009) Chemospecific allylation and domino metathesis of 7-oxanorbornenes for skeletal and appendage diversity. Eur J Org Chem 72–84
127. Paulvannan K (2004) An atom-economical approach to conformationally constrained tricyclic nitrogen heterocycles via sequential and tandem Ugi/intramolecular Diels-Alder reaction of pyrrole. J Org Chem 69:1207–1214
128. Wright DL, Robotham CV, Aboud K (2002) Studies on the sequential multi-component coupling/Diels-Alder cycloaddition reaction. Tetrahedron Lett 43:943–946
129. Lu K, Luo TP, Xiang Z, You ZJ, Fathi R, Chen JH, Yang Z (2005) A concise and diversity-oriented strategy for the synthesis of benzofurans and indoles via Ugi and Diels-Alder reactions. J Comb Chem 7:958–967
130. Akritopoulou Zanze I, Gracias V, Moore JD, Djuric SW (2004) Synthesis of novel fused isoxazoles and isoxazolines by sequential Ugi/INOC reactions. Tetrahedron Lett 45: 3421–3423
131. Akritopoulou-Zanze I, Gracias V, Djuric SW (2004) A versatile synthesis of fused triazolo derivatives by sequential Ugi/alkyne-azide cycloaddition reactions. Tetrahedron Lett 45:8439–8441
132. Akritopoulou-Zanze I, Whitehead A, Waters JE, Henry RF, Djuric SW (2007) Synthesis of novel and uniquely shaped 3-azabicyclo[4.2.0]octan-4-one derivatives by sequential Ugi/[2 + 2] ene-enone photocycloadditions. Org Lett 9:1299–1302
133. Ribelin TP, Judd AS, Akritopoulou-Zanze I, Henry RF, Cross JL, Whittern DN, Djuric SW (2007) Concise construction of novel bridged bicyclic lactams by sequenced Ugi/RCM/Heck reactions. Org Lett 9:5119–5122

134. Piscopio AD, Miller JF, Koch K (1999) Ring closing metathesis in organic synthesis: evolution of a high speed, solid phase method for the preparation of β-turn mimetics. Tetrahedron 55:8189–8198
135. Krelaus R, Westermann B (2004) Preparation of peptide-like bicyclic lactams via a sequential Ugi reaction - olefin metathesis approach. Tetrahedron Lett 45:5987–5990
136. Banfi L, Basso A, Guanti G, Riva R (2003) Application of tandem Ugi reaction/ring-closing metathesis in multicomponent synthesis of unsaturated nine-membered lactams. Tetrahedron Lett 44:7655–7658
137. Anthoine-Dietrich S, Banfi L, Basso A, Damonte G, Guanti G, Riva R (2005) Application of tandem Ugi multi-component reaction/ring closing metathesis to the synthesis of a conformationally restricted cyclic pentapeptide. Org Biomol Chem 3(1):97–106
138. Banfi L, Basso A, Damonte G, De Pellegrini F, Galatini A, Guanti G, Monfardini I, Riva R, Scapolla C (2007) Synthesis and biological evaluation of new conformationally biased integrin ligands based on a tetrahydroazoninone scaffold. Bioorg Med Chem Lett 17:1341–1345
139. Hebach C, Kazmaier U (2003) Via Ugi reactions to conformationally fixed cyclic peptides. Chem Commun 5:596–597
140. Kazmaier U, Hebach C, Watzke A, Maier S, Mues H, Huch V (2005) A straightforward approach toward cyclic peptides via ring-closing metathesis – scope and limitations. Org Biomol Chem 3:136–145
141. Kalinski C, Umkehrer M, Schmidt J, Ross G, Kolb J, Burdack C, Hiller W, Hoffmann SD (2006) A novel one-pot synthesis of highly diverse indole scaffolds by the Ugi/Heck reaction. Tetrahedron Lett 47:4683–4686
142. Umkehrer M, Kalinski C, Kolb E, Burdack C (2006) A new and versatile one-pot synthesis of indol-2-ones by a novel Ugi-four-component-Heck reaction. Tetrahedron Lett 47:2391–2393
143. Dai WM, Shi JY, Wu JL (2008) Synthesis of 3-arylideneindolin-2-ones from 2-aminophenols by Ugi four-component reaction and Heck carbocyclization. Synlett 2716–2720
144. Gracias V, Moore JD, Djuric SW (2004) Sequential Ugi/Heck cyclization strategies for the facile construction of highly functionalized N-heterocyclic scaffolds. Tetrahedron Lett 45:417–420
145. Xiang Z, Luo T, Cui J, Shi X, Fathi R, Chen J, Yang Z (2004) Concise synthesis of isoquinoline via the Ugi and Heck reactions. Org Lett 6:3155–3158
146. Vasudevan A, Verzal MK (2005) A post-Ugi carbonylation/intramolecular amidation approach toward the synthesis of macrolactams. Tetrahedron Lett 46:1697–1701
147. Ma ZB, Xiang Z, Luo TP, Lu K, Xu ZB, Chen JH, Yang Z (2006) Synthesis of functionalized quinolines via Ugi and Pd-catalyzed intramolecular arylation reactions. J Comb Chem 8:696–704
148. Bonnaterre F, Bois-Choussy M, Zhu JP (2008) Synthesis of dihydrophenanthridines by a sequence of Ugi-4CR and palladium-catalyzed intramolecular C-H functionalization. Beilstein J Org Chem 4(10)
149. El Kaim L, Gageat M, Gaultier L, Grimaud L (2007) New Ugi/Pictet-Spengler multicomponent formation of polycyclic diketopiperazines from isocyanides and α-keto acids. Synlett 3:500–502
150. Liu HX, Dömling A (2009) Efficient and Diverse Synthesis of Indole Derivatives. J Org Chem 74:6895–6898
151. Akritopoulou-Zanze I, Whitehead A, Waters JE, Henry RF, Djuric SW (2007) Synthesis of substituted 3, 4-dihydroquinolin-2(1H)-one derivatives by sequential Ugi/acrylanilide [6 pi]-photocyclizations. Tetrahedron Lett 48:3549–3552
152. El Kaim L, Grimaud L, Miranda LD, Vieu E (2006) Ugi/xanthate cyclizations as a radical route to lactam scaffolds. Tetrahedron Lett 47:8259–8261

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Aminoazoles as Key Reagents in Multicomponent Heterocyclizations

Valentin A. Chebanov, Katerina A. Gura, and Sergey M. Desenko

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

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

Contents

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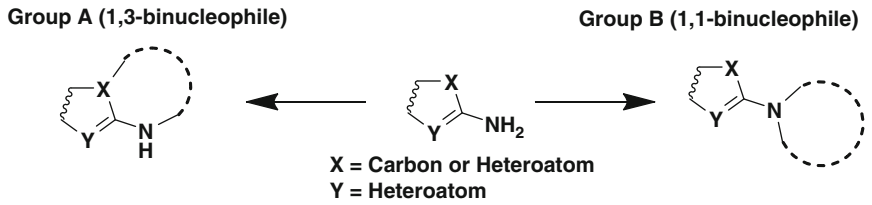
Abbreviations

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

1 Introduction

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

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



Scheme 1 Two main groups of aminozole MCRs

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

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

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

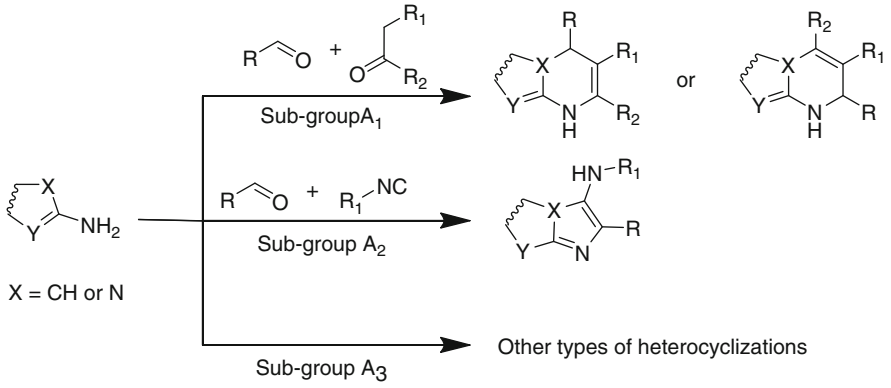
It should be noted that carbonyl compounds, more often aldehydes, are usual second reagent in both the groups. Other building-blocks in these multicomponent processes, leading to the formation of five-, six-, and seven-membered heterocycles, can be numerous acids and their derivatives, β-dicarbonyl compounds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

2 Aminoazoles as 1,3-Binucleophiles

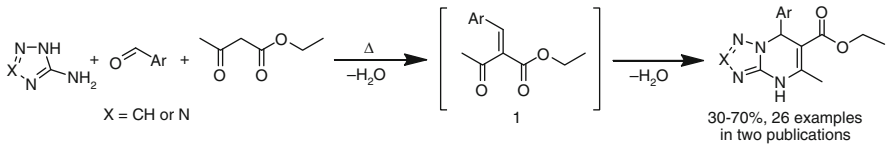
MCRs involving aminoazoles as 1,3-binucleophiles (group A) being the major part of known processes of such type, in turn, can be divided into several additional sub-groups (Scheme 2). The biggest one consists of the treatments of aminoazole with synthetic precursors of α,β-unsaturated carbonyl compounds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

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

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



Scheme 2 Aminoazoles as 1,3-binucleophiles



Scheme 3 MCR of aminoazoles and aldehydes with acetoacetic esters

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

2.1.1 Noncyclic CH-Acids

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

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

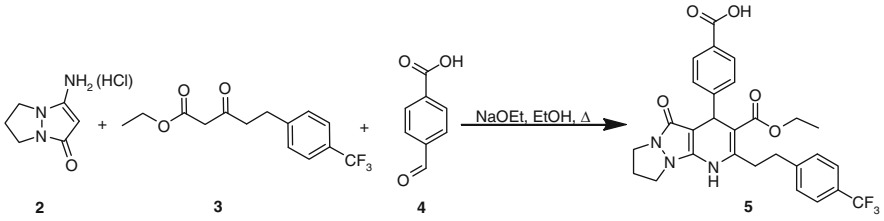
It seems that initial stage of the treatment should be Knoevenagel reaction via the formation of unsaturated derivatives **1** (Scheme 3). This sequence is considered

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

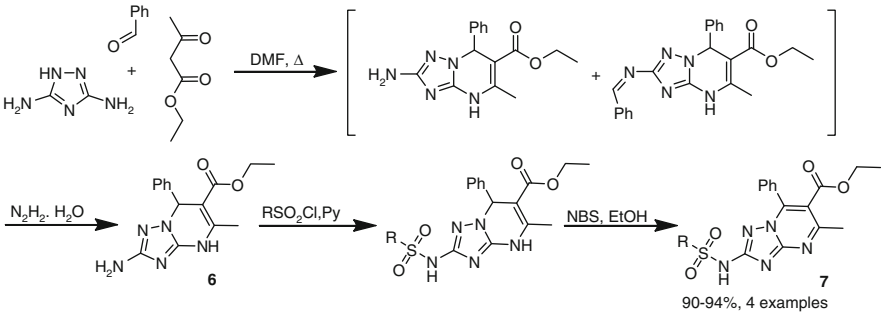
In several subsequent publications, this promising multicomponent synthetic approach was used for the synthesis of certain types of biologically active heterocyclic compounds. For instance, Boros and co-authors [35] reported application of the three-component heterocyclization between bicyclic aminoazole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

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

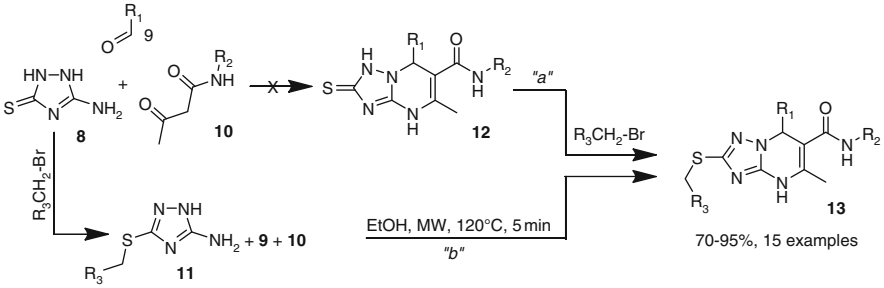
MCRs of aminoazoles and aldehydes with acetoacetamides are also known. For example, combinatorial-oriented synthesis of potentially pharmacologically active dihydrotriazolopyrimidines **13** was described in [38].The authors considered that carrying out S-alkylation at the last step of pathway "a" (Scheme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



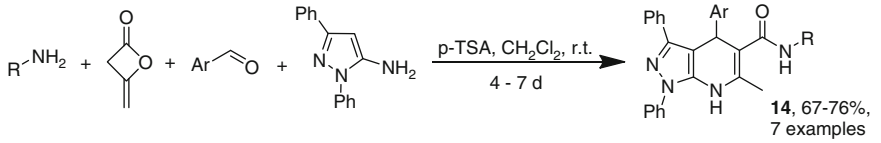
Scheme 4 Synthesis of aza-analog of agonist of the calcetonine receptor



Scheme 5 Synthesis of azolopyrimidines promising in agriculture



Scheme 6 Three-component synthesis of triazolopyrimidinecaroxamides



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

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

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

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

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

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

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

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

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

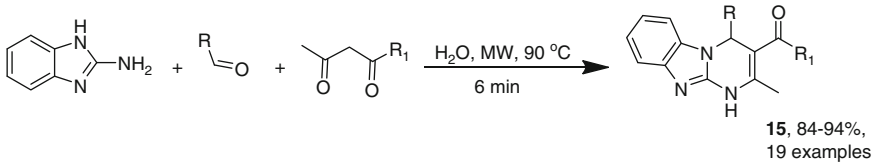
In addition to the abovementioned results consisting only the increasing yields (Scheme 6) [38], another example of effective microwave-assisted synthesis of azolopyrimidine carboxamides should be described. Tu et al. [47] reported eco-friendly three-component reaction of 2-aminobenzimidazole, aromatic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

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

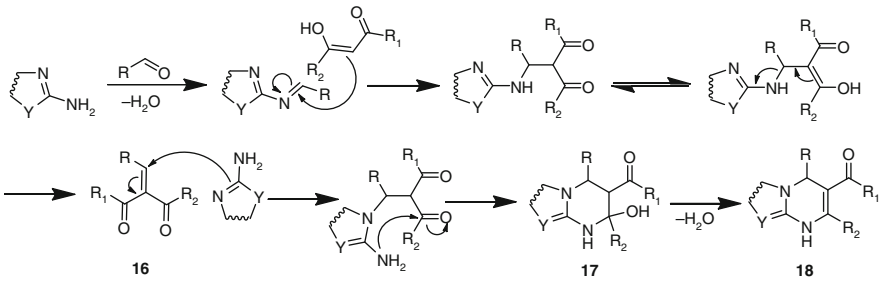
Generally, MCRs based on aminoazoles and synthetic precursors of α,β-unsaturated carbonyl compounds proceed via a sequence of Knoevenagel-type condensation, which was already mentioned (see Scheme 3), Michael-like addition, cyclization, and water elimination. For example, the authors of [47] considered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

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

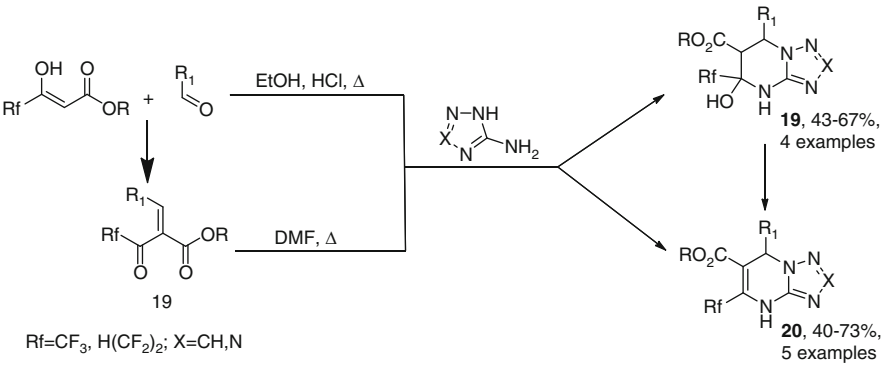
It should be noted that in the most cases MCRs of aminoazoles with CH-acids and aldehydes and linear reactions including preliminary synthesis of α,β-unsaturated carbonyl compounds like **16** yield the same reaction products.



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



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



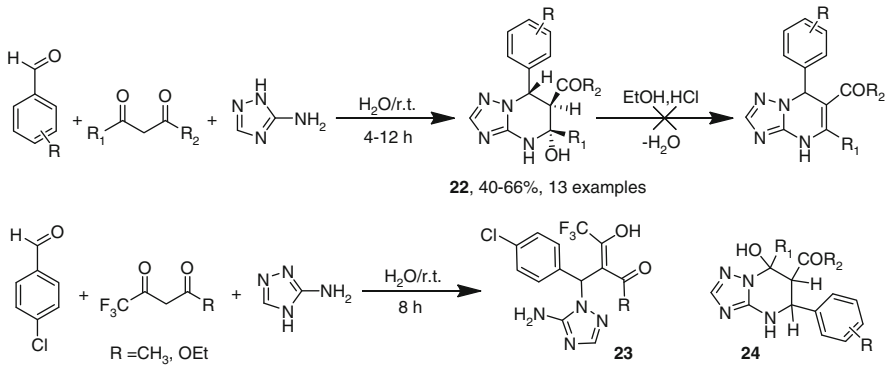
Scheme 10 MCRs of fluorinated 1,3-dicarbonyls

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

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

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

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



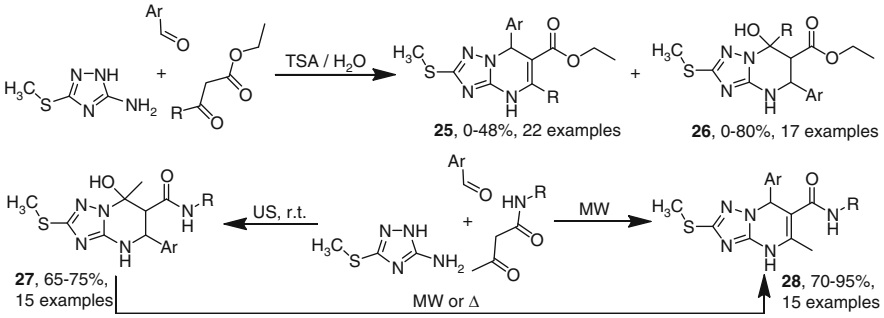
Scheme 11 Unusual directions of aminoazole MCRs

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

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

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

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



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

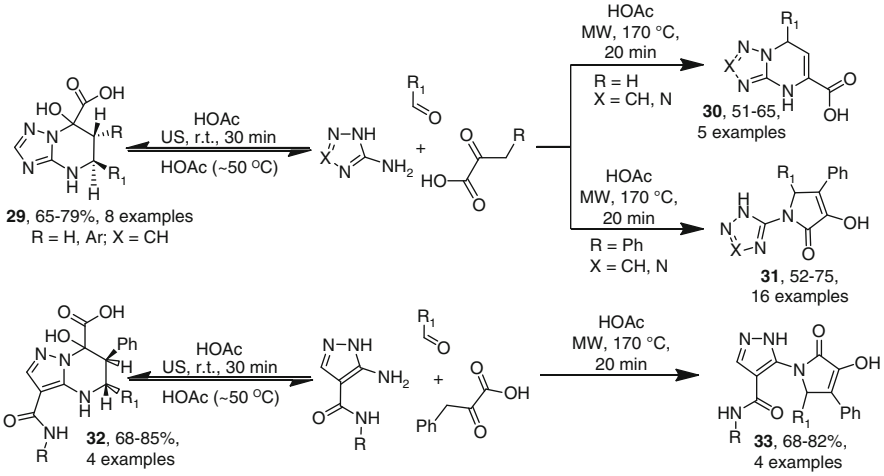
treatment in microwave field at higher temperatures yielded "classical" Biginelli-like heterocycles **28** (Scheme 12). Moreover, compounds **27** can be easily converted into **28** by heating in ethanol.

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

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

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

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



Scheme 13 MCRs under kinetic and thermodynamic control

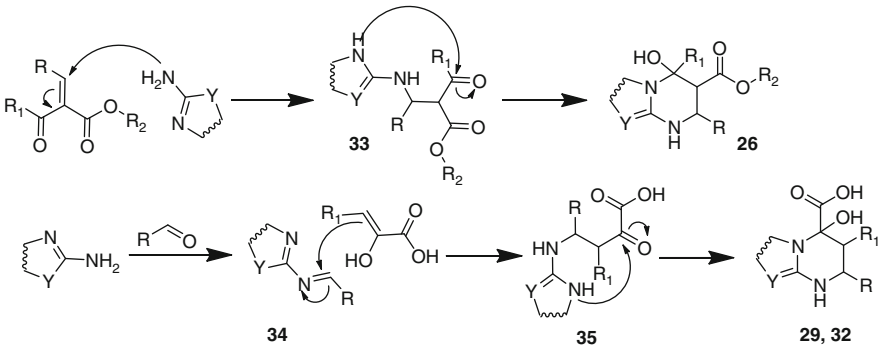
refluxing in acetic acid yields (depending on R substituent) ether carboxylic acids **30** (R = H) or pyrrolones **31**, **33** (R = Ph) [51–53].

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

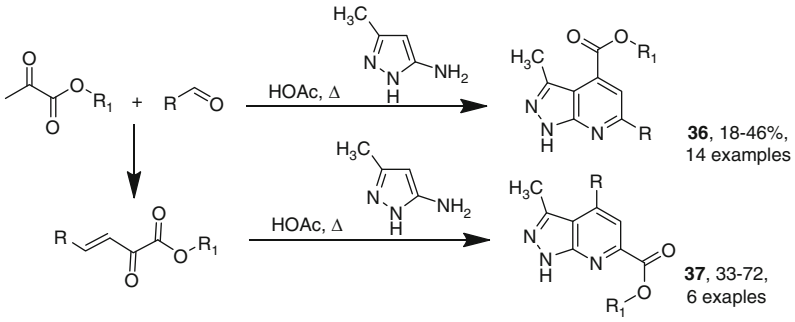
Chen and co-authors in their work [50] offered key stages for mechanism of heterocyclization leading to compounds **25** and **26** (Scheme 12). The reaction sequence for azolopyrimidines **25** formation is very similar to that published in [47] and presented in Scheme 9. Pathway to tetrahydroderivatives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

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

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



Scheme 14 Mechanisms of tetrahydroazolopyrimidines formation



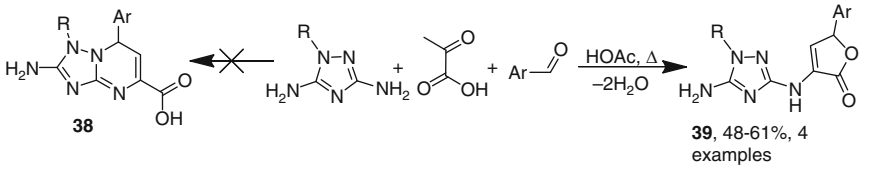
Scheme 15 Synthesis of positional isomers of pyrazolopyridine carboxylic acid derivatives

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

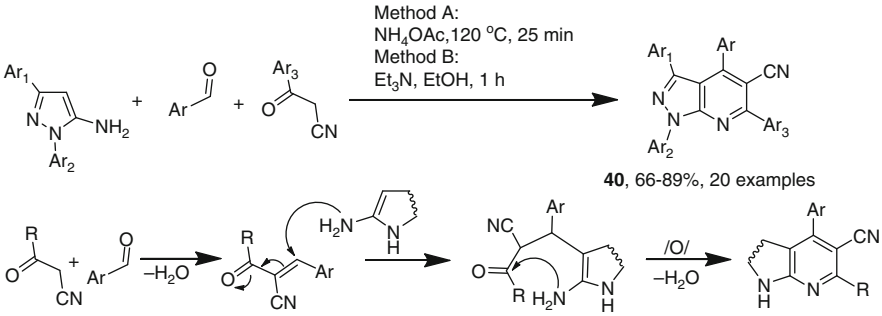
Different products of the three-component and linear treatments in the case of 5-aminopyrazole can be the evidence that this MCR follows independent pathway without formation of in situ α,β-unsaturated carbonyl compound.

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

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



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



Scheme 17 Benzoylacetonitriles in MCRs with aminopyrazoles

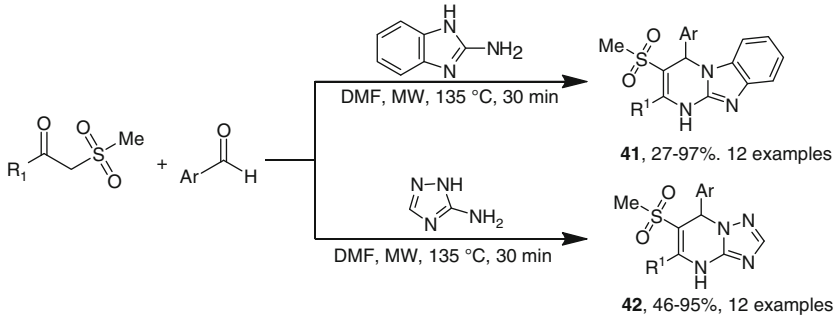
transition states energy or to the decrease in thermodynamic stability of the final heterocycles. Both these factors should favor formation of furanones **39**.

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

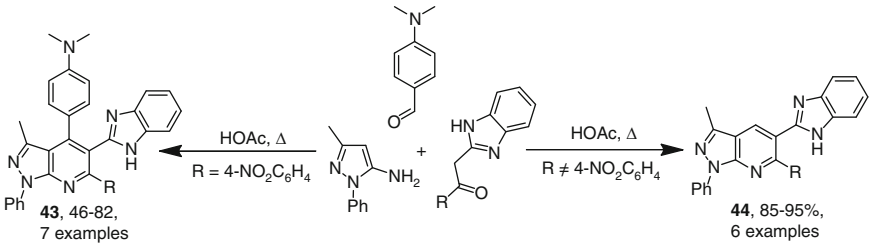
To carry out the similar MCR involving 5-amino-3-methyl-1-phenylpyrazole, aromatic aldehydes, and 3-cyanoacetyl indoles, Zhu et al. [70] used microwave-assisted synthesis in glygol at 150°C. Application of other solvents was less effective and gave either no reaction products (water medium) or led to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

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

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



Scheme 18 Ketosulfones in MCRs with aminoazoles



Scheme 19 Elimination of 4-dimethylaminophenyl substituent

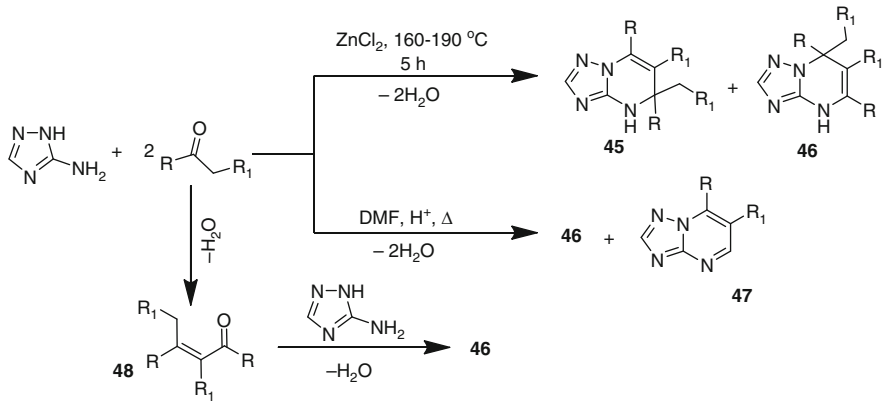
(Scheme 18) [72]. It is interesting to note that this MCR involving 5-aminotetrazole was unsuccessful and only the starting materials were reisolated from the reaction mixture. An explanation for this unreactivity could be the decrease in nucleophilicity comparing 3-amino-1,2,4-triazole and 2-aminobenzimidazole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

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

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

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

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



Scheme 20 Formation of position isomers in MCRs of aminotriazole

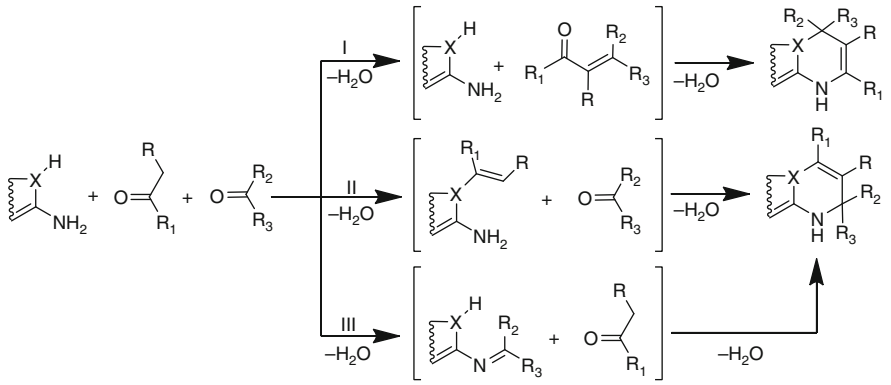
reactions of cyclic CH-acids and will be discussed in Sect. 2.1.2. However, there are several examples for noncyclic active methylene compounds.

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

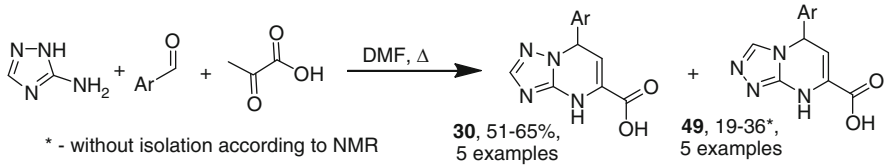
It is possible to suggest at least three mechanisms to explain different directions of the abovementioned MCRs (Scheme 21) [1, 79, 80]. It should be noted that the reaction passing according to pathway **I** is not an independent method for the formation of the dihydroazine system and corresponds to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

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

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



Scheme 21 Mechanisms of position isomers formation



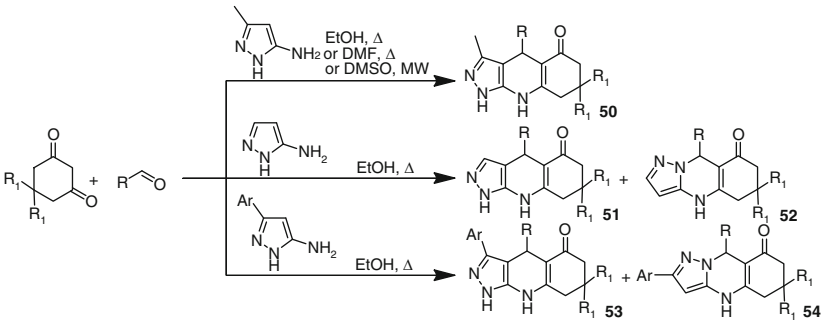
Scheme 22 Formation of regio-isomers in MCRs of 3-amino-1,2,4-triazole, pyruvic acid and aldehydes

2.1.2 Cyclic CH-Acids

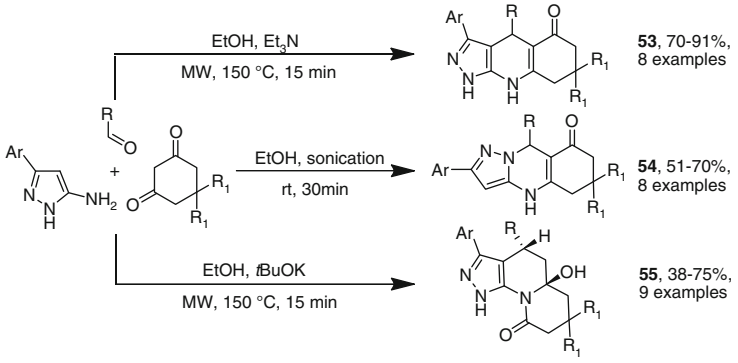
MCRs of Hantzsch and Biginelli-types with participation of aldehydes, aminoazoles, and cyclic CH-acids, first of all 1,3-diketones and Meldrum acid, as well as the treatments discussed in the previous sub-chapter, are in the focus of interest due to high biological activity of their products. However,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

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

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



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



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

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

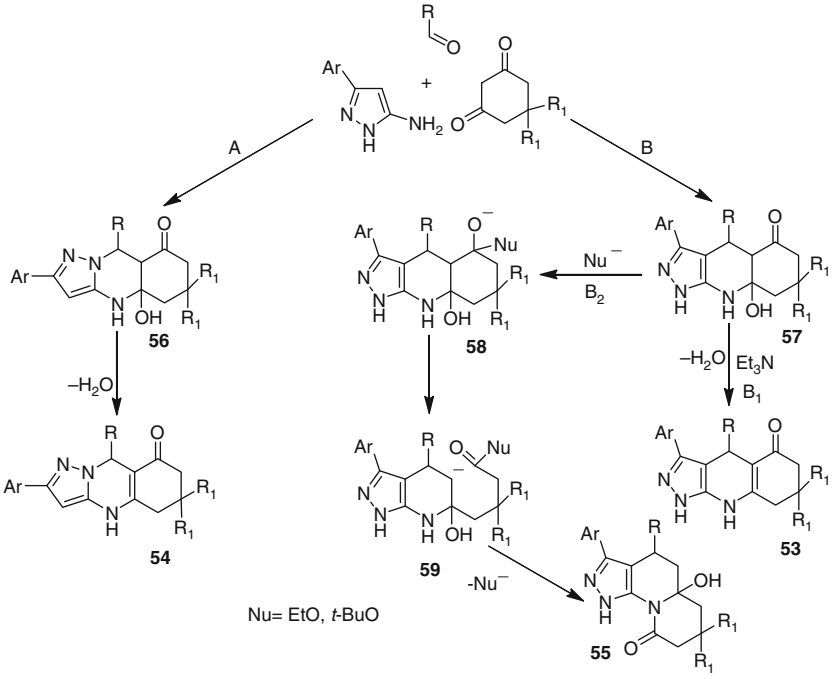
It was reported [59] that temperature in combination with the choice of catalyst is, indeed, the main factor in controlling the direction of this MCR. Under ambient and neutral conditions, the reaction between 5-amino-3-phenylpyrazole, cyclic diketones, and aromatic aldehydes yielded Biginelli-type dihydropyrimidines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

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

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

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

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



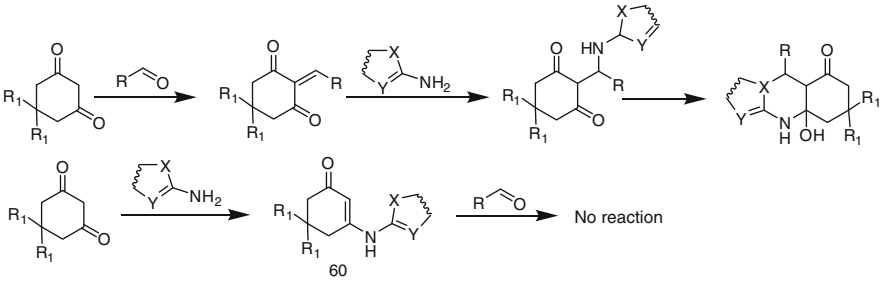
Scheme 25 Key stages for MCRs between 5-aminopyrazoles, aldehydes and cyclic 1,3-diketones

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

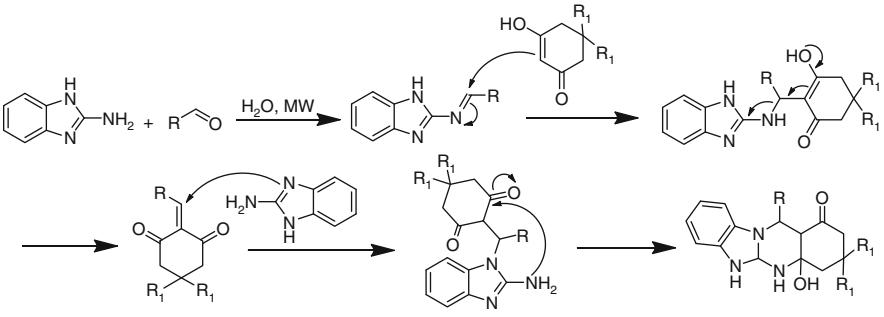
The mechanism of the formation of tricyclic intermediates **56** and **57** is also the important and conflicting matter. For example, Quiroga et al. [83] showed that these MCRs, the most probable, proceed via preliminary Knoevenagel condensation and Michael addition (Scheme 26). At the same time they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

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

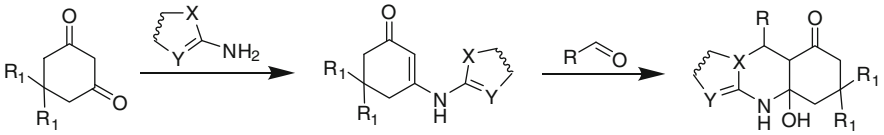
On the other hand, Lipson and co-authors in their publications described numerous MCRs of cyclic β-dicarbonyl compounds and aldehydes with 5-amino-3-methylpyrazole [84], 3-amino-1,2,4-triazole [90], 3-amino-5-methyltio-1,2,4-triazole [91], 2-aminobenimidazole [92], and 2,5-diamino-1,2,4-triazole [93].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



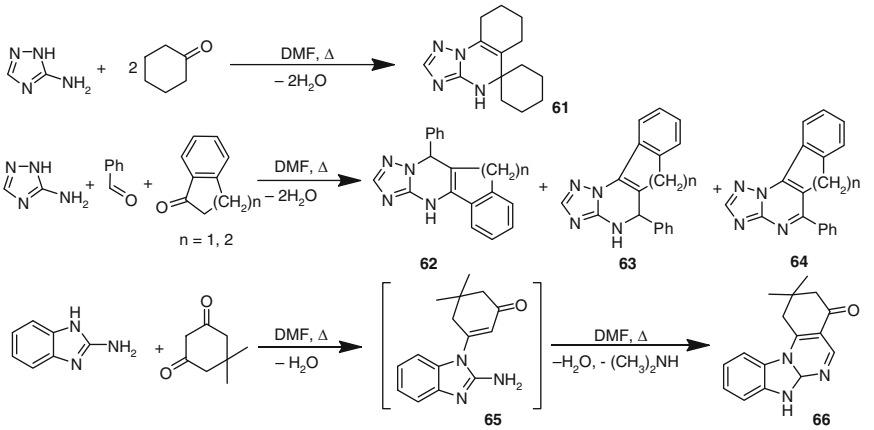
Scheme 26 Possible mechanism of tricyclic intermediate formation



Scheme 27 Microwave-assisted Knoevenagel condensation and Michael addition cascade



Scheme 28 Alternative mechanism of tricyclic intermediate formation



Scheme 29 Formation of angular heterocycles in MCRs

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

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

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

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

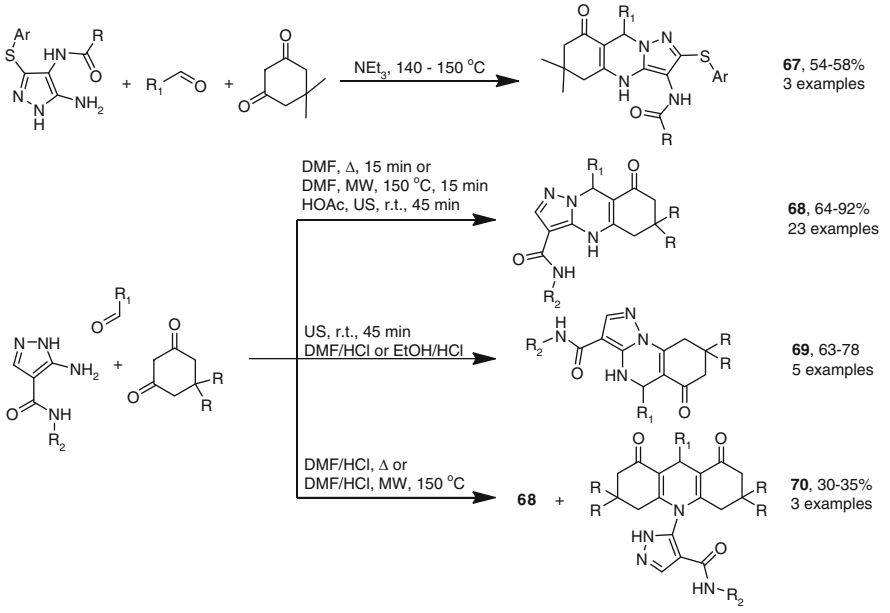
Lipson et al. in several publications [91–93] in the reactions of dimedone and aromatic aldehydes with 2-aminobenzimidazole, 3,5-diamino-1,2,4-triazole, and 3-amino-5-methyltio-1,2,4-triazole described a formation of angular tri- and four-cyclic heterocycles as minor reaction products. However, aldehydes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

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

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

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

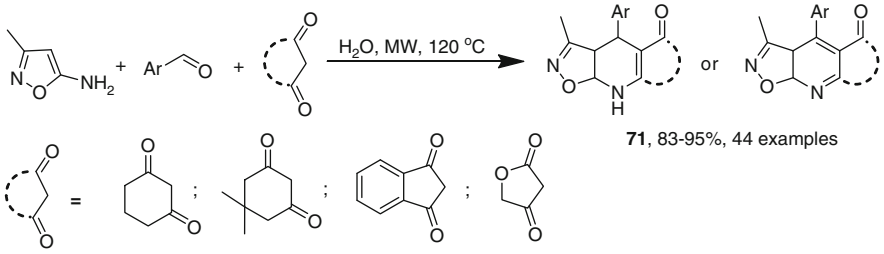
It is very important that this preparative procedure allowed selective synthesis of Biginelli-like fused dihydropyrimidines of type **69** having angular structure. As everyone can see from the other publications cited above in other cases, these heterocycles were usually minor reaction by-products.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



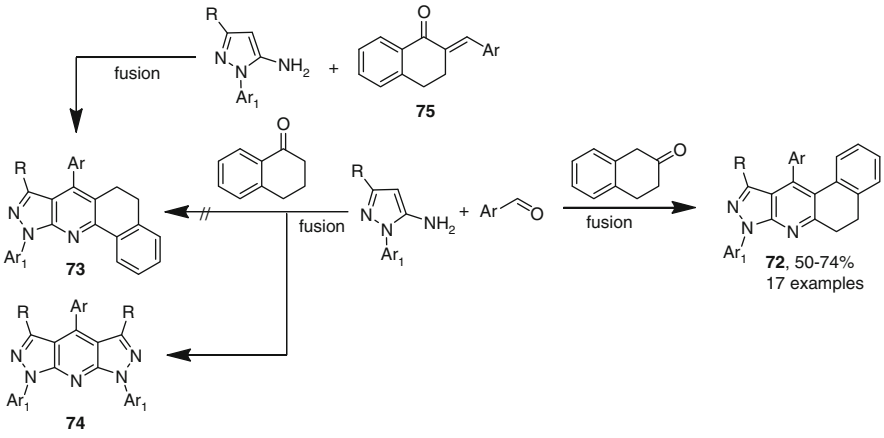
Scheme 30 Tuning of selectivity of MCRs involving carboxamide containing 5-aminopyrazoles

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

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



Scheme 31 MCRs based on "green chemistry" methods



Scheme 32 Tetralones in MCRs with aminoazoles

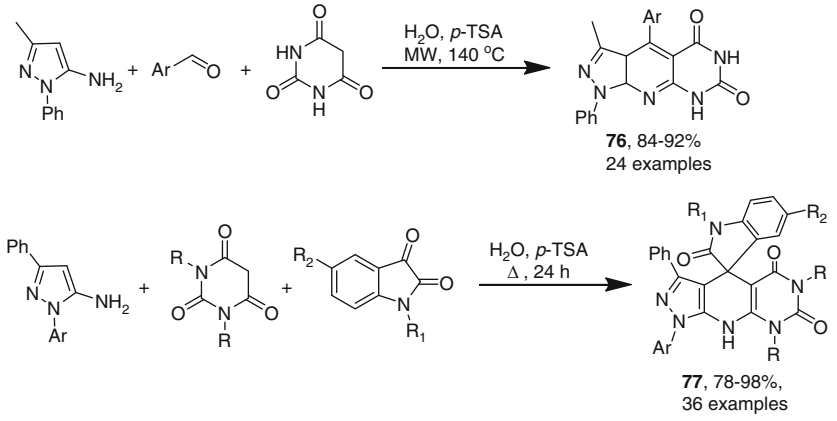
Barbituric acid and its derivatives are other cyclic 1,3-dicarbonyl reagents playing significant role in medicinal-oriented chemistry as well as in material science. Fused heterocyclic compounds having pyrazole, pyridine and pyrimidine moieties simultaneously showed wide spectrum of application such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

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

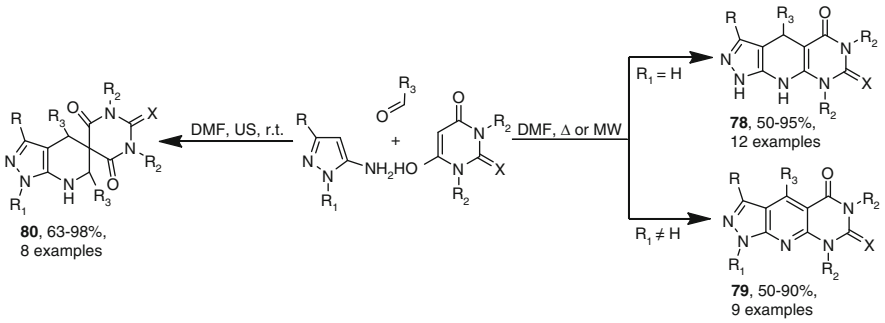
Water-based "green" protocol under conventional heating was used in another publication [112] to carry out three-component treatment between 3-substituted 5-aminopyrazoles, barbituric acids, and several isatines. The reaction gave up required spiroheterocycles **77** in excellent yields and purity (Scheme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

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

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



Scheme 33 MCRs involving barbituric acids



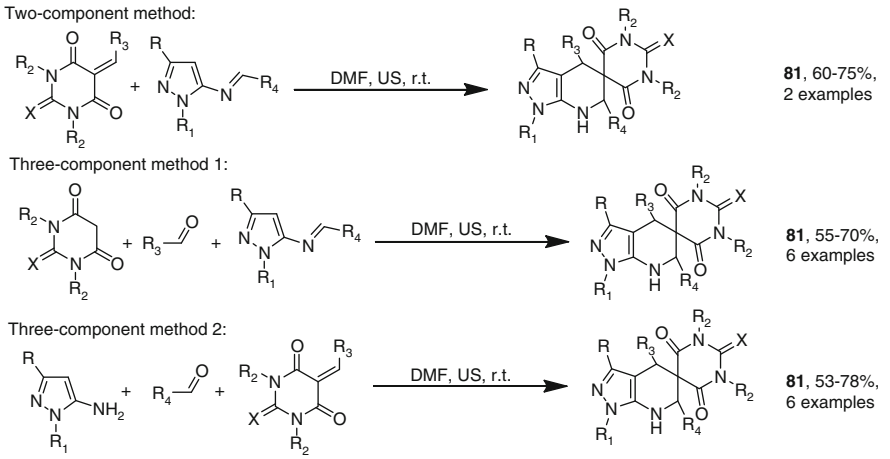
Scheme 34 Selectivity tuning for MCRs involving barbituric acids

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

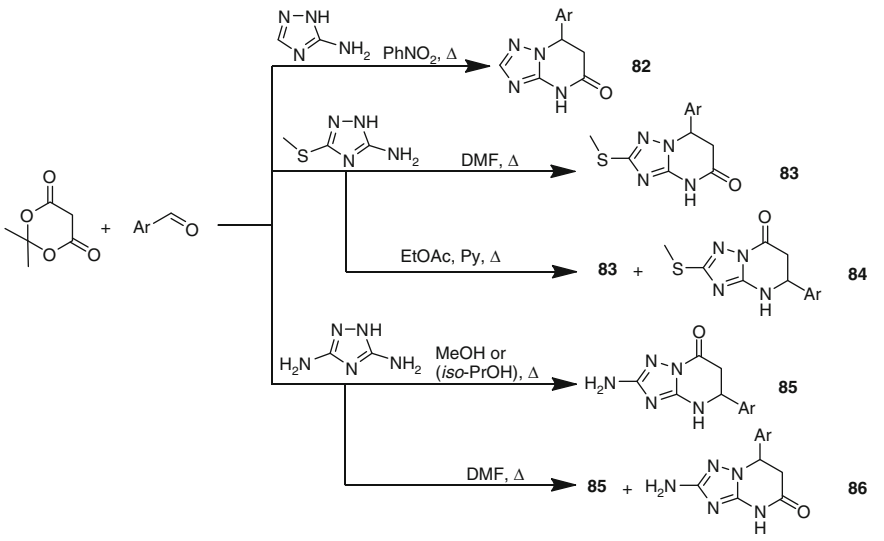
On the other hand, unexpectedly it was additionally established that the same MCR at room temperature under ultrasonication or with the help of simple stirring yielded novel type of spirocompounds **80** in 63–98% yields (Scheme 34). Biginelli-type dihydropyrimidines observed in similar processes involving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

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

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



Scheme 35 Alernative procedures for the sysnthesis of spiroheterocycles



Scheme 36 MCRs of Meldrum's acid

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

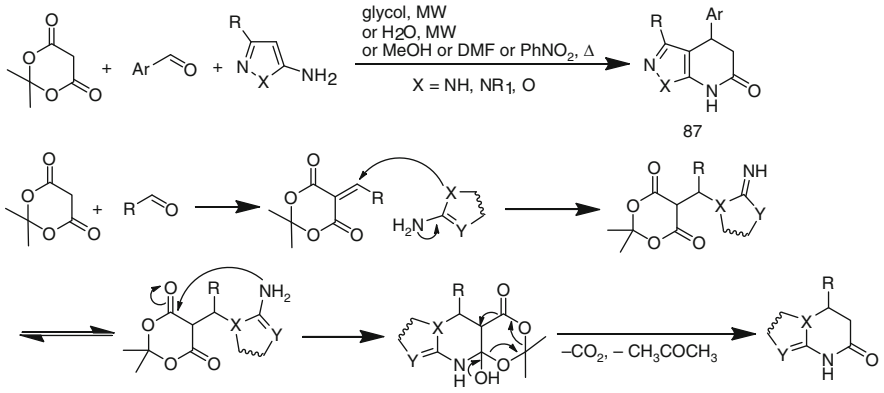
treatment in ethylacetate with catalytic amounts of pyridine led to positional isomeric 7-pyrimidineos **84** in mixture with **83** [116].

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

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

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

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



Scheme 37 Possible mechanism of MCRs involving Meldrum's acid

2.2 *Groebke-Type Heterocyclizations*

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

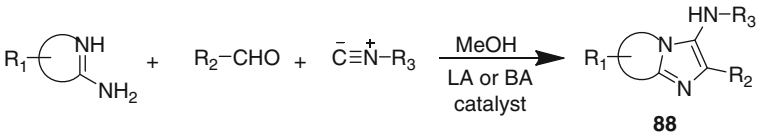
By carrying out the Ugi-reaction with a large number of isonitrils, aldehydes, carboxylic acids, and amines, it was found that formation of different products of the reaction occurred depending on the structure of the amines used. Thus, 3-aminoimidazoles **88** were isolated when aldehyde reacted with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

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

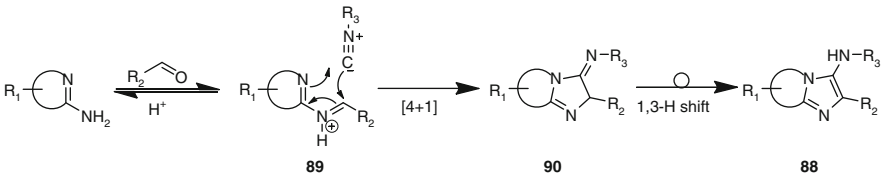
The formation of bicycles **88** occurred through the iminium intermediate 89, in the similar manner as Ugi-reaction. But in contrast to the four-component classical Ugi-reaction, the protonated Schiff base **89**, containing both nucleophilic and electrophilic centers, undergoes [4+1] cycloaddition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

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

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



Scheme 38 Geoebke-type heterocyclizations



Scheme 39 Mechanism of Groebke-type heterocyclizations

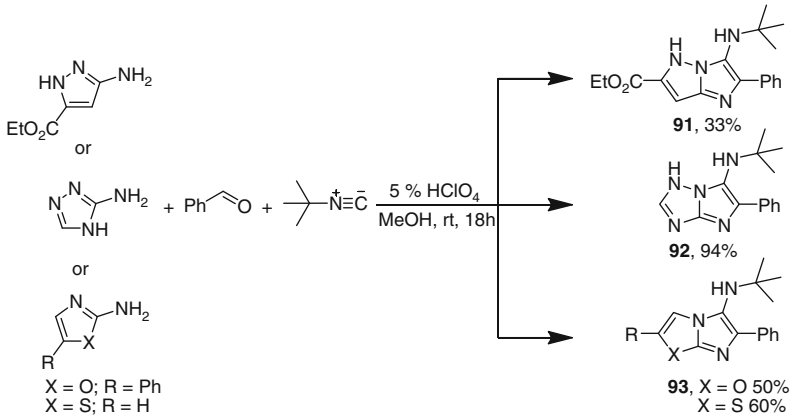
presence of $Sc(OTf)_3$ [129]. Solvent-free microwave facilitated version on the clay (Montmorillonite K10) was also reported [130]. In addition, to disfavor the formation of unwanted side-products, Groebke reaction has been performed using non-polar solvent [131, 132] and involving environment-friendly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

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

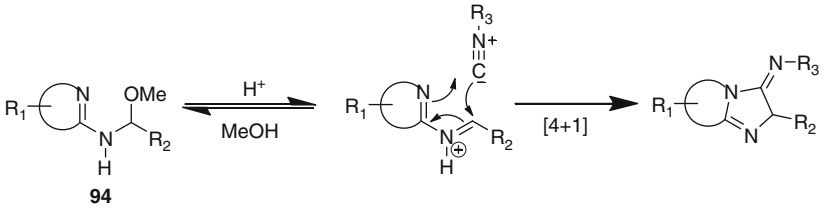
Several imidazo[2,1-b][1,3]thiazoles based on 2-aminothiazoles were successfully prepared by stirring in methanol at ambient temperature in the presence of $HClO_4$ as a catalyst [127]. Additionally, it was shown that Groebke reaction involving 2-aminopyrazoles, 2-aminooxazoles, and 3-amino-5-unsubstituted-1,2,4-triazoles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

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

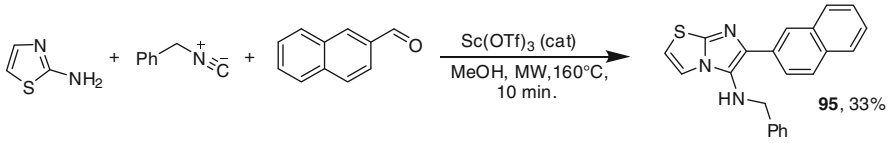
Indeed, the application of less nucleophilic solvent than methanol (e.g., trifluoroethanol) was found to be successful for the improvement of the reaction conversion level and helped to prevent the side-reactions.



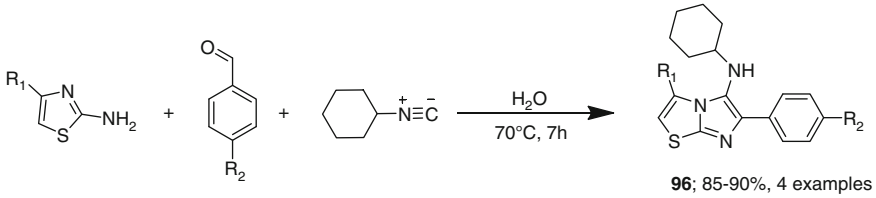
Scheme 40 Synthesis of imidazoazoles



Scheme 41 Side-products in Groebke-type heterocyclization



Scheme 42 MCR of 2-aminothiazole with benzylisocyanide and naphthaldehyde



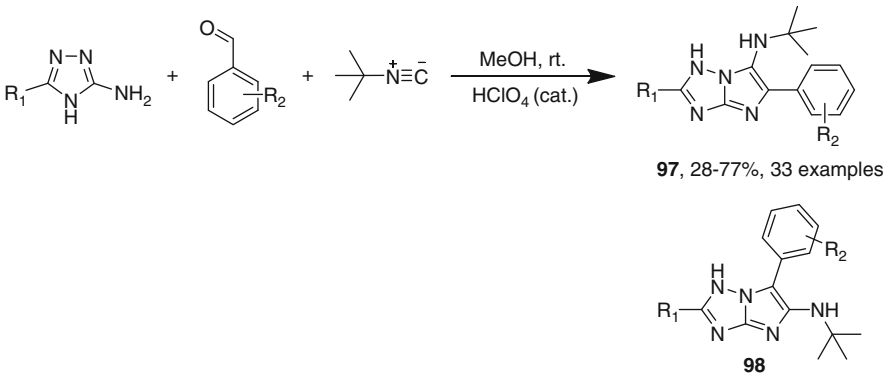
Scheme 43 Water-based procedure for the synthesis of imidazothiazole

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

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

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

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



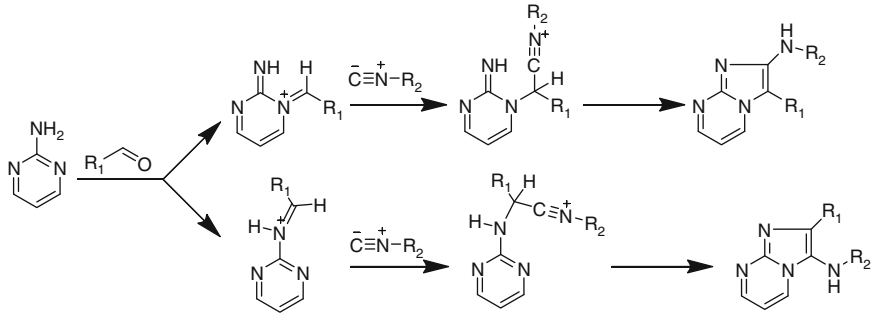
Scheme 44 Synthesis of highly substituted imidazotriazoles

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

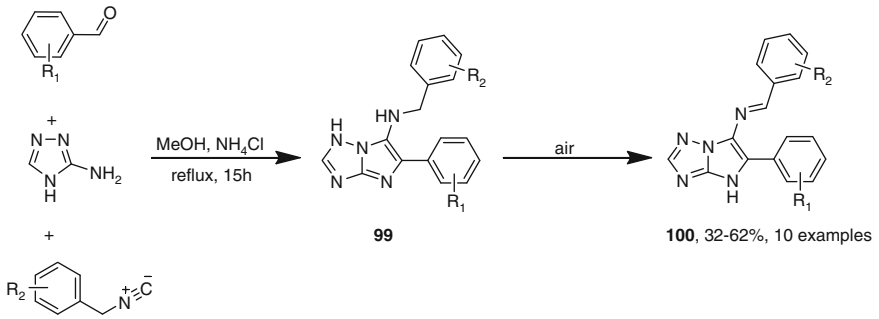
The results obtained showed that both the electron nature of the substituents in 3-amino-1,2,4-triazoles and a space effect of substituents in the aldehyde had an influence on the MCRs' yields. Thus, the presence of electron-donating groups in imidazoles (e.g., R = CH_3 compared to the R = H) led to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

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

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



Scheme 45 Formation of position isomers in Groebke-type reactions



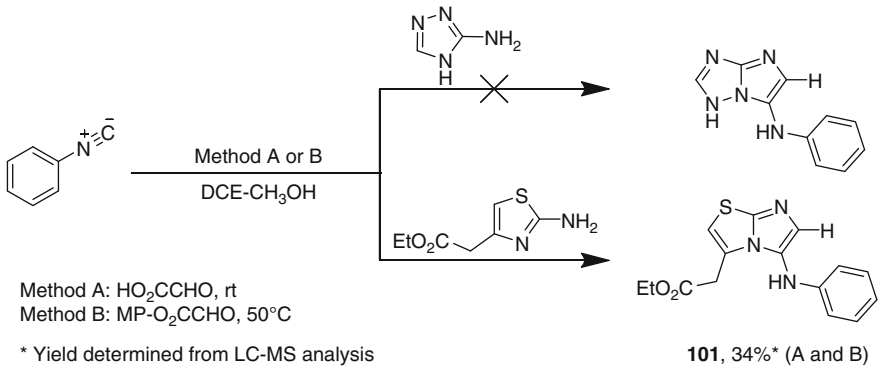
Scheme 46 MCRs involving aliphatic nitriles

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

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

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

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



Scheme 47 Limitation of Groebke-type MCR

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

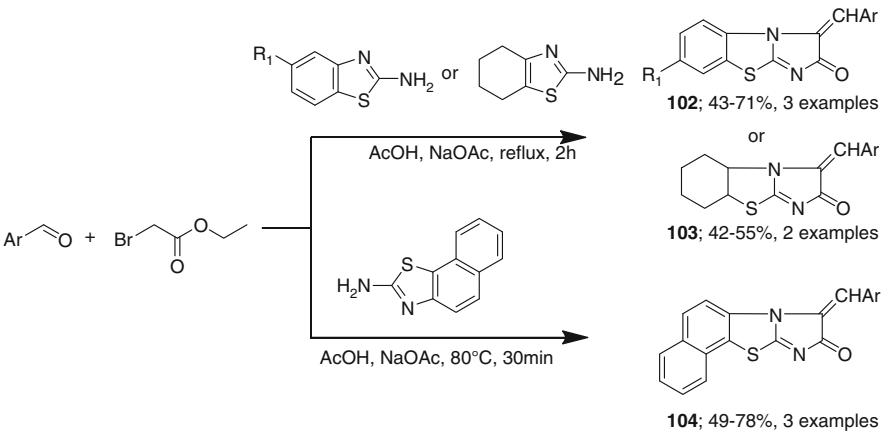
Among binucleophiles used in this reaction 3-amino-1,2,4-triazole and 2-aminothiazole were also selected. However, in the reaction of the latter with phenyl isonitrile and formaldehyde, only the moderate yields of the target product **101** were observed by the LC-MS analysis of the crude reaction mixture.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

2.3 Other Types of Heterocyclizations

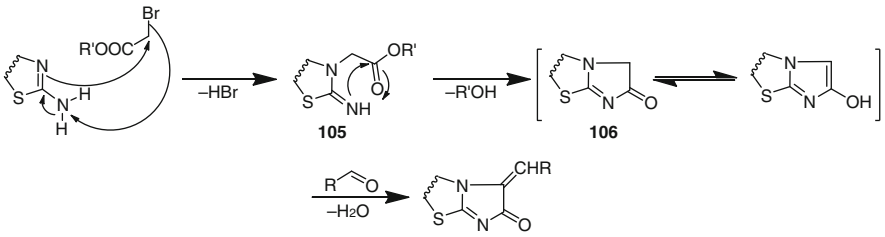
Here we discuss several examples of the multicomponent processes involving aminoazoles, aldehydes, and other organic components such as mercaptoacids, haloacetic acids and their ester, α,β-unsaturated imines, etc., which were not incorporated into the previous two sections of the review.

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

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



Scheme 48 MCRs involving bromacetic esters



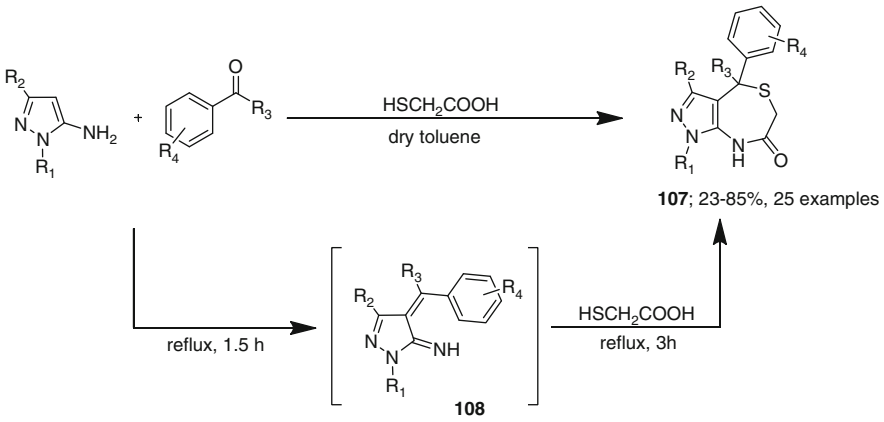
Scheme 49 Mechanism of MCRs involving bromacetic ester

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

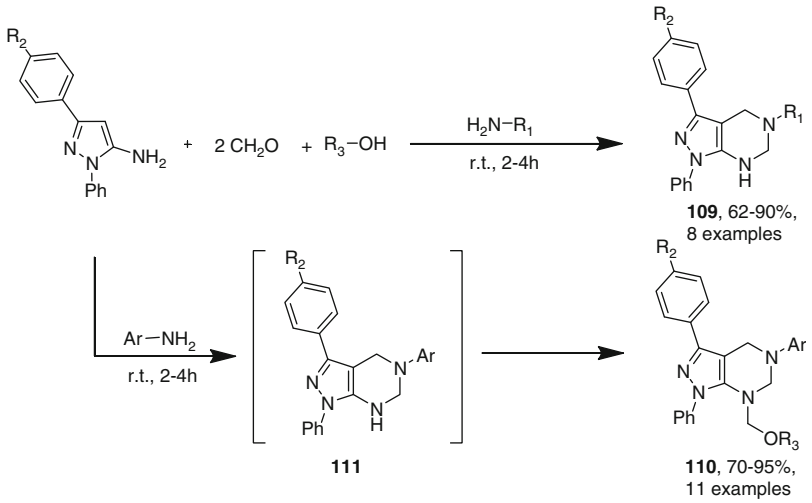
Mercaptoacids were successfully applied in the MRCs with aminozoles on the way to the novel sulfur containing seven-membered heterocycles [145–147]. Thus, condensation of 5-aminopyrazoles with mercaptoacetoacid and aromatic ketones or aldehydes resulted in the formation of pyrazolothiazepines **107**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

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

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



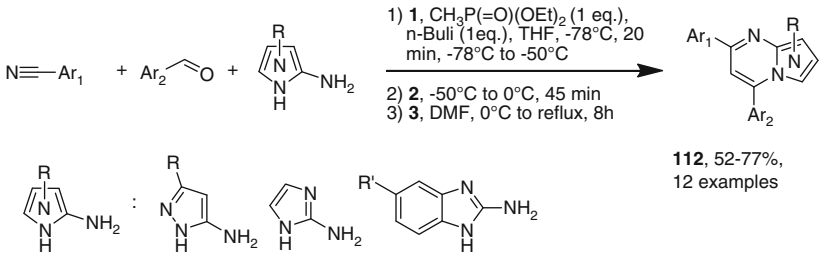
Scheme 50 Multicomponent synthesis of pyrazolothioazepinons



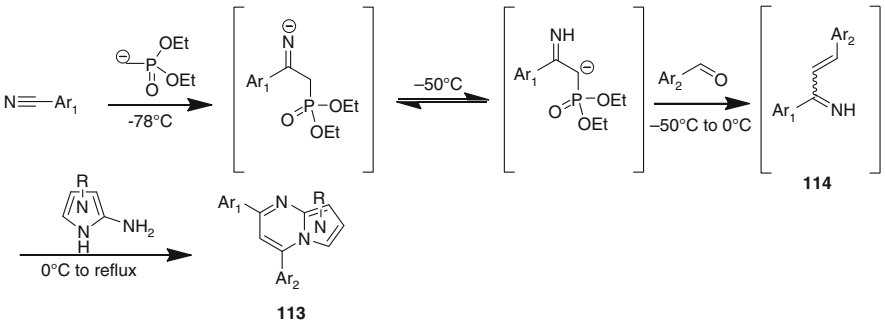
Scheme 51 Mannich reactions of aminopyrazoles

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

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



Scheme 52 MCRs proceeding via unsaturated imines formation



Scheme 53 Mechanism of the MCRs via formation of unsaturated imines

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

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

3 Aminoazoles as 1,1-Binucleophiles

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

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

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

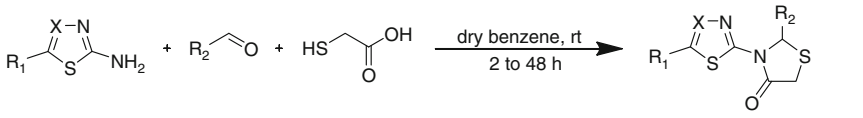
Attempts to perform synthesis of 3-substituted thiazolidinones by the MCR of 2-aminoazoles with mercaptoacetic acid and aldehydes were described by Grasso et al. [164–166].

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

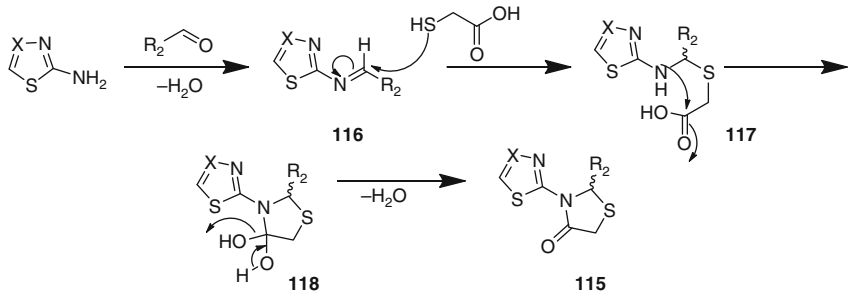
Formation of compounds like **115** seems to have occurred in the similar way as it was established for anilines and other primary amines [167]. The initial step of this reaction is treatment of aldehyde with aminozole giving Schiff base **116**. Further, nucleophilic attack of imine carbon by mercapto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

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

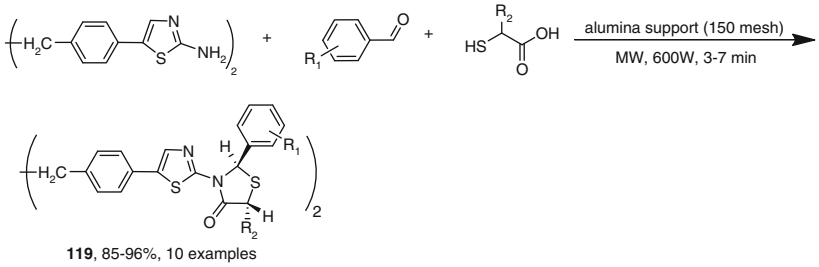
According to the results obtained from the biologic studies, several SAR tendencies were established [167]. By the evaluation of anticancer activities towards tumor cells, the authors found that thiazolyl derivates were generally less active in comparison with thiadiazolyl-containing compounds. The introduction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



Scheme 54 Synthesis of azolyl-4-thiazolidinones



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



119, 85-96%, 10 examples

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

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

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

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

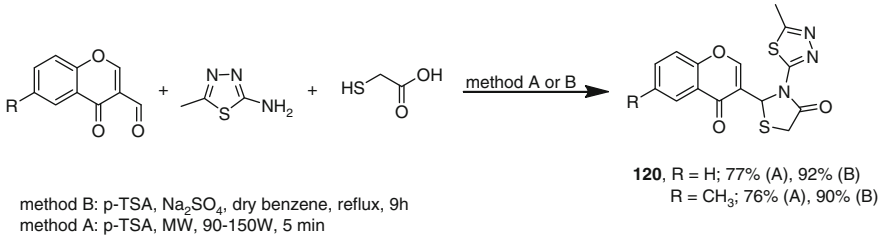
Additionally, it was noted that this MCR had diastereoselective character – only the one *trans*-diastereomer was isolated in all the experiments performed.

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

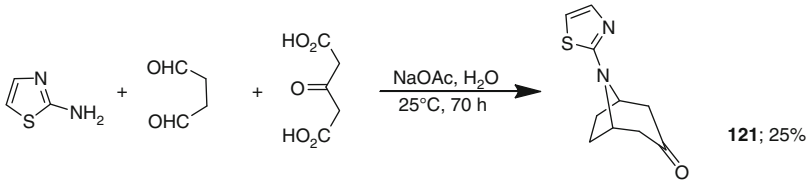
The liquid-phase microwave-assisted approach allowed the dramatic decrease in reaction time and enhancing level of the conversion. The reaction mixture of the starting building blocks in benzene in the presence of catalytic amounts of *p*-toluene sulfonic acid was exposed in microwave field for 5 min,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

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

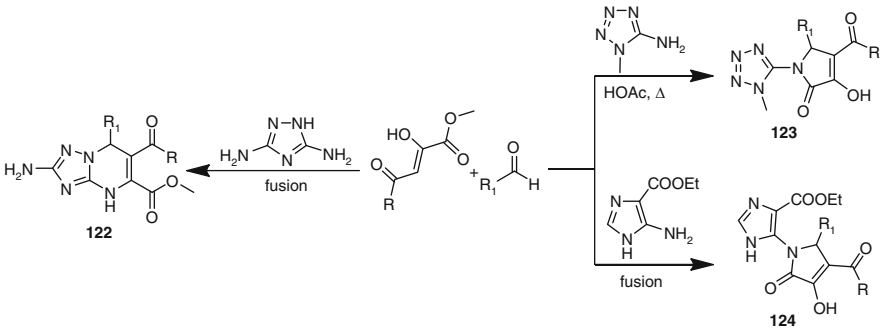
Along with the formation of dihydropyrimidine derivatives, an unusual directions of multicomponent treatment of 2,4-dioxobutanoates with aldehydes and several aminoazoles were described by Gein and co-authors [151]. Thus, fusion of carbonyl compounds with 3,5-diamino-1,2,4-triazole gave as usual for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



Scheme 57 Optimization of MCRs using microwave-assisted synthesis



Scheme 58 Synthesis of nortropinon derivative



Scheme 59 Alternative directions of MCRs 2,4-dioxobutanoates

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

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

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

4 Concluding Remarks

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

Acknowledgments The authors thank University of Konstanz and personally Prof. U. Groth for allowing to access scientific databases, electronic and university libraries.

References

1. Chebanov VA, Desenko SM, Gurley TW (2008) Azaheterocycles based on α, β-unsaturated carbonyls. Springer, Würzburg
2. Chebanov VA, Desenko SM (2006) Curr Org Chem 10:297
3. Desenko SM (1995) Chem Heterocycl Comp 31:125
4. Dias LRS, Santos MB, de Albuquerque S, Castro HC, de Souza AMT, Freitas ACC, DiVaio MAV, Cabral LM, Rodrigues CR (2007) Bioorg Med Chem 15:211
5. Boros EE, Cowan DJ, Cox RF, Mebrahtu MM, Rabinowitz MH, Thompson JB, Wolfe LA (2005) J Org Chem 70:5331
6. Singh SK, Reddy PG, Rao KS, Lohray BB, Misra P, Rajjak SA, Rao YK, Venkatewarlu A (2004) Bioorg Med Chem Lett 14:499
7. Elguero J, Goya P, Jagerovic N, Silva AMS (2002) Targets Heterocycl Syst 6:52
8. Vicente J, Chicote MT, Guerrero R, de Arellano MCR (1999) Chem Commun 16:1541
9. Atwal KS, Moreland S (1999) Bioorg Med Chem Lett 1:291
10. Elguero J (1996) In: Katritzky AR, Rees CW, Scriven EFV (eds) Comprehensive heterocyclic chemistry. Pergamon, New York
11. Huang Z, Ma Q, Bobbitt JM (1993) J Org Chem 18:4837
12. Alajarin R, Avarez-Buila J, Vaquero JJ, Sunkel C, Fau J, Statkov P, Sanz J (1993) Tetrahedron Asymm 4:617
13. Bossert F, Vater W (1989) Med Res Rev 9:291
14. Triggle DJ, Langs DA, Janis RA (1989) Med Res Rev 9:123
15. Atwal KS, Vaccaro W, Lloyd J, Finlay H, Yan L, Bhandaru RS (2007) US 099899
16. Tsuda Y, Mishina T, Obata M, Araki K, Inui J, Nakamura T (1987) EP.0217142
17. Tsuda Y, Mishina T, Obata M, Araki K, Inui J, Nakamura T (1986) JP 61227584
18. Tsuda Y, Mishina T, Obata M, Araki K, Inui J, Nakamura T (1985) WO 8504172
19. Magedov IV, Manpadi M, Van slambrouck S, Steelant WFA, Rozhkova E, Przheval'skii NM, Rogelj S, Kornienko A (2007) J Med Chem 50:5183
20. Druzhinin SV, Balenkova ES, Nenajdenko VG (2007) Tetrahedron 63:7753
21. Desenko SM, Orlov VD (1998) Azaheterocycles based on aromatic unsaturated ketones. Folio, Kharkov
22. Insuasty B, Quiroga H, Meier H (1997) Trends Heterocycl Chem 5:83
23. Sausins A, Duburs G (1992) Chem Heterocycl Comp 28:363
24. Sausins A, Duburs G (1988) Heterocycles 27:269
25. Simon C, Constantieux T, Rodriguez J (2004) Eur J Org Chem:4957
26. Groenendaal B, Ruijter E, Orru RVA (2008) Chem Commun:5474
27. Orru RVA, de Greef M (2003) Synthesis:1471
28. Bagley MC, Lubinu MC (2006) Top Heterocycl Chem 1:31
29. Kappe CO, Dallinger D (2009) Mol Divers 13:71
30. Isambert N, Lavilla R (2008) Chem Eur J 14:8444
31. Anwar HF, Elnagdic MH (2009) ARKIVOC i:198
32. Tejedor D, García-Tellado F (2007) Chem Soc Rev 36:484
33. Fedorova OV, Zhidovinova MS, Rusinov GL, Ovchinnikova IG (2003) Russ Chem Bulletin 52:1768
34. Desenko SM, Gladkov ES, Sirko SN, Khanetsky BB (2003) Vestnik Kharkovskogo Natsionalnogo Universiteta 10:56
35. Boros EE, Cowan DJ, Cox RF, Mebrahtu MM, Rabinowitz MH, Thompson JB, Wolfe LA III (2005) J Org Chem 70:5334

36. Bhandari A, Boros EE, Cowan DJ, Handlon AL, Hyman CE, Oplinger JA, Rabinowitz MH, Turnbull PS (2003) WO 076440
37. Chernyshev VM, Sokolov AN, Taranushich VA (2007) Russ J Appl Chem 80:1691
38. Chebanov VA, Muravyova EA, Desenko SM, Musatov VI, Knyazeva IV, Shishkina SV, Shishkin OV, Kappe CO (2006) J Comb Chem 8:427
39. Shaabani A, Seyyedhamzeh M, Maleki A, Behnam M, Rezazadeh F (2009) Tetrahedron Lett 50:2911
40. Shaabani A, Seyyedhamzeh M, Maleki M, Rezazadeh F, Behnam M (2009) J comb Chem 11:375
41. Yao C, Lei S, Wang C, Yu C, Tu S (2008) J Heterocycl Chem 45:1609
42. Caddick S, Fitzmaurice R (2009) Tetrahedron 65:3325
43. Loupy A (ed) (2006) Microwaves in organic synthesis. Wiley-VCH, Weinheim
44. Kappe CO, Stadler A (2005) Microwaves in organic and medicinal chemistry. Wiley, Weinheim
45. Roberts BA, Strauss CR (2005) Acc Chem Res 38:653
46. Wender PA, Handy ST, Wright DL (1997) Chem Ind:765
47. Tu S, Shao Q, Zhou D, Cao L, Shi F, Li C (2007) J Heterocycl Chem 44:1401
48. Pryadeina MV, Burgart YV, Saloutin VI, Kodess MI, Ulomskii EN, Rusinov VL (2004) Russ J Org Chem 40:902
49. Shaabani A, Rahmati A, Rezayan AH, Darvishi M, Badri Z, Sarvari A (2007) QSAR Comb Sci 26:973
50. Chen Q, Jiang L-L, Chen C-N, Yang G-F (2009) J Heterocycl Chem 46:139
51. Sakhno YI, Desenko SM, Shishkina SV, Shishkin OV, Sysoyev DO, Groth U, Kappe CO, Chebanov VA (2008) Tetrahedron 64:11041
52. Sakhno YI, Shishkina SV, Shishkin OV, Musatov VI, Desenko SM, Chebanov VA (2009) Mol Divers (in press) doi: 10.1007/s11030-010-9226-9
53. Sakhno YA (2009) PhD dissertation, Kharkov
54. Muravyova EA, Chebanov VA, Shishkina SV, Musatov VI, Desenko SM (2009) An influence of temperature and activations regime on the multicomponent heterocyclizations of some aminoazoles. 5th international conference “chemistry of nitrogen containing heterocycles”, Kharkiv, Ukraine, 104
55. Mason TJ, Luche J-L (1997) Ultrasound as a new tool for synthetic chemists. In: van Eldick R, Hubbard CD (eds) Chemistry under extreme or non-classical conditions. Wiley, Stony Brook, pp 317–380
56. Cravotto G, Cintas PJ (2006) Chem Soc Rev 35:180
57. Cella R, Stefani HA (2009) Tetrahedron 65:2619
58. Muravyova EA, Shishkina SV, Musatov VI, Shishkin OV, Desenko SM, Chebanov VA (2009) Synthesis:1375
59. Chebanov VA, Saraev VE, Desenko SM, Chernenko VN, Knyazeva IV, Groth U, Glasnov T, Kappe CO (2008) J Org Chem 73:5110
60. Chebanov VA, Saraev VE, Desenko SM, Chernenko VN, Shishkina SV, Shishkin OV, Kobzar KM, Kappe CO (2007) Org Lett 9:1691
61. Chebanov VA, Sakhno YI, Desenko SM, Chernenko VN, Musatov VI, Shishkina SV, Shishkin OV, Kappe CO (2007) Tetrahedron 63:1229
62. Chebanov VA, Sakhno YI, Desenko SM, Shishkina SV, Musatov VI, Shishkin OV, Knyazeva IV (2005) Synthesis:2597
63. Atwell GJ, Baguley BC, Denny WA (1989) J Med Chem 32:396
64. Epling GA, Lin KY (1987) J Heterocycl Chem 24:853
65. Saggiomo A, Kato K, Kaiya T (1968) J Med Chem 11:277
66. Bergman J, Brynolf A (1990) Tetrahedron 46:1295
67. Um S-J, Park S-H, Park C-H, Park C-H, Chang B-H, Yoon J-H, Sin H-S (2003) Bull Korean Chem Soc 24:677
68. Bjergarde K, Nair A, Patek M, Ackerman-Berrier M, Smrcina M, Bacque E, Tabart M, Ronan B, Leroy V, Viviani F, Dodson M, Souaille C (2008) US 2008/182844

69. Jachak MN, Avhale AB, Ghotekar BK, Kendre DB, Toche RB (2008) J Heterocycl Chem 45:1221
70. Zhu S-L, Ji S-J, Zhao K, Liu Y (2008) Tetrahedron Lett 49:2578
71. Quiroga J, Cruz S, Insuasty B, Abonia R (2000) Heterocycl Commun 6:275
72. Gladkov ES, Chebanov VA, Desenko SM, Shishkin OV, Shishkina SV, Dallinger D, Kappe CO (2007) Heterocycles 73:469
73. Chebanov VA, Desenko SM, Kuzmenko SA, Borovskoy VA, Musatov VI, Sadchikova YV (2004) Russ Chem Bull 53:2845
74. Han W, Hu Z (2007) WO 27454
75. Dzvinchuk IB (2007) Chem Heterocycl Comp 43:474
76. Dzvinchuk IB, Tolmacheva NA (2001) Chem Heterocycl Comp 37:506
77. Pyrko AN (2002) Russ J Org Chem 38:1817
78. Chebanov VA, Saraev VE, Gura EA, Desenko SM, Musatov VI (2005) Collect Czech Chem Commun 70:350
79. Wermann K, Hartman M (19991) Synthesis:189
80. Desenko SM, Orlov VD, Getmanskii NV, Shishkin OV, Lindeman SV, Struchkov YT (1992) Dokl Akad Nauk 324:801
81. Zhou ZZ, Huang W, Ji FQ, Ding MW, Yang GF (2007) Heteroat Chem 18:381
82. Quiroga J, Insuasty B, Hormaza A, Saitz C, Jullian C (1998) J Heterocycl Chem 35:575
83. Quiroga J, Mejia D, Insuasty B, Abonia R, Nogueras M, Sanchez A, Cobo J, Low JN (2001) Tetrahedron 57:6947
84. Lipson VV, Shirobokova MG, Shishkin OV, Shishkina SV (2006) Russ J Org Chem 42:1015
85. Bremner WS, Organ MG (2007) J Comb Chem 9:14
86. Drizin I, Holladay MW, Yi L, Zhang GQ, Gopalakrishnan S, Gopalakrishnan M, Whiteaker KL, Buckner SA, Sullivan JP, Carroll WA (2002) Bioorg Med Chem Lett 12:1481
87. Houser CR, Swamer FW, Ringler BI (1948) J Am Chem Soc 70:4023
88. Bates HA, Deng P-N (1983) J Org Chem 48:4479
89. Shao Q, Tu S, Li C, Cao L, Zhou D, Wang Q, Jiang B, Zhang Y, Hao W (2008) J Heterocycl Chem 45:411
90. Lipson VV, Desenko SM, Shirobokova MG, Borodina VV (2003) Chem Heterocycl Comp 39:1213
91. Lipson VV, Borodina VV, Shirobokova MG, Karnozhitskaya TM (2002) Phizyologichno Actyvni Spoluky 34:10
92. Lipson VV, Desenko SM, Shishkina SV, Shirobokova MG, Shishkin OV, Orlov VD (2003) Chem Heterocycl Comp 39:1041
93. Lipson VV, Desenko SM, Borodina VV, Shirobokova MG, Musatov VI (2005) Russ J Org Chem 41:114
94. Desenko SM, Orlov VD, Estrada K (1990) Chem Heterocycl Comp 26:839
95. Desenko SM, Orlov VD, Getmanskii NV, Shishkin OV, Lindeman SV, Struchkov YT (1993) Chem Heterocycl Comp 29:406
96. Popil'nichenko SV, Pil'no SG, Brovarets BS, Chernega AN, Drach BS (2005) Russ J Gen Chem 75:1816
97. Chebanov VA, Sakhno YI, Saraev VE, Muravyova EA, Andrushchenko AY, Desenko SM (2009) Multicomponent heterocyclizations: control of chemo- and regioselectivity. Fourth international conference "multi-component reactions and related chemistry", Ekaterinburg, Russia, I–3
98. Chebanov VA, Muravyova EA, Sakhno YI, Saraev VE, Kappe CO, Desenko SM (2009) Microwaves vs. ultrasonication: towards control of chemoselectivity. Microwave and flow chemistry conference, Jolli Beach, Antigua, 52
99. Chebanov VA, Saraev VE, Desenko SM, Chernenko VN, Shishkin OV, Lukinova EV, Kappe CO (2007) Microwave-assisted and ultrasonic-promoted regio- and chemoselective three-component reactions of 3-aryl-6-aminopyrazoles, aldehydes and 1,3-diketones. 2nd symposium on microwave accelerated synthesis, Düsseldorf, Germany, 32

100. Tu S-J, Zhang X-H, Han Z-G, Cao X-D, Wu S-S, Yan S, Hao W-J, Zhang G, Ma N (2009) J Comb Chem 11:428
101. Quiroga J, Portilla J, Serrano H, Abonra R, Insuasty B, Nogueras M, Cobo J (2007) Tetrahedron Lett 48:1987
102. Selleri S, Burni F, Castanzo A, Guerrini G, Malmberg-Aiello P, Iavarone G, Martini C (1992) J Med Chem 27:985
103. Sanghvi YS, Larson SB, Wills RC, Robins RK, Revankar GR (1989) J Med Chem 32:945
104. Rosowsky A, Chen H, Fu H, Queener SF (2003) Bioorg Med Chem 11:59
105. Farghaly AM, Habib NS, Hazzaa AB, El-Sayed OA (1989) J Pharm Sci 3:90
106. Bell MR, Ackerman JH (1990) US 4920128
107. Yutaka K (1991) JP 02277050
108. Muszynski M, Hahn WE (1986) Pol Patent 130681
109. Yutaka K, (1991) JP 02220050
110. Tseng CP (1990) US 4838925
111. Shi F, Zhou D, Tu S, Li C, Cao L, Shao Q (2008) J Heterocycl Chem 45:1305
112. Ghahremanzadeh R, Sayyafi M, Ahadi S, Bazgir A (2009) J Comb Chem 11:393
113. Lipson VV, Gorobets NY (2009) Mol Divers 13:399
114. Lipson VV, Orlov VD, Desenko SM, Karnozhitskaya TM, Shirobokova MG (1999) Chem Heterocycl Comp 35:595
115. Lipson VV, Borodina VV, Shirobokova MG (2005) Ukrainskii Khimicheskii Zhurnal 71:95 (Russian edition)
116. Lipson VV, Desenko SM, Borodina VV, Shirobokova MG, Karnozhitskaya TM, Musatov VI, Kravchenko SV (2005) Chem Heterocycl Comp 41:216
117. Lipson VV, Borodina VV, Musatov VI (2006) Zh Org Farm Khim 4:62
118. Lipson VV, Orlov VD, Desenko SM, Shishkina SV, Shishkin OV, Shirobokova MG (2001) Chem Heterocycl Comp 36:1039
119. Lipson VV, Desenko SM, Shirobokova MG, Shishkin OV, Shishkina SV (2006) Russ J Org Chem 42:1022
120. Kung DW, Wager TT (2004) US 2004/266815
121. Tu S, Wang Q, Zhang Y, Xu J, Zhang J, Zhu J, Shi F (2007) J Heterocycl Chem 44:811
122. Drizin I, Altenbach RJ, Buckner SA, Whiteaker KL, Scott VE, Darbyshire JF, Jayanti V, Henry RF, Coghlan MJ, Gopalakrishnan M, Carroll WA (2004) Bioorg Med Chem 12:1895
123. Drizin I, Altenbach RJ, Carroll WA (2002) US 2002/7059
124. Manpadi M, Uglinskii PY, Rastogi SK, Cotter KM, Wong Y-SC, Anderson LA, Ortega AJ, Van slambrouck S, Steelant WFA, Rogelj S, Tongwa P, Antipin MY, Magedov IV, Kornienko A (2007) Org Biomol Chem 5:3865
125. Groebke K, Webel L, Mehlin F (1998) Synlett:661
126. Blackburn C, Guan B, Fleming P, Shiasaki K, Shirling T (1998) Tetrahedron Lett 39:3635
127. Bienayme H, Bouzid K (1998) Angew Chem Int Ed 37:2234
128. Dömling A (2006) Chem Rev 106:17
129. Ireland SM, Tye H, Whittaker M (2003) Tetrahedron Lett 44:4369
130. Varma RS, Kumar D (1999) Tetrahedron Lett 40:7665
131. Parchinsky VZ, Shuvalova O, Ushakova O, Kravchenko DV, Krasavin M (2006) Tetrahedron Lett 47:947
132. Umkehrer M, Ross G, Jäger N, Burdack C, Kolb J, Hu H, Alvim-Gaston M, Hulme C (2007) Tetrahedron Lett 48:2213
133. Adib M, Mahdavi M, Noghani M, Mirzaei (2007) Tetrahedron Lett 48:7263
134. Shaabani A, Soleimani E, Maleki A (2006) Tetrahedron Lett 47:3031
135. Blackburn C (1998) Tetrahedron Lett 39:5469
136. Blackburn C, Guan B (2000) Tetrahedron Lett 41:1495
137. Chen JJ, Golebiowski A, McClenaghan J, Klopfenstein SR, West L (2001) Tetrahedron Lett 42:2269
138. Huang Y, Hu X-Q, Shen D-P, Chen Y-F, Xu P-F (2007) Mol Divers 11:73

139. Mandair GS, Light M, Russell A, Hursthouse M, Bradley M (2002) Tetrahedron Lett 43:4267
140. Parchinsky VZ, Koleda VV, Ushakova O, Kravchenko DV, Krasavin M (2006) Tetrahedron Lett 47:6891
141. Lyon MA, Kercher TS (2004) Org Lett 6:4989
142. Paolini JP, Lendvay LJ (1969) J Med Chem 12:1031
143. Ogura H, Itoh T (1970) Chem Pharm Bull 18:1981
144. Krasovskii AN, Bogatyreva EI, Soroka II, Kochergin PM, Grin NP (1977) Pharm Chem J 11:778
145. Swett LR, Ratajczyk JD, Nordeen CW, Aynilan GH (1975) J Heterocycl Chem 12:1137
146. Joshi KC, Dubey K (1979) Pharmazie 34:716
147. Joshi KC, Dubey K, Dandia A (1980) Heterocycles 16:71
148. Joshi KC, Pathak VN, Garg U (1980) J Heterocycl Chem 17:789
149. Hozien ZA, Sarhan AAO, El-Sherief HAH, Mahmoud AM (1997) Z Nat Forsch B Chem Sci 52:1401
150. Kiselyov AS, Smith L II (2006) Tetrahedron Lett 47:2611
151. Gein VL, Tsyplyakova EP, Stashina GA, Bakulev VA (2008) Russ J Org Chem 44:478
152. Doran WJ, Shonle HA (1939) J Org Chem 3:193
153. Troutman HD, Long LM (1948) J Am Chem Soc 70:3439
154. Lakhar R (1982) Agric Biol Chem 46:557
155. Vigorita MG, Ottana R, Monforte F, Maccari R, Trovato A, Monforte MT, Taviano MF (2001) Bioorg Med Chem Lett 11:2791
156. Diurno MV, Mazzoni O, Izzo AA, Bolognese A (1997) Il Farmaco 52:237
157. Desai SB, Desai PB, Desai KR (1999) Asian J Chem 2:363
158. Previtera T, Vigorita MG, Bisila M, Orsini F, Benetolla F, Bombieri G (1994) Eur J Med Chem 29:317
159. Rawal RK, Prabhakar YS, Katti SB, De Clercq E (2005) Bioorg Med Chem 13:6771
160. Kato T, Ozaki T, Tamura K (1999) J Med Chem 42:3134
161. Tanabe Y, Suzukamo G, Komuro Y, Imanishi N, Morooka S, Enomoto M, Kojima A, Sanemitsu Y, Mizutani M (1991) Tetrahedron Lett 32:379
162. Oleson JJ, Sloboda A, Troy WP, Halliday SL, Landes MJ, Angier RB, Semb RB, Williams JH (1955) J Am Chem Soc 77:6713
163. Hill DL (1980) Cancer Chemother Parmacol 4:215
164. Grasso S, Chimirri A, Monforte P, Fenech G (1984) Il Farmaco Ed Sci 39:505
165. Chimirri A, Grasso S, Monforte P, Fenech G, Zappala M (1986) Il Farmaco Ed Sci 41:839
166. Grasso S, Chimirri A, Monforte P, Fenech G, Zappala M, Monforte AM (1988) Il Farmaco Ed Sci 43:851
167. Bolognese A, Correale G, Manfra M, Lavecchia A, Novellino E, Baronec V (2004) Org Biomol Chem 2:2809
168. Veerabhadraian U, Rao VR, Rao TV (1990) Czech Chem Commun 55:535
169. Parekh HH, Parikh KA, Parikh AR (2004) J Sci Repub Iran 15:143
170. Desai SB, Desai PB, Desai KR (2001) Heterocycl Commun 7:83
171. Rao VP, Kumar PV, Reddy VR (2005) Heterocycl Commun 11:273
172. Rawal RK, Tripathi R, Katti SB, Pannecouque C, De Clercq E (2007) Bioorg Med Chem 15:1725
173. Rawal RK, Tripathi R, Katti SB, Pannecouque C, De Clercq E (2008) Eur J Med Chem 43:2800
174. Siddiqui IR, Singh PK, Singh J, Singh J (2004) J Chem Res Synop 8:554
175. Stoll A, Jucker E, Lindemann A (1954) Helv Chim Acta 37:649
176. Robinson R (1917) J Chem Soc Trans 111:762

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The Piperazine Space in Isocyanide-based MCR Chemistry

Yijun Huang, Kareem Khoury, and Alexander Dömling

Abstract Piperazines and its congeners, (di)keto piperazines are valuable tools in drug discovery, providing a natural path for the process peptide > peptidomimetic > small molecule also called depeptisation. Moreover, they can provide molecular probes to understand molecular pathways for diseases of unmet medical need. However, in order to better understand the design of such value added compounds, the detailed understanding of scope and limitation of their synthesis as well as their 3D structures and associated physicochemical properties is indispensables. Isocyanide multicomponent reaction (MCR) chemistry provides a prime tool for entering the chemical space of (di)(keto)piperazines since not less then 20 different ways exist to access a diversity of related scaffolds.

Keywords Multicomponent reaction · Isocyanide · Ugi · van Leusen · Medicinal chemistry · Molecular probes · Piperazine · Keto-piperazine · Diketo-piperazine

Contents

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1 Piperazines in Chemistry, Medicine, and Biology

Piperazine is a functional group that consists of a six-membered ring containing two opposing nitrogen atoms. A broad range of chemical compounds with important pharmacological properties contains a core or "side-chain" piperazine. The representative piperazine scaffold types and the distributions of commercial available derivatives are shown in Fig. 1. Notably, 73 drug entries of piperazine derivatives are deposited in the Drug Bank [2]. Piperazine was first introduced as an anthelmintic in 1953, especially useful in the treatment of partial intestinal obstruction [3]. The piperazine ring is a privileged structure shown in a number of drugs, such as cyclizine, dapiprazole, flunarizine, olanzapine, and pirenzepine. Ketopiperazines and piperazine scaffolds fused with bi- and tricyclic ring systems also exist in drug entries, such as piperacillin and praziquantel. Therefore, piperazine scaffolds can be considered as privileged structures for lead discovery and optimization.

Piperazine derivatives have been intensively investigated in structural biology studies due to their unique scaffolds. According to a substructure search in Relibase

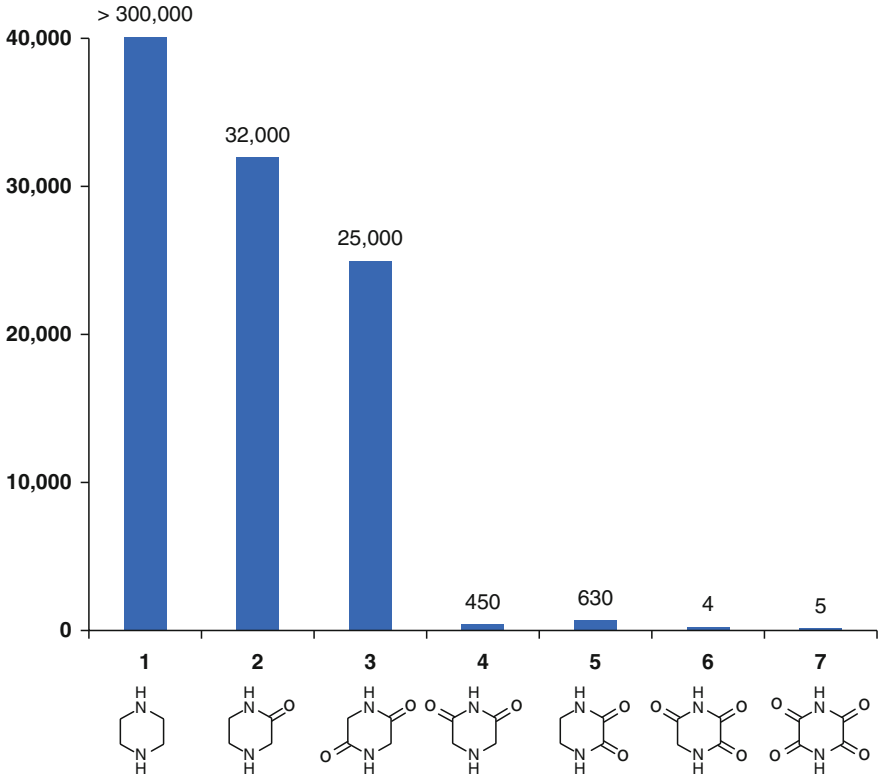


Fig. 1 Basic piperazine and ketopiperazine scaffolds and the number of commercial available derivatives according to substructure search from eMolecules [1]

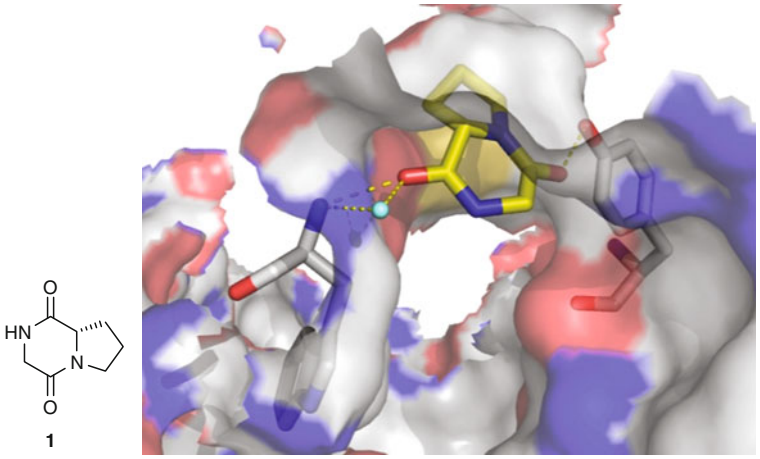


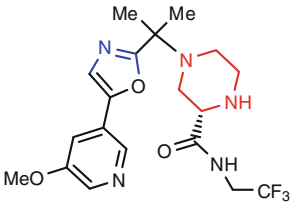
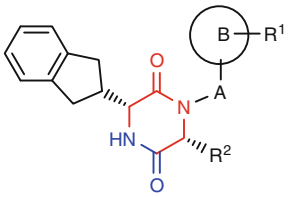
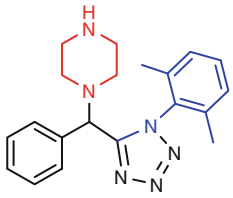
Fig. 2 X-ray co-crystal structure of diketopiperazine-chitinase complex (PDB ID: 1W1P). Diketopiperazine inhibitor is shown as *yellow sticks*, and the receptor binding site is shown as *transparent surface*. The hydrogen bonding with the key Trp97, Tyr214, and water (cyan ball) is shown as *yellow dots*

[4], 1,011 ligands containing piperazine motif were found in Protein Data Bank. Some of the ligands serve as molecular probes of proteins, as well as leads of small molecular weight inhibitors. For example, chitinase inhibitors in complex with chitinase B reveal that the common cyclo-(Gly–Pro) substructure is sufficient for binding [5]. The co-crystal structure of piperazine lignad/protein complex is shown in Fig. 2. Two carbonyl groups of the diketopiperazine scaffold **1** form hydrogen binding network with the target protein amino acid residues.

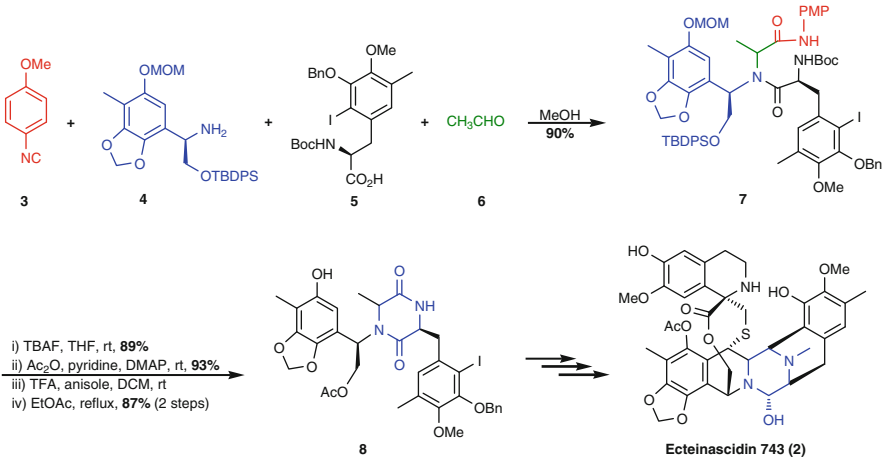
A recent literature survey revealed >3,000 piperazine substructure containing compounds accessed by isocyanide-based MCRs. Many of these piperazines are of commercial interest and therefore are described in patents as a primary literature source. Moreover, 430,000 piperazine derivatives are commercially available (according to a substructure search in eMolecules) [1]. Inspecting the general scaffold types in the database of the commercially available piperazine derivatives, it can be speculated that a considerable fraction of them were made by MCR technology. Some examples of piperazine derivatives via isocyanide-based MCRs from patent literature are listed in Table 1.

Isocyanide-based MCR was also applied for the total synthesis studies of natural products containing piperazine substructure. For example, trabectedin (also known as ecteinascidin 743 or ET-743) is undergoing clinical trials for the treatment of breast, prostate, and pediatric sarcomas. Ecteinascidin 743 (**2**) is an extremely potent antitumor agent isolated from a marine tunicate, *Ecteinascidia turbinate* [12]. Fukuyama et al. developed the total synthesis of ecteinascidin 743 from a Ugi reaction [13]. The reaction of *p*-methoxyphenyl isocyanide **3** gave Ugi product **7**, which was cyclized to DKP intermediate **8** (Scheme 1).

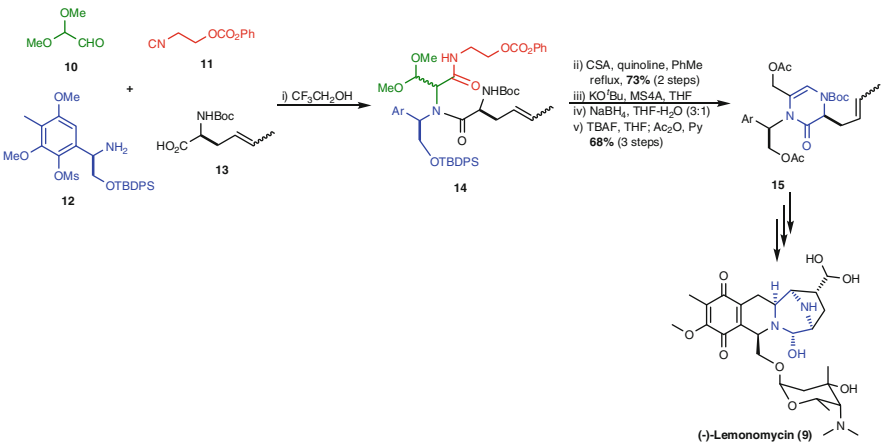
Table 1 Patent examples of isocyanide-based MCRs for the assembly of piperazine scaffolds in medicinal chemistry and their use

Example	Use (target, indication)	Company	References
	Intermediate of HIV protease inhibitor	Merck & Co Inc.	[6, 7]
	Oxytocin receptor antagonist	GSK	[8–10]
	Melanin concentrating hormone receptor antagonist	Amgen, Inc.	[11]

The piperazine scaffold and the isocyanide part are shown in *red* and *blue*, respectively



Scheme 1 Ugi reaction as a central step in the total synthesis of Ecteinascidin 743 by Fukuyama et al.



Scheme 2 Ugi reaction for the synthesis of (−)-lemonomycin intermediate **15**

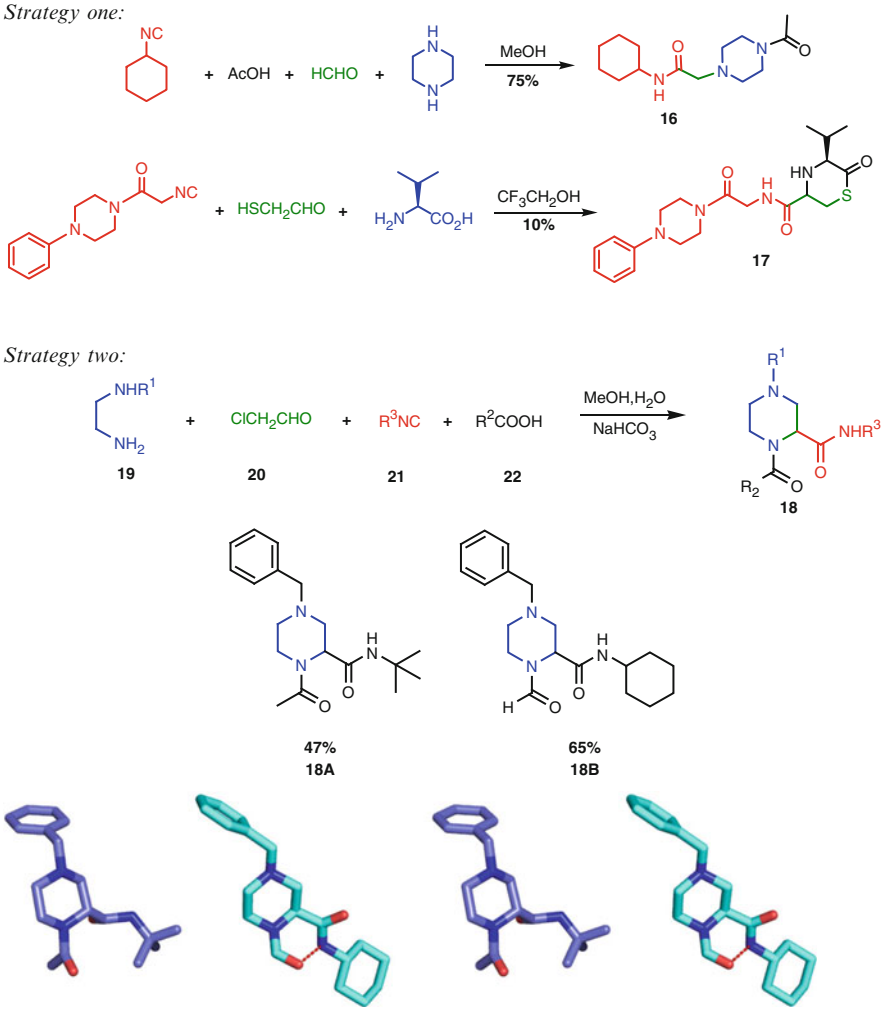
Recently, the piperazine intermediate **15** for the total synthesis of (−)-lemonomycin (**9**) was reported by Fukuyama et al. [14]. (−)-Lemonomycin possesses interesting antibiotic activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, as well as cytotoxicity against the human colon tumor cell line HCT-116 [15]. The reaction of 2-isocyanoethyl phenyl carbonate **11** gave Ugi product **14**, which was further transformed to a piperazine intermediate **15** (Scheme 2).

The reader is further directed to the excellent reviews of Fischer and Hortan et al. on the chemistry and biology of the privileged structure of the piperazine scaffold [16, 17]. Moreover, Dinsmore et al. and Martins et al. provided a systematic, comprehensive, and contemporary overview on the synthetic methods to DKP with a focus on the classical sequential syntheses [18, 19].

2 The MCR Piperazine Space

Generally, one can distinguish two distinct strategies to assemble the piperazine moiety in target molecules according to the synthetic aspects. Strategy one introduces the piperazine substructure via one of the starting materials of the MCR. In the second strategy, the piperazine substructure is assembled in the course of the MCR. Both strategies are very powerful and have been widely used. Representative examples of piperazine synthetic aspects are shown in Scheme 3.

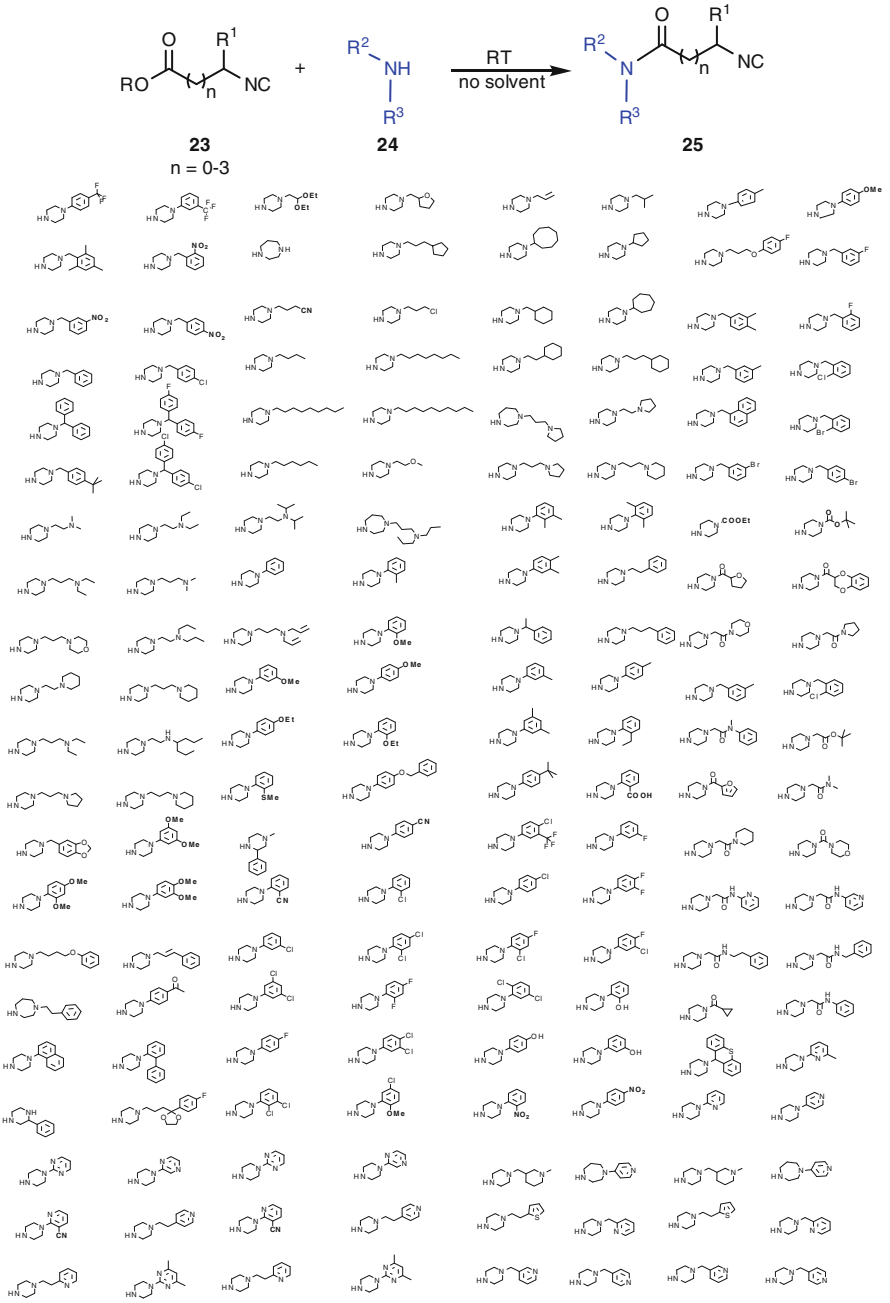
For instance, basic piperazine scaffold can be introduced via MCR into the following two strategies. The first strategy, either piperazine or isocyanide, containing piperazine substructure was used as starting material of the MCR [20, 21]. The second strategy, the piperazine ring, is formed via MCR. Piperazine-2-carboxamide **18**, for example, is prepared by a one-pot, four-component Ugi condensation among



Scheme 3 Synthetic aspects of two conceptually different strategies for the introduction of piperazines via isocyanide based MCRs and two representative 3D conformations of **18A** (*blue*) and **18B** (*cyan*). An intramolecular hydrogen bond in compound **18B** was shown in red dots

an *N*-alkylethylenediamine **19**, chloroacetaldehyde **20**, an isonitrile **21**, and a carboxylic acid **22** [22].

A particular fruitful way to arrays of piperazine moiety containing isocyanides has been recently described [23]. This efficient, scalable, and versatile procedure comprises the simple solventless mixing of a suitable α-amino acid methylester-derived isocyanide **23** with an aliphatic amine **24** (such as a substituted piperazine), filtration and washing of the resulting precipitate. Thus the array of isocyanides **25** shown in Scheme 4 was synthesized on a multigram scale mostly derived from achiral glycine and exemplary of other amino acids as well. These piperazine



Scheme 4 A 168 compounds comprising building block library of piperazine containing isocyanides as versatile building blocks for MCR scaffolds

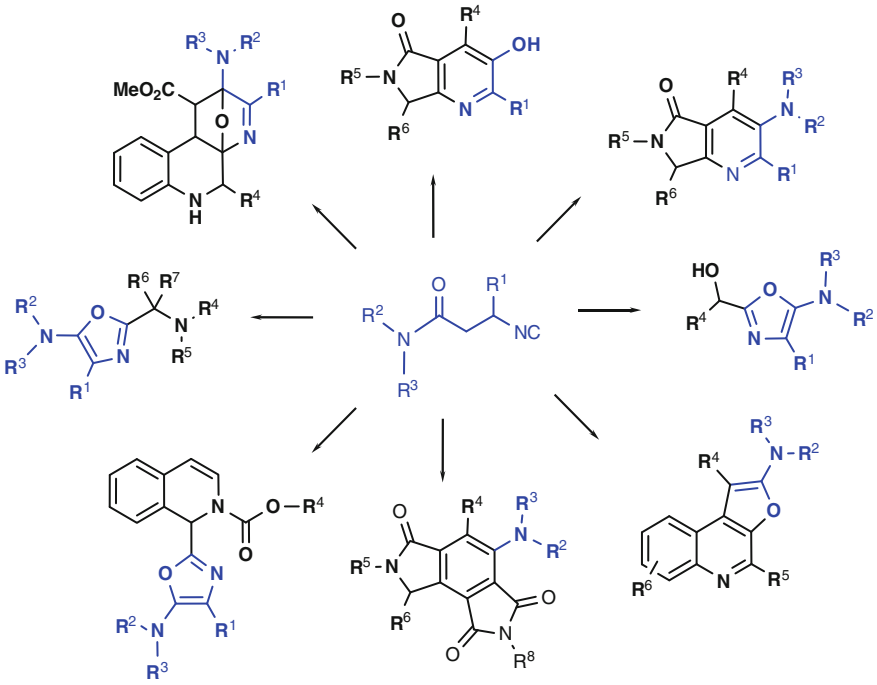


Fig. 3 α-Isocyanoamides as the starting materials for a plethora of combinatorial scaffolds. The isocyanide borne moiety in the scaffolds is marked *blue*

building blocks are invaluable because the corresponding isocyanides are very versatile starting materials for a plethora of scaffolds (Fig. 3).

The piperazine scaffolds based on MCR chemistry and some of their physicochemical properties are summarized in Fig. 4. Such scaffolds are suitable for lead generation in terms of drug-like properties (molecular weight, H-bond acceptors and donors, and sp^3 character). In the following, the different piperazine scaffolds, their 3D structures, and the synthetic approaches are discussed.

3 Monocyclic Piperazines

3.1 Piperazine

The first multicomponent reaction of a piperazine was described by Rossen et al. [22]. It was achieved by a four-component Ugi condensation in a one-pot reaction among a mono-*N*-alkylethylendiamine, a chloroacetaldehyde, an isocyanide, and a carboxylic acid to give a resulting piperazine (Scheme 3). This reaction is performed by adding equimolar amounts of all four components, with one equivalent of sodium bicarbonate in methanol for 2 days. The reaction works well with a variety of different starting materials and gives yields in the range of 30–100%.

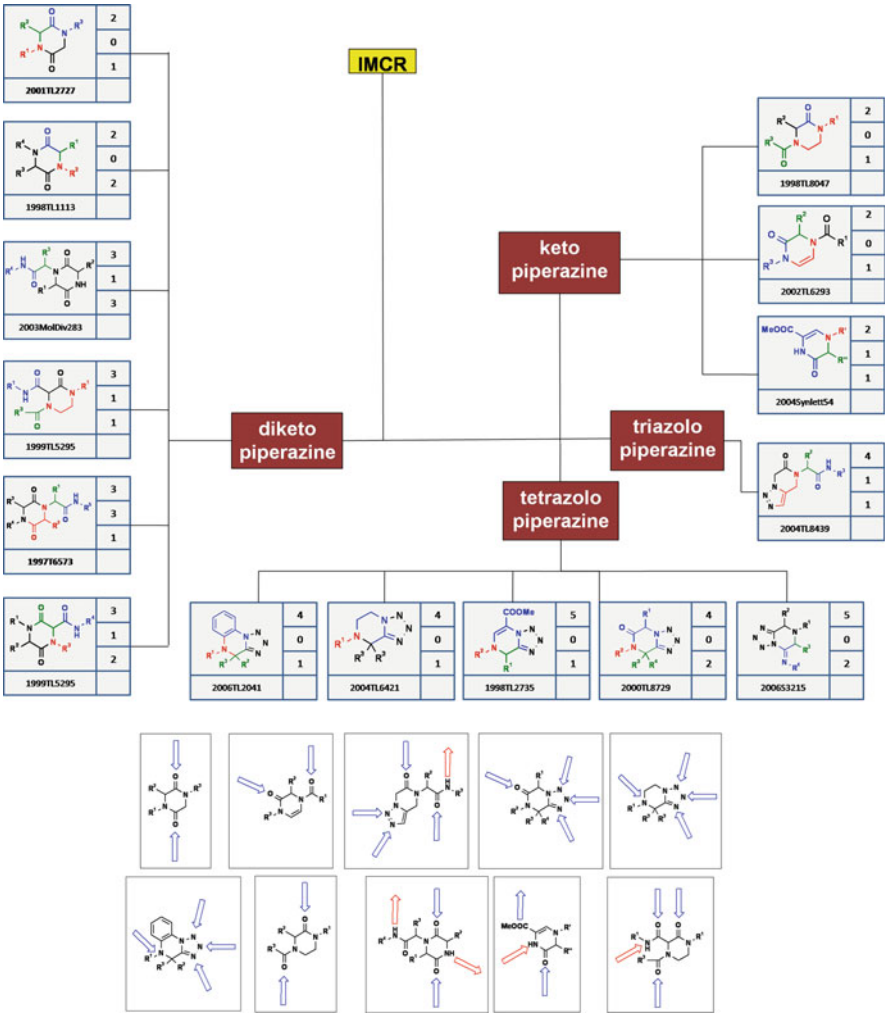


Fig. 4 The piperazine scaffold space offered by IMCR. (Above) The relationship of 16 different piperazine scaffolds based on different heterocyclic systems and also including hydrogen bond donor–acceptor features and sp^3 character is depicted (*right column*). (Below) Several piperazine scaffolds are shown with their immanent 2D hydrogen bond donor–acceptor propensity (*blue* and *red arrows*, H-bond acceptors and donors, respectively)

This procedure can be used to synthesize the key intermediate **34** of Merck's HIV protease inhibitor Crixivan **35** (Fig. 5) [25]. This reaction is done using dichloroacetaldehyde **26** instead of chloroacetaldehyde, forming the classical Ugi product **30**. This intermediate is then treated with triethylamine to obtain the corresponding vinylchloride **31**. Cyclization with KO^{t}Bu followed by stereoselective hydrogenation using the chiral catalyst Rh-BINAP afforded the Crixivan intermediate **34**. (Scheme 5) The classical way to make this intermediate requires five steps, and thus makes the MCR route more attractive [25].

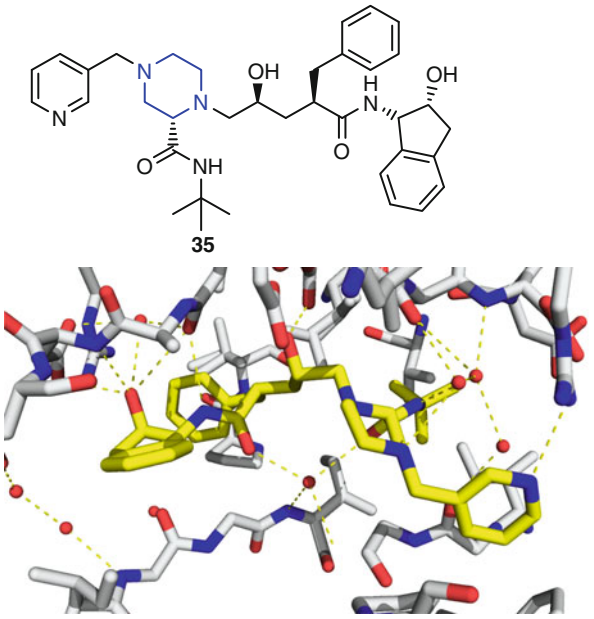
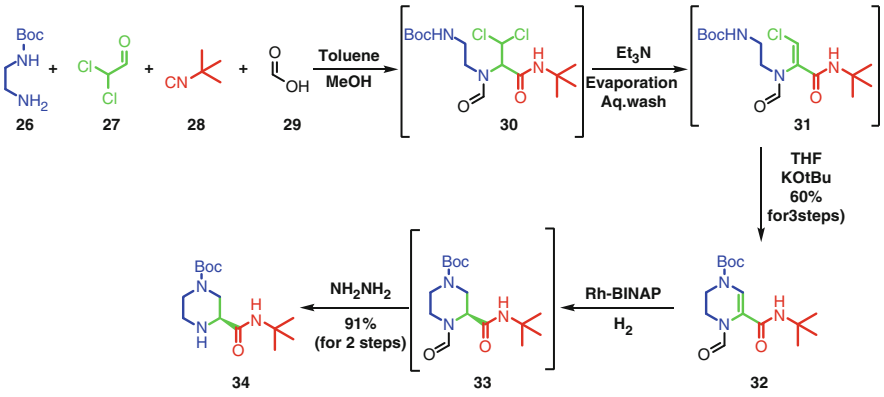
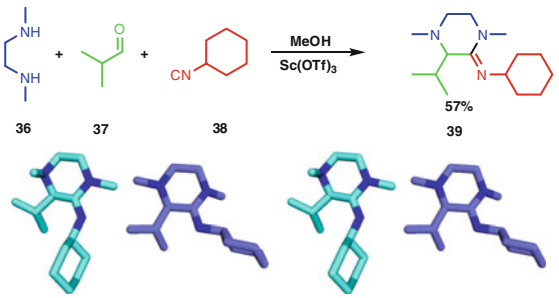


Fig. 5 HIV protease inhibitor Crixivan **35** (*yellow*) bound to HIV protease (*grey*) [24]. The piperazine moiety of Crixivan comprises scaffolding as well binding qualities as depicted by the piperazine hydrogen bonds (PDB ID: 1SDU)

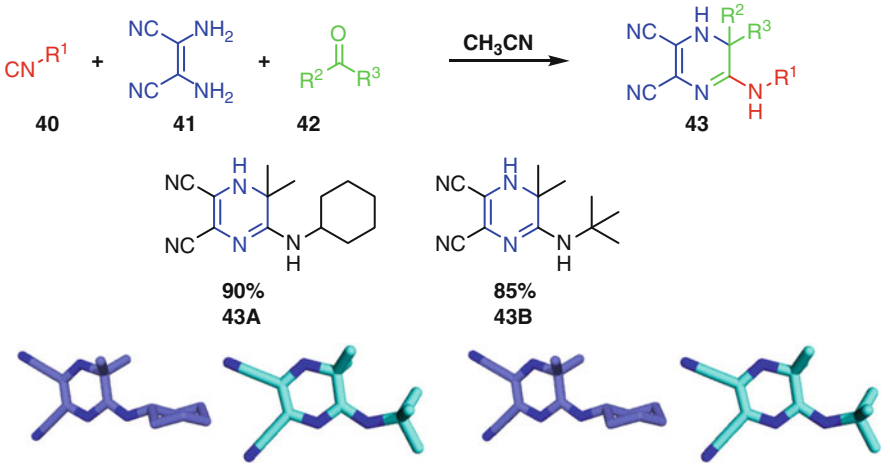


Scheme 5 Asymmetric MCR synthesis to piperazine intermediate (**34**) of the Merck HIV protease inhibitor Crixivan (BINAP: 2,2′-bis(diphenylphosphino)-1,10-binaphthyl; COD: cyclo-octadiene)

Keung et al. describes the optimization of 2-imino-piperazines using Lewis acids to catalyze the multicomponent α-amino amidine synthesis to make piperazines **39** (Scheme 6) [26]. *N*,*N*′-dimethylethylenediamine **36** was used with an aldehyde **37** and isocyanide **38** in methanol with scandium (III) trifluoromethane sulfonate ($Sc(OTf)_3$) as a catalyst to obtain the piperazine **39** in 57% yield.



Scheme 6 Use of Lewis acid catalyst for 3-CR 2-imino-piperazine synthesis and representative 3D conformations of the *cis*- and *trans*-stereoisomer **39** are shown. Two 3D structures of the *cis*- and *trans*-stereoisomer **39** are shown



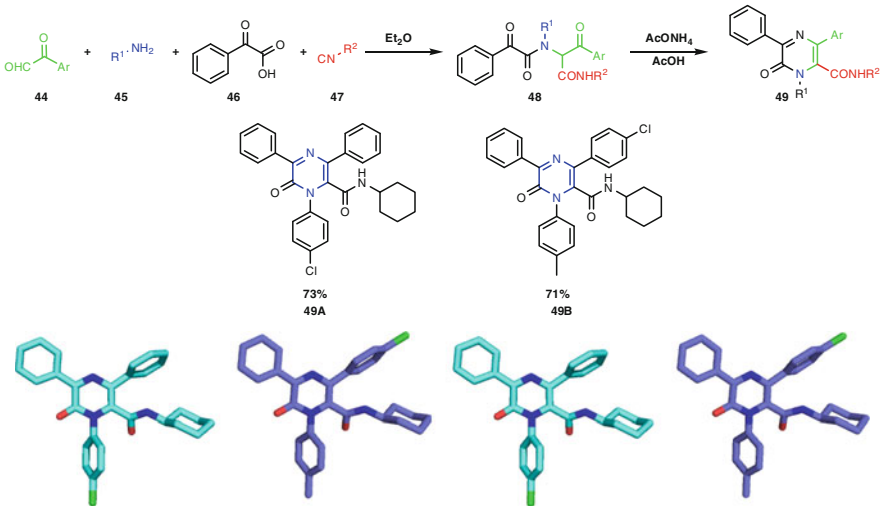
Scheme 7 Synthesis of 1,6 dihydropyrazine derivatives and two representative 3D conformations of **43A** (*cyan*) and **43B** (*blue*)

Shaabani et al. developed a one-pot MCR for the synthesis of 1,6 dihydropyrazine derivatives from condensation reactions among diketene **42**, an isocyanide **40**, and 2,3-diaminomaleonitrile **41** (Scheme 7) [27].

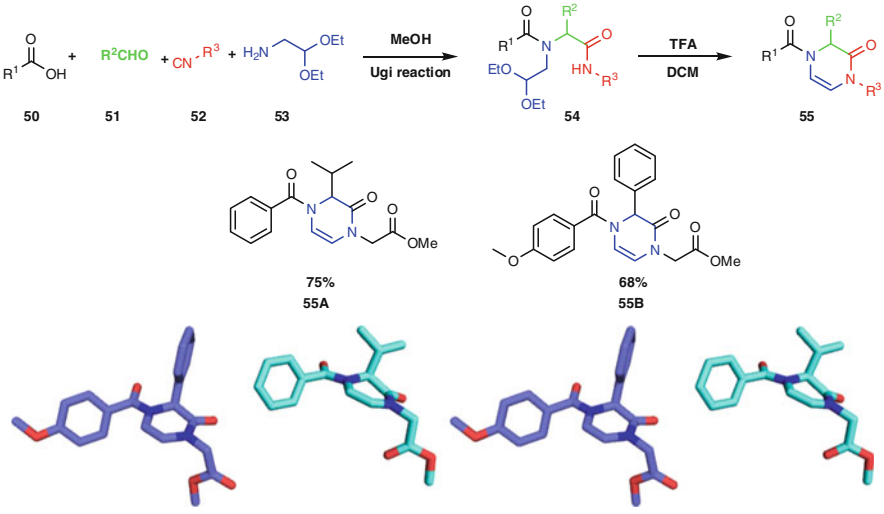
Faggi et al. describes the synthesis of a 1,6-dihydro-6-oxopyrazine-2-carboxylic acid derivative via the Ugi four-component reaction (Scheme 8) [28]. Arylglyoxals **44**, an amine **45**, benzoylformic acid **46**, and an isocyanide **47** afforded the Ugi intermediate **48**, which was cyclized in a [5+1] fashion with ammonium acetate to give the final product **49** in good yields.

3.2 Ketopiperazine

Cheng et al. describes an efficient solution phase and solid phase synthesis of 2-oxopiperazines [29]. These reactions involve a novel Ugi condensation-*N*-acyliminium condensation reaction (Scheme 9). A carboxylic acid **50**, an aldehyde **51**,

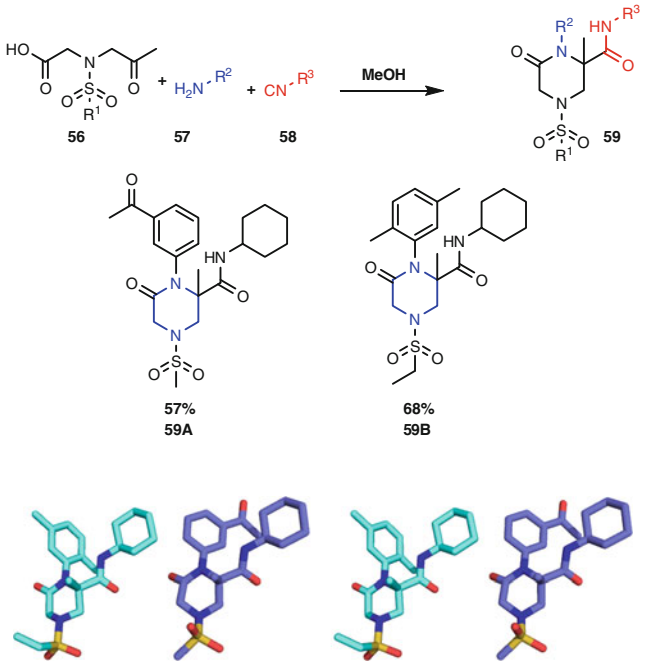


Scheme 8 Synthesis of a 1,6-dihydro-6-oxopyrazine-2-carboxylic acid derivatives via the Ugi four-component reaction and two representative 3D conformation of **49A** (*cyan*) and **49B** (*blue*). Yield shown represents yield over all steps



Scheme 9 Solution phase synthesis of oxopiperazine with Ugi intermediate and two representative 3D conformations of **55A** (*blue*) and **55B** (*cyan*). Yield shown represents yield over all steps

aminoacetaldeyde diethyl acetal **52**, and an isocyanide **53** are added to a mixture of methanol and chloroform for 24 h at room temperature. After this reaction is complete, the intermediate Ugi product **54** is treated with 50% TFA in dichloromethane.

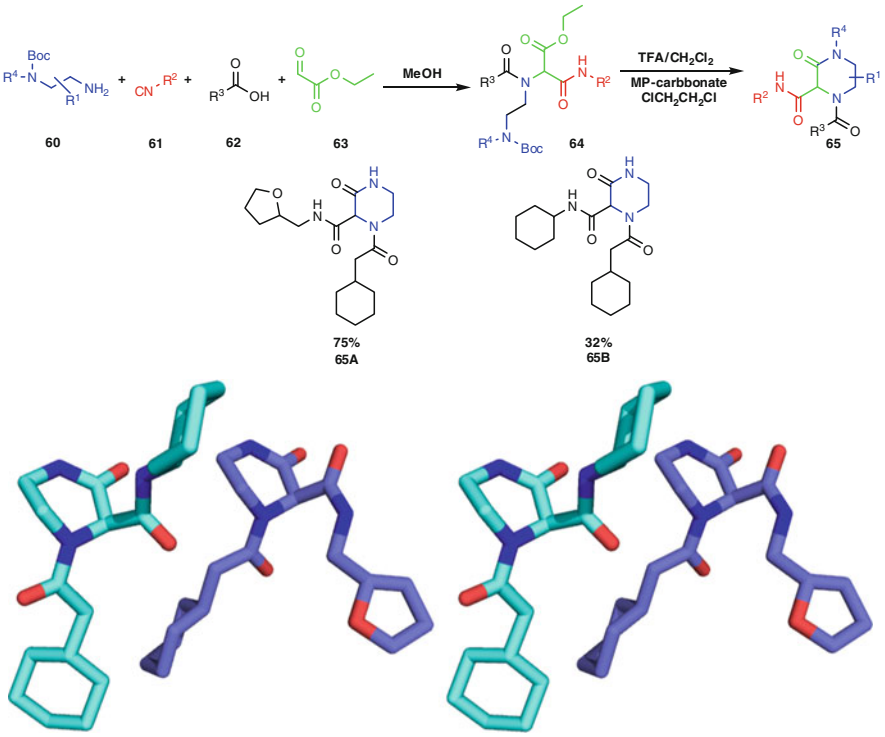


Scheme 10 Use of a bi-functional *N*-sulfonyl-*N*-(2-oxoproply) glycines for the 3CR synthesis of ketopiperazines and two representative 3D conformations of **59A** (*cyan*) and **59B** (*blue*)

The cyclization completes within 2–4 h, and the purified product **55** is obtained in 65–75% yield. The solid phase synthesis is conducted with the same starting materials; however, resin bound isocyanide is used and yields are greater than 90% based on the resin loading.

Ilyin et al. reported the first example of using the Ugi reaction of a bis-functional sulfonoamide ketoacids **56** with an amine **57** and an isocyanide **58** to construct 5-carbamoyl-4-sulfonyl-2-piperazinones **59** (Scheme 10) [30]. This scaffold differs from other piperazine moieties due to its high steric congestion surrounding the *N*1. This reaction took place in a methanolic solution in which the product precipitated out after 8 h and therefore requires no chromatographic purification. This procedure afforded the synthesis of a 218 member library of this scaffold, all of which had yields in the range of 45–75%. The sulfonoamide ketoacids were prepared from ethyl glycinate involving sequential sulfonylation, alkylation, and ester hydrolysis.

Hulme et al. describes the novel use of ethyl glyoxalate in the Ugi-4CR to create ketopiperazines [31]. *N*-alkylated/Boc-protected ethylene diamines **60** reacted with an isocyanide **61**, a carboxylic acid **62**, and ethyl 2-oxoacetate **63** in stoichiometric ratio of 1/1/1/1.25 in methanol. Deprotection and cyclization is completed using TFA and MP-carbonate (a macroporous polystyrene

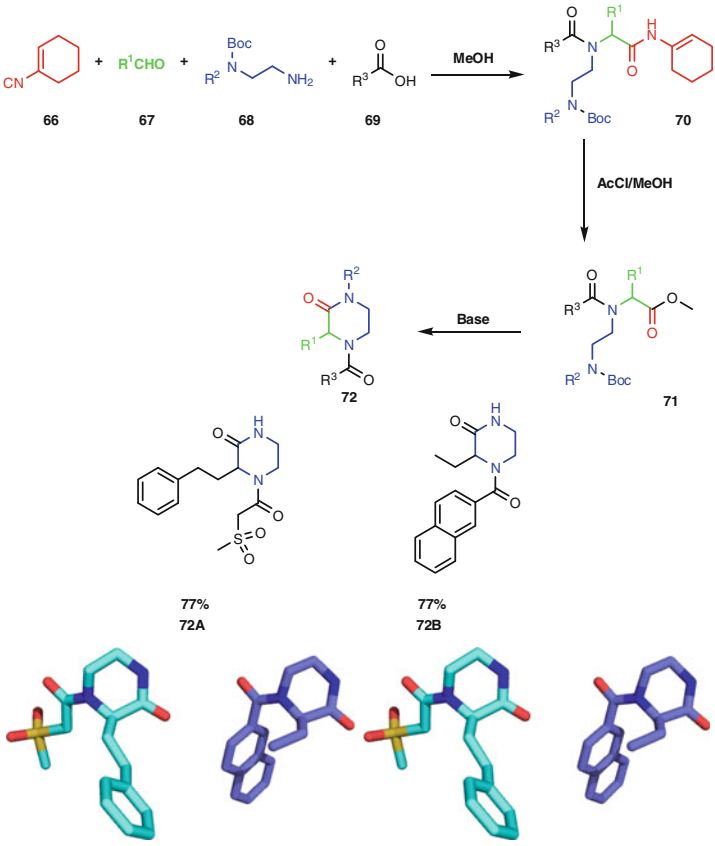


Scheme 11 3-CR synthesis of ketopiperazines using ethyl glyoxalate and two representative 3D conformations of **65A** (*cyan*) and **65B** (*blue*). Yield shown represents yield over all steps

anion-exchange resin), respectively, and yields varied from 50–89% (Scheme 11). The same reaction was prepared as a one step procedure using a non-alkylated, non-Boc-protected ethylene diamine. Even though this afforded products with roughly the same yield, and only took one step, it offers one less variability point then the previous example.

Hulme et al. describes the use of a convertible isonitrile for the generation of a ketopiperazine library (Scheme 12) [32]. Using a mono-*N*-Boc diamine **68** in the classical Ugi reaction followed by Boc deprotection and base-facilitated cyclization (3 steps, 1 pot) afforded the ketopiperazine **72** in relatively high yields.

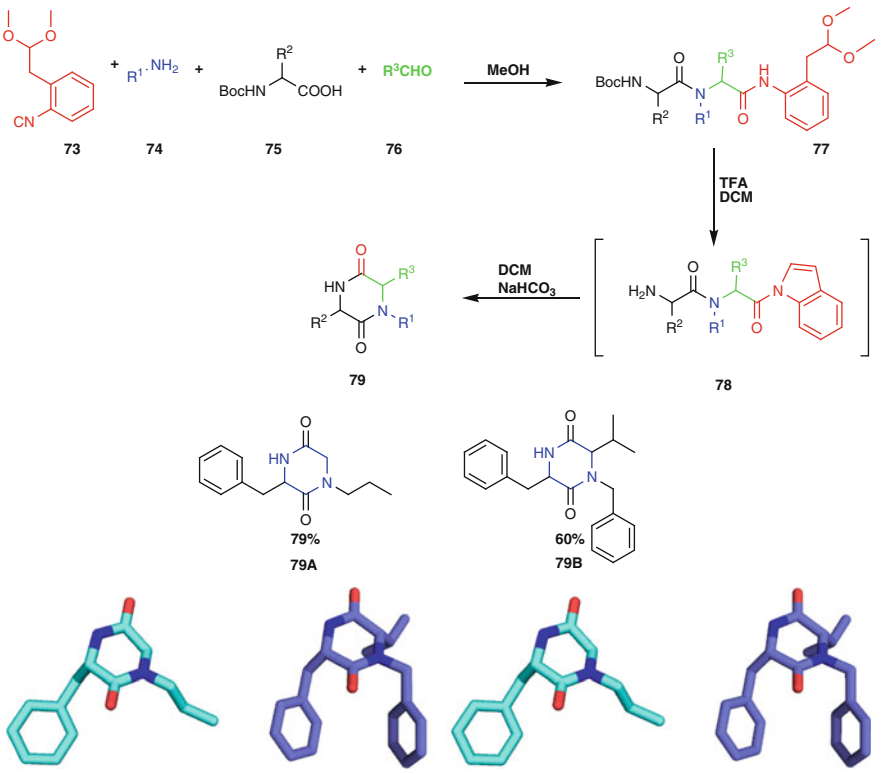
Convertible isocyanide reagent **66** allows a mild and chemoselective in situ post-Ugi activation of the isonitrile born amide with simultaneous deprotection of the nucleophilic amine, that is, liberation and activation of two Ugi-reactive groups, if desired also under subsequent lactam formation [33]. Another recently introduced convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl)-benzene **73**, was shown effective by Rhoden et al. In the course of this short sequence, a hydrolytically labile *N*-acylindole **78** is formed, which is displaced intramolecularly by the amine portion of the former Boc-protected amino acid **75** (Scheme 13).



Scheme 12 Use of a convertible isocyanide for synthesis of DKP's. Two examples of ketopiperazines derived from use of convertible isocyanide and two representative 3D conformations of **72A** (*blue*) and **72B** (*cyan*). Yield shown represents yield over all steps

3.3 2,5-Diketopiperazine

N,*N*,*C*-trisubstituted 2,5-DKP **85** have been described by Bossio et al. by reacting chloroacetic acid **80**, primary amines **81**, aldehydes **82**, and isocyanides **83** in an Ugi-4CR [34]. The intermediate Ugi product can be cyclized under basic conditions and using ultrasound via a S_N2 reaction to give good yields of 2,5-DKP. The Ugi reaction tolerates many aldehydes; however, the secondary ring closure can be performed only with aromatic benzaldehydes (Scheme 14). This backbone is also accessible using classical stepwise chemistry starting from α-amino acid amides and chloroacetylation thereof and subsequent cyclization. Clearly the MCR approach is advantageous in terms of facile reaction conditions, scope of the starting materials, broadness of synthetic variations, and synthetic efficacy.



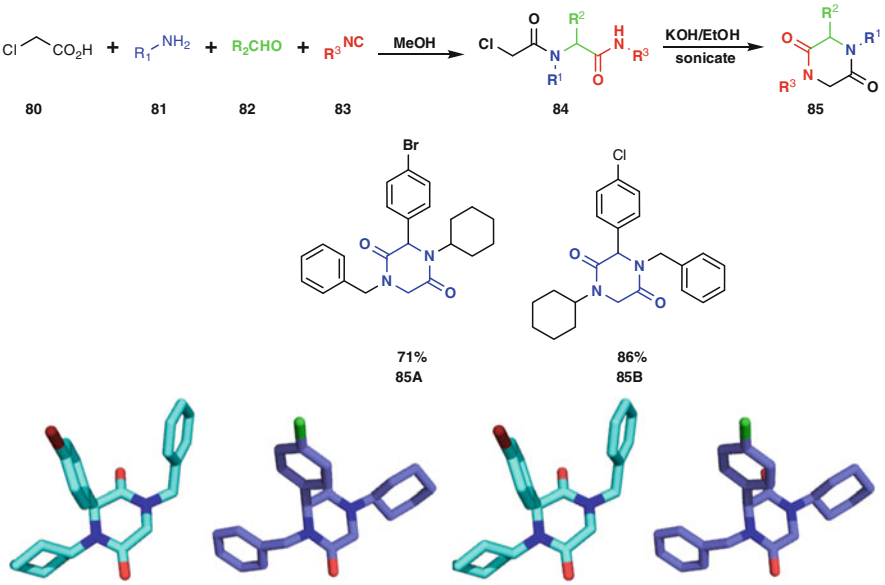
Scheme 13 Use of a convertible isonitrile to form a 2,5-DKP and two representative 3D conformations of **79A** (*blue*) and **79B** (*cyan*). Yield shown represents yield over all steps

This scaffold comprises two hydrogen bond acceptors and no hydrogen bond donor. The molecular weight of the scaffold is low (MW = 156). Two of the residues exit the scaffold in plane, whereas the aldehyde emerging substituent is attached to a sp^3 carbon (Fig. 6).

Substructure search of this backbone (smiles O = C(N(C)C1C)CN(C)C1=O) reveals several hundreds commercially available compounds, which likely have been synthesized by the above synthetic route [1]. This backbone can also be considered as a peptide mimetic by using α-amino acid derived isocyanide and amine components and will be of value for biological studies and for the discovery of hydrolysis resistant and biologically active peptide fragments (Fig. 6).

Wyatt et al. describes the use of *C*- and *N*-protected amino acids to synthesize DKPs (Scheme 15) [35]. An *N*-protected amino acid **87**, an aldehyde **88**, a *C*-protected amino acid **89**, and an isocyanide **90** are used to form the Ugi intermediate **91**, followed by deprotection and cyclization with TFA and triethylamine.

This scaffold recently gained high attention since compound GSK-221149A currently underwent advanced clinical trials as an oxytocin receptor antagonist



Scheme 14 Two-step MCR synthesis of *N*,*N*,*C*-trisubstituted 2,5-DKPs with two representative 3D conformations of **85A** (*blue*) and **85B** (*cyan*). Yield shown represents yield over all steps

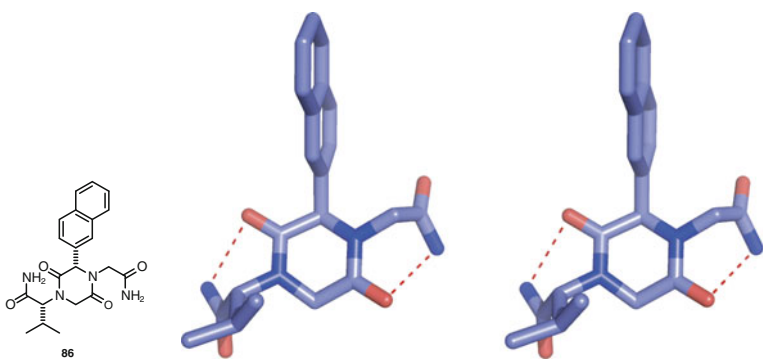
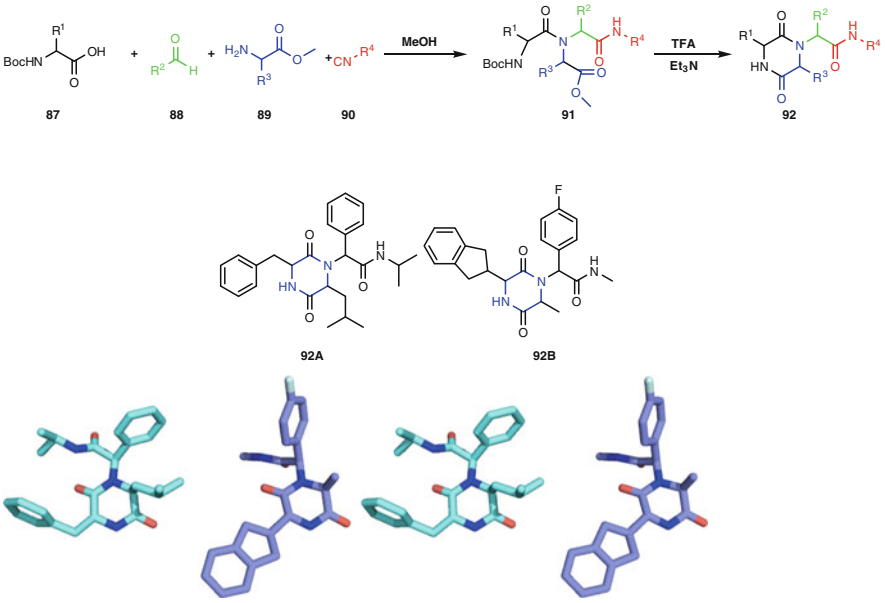


Fig. 6 2D and 3D structure of a peptidomimetic 2,5-DKP. The scaffold can undergo two intermolecular hydrogen bond, thus rendering it conformationally rigid

[36]. In an HT-screening, compound **108** was discovered as an oxytocin receptor antagonist hit. To investigate SAR, all eight possible stereoisomers had to be synthesized separately on a preparative scale. In an expeditious undertaking, several strategies have been devised to synthesize all eight stereoisomers in a stereoselective manner and using three different Ugi MCR strategies (Scheme 16). This



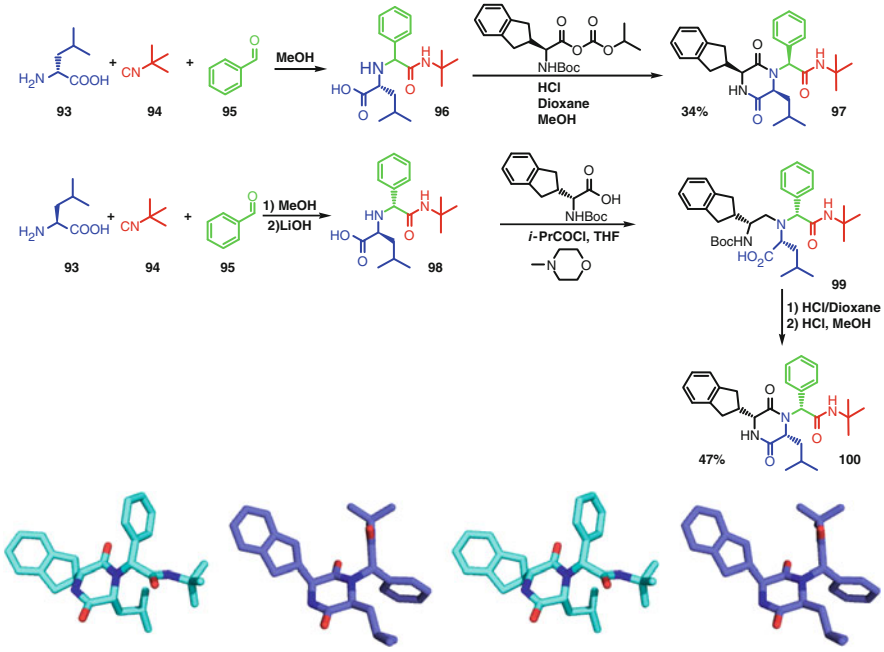
Scheme 15 Use of both *N*- and *C*-protected amino acid to synthesize 2,6 DKPs with two representative 3D conformations of **92A** (*blue*) and **92B** (*cyan*). *Yields not reported

example nicely underscores the usefulness of alternative MCR approaches to a particular piperazine scaffold.

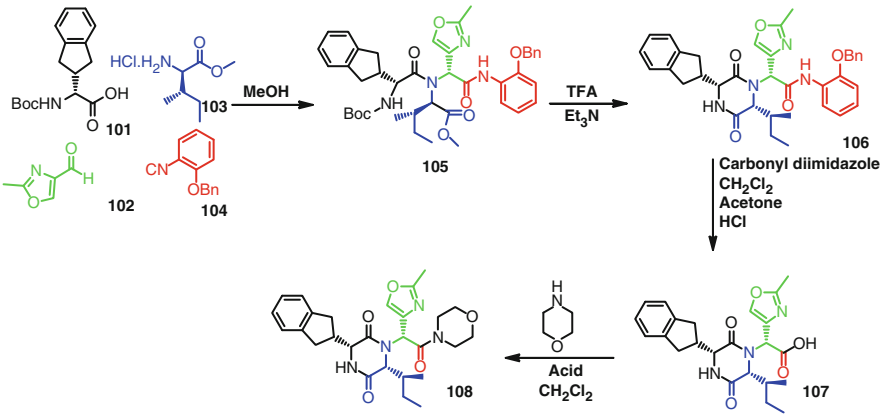
Extensive medicinal chemistry optimization of potency, selectivity pharmacokinetic, and pharmacodynamic properties finally led to potent, selective, and orally bioavailable GSK-221149A, which is synthesized as shown on Scheme 17 [35, 37, 38]. Peptidic oxytocin receptor antagonists are currently used to treat preterm labor, the main reason for infant death. The peptide derivatives by their nature are not orally bioavailable but must be administered i.v. Surprisingly, the peptide derivatives are less potent and less selective against several related receptors than GSK-221149A with half the molecular weight [39].

GSK-221149A is believed to mimic Tyr2 and Ile2 of oxytocin (Fig. 7). The role of the exocyclic side chain is speculated to reduce the rotational degrees of freedom of the Ile side chain at the DKP scaffold. DKP derivatives lacking this side chain are inactive [38].

Habashita et al. reported the discovery of a spirodiketopiperazine, which can be used as a potent and selective CCR5 antagonist [40]. CCR5 is a chemokine, which are large families of small cytokines that selectively control adhesion, chemotaxis, activation of various leukocyte populations, and have been shown to be involved in the initiation and progress of inflammation during allergic diseases. Human immunodeficiency virus (HIV) has been shown to bind to CCR5, which leads to the infection of its target cells by HIV. Interference with this receptor may open new



Scheme 16 Two different ways to stereoselectively create 2,5-DKP's via Ugi reaction with two representative 3D conformations of **97** (*blue*) and **100** (*cyan*). Yield shown represents yield over all steps



Scheme 17 Synthesis of the clinical candidate GSK221149A **108**. Yields not reported

avenues for the development of a novel class of anti-inflammatory drugs, anti-allergic drugs, immunosuppressants, and most importantly as antiviral drugs for HIV infection. This reaction made use of Ugi MCR on solid phase followed by

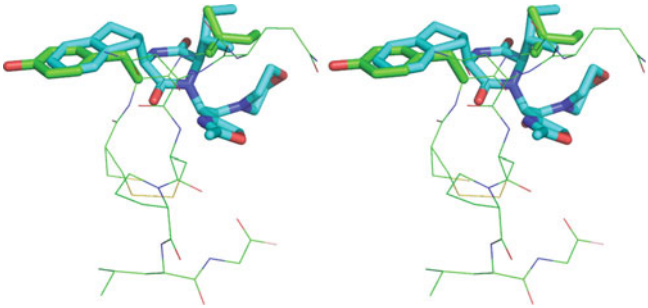
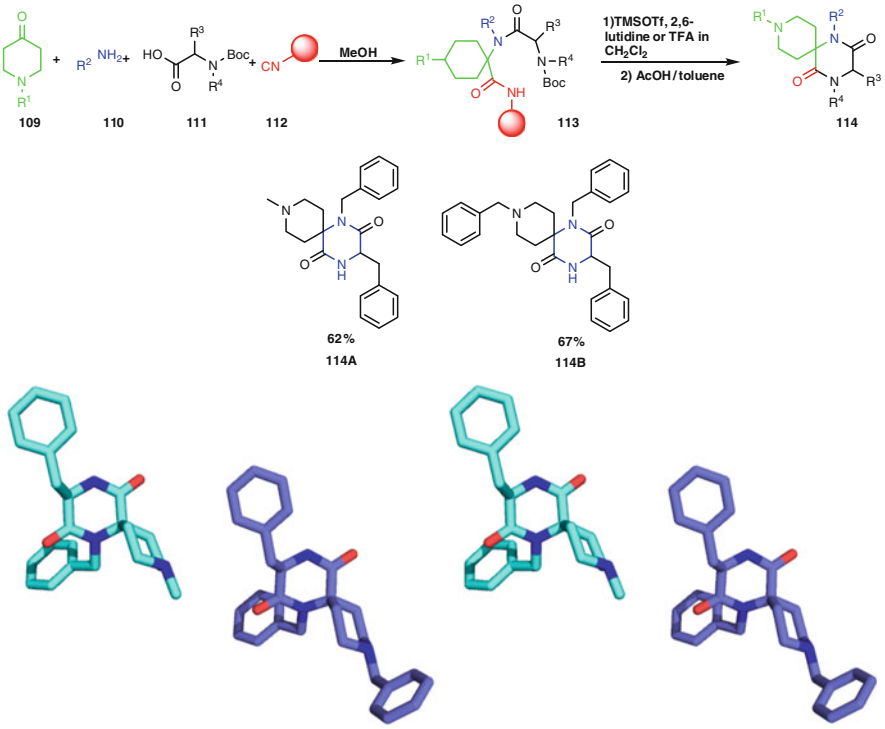


Fig. 7 Stereopicture of the alignment of the key oxytocin amino acids Tyr2 and Ile3 (*green sticks*, PDB ID: 1XY2) with the Ugi-DKP compound GSK-221149A (*cyan sticks*)

cyclative cleavage from the resin. The reaction of either Rink-isonitrile resin or methylene-isonitrile resin **112** with amine **110**, piperidone **109**, and Boc-protected *N*-alkylated amino acid **111** was done in methanol, followed by deprotection with either trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,6-lutidine (for Rink-isonitrile resin) or TFA (for methylene-isonitrile) in dichloromethane and cyclization via AcOH in toluene (Scheme 18). This afforded yields in the range of 72–97%. From this Habashita et al. was able to identify several potent CCR5 antagonists. An advanced optimized compound out of this series did undergo clinical trials.

A similar reaction (Scheme 19) was used to create a thiol-containing DKP as a novel inhibitor of matrix metalloprotease (MMPs) [41]. The MMPs are a family of zinc dependent enzymes involved in the construction and degradation of the cellular matrix. They have been shown to be important therapeutic targets in cancer and arthritis. Szardenings et al. describes the creation of a library of thiol-containing DKPs where potency was improved from 15 μM to 30 nM. Instead of solid support being done on the isonitrile, solid support was put on the amine component **115** of the Ugi reaction using TentaGel S-OH or ArgoGel-OH.

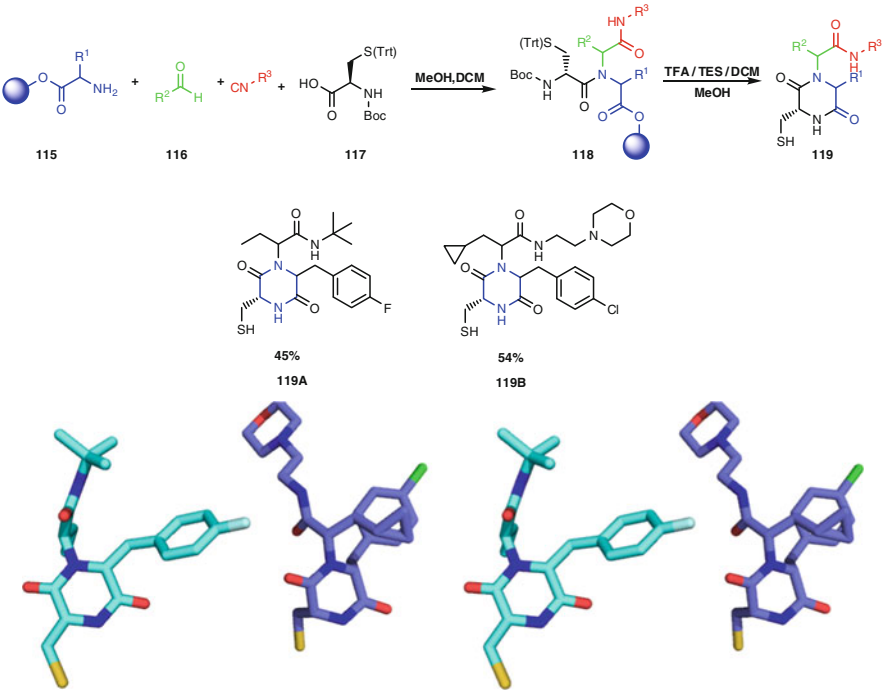
Cho et al. describes an alternative synthesis (Scheme 20) of the 2,5 DKP scaffold **92 = 123** via a bifunctional dipeptide **120**, an aldehyde **121**, and an isocyanide **122** [42]. These commercially available starting materials were added in equimolar amounts to trifluoroethanol at −40°C under nitrogen. The reaction was brought to room temperature and allowed to complete. The standard Ugi workup was used followed by column chromatography. Yields were shown in the range of 21–87%. When this reaction was done in a microwave, time taken for the reaction to complete was decreased significantly and yields increased by a factor of 4. The substitution pattern of this and the previously described (in Scheme 15) are identical; however, the reactions use different types of starting materials, for example, dipeptide vs. *N*- and *C*-protected amino acids. Thus different stereochemical outcomes can be expected for the two syntheses.



Scheme 18 Solid phase synthesis of spirodiketopiperazine CCR5 inhibitors with two representative 3D conformations of **114A** (*blue*) and **114B** (*cyan*). Yield shown represents yield over all steps

Tryptophan DKPs have shown to be an attractive subclass of this reaction with many active compounds including tryprostatin B and fumitremorgin B (Fig. 8), which are potent inhibitors of mammalian cell progression at the G2/M transition. Rhoden et al. describes the synthesis of a library of trypophan containing DKPs [43]. In this reaction (Scheme 21) *N*-protected tryptophan **124** with different combinations of amines **126**, isocyanides **127**, and aldehydes **125** were combined in methanol and heated. The reaction was heated either via reflux or by microwave; though yield did not increase significantly, time was reduced by 50-fold when reaction was heated via microwave. These reactions proved to be fast, scalable, and allow for extensive variation.

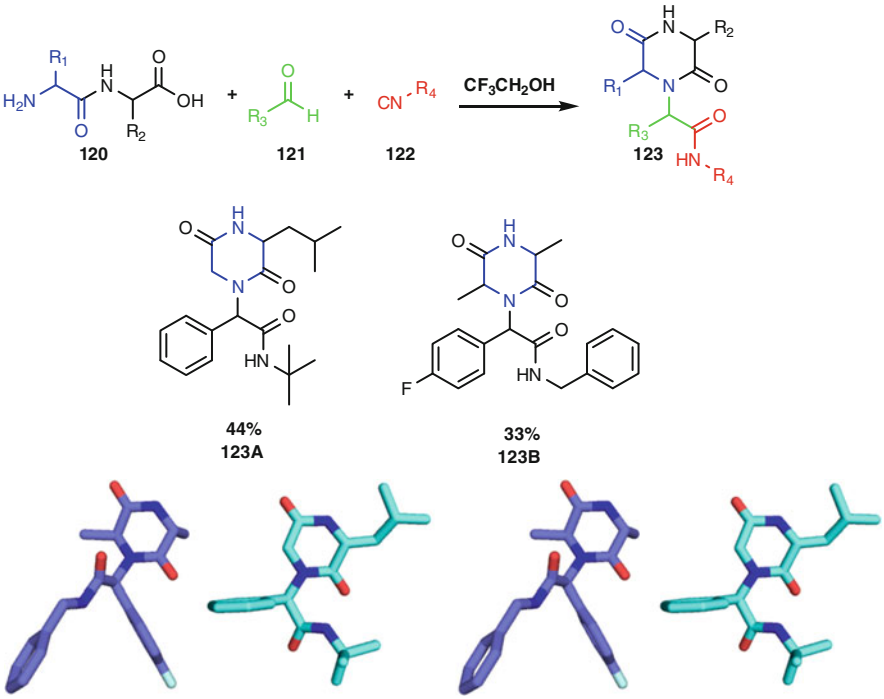
A similar reaction was performed by Szardenings et al., however, as a solid phase Ugi reaction (Scheme 22) with the amine component on the resin **126** [44]. In this case either tentagel S-OH or PAM resin was used. The same synthetic operations were used as in previous solid phase DKP and yields were shown to be 28–91%. Previous attempts to make these compounds took six steps, resulted in single digit yields, and still contained impurities [44]. The Ugi route proves to be a much better access to those compounds.



Scheme 19 Synthesis of thiol containing 2,5-DKP's for use in MMP inhibition. Solid support was done using TentaGel S OH or ArgoGel-OH. (Trt = triphenylmethyl, TES = triethylsilane). Two representative 3D conformations of **119A** (*blue*) and **119B** (*cyan*). Yield shown represents yield over all steps

Lin et al. describes the generation of a library of high purity DKPs using small molecule macroarray synthesis [45]. This has several advantages over solid phase synthesis; the compound arrays are straightforward to manipulate, inexpensive, and amenable to numerous screening applications, where the array compounds are either bound to or cleaved from the planar support. Lin et al. was also able to show that microwave-assisted reaction of the macroarrays accelerated the library synthesis. This reaction used amino-derived cellulose support **138**, an aldehyde **139**, an amino protected amino acid **140**, and a convertible isocyanide **141** (Scheme 23). The combination of these compounds in water is followed by deprotection, cyclization, and release from the microarray. This same reaction can be done via solution phase synthesis in reasonable yields as shown by Hulme et al. [46].

Another macroarray study was described by Campbell et al. using an amino acid bound to the support via the carboxyl group **143** (Scheme 24) [47]. This allows for two more points of diversity as opposed to the above scaffold; allowing for a substitution on the amino acid as well as an isocyanide, as the convertible isocyanide is no longer needed. Isolated yields were in the range of 82–99%.



Scheme 20 Synthesis of 2,5-DKPs via Ugi three-center four-component reaction with two representative 3D conformations of **123A** (*blue*) and **123B** (*cyan*). Yield shown represents yield over all steps

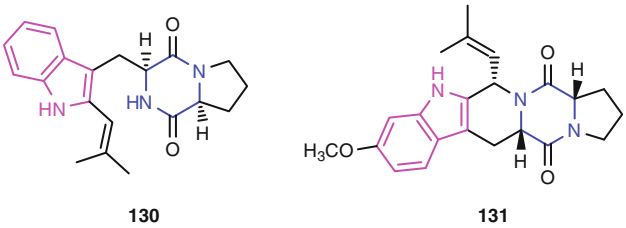
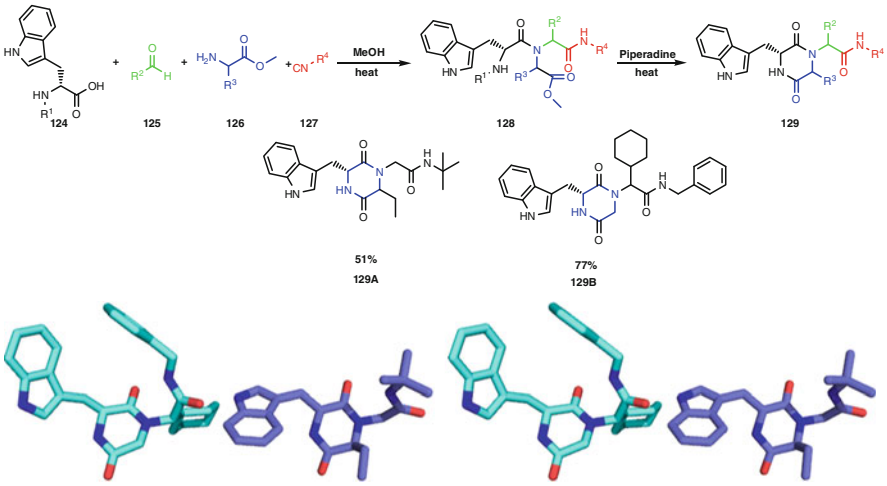


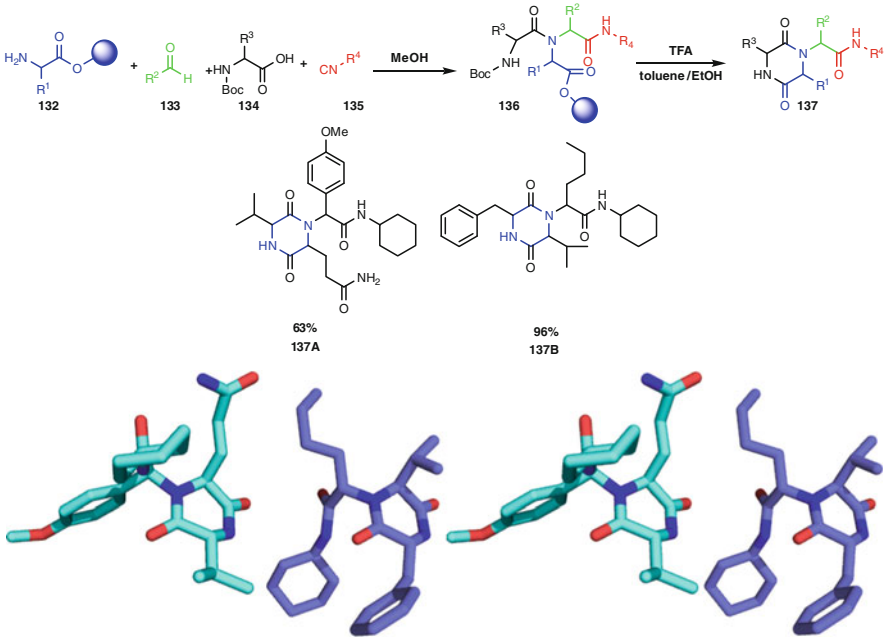
Fig. 8 Tryptophan moiety (*magenta*) containing piperazine natural products tryprostatin B **130** and fumitremorgin **131** are two inhibitors of mammalian cell progression at the G2/M transition

3.4 2,6-Diketopiperazine

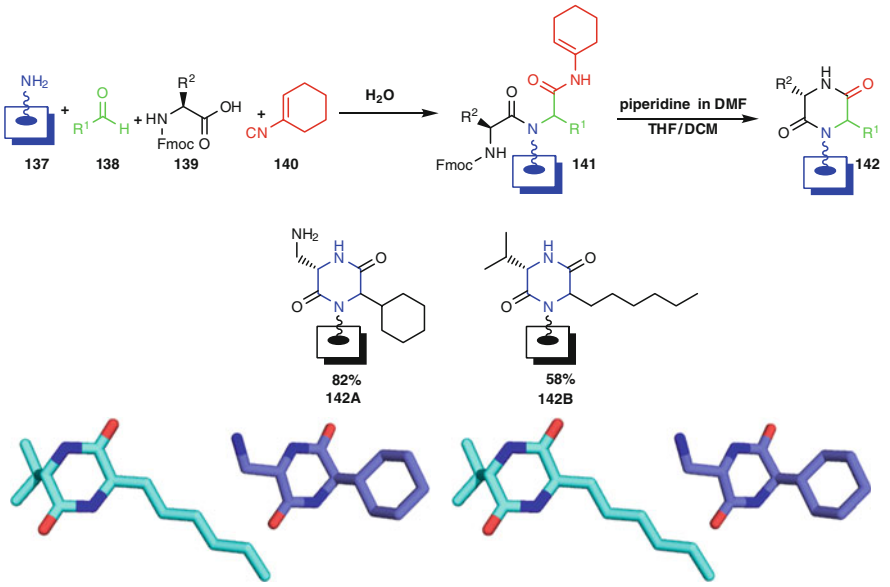
2,6-DKP as opposed to 2,5-DKPs are rather rarely described by isocyanide-based MCRs. Ugi et al. describes the only 2,6-DKP synthesized by isocyanide MCR [48]. This reaction (Scheme 25) uses the well known five-center-four-component reaction (U-5C-4CR) of an α-amino acid, an aldehyde or ketone, an isocyanide,



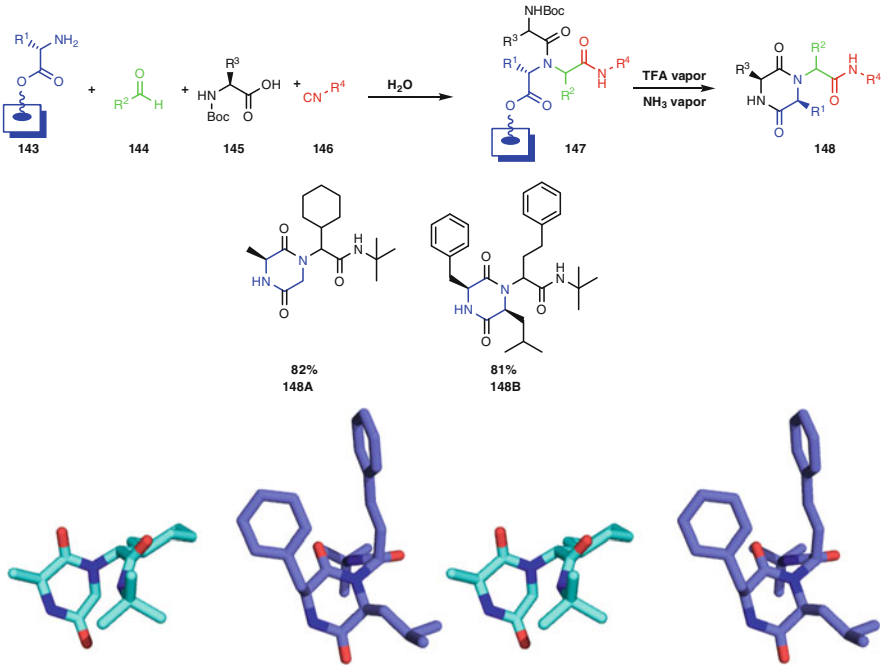
Scheme 21 Synthesis of tryptophan derived 2,5-DKPs with two representative 3D conformations of **129A** (*cyan*) and **129B** (*blue*). (PG = Protecting group; Fmoc or Boc) Yield shown represents yield over all steps



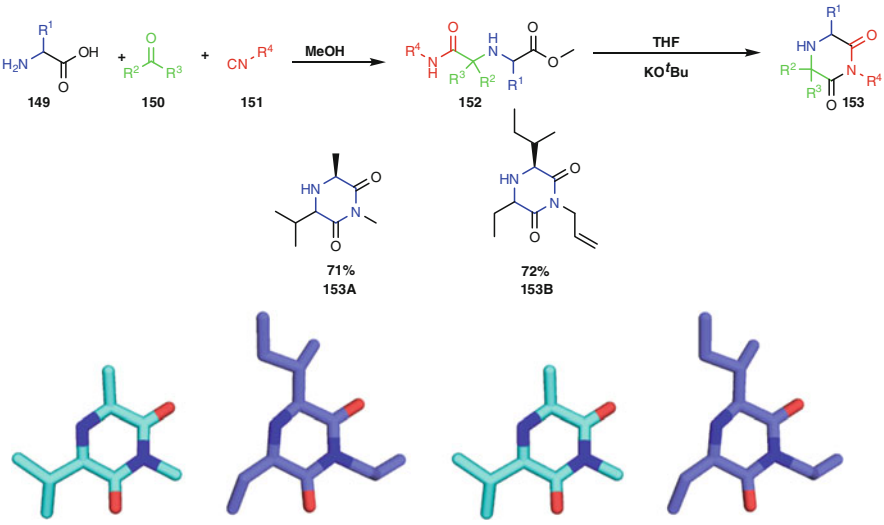
Scheme 22 Solid phase synthesis of 2,5-DKP's, with two representative 3D conformations of **137A** (*blue*) and **137B** (*cyan*). Yield shown represents yield over all steps



Scheme 23 Cellulose-based macroarray synthesis of 2,6-DKPs with two representative 3D conformations of **142A** (*cyan*) and **142B** (*blue*). Yield shown represents yield over all steps



Scheme 24 Macroarray synthesis of DKPs using a cellulose supported *C*-bound α-amino acid attached to the microarray with two representative 3D conformations of **148A** (*blue*) and **148B** (*cyan*).Yield shown represents yield over all steps



Scheme 25 The only known synthesis of 2,6-DKPs using isocyanide-based MCR chemistry with two representative 3D conformations of **153A** (*blue*) and **153B** (*cyan*). Yield shown represents yield over all steps

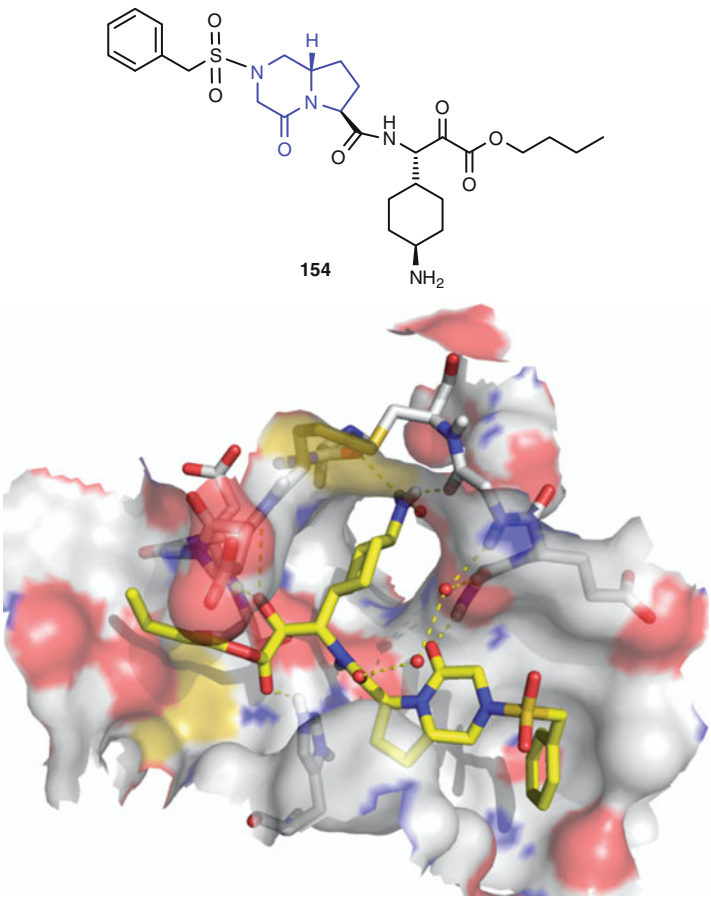
and methanol. The intermediate Ugi **152** is then treated with K^{t}BuO in THF to afford **153**.

4 Condensed Bicyclic Piperazines

Compared with monocyclic piperazine scaffolds, bicyclic piperazines often provide platforms with even more points of diversity compared to monocyclic piperazines. Condensed bicyclic piperazines enlarge the chemical space of piperazine scaffolds, as well as the family of target proteins. For example, bicyclic piperazinones were prepared and evaluated *in vitro* and *in vivo* as thrombin inhibitors [49]. The co-crystal structure of a bicyclic piperazinone inhibitor **154** with thrombin was shown in Fig. 9. So far, chemists have developed many MCR methods to synthesize a variety of bicyclic piperazine scaffolds.

Preparation of diketopiperazine as part of a bicyclic system was developed by a one-pot Ugi-4-center-3-component reaction (U-4C-3CR) [50]. A 3-keto or aldo acid **155** was used as bifunctional educt for an intramolecular Ugi reaction forming a five-membered ring. The application of *C*-protected amino acids **156** as amine components enables an intramolecular cyclization forming 2,6-piperazinediones **158** (Scheme 26).

A bicyclic diketopiperazine **159** as a potential peptide β-turn mimetic was developed via solid-supported synthesis [51]. The Ugi reaction among the resin



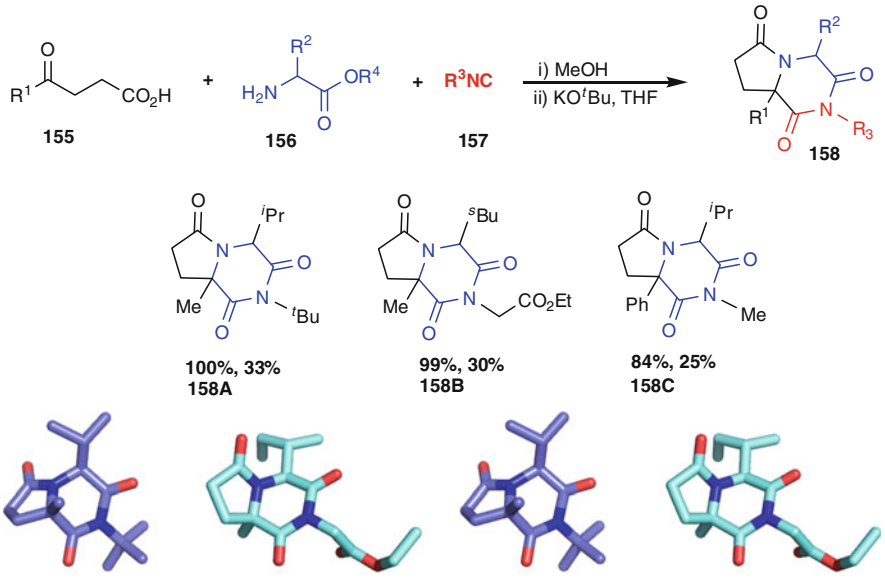
154

Fig. 9 X-ray structure of bicyclic piperazinone inhibitor with thrombin (PDB ID: 1G37). Piperazinone inhibitor is shown as *yellow sticks*, and the receptor binding site is shown as transparent surface. The extensive hydrogen bonding network with receptor and water is shown as *yellow dots*

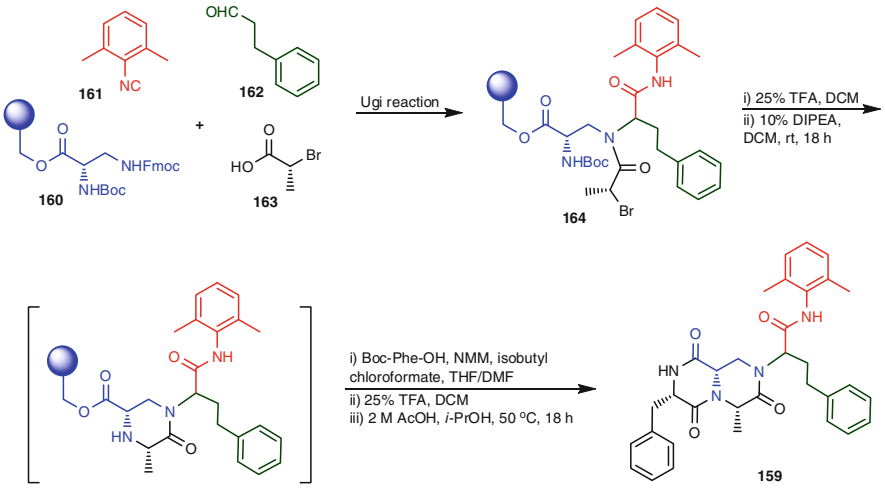
ester of α-*N*-Boc-diaminopropionic acid **160** (an amine input), 2,6-dimethylphenyl isocyanide **161**, hydrocinnamaldehyde **162**, and α-bromo acetic acid **163** is the key step in this protocol (Scheme 27). The Ugi product **164** was transformed to **159** in five steps, which was isolated in overall 20% yield.

The scope and limitations of the solid-supported synthesis of bicyclic diketopiperazines **165** as peptide β-turn mimetic were further investigated by Golebiowski et al. [52]. The four-component Ugi reaction of α-*N*-Boc-diaminopropionic acid resin ester **160** (an amine input) and optically active α-bromoacid **163** with various isocyanides **166** and aldehydes **167** yields a series of bicyclic diketopiperazines **165** (Scheme 28).

A solution phase synthesis of an array of biologically relevant quinoxalinones **168** was developed by Nixey et al. in a simple two-step procedure [53]. The Ugi

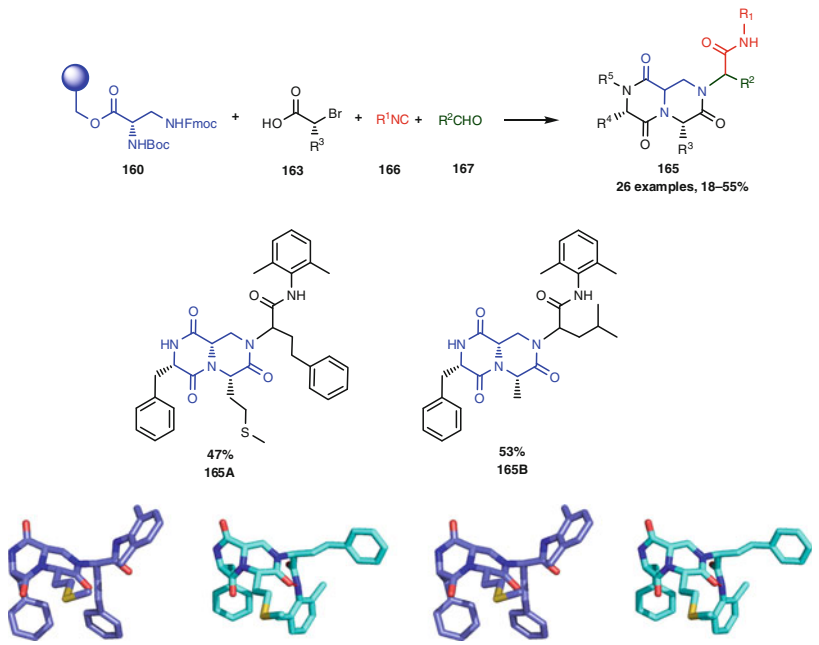


Scheme 26 Synthesis of bicyclic diketopiperazines and two representative 3D conformations of **158A** (*blue*) and **158B** (*cyan*)



Scheme 27 Synthesis of bicyclic diketopiperazine **159**

products **173** were obtained by the reaction of glyoxylic acids **169** and mono-Boc protected *ortho*-phenylene diamine **170** with various aldehydes **171** and isocyanides **172** (Scheme 29). Subsequent acid treatment and evaporation afford quinoxalinones **168** in good to excellent yields.

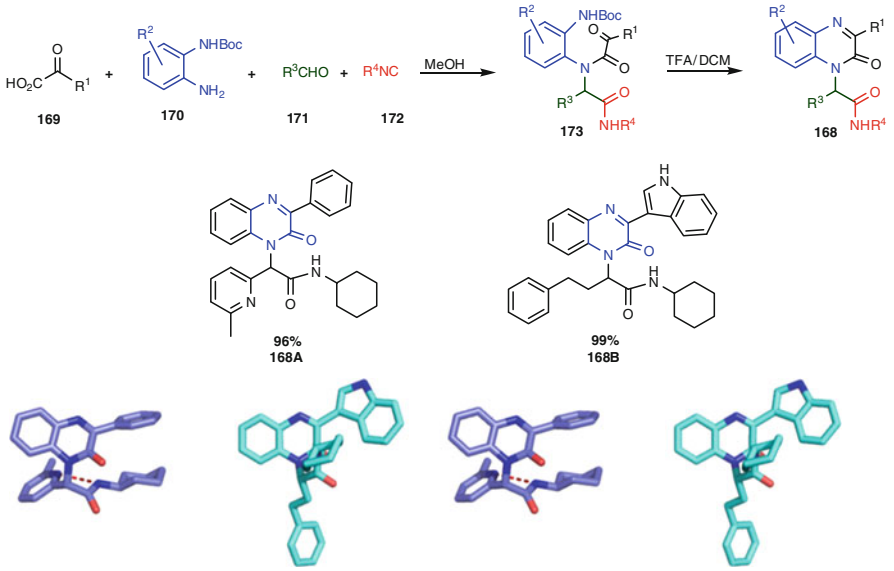


Scheme 28 Variations of bicyclic diketopiperazines **165**. Two representative diastereomers of **165A** are drawn in *blue* and *cyan* and intramolecular hydrogen bonds are shown in *red dots*

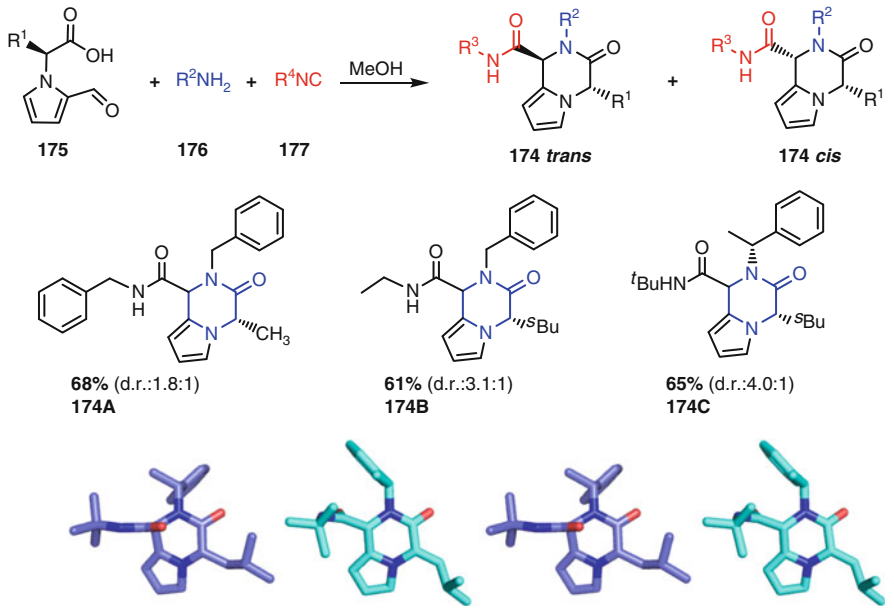
The synthesis of chiral pyrroloketopiperazines **174** was achieved via diastereoselective Ugi reaction, with chiral 2-(2-formyl-1*H*-pyrrol-1-yl)acetic acids **175** conveniently derived from α-amino acids [54]. The reaction proceeds with moderate diastereoselectivity (*trans*:*cis*, up to 4:1) to give the target compounds **174** in good yields (Scheme 30). Noteworthy, the mixture of diastereomeres was separated by column chromatography and could be isolated as single diastereomeres.

Umkehrer et al. developed the synthesis of tetrazolopiperazine building blocks **178** via Ugi five-center-four-component reaction (U-5C-4CR) of primary amines **179**, aldehydes **180**, trimethylsilylazide **181**, and 2-isocyanoethyltosylate **182** [54]. The *in situ* generated secondary amine finally gets alkylated by the toluenesulfonate, leading to the expected fused tetrazoles **178** (Scheme 31). The primary amines and the aldehydes can be varied broadly, which allows to produce products with two potential diversity points.

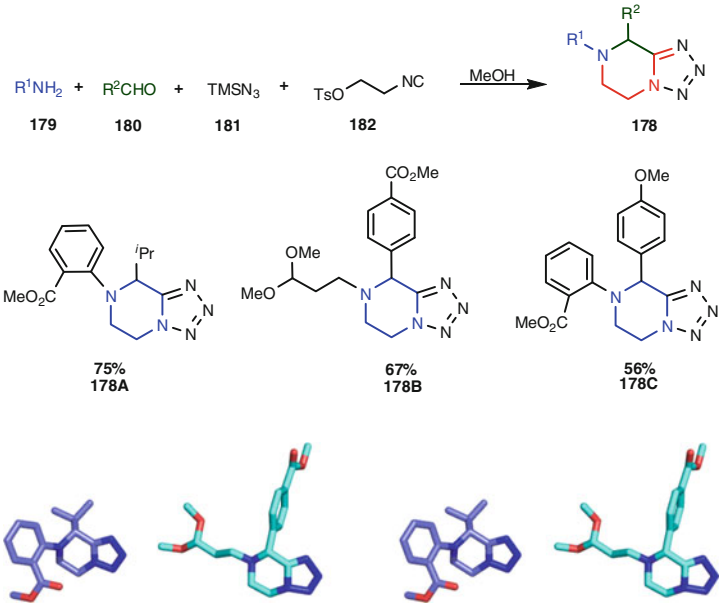
A library of piperazine containing fused azepine-tetrazoles **183** was built by Nixey et al. via Ugi reaction in the solution phase [55]. This library comprises an example of a building block introduced piperazine (Scheme 32). The reaction of *N*-Boc-α-amino aldehyde **184**, methyl isocyanoacetate **185**, substituted piperazines **186**, and trimethylsilylazide **181** in methanol, followed by acid treatment, proton scavenging, and reflux affords bicyclic azepine-tetrazoles **183**. This efficient protocol with three diversity points can be used to generate arrays of biologically



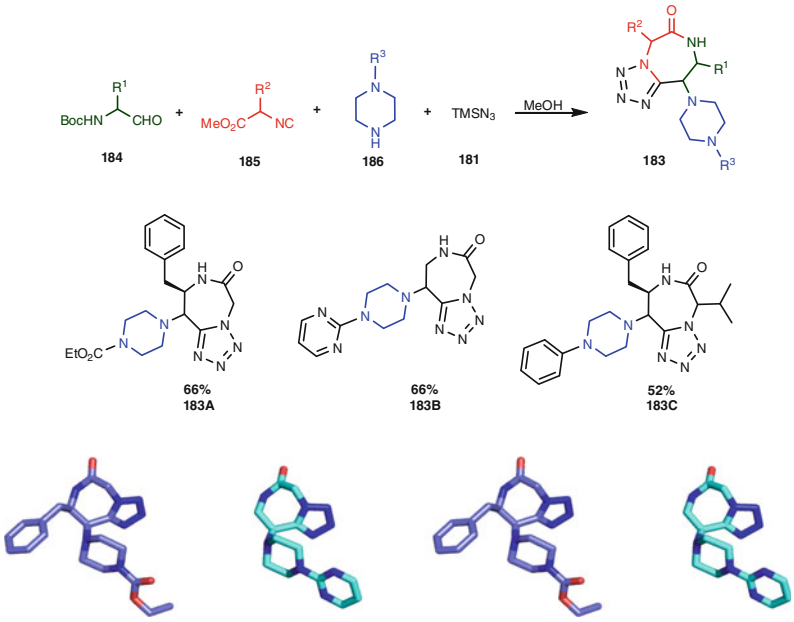
Scheme 29 Synthesis of quinoxalinones **168** and two representative 3D conformations of **168A** (*blue*) and **168B** (*cyan*). An intramolecular hydrogen bond in compound **168A** is shown in *yellow dots*



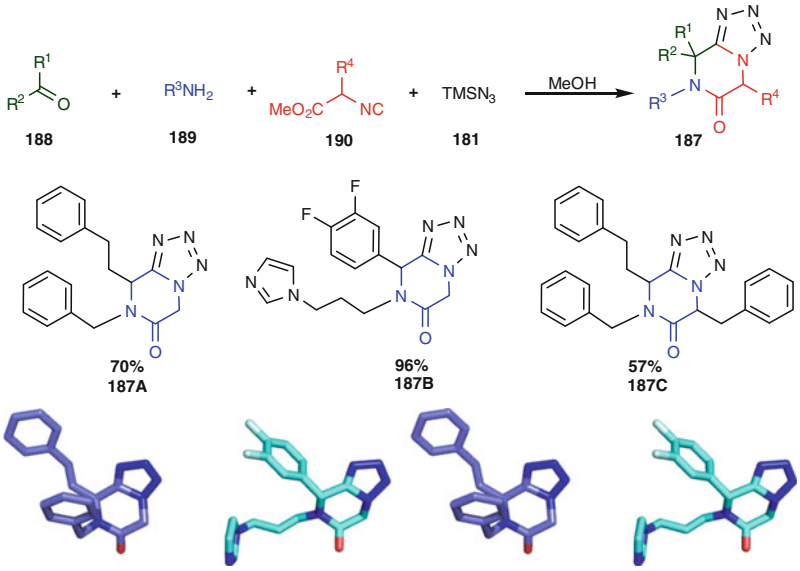
Scheme 30 Synthesis of pyrroloketopiperazines **174**. Two representative diastereomers of **174C** are drawn in *blue* and *cyan*



Scheme 31 Synthesis of tetrazolopiperazines **178** and two representative 3D conformations of **178A** (*blue*) and **178B** (*cyan*)



Scheme 32 Synthesis of piperazine incorporating fused azepine-tetrazoles **183** and two representative 3D conformations of **183A** (*blue*) and **183B** (*cyan*)



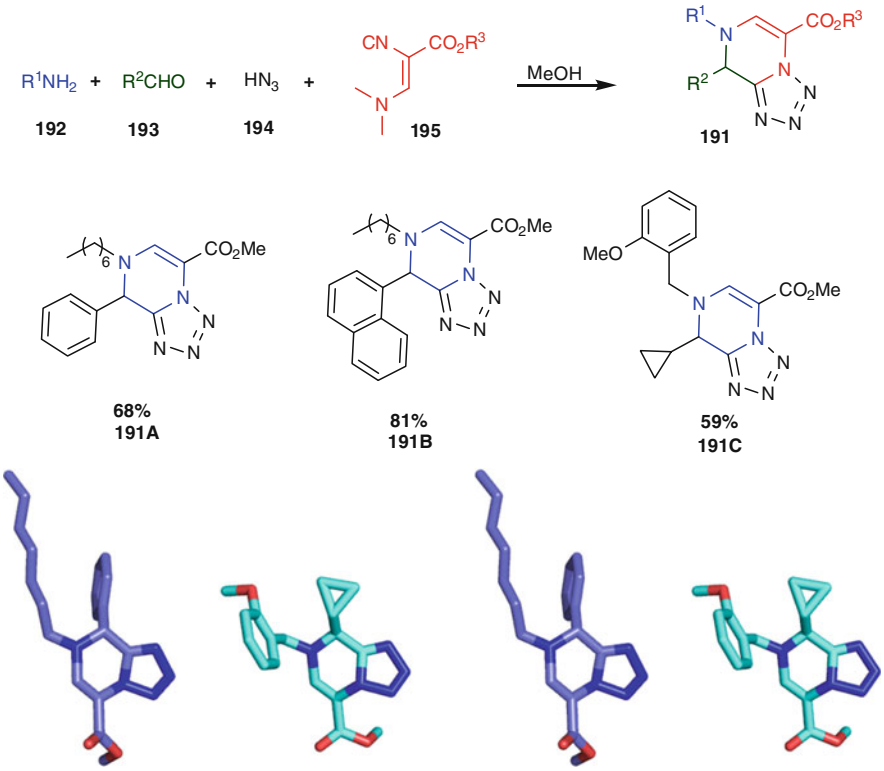
Scheme 33 Synthesis of fused tetrazole-ketopiperazines **187** and two representative 3D conformations of **187A** (*blue*) and **187B** (*cyan*)

relevant small molecules. Such piperazino tetrazoles are known to preferentially interact with GPCRs, the major drug target class [11].

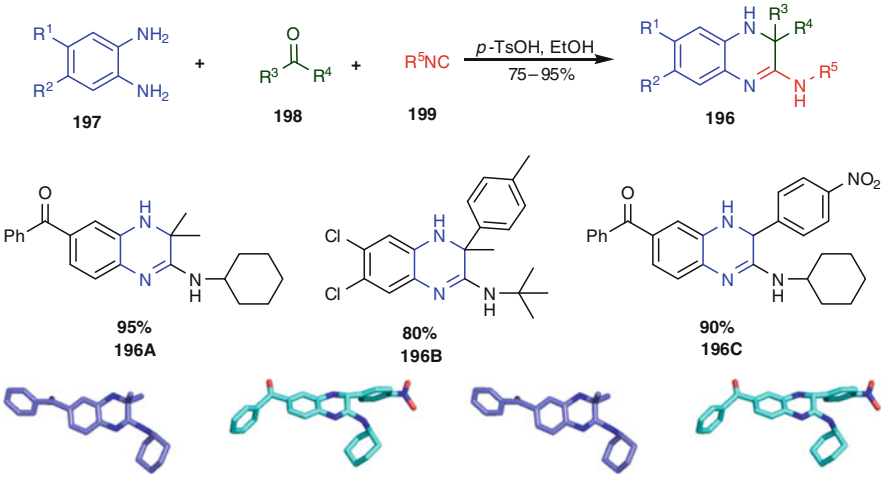
A library of fused tetrazole-ketopiperazines **187** was obtained by Nixey et al. via Ugi four-component reaction in the solution phase [56]. The reaction of an oxo component **188**, primary amine **189**, methyl isocyanoacetate **190**, and trimethylsilylazide **181** in methanol at reflux affords bicyclic tetrazole-ketopiperazines **187** in good yield (Scheme 33). The cyclization to afford the tetrazole-ketopiperazines is performed spontaneously under the reaction conditions.

The synthesis of tetrazolopiperazines **191** was achieved by Bienaymé et al. via Ugi reaction of primary amines **192**, aldehydes **193**, hydrazoic acid **194**, and Schöllkopf isocyanide **195** [57]. This transformation was used to prepare large arrays of drug-like molecules (Scheme 34). Overall yields for this highly efficient process were fair to good.

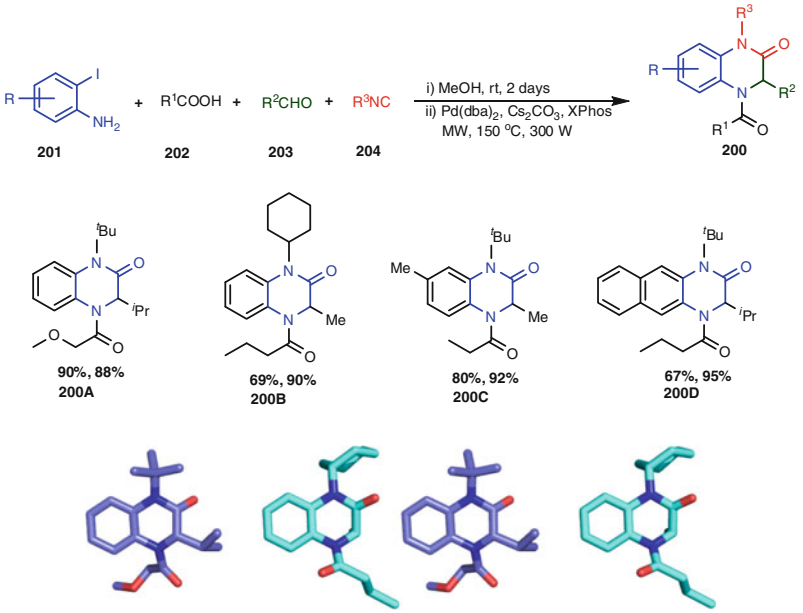
Libraries of highly substituted 3,4-dihydroquinoxaline-2-amine derivatives **196** including spirocyclic compounds were synthesized by Neochoritis et al. and Shabaani et al. employing a three-component condensation [58, 59]. The reaction of *o*-phenylenediamines **197**, diverse carbonyl compounds **198**, and isocyanides **199** in the presence of a catalytic amount of *p*-toluenesulfonic acid provides **196** in good to excellent yields (Scheme 35). Compounds based on this scaffold have recently attracted considerable attention as agonists for the glucagon-like peptide 1 receptor, as novel anti-diabetic experimental drugs [60].



Scheme 34 Synthesis of tetrazolopiperazines **191** and two representative 3D conformations of **191A** (*blue*) and **191B** (*cyan*)



Scheme 35 Synthesis of 3,4-dihydroquinoxalin-2-amine derivatives **196** and two representative 3D conformations of **196A** (*blue*) and **196C** (*cyan*)



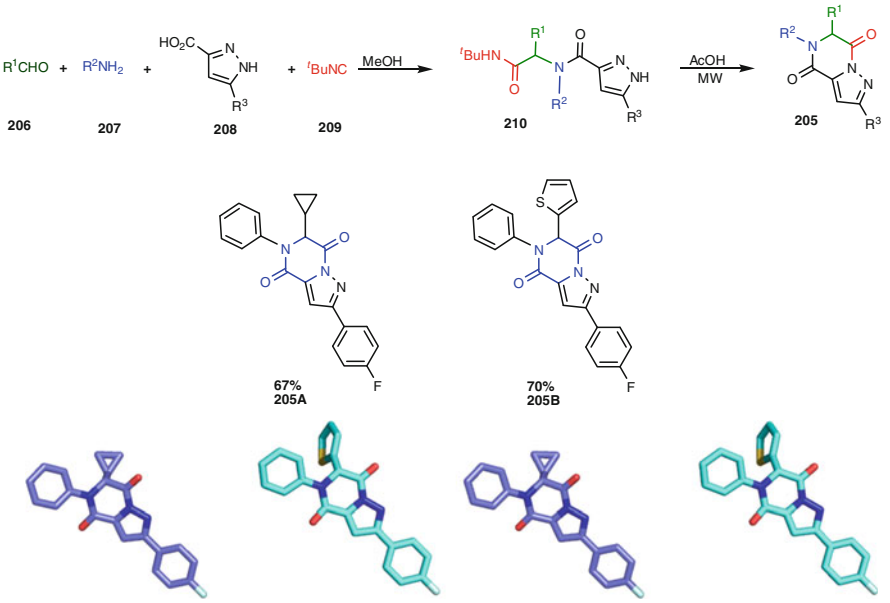
Scheme 36 4CR synthesis of benzopiperazinones **200** and two representative 3D conformations of **200A** (*blue*) and **200B** (*cyan*)

Benzopiperazinones **200** were prepared by Erb et al. via the Ugi four-component reaction followed by palladium-catalyzed intramolecular *N*-arylation [61]. XPhos was used as a supporting ligand to afford the 3,4-dihydroquinoxalin-3-ones **200** (Scheme 36). Microwave irradiation was found to be determinant on the reaction efficiency.

Dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **205** were synthesized by Nikulnikov et al. using *tert*-butyl isocyanide **209** as a convertible isocyanide [62]. The Ugi reaction of *tert*-butyl isocyanide and pyrazole-3-carboxylic acids **208** with various aldehydes **206** and amines **207** yields *tert*-butyl amides **210**, which undergo cyclization into glacial acetic acid under microwave irradiation (Scheme 37).

5 Polycyclic Fused Piperazines

Piperazine fused polycyclic ring systems are unique in terms of structures and properties. Praziquantel **211** is the primary medication for human schistosomiasis, for which it is usually effective in a single dose treatment. As shown in Fig. 10, praziquantel consists of a ketopiperazine fused ring system. A co-crystal of praziquantel and glutathione-*S*-peroxidase of the helminth *Schistosoma japonica* was known [63]. Praziquantel binds in a channel joining the two xenobiotic substrate



Scheme 37 Synthesis of dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **205** and two representative 3D conformations of **205A** (*blue*) and **205B** (*cyan*)

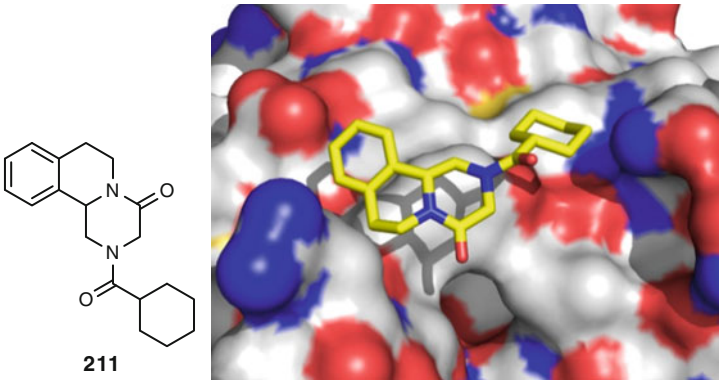
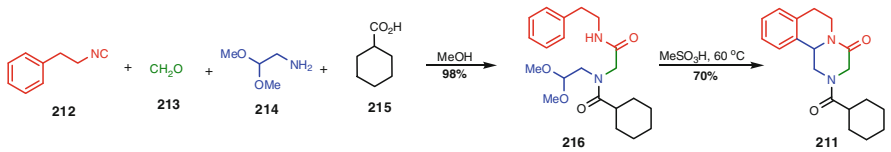


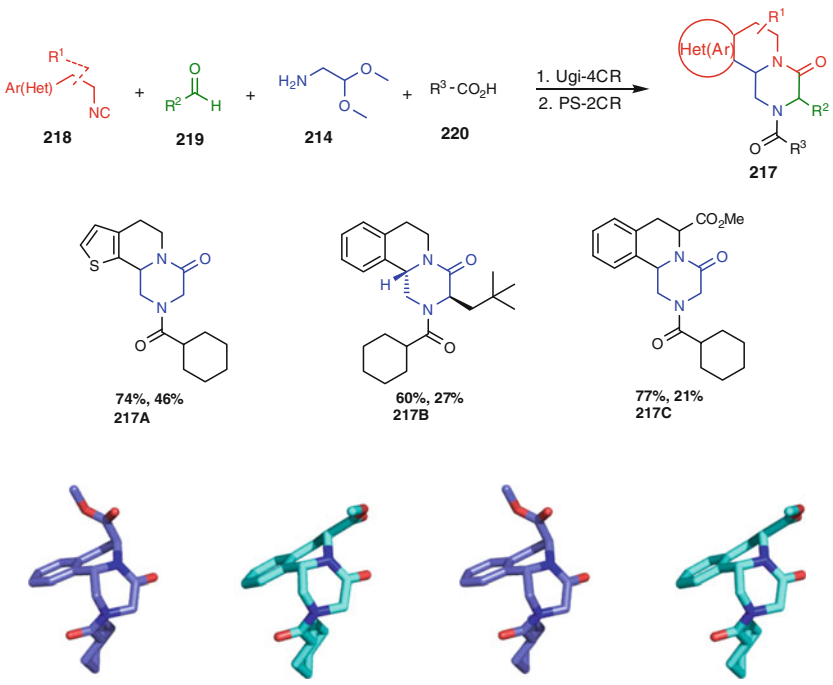
Fig. 10 X-ray co-crystal structure of praziquantel **211** and glutathione-*S*-peroxidase complex (PDB ID: 1GTB). Praziquantel is shown as *yellow sticks* and the receptor binding site is shown as hydrophobic surface

binding sites of the dimer due to its hydrophobic nature. The mode-of-action of Praziquantel, however, likely involves other target(s).

Many syntheses to praziquantel and derivatives have been discovered by ingenious chemists after the first synthesis in 1977 [64]. Until recently, the synthesis of praziquantel was developed by Dömling et al. in three steps from bulk starting



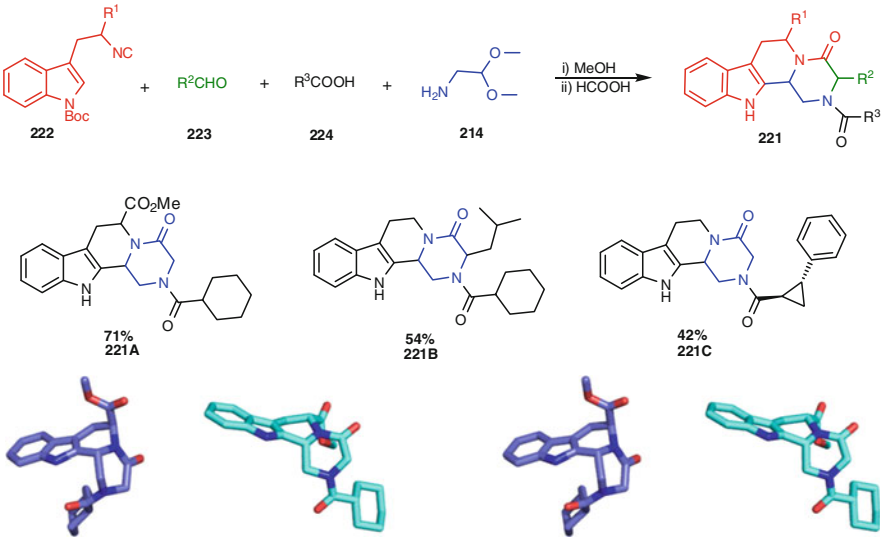
Scheme 38 Efficient synthesis of praziquantel based on Ugi MCR



Scheme 39 Convergent MCR approach towards praziquantel derivatives **217**. Two representative diastereomers of **217C** are drawn in *blue* and *cyan*

materials using MCR technology [65]. As shown in Scheme 38, 2-phenylethylisocyanide **212** reacts with paraformaldehyde **213**, aminoacetaldehyde dimethylacetal **214**, and cyclohexylcarboxylic acid **215** to quantitatively yield the precursor **216**. Praziquantel was then obtained by the treatment of the Ugi product **216** with methanesulfonic acid in a Pictet–Spengler cyclization.

A general strategy towards praziquantel derivatives **217** was developed by Liu et al. based on an Ugi four-component condensation (Ugi-4CR) followed by a Pictet–Spengler cyclization (PS-2CR) [66]. The variations of the groups and substitutents in these scaffolds arise from the four starting materials: isocyanide **218**, aldehyde **219**, amine **214**, and carboxylic acid **220** (Scheme 39). This process produces ketopiperazine fused ring systems that mimic the scaffold of praziquantel.



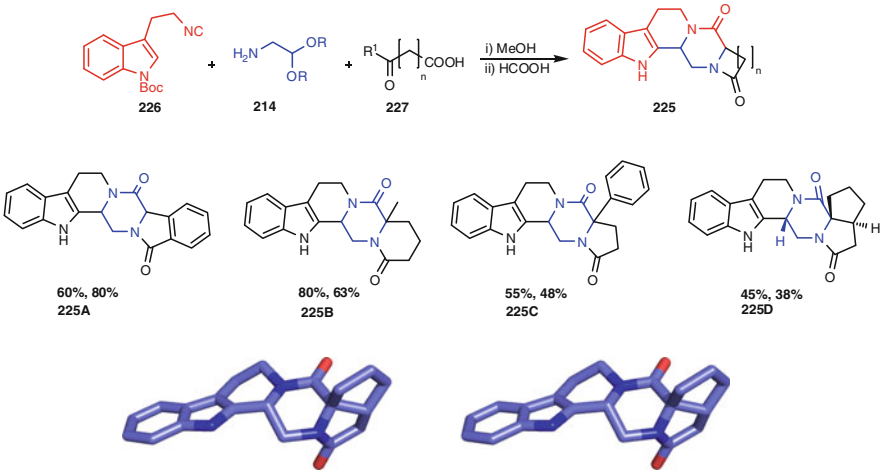
Scheme 40 Synthesis of the tetrahydro-β-carboline scaffold **221**. Two representative diastereomers of **221A** are drawn in *blue* and *cyan*

Combination of MCR with the Pictet–Spengler cyclization also leads to different types of scaffolds with ketopiperazine fused ring systems. Tetrahydro-β-carboline scaffold **221** was prepared in a convergent, two-step procedure [67]. An array of indole derivatives was prepared by the reaction of tryptophan derivative **222**, aldehyde **223**, carboxylic acid **224**, and bifunctional amine **214** (Scheme 40).

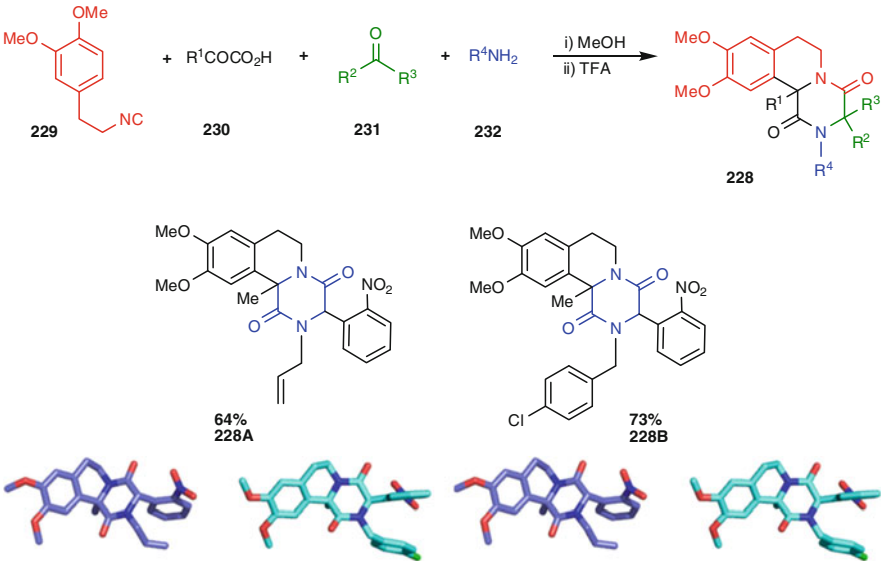
Moreover, polycyclic indole alkaloid-type molecules **225** with a ketopiperazine were prepared by Wang et al. using Ugi-Pictet–Spengler process [68]. Ketocarboxylic acids **227** were used as bifunctional substrates in Ugi reaction to yield lactams of varying ring sizes (Scheme 41). A diastereomer of hexacyclic indole derivative was crystallized and yielded X-ray diffraction suitable crystal to assign the stereochemistry.

Another example of Ugi/Pictet–Spengler two-step procedure was employed by El Kaim et al. to prepare polycyclic 1,4-diketopiperazines **228** [69]. The four-component Ugi reaction of homoveratryl isocyanide **229** and α-ketocarboxylic acids **230** allows the formation of Ugi products, which were treated with trifluoroactic acid to afford tricyclic 2,5-diketopiperazines **228** in a Pictet–Spengler-type cyclization (Scheme 42).

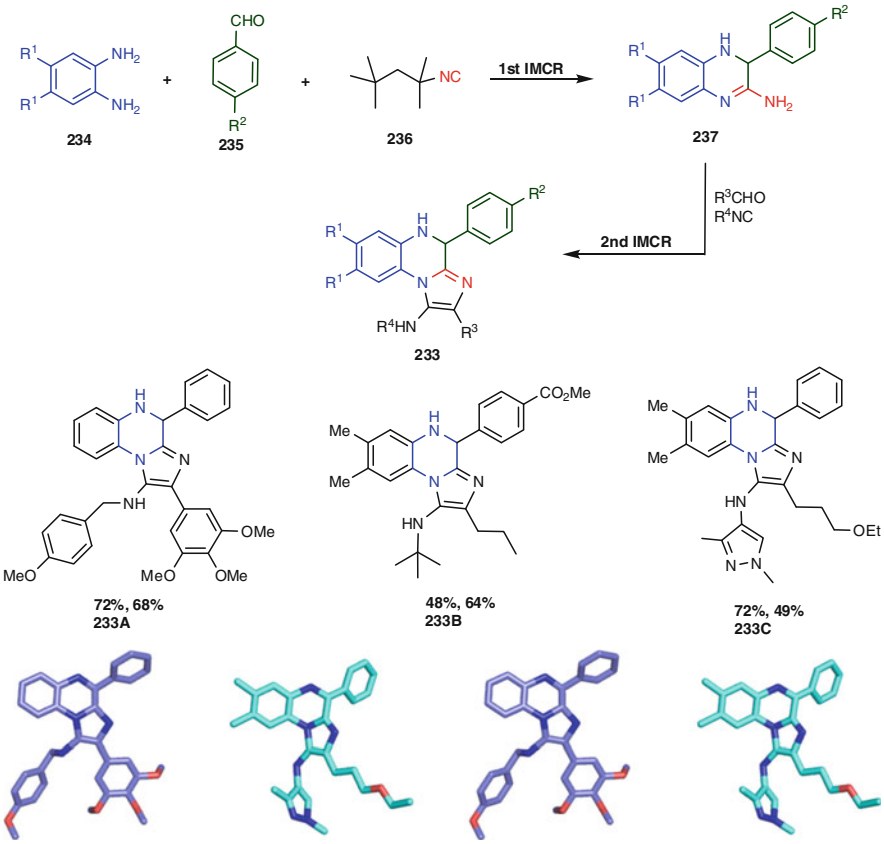
The imidazo[1,2-*a*]quinoxaline scaffold **233** was developed by Krasavin et al. via two isocyanide-based multicomponent reactions sequentially introducing four diversity elements to the final products [70]. The first step involves the synthesis of quinoxalines **237** from *o*-phenylenediamines **234** and followed by the Groebke–Blackburn–Bienayme multicomponent reaction (Scheme 43). The described methodology provides a tool to construct the medicinally relevant heterocycles.



Scheme 41 Synthesis of polycyclic indole alkaloid-type compounds **225**. The X-ray structure of compound **225D** is shown in *blue sticks* (CCDC-749252)



Scheme 42 Ugi/Pictet–Spengler formation of 2,5-diketopiperazine **228** and two representative 3D conformations of **228A** (*blue*) and **228C** (*cyan*)



Scheme 43 Synthesis of imidazo[1,2-*a*]quinoxalines **233** and two representative 3D conformations of **233A** (*blue*) and **233C** (*cyan*)

6 Conclusion

Piperazines and derivatives are archaetypical scaffolds and can be considered as efficient, however, structurally simple peptidomimics. The scaffolds combine conformational rigidity with peptide-like spacial placement of amino acid side chains or isosteres thereof. Moreover, piperazines can be used to confine compounds with beneficial properties such as water solubility. Piperazines are therefore in the center of synthetic interest and many different synthetic pathways have been designed [16–19]. A preferred way to synthesize different piperazine scaffolds with plenty of variability provides MCR chemistry. Several piperazine scaffolds are currently only accessible by isocyanide-based MCR. Likely they could be assembled by sequential synthesis as well; however, the synthetic efficiency, the diversity, and the size of the alternative chemical space will be inferior. The application of

isocyanide-based MCRs is one of the best and versatile methods for the synthesis of many different (keto)piperazine scaffolds, owing to the high yields, the simplicity of the synthetic procedure, and the mild reaction conditions. Like no other method in organic chemistry, IMCR gives access to a very large chemical space for the everlasting search for compounds to find cures in areas of unmet medical need.

References

1. eMolecules (2010) http://www.emolecules.com
2. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, Gautam B, Hassanali M (2008) DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic Acids Res 36(suppl 1):D901–D906
3. Borio P (1953) The anthelmintic action of papain and of piperazine diphenylacetate (DPP). Minerva Farm 2(4):141–142
4. Hendlich M, Bergner A, Gunther J, Klebe G (2003) Relibase: design and development of a database for comprehensive analysis of protein-ligand interactions. J Mol Biol 326(2): 607–620
5. Houston DR, Synstad B, Eijsink VGH, Stark MJR, Eggleston IM, van Aalten DMF (2004) Structure-based exploration of cyclic dipeptide chitinase inhibitors. J Med Chem 47(23): 5713–5720
6. Miller RA, Karady S, Reider PJ (2003) Piperazinecarboxamide intermediates of HIV protease inhibitors and processes for their preparation. US Pat Appl Publ US 2003191121 A1 20031009
7. Ikemoto N, Miller RA, Fleitz FJ, Liu J, Petrillo DE, Leone JF, Laquidara J, Marcune B, Karady S, Armstrong Iii JD, Volante RP (2005) Approaches to installing a N-gem-dimethylmethylene-2-oxazolyl group and application to the synthesis of a second generation HIV protease inhibitor. Tetrahedron Lett 46(11):1867–1871
8. Leach CA, Liddle J, Peace S, Philp J, Smith IED, Terrell LR, Zhang J (2006) Preparation of 1,6-disubstituted-(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-2,5-piperazinedione derivatives as oxytocin receptor antagonists for the treatment of pre-term labor, dysmenorrhea and endometriosis. PCT Int Appl WO 2006067462 A1 20060629
9. Borthwick AD, Hickey DMB, Liddle J, Mason AM (2006) Preparation of diketopiperazines as oxytocin receptor antagonists. 2005-EP6760 WO2006000399, 20050621
10. Borthwick AD, Hickey DMB, Liddle J, Mason AM, Pollard DR, Sollis S (2006) Preparation of diketopiperazines as oxytocin antagonists. 2005-GB2448 WO2006000759, 20050621
11. Hulme C, Tempest P, Ma V, Nixey T, Balow G (2005) Preparation of tetrazolylmethylpiperazines as melanin concentrating hormone receptor antagonists. 2004-US26021 WO2005019167, 20040811
12. Rinehart KL, Holt TG, Fregeau NL, Stroh JG, Keifer PA, Sun F, Li LH, Martin DG (2002) Ecteinascidins 729, 743, 745, 759A, 759B, and 770: potent antitumor agents from the Caribbean tunicate Ecteinascidia turbinata. J Org Chem 55(15):4512–4515
13. Chen J, Chen X, Bois-Choussy M, Zhu J (2005) Total synthesis of ecteinascidin 743. J Am Chem Soc 128(1):87–89
14. Rikimaru K, Mori K, Kan T, Fukuyama T (2005) Synthetic studies on (-)-lemonomycin: stereocontrolled construction of the 3,8-diazabicyclo[3.2.1] skeleton. Chem Commun (3) 394–396
15. He H, Shen B, Carter GT (2000) Structural elucidation of lemonomycin, a potent antibiotic from *Streptomyces candidus*. Tetrahedron Lett 41(13):2067–2071
16. Fischer PM (2003) Diketopiperazines in peptide and combinatorial chemistry. J Pept Sci 9(1):9–35

17. Horton DA, Bourne GT, Smythe ML (2002) Exploring privileged structures: the combinatorial synthesis of cyclic peptides. Mol Divers 5(4):289–304
18. Martins MB, Carvalho I (2007) Diketopiperazines: biological activity and synthesis. Tetrahedron 63(40):9923–9932
19. Dinsmore CJ, Beshore DC (2002) Recent advances in the synthesis of diketopiperazines. Tetrahedron 58(17):3297–3312
20. Srivastava S, Beck B, Herdtweck E, Khoury K, Dömling A (2009) A novel delta-thiolactone scaffold by a versatile intramolecular multicomponent reaction. Heterocycles 77(2):731–738
21. Giovenzana GB, Tron GC, Paola SD, Menegotto IG, Pirali T (2006) A mimicry of primary amines by bis-secondary diamines as components in the Ugi four-component reaction13. Angew Chem 118(7):1117–1120
22. Rossen K, Sager J, DiMichele LM (1997) An efficient and versatile synthesis of piperazine-2-carboxamides. Tetrahedron Lett 38(18):3183–3186
23. Dömling A, Beck B, Fuchs T, Yazbak A (2006) Parallel synthesis of arrays of amino-acid-derived isocyanoamides useful as starting materials in IMCR. J Comb Chem 8(6):872–880
24. Mahalingam B, Wang Y-F, Boross PI, Tozser J, Louis JM, Harrison RW, Weber IT (2004) Crystal structures of HIV protease V82A and L90M mutants reveal changes in the indinavir-binding site. Eur J Biochem 271(8):1516–1524
25a. Rossen K, Pye PJ, DiMichele LM, Volante RP, Reider PJ (1998) An efficient asymmetric hydrogenation approach to the synthesis of the Crixivan (R) piperazine intermediate. Tetrahedron Lett 39(38):6823–6826
25b. Askin D, Eng KK, Rossen K, Purick RM, Wells KM, Volante RP, Reider PJ (1994) Highly diastereoselective reaction of a chiral, non-racemic amide enolate with (*S*)-glycidyl tosylate. Synthesis of the orally active HIV-1 protease inhibitor L-735, 524. Tetrahedron Lett 35(5):673–676
26. Keung W, Bakir F, Patron AP, Rogers D, Priest CD, Darmohusodo V (2004) Novel alpha-amino amidine synthesis via scandium(III) triflate mediated 3CC Ugi condensation reaction. Tetrahedron Lett 45(4):733–737
27. Shaabani A, Maleki A, Moghimi-Rad J (2007) A novel isocyanide-based three-component reaction: synthesis of highly substituted 1, 6-dihydropyrazine-2, 3-dicarbonitrile derivatives. J Org Chem 72(16):6309–6311
28. Faggi C, Garcia-Valverde M, Marcaccini S, Pepino R, Pozo MC (2003) Studies on isocyanides and related compounds: a facile synthesis of 1,6-dihydro-6-oxopyrazine-2-carboxylic acid derivatives via Ugi four-component condensation. Synthesis (10) 1553–1558
29. Cheng JF, Chen M, Arrhenius T, Nadzan A (2002) A convenient solution and solid-phase synthesis of delta(5)-2-oxopiperazines via N-acyliminium ions cyclization. Tetrahedron Lett 43(36):6293–6295
30. Ilyin AP, Trifilenkov AS, Kurashvili ID, Krasavin M, Ivachtchenko AV (2005) One-step construction of peptidomimetic 5-carbamoyl-4-sulfonyl-2-piperazinones. J Comb Chem 7(3):360–363
31. Hulme C, Cherrier MP (1999) Novel applications of ethyl glyoxalate with the Ugi MCR. Tetrahedron Lett 40(29):5295–5299
32. Hulme C, Peng J, Louridas B, Menard P, Krolikowski P, Kumar NV (1998) Applications of N-BOC-diamines for the solution phase synthesis of ketopiperazine libraries utilizing a Ugi/De-BOC/Cyclization (UDC) strategy. Tetrahedron Lett 39(44):8047–8050
33. Rhoden CRB, Rivera DG, Kreye O, Bauer AK, Westermann B, Wessjohann LA (2009) Rapid Access to N-substituted diketopiperazines by one-pot Ugi-4CR/deprotection + activation/cyclization (UDAC). J Comb Chem 11(6):1078–1082
34. Marcaccini S, Pepino R, Pozo MC (2001) A facile synthesis of 2,5-diketopiperazines based on isocyanide chemistry. Tetrahedron Lett 42(14):2727–2728

35. Wyatt PG, Allen MJ, Borthwick AD, Davies DE, Exall AM, Hatley RJD, Irving WR, Livermore DG, Miller ND, Nerozzi F, Sollis SL, Szardenings AK (2005) 2,5-diketopiperazines as potent and selective oxytocin antagonists - 1: identification, stereochemistry and initial SAR. Bioorg Med Chem Lett 15(10):2579–2582
36. Sollis SL (2005) Short and novel stereospecific synthesis of trisubstituted 2,5-diketopiperazines. J Org Chem 70(12):4735–4740
37. Borthwick AD, Davies DE, Exall AM, Hatley RJD, Hughes JA, Irving WR, Livermore DG, Sollis SL, Nerozzi F, Valko KL, Allen MJ, Perren M, Shabbir SS, Woollard PM, Price MA (2006) 2, 5-Diketopiperazines as potent, selective, and orally bioavailable oxytocin antagonists. 3. Synthesis, pharmacokinetics, and in vivo potency. J Med Chem 49(14): 4159–4170
38. Borthwick AD, Davies DE, Exall AM, Livermore DG, Sollis SL, Nerozzi F, Allen MJ, Perren M, Shabbir SS, Woollard PM, Wyatt PG (2005) 2, 5-Diketopiperazines as potent, selective, and orally bioavailable oxytocin antagonists. 2. Synthesis, chirality, and pharmacokinetics. J Med Chem 48(22):6956–6969
39. Liddle J, Allen MJ, Borthwick AD, Brooks DP, Davies DE, Edwards RM, Exall AM, Hamlett C, Irving WR, Mason AM, McCafferty GP, Nerozzi F, Peace S, Philp J, Pollard D, Pullen MA, Shabbir SS, Sollis SL, Westfall TD, Woollard PM, Wu C, Hickey DMB (2008) The discovery of GSK221149A: a potent and selective oxytocin antagonist. Bioorg Med Chem Lett 18 (1):90–94
40. Habashita H, Kokubo M, Hamano S, Hamanaka N, Toda M, Shibayama S, Tada H, Sagawa K, Fukushima D, Maeda K, Mitsuya H (2006) Design, synthesis, and biological evaluation of the combinatorial library with a new spirodiketopiperazine scaffold. Discovery of novel potent and selective low-molecular-weight CCR5 antagonists. J Med Chem 49(14):4140–4152
41. Szardenings AK, Antonenko V, Campbell DA, DeFrancisco N, Ida S, Shi LH, Sharkov N, Tien D, Wang YW, Navre M (1999) Identification of highly selective inhibitors of collagenase-1 from combinatorial libraries of diketopiperazines. J Med Chem 42(8):1348–1357
42. Cho S, Keum G, Kang SB, Han SY, Kim Y (2003) An efficient synthesis of 2, 5-diketopiperazine derivatives by the Ugi four-center three-component reaction. Mol Divers 6(3–4): 283–286
43. Rhoden CRB, Westermann B, Wessjohann LA (2008) One-pot multicomponent synthesis of N-substituted tryptophan-derived diketopiperazines. Synthesis (Stuttg) (13):2077–2082
44. Szardenings AK, Burkoth TS, Lu HH, Tien DW, Campbell DA (1997) A simple procedure for the solid phase synthesis of diketopiperazine and diketomorpholine derivatives. Tetrahedron 53(19):6573–6593
45. Lin Q, Blackwell HE (2006) Rapid synthesis of iketopiperazine macroarrays via Ugi four-component reactions on planar solid supports. Chem Commun (27):2884–2886
46. Hulme C, Morrissette MM, Volz FA, Burns CJ (1998) The solution phase synthesis of diketopiperazine libraries via the Ugi reaction: novel application of Armstrong's convertible isonitrile. Tetrahedron Lett 39(10):1113–1116
47. Campbell J, Blackwell HE (2009) Efficient construction of diketopiperazine macroarrays through a cyclative-cleavage strategy and their evaluation as luminescence inhibitors in the bacterial symbiont *Vibrio fischeri*. J Comb Chem 11(6):1094–1099
48. Ugi I, Hörl W, Hanusch-Kompa C, Schmid T, Herdtweck E (1998) MCR 6: chiral 2, 6-piperazinediones via Ugi reactions with alpha-amino acids, carbonyl compounds, isocyanides and alcohols. Heterocycles 47(2):965–975
49. Bachand B, Tarazi M, St-Denis Y, Edmunds JJ, Winocour PD, Leblond L, Siddiqui MA (2001) Potent and selective bicyclic lactam inhibitors of thrombin. Part 4: transition state inhibitors. Bioorg Med Chem Lett 11(3):287–290
50. Hanusch-Kompa C, Ugi I (1998) Multi-component reactions 13: synthesis of [gamma]-lactams as part of a multiring system via Ugi-4-centre-3-component reaction. Tetrahedron Lett 39(18):2725–2728

51. Golebiowski A, Klopfenstein SR, Shao X, Chen JJ, Colson A-O, Grieb AL, Russell AF (2000) Solid-supported synthesis of a peptide β-turn mimetic. Org Lett 2(17):2615–2617
52. Golebiowski A, Jozwik J, Klopfenstein SR, Colson A-O, Grieb AL, Russell AF, Rastogi VL, Diven CF, Portlock DE, Chen JJ (2002) Solid-supported synthesis of putative peptide β-turn mimetics via Ugi reaction for diketopiperazine formation. J Comb Chem 4(6):584–590
53. Nixey T, Tempest P, Hulme C (2002) Two-step solution-phase synthesis of novel quinoxalinones utilizing a UDC (Ugi/de-Boc/cyclize) strategy. Tetrahedron Lett 43(9):1637–1639
54. Nenajdenko VG, Reznichenko AL, Balenkova ES (2007) Diastereoselective Ugi reaction without chiral amines: the synthesis of chiral pyrroloketopiperazines. Tetrahedron 63: 3031–3041
55. Nixey T, Kelly M, Semin D, Hulme C (2002) Short solution phase preparation of fused azepine-tetrazoles via a UDC (Ugi/de-Boc/cyclize) strategy. Tetrahedron Lett 43(20): 3681–3684
56. Nixey T, Kelly M, Hulme C (2000) The one-pot solution phase preparation of fused tetrazole-ketopiperazines. Tetrahedron Lett 41(45):8729–8733
57. Bienaym H, Bouzid K (1998) Synthesis of rigid hydrophobic tetrazoles using an Ugi multicomponent heterocyclic condensation. Tetrahedron Lett 39(18):2735–2738
58. Neochoritis C, Stephanidou-Stephanatou J, Tsoleridis CA (2009) Heterocyclizations via TosMIC-based multicomponent reactions: a new approach to one-pot facile synthesis of substituted quinoxaline derivatives. Synlett 2009(02):302–305
59. Shaabani A, Maleki A, Mofakham H, Khavasi HR (2008) Novel isocyanide-based three-component synthesis of 3, 4-dihydroquinoxalin-2-amine derivatives. J Comb Chem 10 (2):323–326
60. Knudsen LB, Kiel D, Teng M, Behrens C, Bhumralkar D, Kodra JT, Holst JJ, Jeppesen CB, Johnson MD, de Jong JC, Jorgensen AS, Kercher T, Kostrowicki J, Madsen P, Olesen PH, Petersen JS, Poulsen F, Sidelmann UG, Sturis J, Truesdale L, May J, Lau J (2007) Small-molecule agonists for the glucagon-like peptide 1 receptor. Proc Natl Acad Sci 104(3):937–942
61. Erb W, Neuville L, Zhu JP (2009) Ugi-post functionalization, from a single set of Ugi-adducts to two distinct heterocycles by microwave-assisted palladium-catalyzed cyclizations: tuning the reaction pathways by ligand switch. J Org Chem 74(8):3109–3115
62. Nikulnikov M, Tsirulnikov S, Kysil V, Ivachtchenko A, Krasavin M (2009) *tert*-Butyl isocyanide as a convertible reagent in Ugi reaction: microwave-assisted preparation of 5,6-dihydropyrazolo[1, 5-a]pyrazine-4, 7-diones. Synlett 2009(02):260–262
63. McTigue MA, Williams DR, Tainer JA (1995) Crystal structures of a schistosomal drug and vaccine target: glutathione S-transferase from *Schistosoma japonica* and its complex with the leading antischistomal drug praziquantel. J Mol Biol 246(1):21–27
64. Dömling A, Khoury K (2010) Praziquantel and schistosomiasis. Angew Chem Int Ed (in press)
65. Dömling A (2009) Preparation of praziquantel. 2009-EP2042 WO2009115333, 20090319
66. Liu H, Dömling A (2010) MCR synthesis and biological evaluation of novel praziquantel derivatives. Submitted
67. Liu H, Dömling A (2009) Efficient and diverse synthesis of indole derivatives. J Org Chem 74(17):6895–6898
68. Wang W, Herdtweck E, Dömling A (2010) Polycyclic indole alkaloid-type compounds by MCR. Chem Commun 46(5):770–772
69. El Kaim L, Gageat M, Gaultier L, Grimaud L (2007) New Ugi/Pictet–Spengler multicomponent formation of polycyclic diketopiperazines from isocyanides and alpha-keto acids. Synlett 2007(03):0500–0502
70. Krasavin M, Shkavrov S, Parchinsky V, Bukhryakov K (2009) Imidazo[1,2-a]quinoxalines accessed via two sequential isocyanide-based multicomponent reactions. J Org Chem 74(6): 2627–2629

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α-Acidic Isocyanides in Multicomponent Chemistry

Niels Elders, Eelco Ruijter, Valentine G. Nenajdenko, and Romano V. A. Orru

Abstract The exceptional reactivity connected to isocyanides, as discussed here, is unrivaled by other functional groups and has led to many synthetically useful novel reactions. This chapter deals with multicomponent reactions (MCRs) involving isocyanides as one of the inputs for the synthesis of heterocycles. We focus on the α-acidic isocyanides, which are an appealing class of versatile building blocks. Their use has led to a range of versatile isocyanide-based MCRs (IMCRs), as will become clear from this chapter. From a set of only three different types of α-acidic isocyanides, sometimes inspired by the early work of Schöllkopf and van Leusen, a wide range of novel reaction paths were discovered in the last decade. In this way a plethora of mainly heterocyclic scaffolds can be synthesized in a straightforward fashion. The IMCRs discussed are usually robust reactions that can be easily combined in very short sequences with other complexity-generating processes, like cycloadditions or even additional MCRs, leading to yet other classes of heterocyclic motifs. This offers exciting opportunities for library design of highly functionalized heterocyclic scaffolds employing diversity-oriented synthesis approaches.

Keywords Complexity · Diversity · Isocyanides · Multicomponent reactions · Synthesis

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Contents

Abbreviations

Ac	Acetyl
Ar	Aryl
bmim	1-Butyl-3-methylimidazolium
Bn	Benzyl
Bu	Butyl
*c*hex	Cyclohexyl
CR	Component reaction
d	Day(s)
DABCO	1,4-Diazabicyclo[2.2.2]-octane
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCM	Dichloromethane
DHOP	Dihydrooxazolopyridine
DMF	Dimethylformamide
DOS	Diversity-oriented synthesis
e.g.	*exempli gratia* (for example)
eq.	Equivalent(s)
Et	Ethyl
EWG	Electron withdrawing group
h	Hour(s)
i.e.	*id est* (that is)
*i*Bu	Isobutyl
IMCRs	Isocyanide based multicomponent reactions
*i*Pr	Isopropyl
MCR	Multicomponent reaction
Me	Methyl
*n*Bu	Normal butyl

NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
Ph	Phenyl
Pr	Propyl
py	Pyridine
RT	Room temperature
SRR	Single reactant replacement
TBAF	Tetrabutylammonium fluoride
*t*Bu	tert-Butyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl, 4-methylphenyl
TosMIC	*p*-Toluenesulfonylmethyl isocyanide
Ts	Tosyl, 4-toluenesulfonyl
vL-3CR	van Leusen 3-component reaction

1 Introduction

During the past 160 years, multicomponent reactions (MCRs) [1–12] developed from isolated reaction examples to key methods in natural product synthesis, in diversity-oriented synthesis (DOS), and in the construction of focused libraries of bioactive compounds both in the pharmaceutical and agrochemical industry. By definition, MCRs are one-pot processes in which at least three substrates react to a single product that contains essentially all the atoms of the starting materials. Ideally, the substrates can be mixed simultaneously, resulting in a single-operation procedure. Despite early examples of MCRs like the Strecker (1850) [13, 14], Hantzsch (1882) [15], Biginelli (1891) [16, 17], and Mannich reaction (1912) [18], true cornerstone examples of MCRs were introduced only much later with the reports of the Passerini (1921) [19, 20] and Ugi reactions (1959) [21, 22]. The latter are the most prominent representatives of a subclass of MCRs, the isocyanide-based MCRs (IMCRs) [11] (Figs. 1 and 2).

Since their first isolation (Lieke, 1859 [23]), exceptional reactivity has been observed for isocyanides. For example, their easy formation of radicals and their ability to react both as a nucleophile and as an electrophile at the same atom (α-addition) is unrivaled by other functional groups. Although they are overall in the minority, IMCRs are considered to be more versatile and diverse than other MCRs.

A third property that characterizes the reactivity of isocyanides is their α-acidity. Introduction of an electron withdrawing group (EWG) at the α-position of isocyanides considerably lowers the pK_a-value of the α-hydrogens. Consequently, α-acidic isocyanides have, besides the already unusual reactivity of the isocyanide functional group, an additional nucleophilic center upon proton abstraction. This opens different reaction paths towards a range of interesting products, including heterocycles.

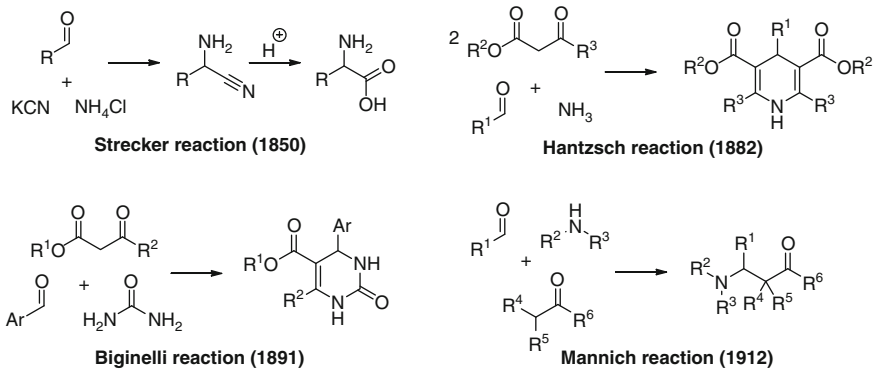


Fig. 1 Early examples of multicomponent reactions

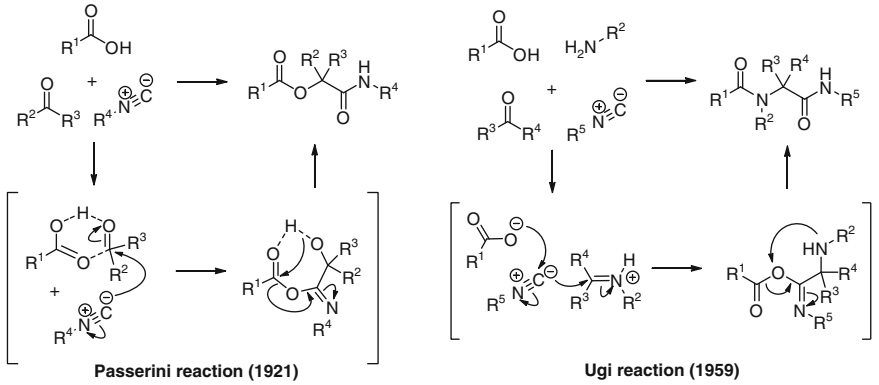


Fig. 2 The Passerini and Ugi reaction, the most prominent examples of the isocyanide-based multicomponent reactions

Among the α-acidic isocyanides, isocyano esters (**1**) (for the first isolated example of α-acidic isocyano ester see [24]), isocyano amides (**2**) (for the first isolated example of α-acidic isocyano amide see [25]), and arylsulfonyl methyl isocyanides (**3**) (for the first report of TosMIC see [26]) have been studied predominantly, and therefore this mini review will mainly focus on the MCRs involving these species.

2 Synthesis of α-Acidic Isocyanides

Several synthetic routes for the construction of α-acidic isocyanides (**1**–**3**) have been reported. The most general methods are depicted in Fig. 3. For example, because of the acidity of the α-protons, α-substituted α-acidic isocyanides can be prepared from their (commercially available) α,α-unsubstituted analogs (**4**) by deprotonation

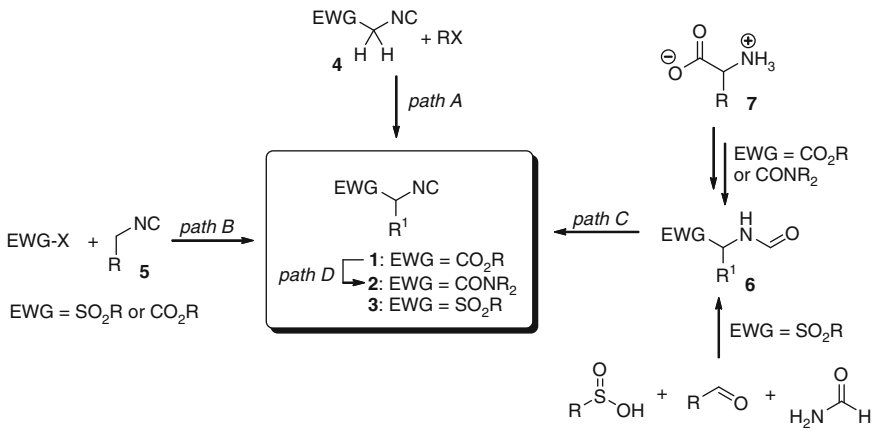


Fig. 3 General methods for the preparation of isocyano esters (**1**), isocyano amides (**2**), and arylsulfonyl methyl isocyanides (**3**) (R = alkyl and/or H)

followed by alkylation under basic conditions (*path A*). Although dialkylation is a problem often observed for all three classes of α-acidic isocyanides [27–29], several methods for the selective formation of monoalkylated derivatives have been described in literature. For arylsulfonyl methyl isocyanides (**3**), phase transfer catalysis using tetraalkylammonium halides and NaOH in DCM is often the method of choice, although this method is reported only for the use of primary halides [30].

Monoalkylation of isocyano amides can be accomplished by a Michael reaction with an α,β-unsaturated ketone in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) in THF, as indicated by Ito in 1989 [31]. In addition, Zhu recently reported the selective monoalkylation of isocyano amides by using $CsOH{\cdot}H_2O$ (1.5 eq.) in MeCN at 0°C [32]. A slight excess of alkylating agent (1.2 eq.) can be used under the optimized conditions, which generates the monoalkylated products for a wide range of primary halides (X = Br or I) after 24 h.

Monoalkylation of α-isocyano esters by using tert-butyl isocyano acetate (R^1 = *t*Bu) has been reported by Schöllkopf [28, 33]. Besides successful examples using primary halides, 2-iodopropane has been reported to produce the α-alkylated product (**1**) as well by this method (KO*t*Bu in THF). In the years 1987–1991, Ito reported several methods for the monoalkylation of isocyano esters, including the Michael reaction under TBAF catalysis as described earlier [31], Claisen rearrangements [34], and asymmetric Pd-catalyzed allylation [35]. Finally, Zhu recently reported the first example of the introduction of an aromatic substituent by means of a nucleophilic aromatic substitution ($CsOH{\cdot}H_2O$, MeCN, 0°C) in the synthesis of methyl α-isocyano *p*-nitrophenylacetate [36].

Arylsulfonyl methyl isocyanides (**3**) and isocyano esters (**1**) can also be prepared by the deprotonation of alkylisocyanides (**5**) by strong bases (*n*BuLi or NaH) followed by the addition of TosF and dialkyl carbonates or ethyl chloroformate, respectively (*path B*) [37, 38]. However, the use of "small" and foul-smelling alkyl isocyanides makes this route less attractive.

Like isocyanides, in general, α-acidic isocyanides can be synthesized from the corresponding formamides (**6**) by the usual methods reported for dehydration (*path C*, e.g., (tri)phosgene or $POCl_3$ under basic conditions). In the case of arylsulfonyl methyl isocyanides, the corresponding formamides can be generated using a 3-CR between sulfinates (or sulfinic acids), aldehydes, and formamide while heating in formic acid. Using this procedure, first reported in 1972 by Olijnsma [39], a wide range of (optically pure) sulfinates can be converted to their corresponding arylsulfonyl methyl isocyanides (**3**) [39–41]. The scope according to the aldehyde input, however, remained limited to formaldehyde and benzaldehyde. Using a modified method reported in 1996 by Sisko (+TMSCl, solvent = toluene:MeCN (1:1), 50°C, 5 h), the reaction is reported to work well for a wide range of aldehydes, generating the formamides in multikilogram scale [42].

Formamido esters and amides can be generated in two steps starting from (natural) α-amino acids (**7**). Owing to the wide availability of optically pure formamides, the synthesis of optically pure α-substituted α-acidic isocyano amides (**2**) and esters (**1**) has been envisioned using the dehydration route.

Although the synthesis of optically active α-chiral α-acidic isocyano esters has been reported in literature by the dehydration of the corresponding formamides using $POCl_3$ [43], phosgene [44, 45], diphosgene [46–50], or triphosgene [51], the isolation of such compounds is not trivial. Limited information about the enantiomeric excess of the α-chiral center is generally provided, although racemization during the dehydration step is known to cause major problems [52]. In 2009, the research group of Danishefsky compared several procedures and confirmed that the traditional method using triphosgene and NMM at −78 to −30°C gave optimal results ($POCl_3/Et_3N$ gave full racemization) [53]. Using this mild protocol, several α-alkyl substituted isocyano esters could be synthesized in high yield, with enantiomeric ratios up to >99:1.

The synthesis of α-chiral isocyano amides has also been reported using various dehydration methods [47, 53–66]. Because of the lower acidity of the α-proton in α-isocyano amides, high stereoinductions can be obtained using relatively harsh dehydration methods ($POCl_3/Et_3N$, −20°C) [62]. However, the triphosgene/NMM protocol remains the method of choice [53].

Finally, isocyano esters can be converted to the corresponding amides upon treatment with an amine (typically just stirring in MeOH) [32, 43, 47, 67–71]. Although this procedure (*path D*) works well for α,α-unsubstituted isocyano esters and for a wide variety of primary and secondary amines, steric bulk around both the α-carbon and the amine component should be avoided.

3 Reactivity of α-Acidic Isocyanides

α-Acidic isocyanides of type **1**, **2**, and **3** (for an excellent review on the synthetic use of tosylmethyl isocyanide (Tos-MIC) see[72]) have found widespread application in the construction of heterocyclic compounds (Figs. 4 and 5). Most examples

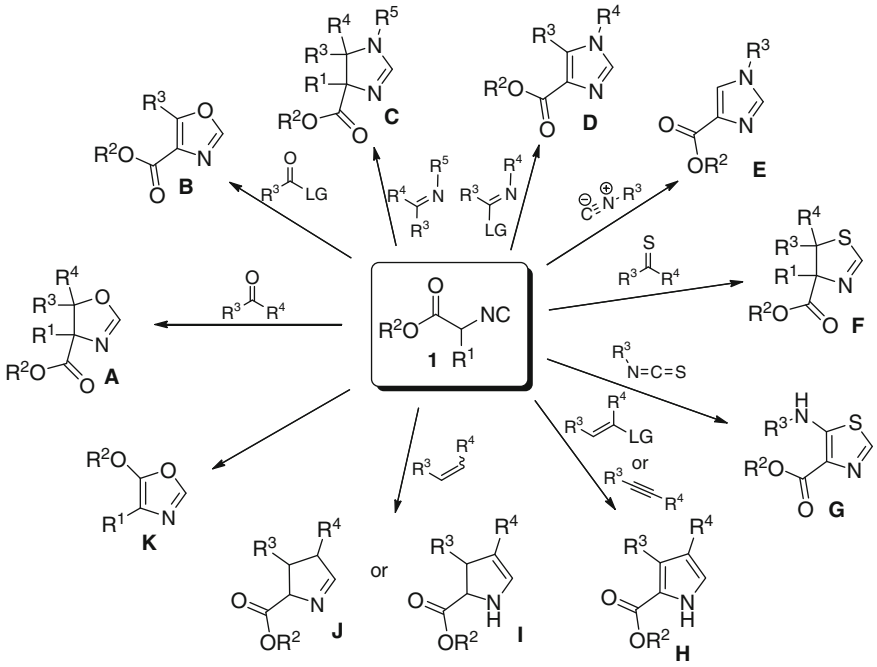


Fig. 4 Selected examples for the formation of heterocycles starting from isocyano esters

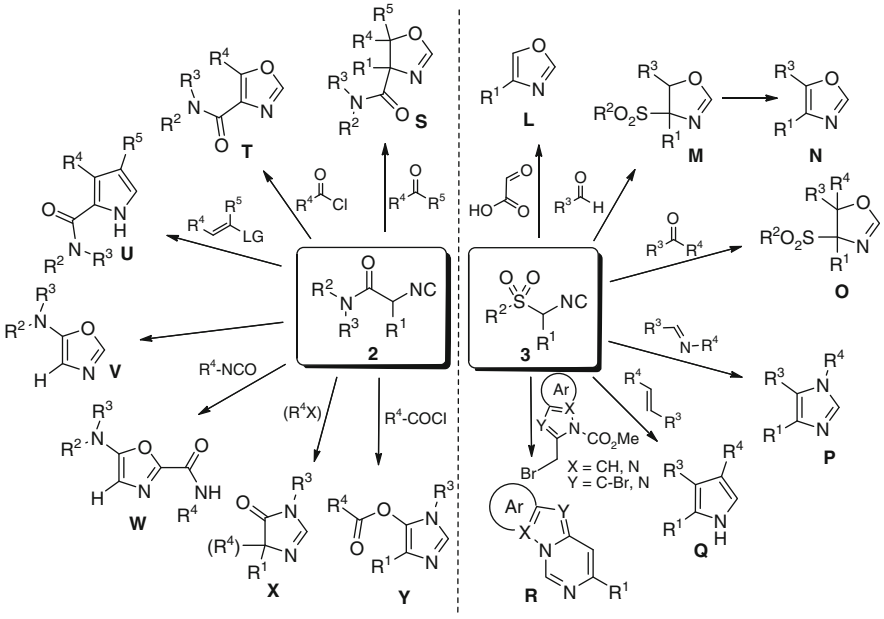


Fig. 5 Selected examples for the formation of heterocycles starting from either isocyano amides (**2**) or sulfonylmethyl isocyanides (**3**)

reported in literature involve [3 + 2] cycloadditions with carbon heteroatom double bonds under (highly) basic conditions. For example, cycloadditions of deprotonated isocyano esters (for a review on applications of α-metalated isocyanides see [73]) (Fig. 4) with C=O, C=N, or C=S double bonds yield oxazolines (**A**) [74, 75], imidazolines (**C**) [76–79], and thiazolines (**F**) [80] ring systems, respectively. The corresponding aromatized heterocyclic ring systems **B** (oxazoles) [81–85] and **D** (imidazoles) [86–88] can be obtained when the leaving groups are attached to the carbon heteroatom double bonds. In addition, imidazoles of type **E** can be obtained by the cycloaddition of the anion of **1** with other isocyanides [89–91], although the number of diversity points via this procedure is reduced to two. Thiazoles (**G**) can be obtained by the treatment of **1** with isothiocyanates, under basic conditions [92–94].

Cycloadditions of deprotonated **1** with electron deficient alkenes as dipolarophiles yielding pyrroles (**H**) could be performed using isocyanoalkenes [95–97], nitroalkenes [98–102], α,β-unsaturated sulfones [103–106], and α,β-unsaturated nitriles [107]. Even alkynes [108–110] could be used to give the pyrrole (**H**) ring system. Similar cycloadditions of **1** with activated olefins yielding pyrrolines (**I** and **J**) is accomplished upon Cu_2O catalysis [74], AgOAc catalysis [89, 111], or organocatalysis [111], although the uncatalyzed reaction using [60]fullerene has also been reported [112].

Finally, treatment of α-acidic isocyano esters (**1**) with base in the absence of other reagents is reported to furnish 5-alkoxy oxazoles (**K**) via ring closure [113, 114].

As in the case of isocyano esters (**1**, Fig. 4.), isocyano amides (**2**) and arylsulfonyl methyl isocyanides (**3**) have also found widespread application in the construction of heterocyclic compounds (Fig. 5).

For arylsulfonyl methyl isocyanides (**3**), [3 + 2] cycloadditions with aldehydes yielding 4,5-disubstituted oxazoles (**N**) have been reported [115]. The cycloaddition takes place in the same manner as with the use of isocyano esters (**A**, $R^3 = H$); however, owing to the facile elimination of RSO_2H, the reaction typically does not stop at the trisubstituted oxazoline (**M**) stage [115, 116]. With the use of ketones, however, elimination of RSO_2H is blocked and consequently the corresponding oxazolines (**O**) can be isolated instead [40, 117]. Monosubstituted oxazoles of type (**L**) can be obtained by using glyoxylic acid [118]. Imidazoles (**P**) and pyrroles (**Q**) can be obtained by using aldimines [119] and alkenes [115, 120, 121], respectively. Finally, azopyrimidine derivatives (**R**) could be obtained by the unprecedented reactivity of arylsulfonyl methyl isocyanide toward *N*-protected bromomethylazoles under phase transfer conditions [122].

For isocyano amides (**2**), [3 + 2] cycloadditions with carbonyl compounds yielding oxazolines (**S**) [123, 124] and oxazoles (**T**) [125] have been reported. In addition, the formation of pyrroles (**U**) starting from nitro ([98, 100]; for examples using Weinreb amides see [126]) or isocyanoalkenes [97] have been reported. In addition to the [3 + 2] cycloadditions described earlier, intramolecular ring closures of α-acidic isocyano amides (**2**) have also been described. For example, unsubstituted isocyano amides ($R^1 = H$) readily cyclize via the amide oxygen, resulting in the formation of 2*H*-5-aminooxazole (**V**) [127], while the addition of an isocyanate results

in the formation of the 2-amido analog **W** [128]. Cyclization via the amide nitrogen (R^2 = H) results in the formation of imidazolin-5-one (**X**) [129, 130], where an additional substituent may be added at C4 upon alkylation. When the additional substituent is not introduced, addition of an acid chloride provides **Y** [130].

4 MCRs Involving α-Acidic Isocyanides

Besides numerous applications of α-acidic isocyanides in classical IMCRs, such as the Ugi and Passerini reaction, the presence of an α-acidic proton enables other reaction paths and, subsequently, the development of novel MCRs. Here we focus on novel MCRs involving α-acidic isonitriles that have been described in literature since 1998.

4.1 van Leusen Imidazole MCR

The first MCR involving the explicit use of α-acidic isonitriles was reported in 1998 by Sisko [131]. The reaction involves the cycloaddition of a TosMIC derivative (**8**) to an (in situ-generated) imine (**10**) followed by the elimination of *p*-toluenesulfinic acid (TsH) as described in 1977 by van Leusen for preformed imines (Fig. 5, scaffold **P**) [119]. Although several potential pitfalls for the conversion of the traditional van Leusen [3 + 2] cycloaddition to the so-called "van Leusen three-component reaction (vL-3CR)" of imidazoles were expected by the author,[1] simply stirring the aldehyde and amine for 20 min followed by addition of the TosMIC derivative and base resulted in the isolation of the corresponding imidazole (**9**) in high yield [131].

Removal of water from the reaction mixture by adding $MgSO_4$ of molecular sieves did not have a major effect on the reaction outcome. Further optimization studies indicated that the reaction works well in a wide range of common organic solvents (EtOAc, THF, MeCN, DMF, DCM, and MeOH) and only a mild base like piperazine, morpholine, or K_2CO_3 is required to promote the reaction. A wide variety of functional groups are tolerated, including alcohols, esters, alkenes, and even additional aldehydes, without the need of protecting groups. In addition to the broad scope regarding the amine and carbonyl input, various α-aryl (and biaryl)-substituted TosMICs (**8**) could be used in the vL-3CR. Remarkably, despite their successful application in the stepwise [3 + 2] cycloaddition [119], experiments using α-alkyl-substituted TosMICs (R^1 = alkyl) and TosMIC itself (**8a**, R^1 = H) showed to be quite unreactive in the multicomponent approach (In the original

[1] Initially, the presence of water and competition between the aldehyde and imine were expected to cause problems in the reaction setup.

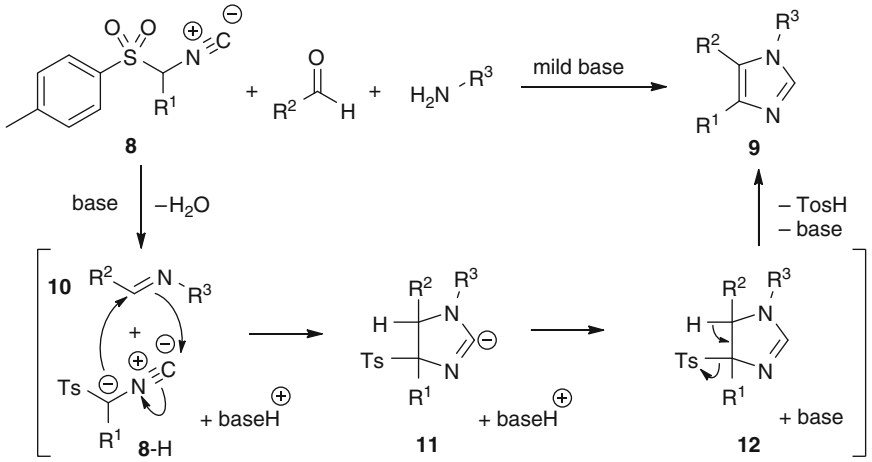


Fig. 6 Two representative examples of the application of the van Leusen 3-CR in the synthesis of biologically active compounds

3 + 2 cycloaddition, NaH as a base was found to be essential [119]. Recently, allyl TosMIC was found to give the desired oxazole although the yield was moderate (32%); see [132]), probably due to the increased pK_a of the α-proton.

The broad substrate scope for vL-3CR for the synthesis of imidazoles (**9**) in combination with the easy and straightforward reaction setup resulted in several examples of this MCR as a key step in the development of biologically active compounds. For example, Sisko initially developed the vL-3CR for the synthesis of **9a** [131], which is a representative of a general class of compounds that exhibit potent binding affinities for p38 MAP kinase, a protein kinase that appears to be involved in an inflammation regulatory pathway [133]. In addition, the construction of a focused library of about 60 bioactive trisubstituted imidazoles by Dömling resulted in the design of novel α-helix mimetics in a single reaction step [134]. Initial screen results indicated the disruption of the interaction between Bcl-w and Bak-BH3 peptide, which could constitute an effective and selective way for the treatment of cancer, making this novel class of lead molecules interesting and well suited compounds for further optimization (Fig. 7).

4.2 2,6,7-Trisubstituted Quinozaline MCR

In 2009, the MCR between *o*-phenylenediamines (**13**), aldehydes, and TosMIC (**8a**) which yields 2,6,7-trisubstituted quinozalines (**14**) has been described [135]. The mechanism probably proceeds via the initial attack of deprotonated TosMIC at the in situ-generated imine affording intermediate **16** (Fig. 8). Apparently, attack of the secondary amine in **16** at the terminal isonitrile C-atom that yields the

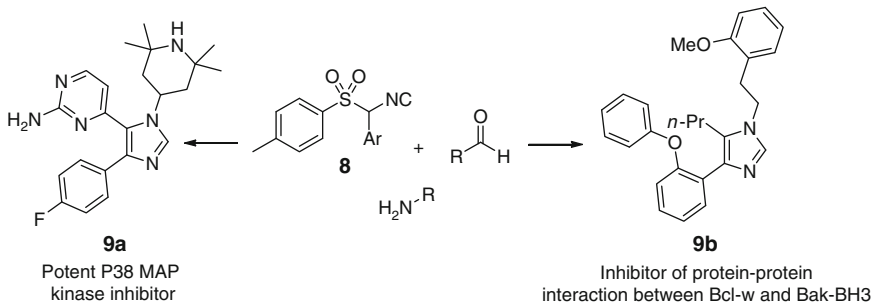


Fig. 7 Formation of 2,6,7-trisubstituted quinozalines (**14**) from the MCR between *o*-phenylenediamines (**13**), aldehydes, and TosMIC (**8a**)

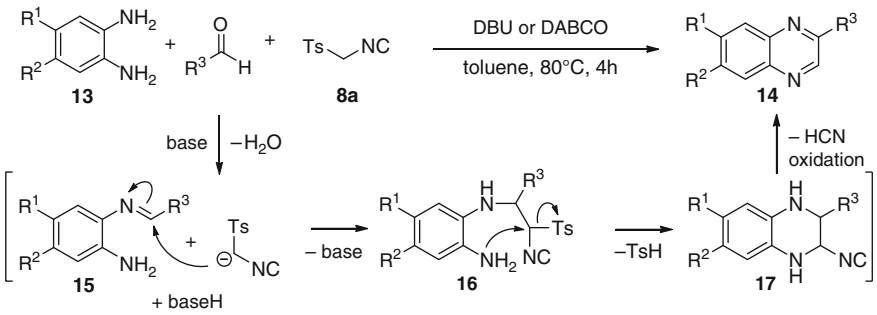


Fig. 8 Reaction mechanism for the van Leusen 3-CR toward imidazoles

corresponding imidazole (vL-3CR, Fig. 6) is not favored in this case. Instead, S_N2 substitution of Ts by the NH_2 at the α-carbon followed by elimination of HCN and oxidation under the reaction conditions used afforded product **14**. Unfortunately, only reaction entries using aromatic aldehydes and the parent TosMIC input have been reported. However, isolation of the otherwise difficult-to-access quinozaline derivatives in moderate-to-high yield (46–91%) in combination with the unusual reactivity of TosMIC (contributing only CH to the reaction) makes this MCR appealing for further investigations.

4.3 4,5-Disubstituted Oxazole MCR

Also in 2009, an elegant combination of two original van Leusen reactions was reported, leading to a MCR toward 4,5-disubstituted oxazoles (**19**) [136]. The MCR involves the base-induced mono-alkylation of TosMIC (**8a**) followed by the formal cycloaddition with an aldehyde (Fig. 9). Although dialkylation is a problem often

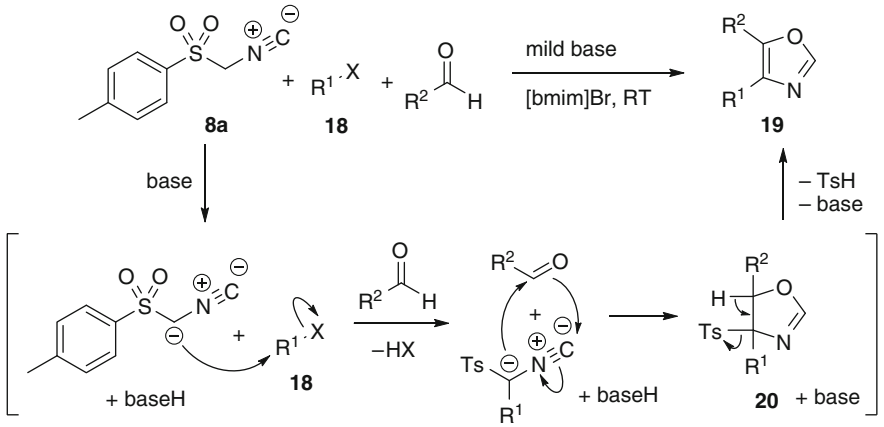


Fig. 9 MCR between TosMIC (**8a**), aliphatic halides (**18**), and aldehydes which yields 4,5-disubstituted oxazoles (**19**)

observed with TosMIC, selecting K_2CO_3 as the base while performing the reaction in an ionic liquid resulted in the clean conversion to the monoalkylated TosMIC derivative in 12 h. Owing to the similar basic reaction conditions requirement for the van Leusen synthesis of oxazoles, the second reaction step could be performed in the same pot, which gives the 4,5-disubstituted oxazole (**19**) in high yields ($\geq$75%). The scope of compatible aldehyde inputs turned out to be very broad, including aliphatic, aromatic, and heteroaromatic carbonyl entries. Both primary and secondary aliphatic halides (X = Cl, Br, I) could be used, but naturally, the S_N2-type reaction using tertiary halides proved to be unsuccessful. Absolute anhydrous conditions were found not to be necessary, which simplifies the experimental procedure. In addition, the ionic liquid could be reused at least 5 times with only a slight decrease in the reaction yield after each run.

4.4 Nitropyrrole MCR

The reactivity of TosMIC and α-acidic isocyano esters toward nitroalkenes, developed by van Leusen [120, 121] and Zard [98, 100], respectively, has also been modified to a 3-CR in 2009 (Fig. 10) [137]. In this MCR approach toward nitropyrroles (**23**), TosMIC is treated with 2.0 eq. of *n*BuLi[2] at −78°C followed by the addition of a carbonochloridate (**21**) generating deprotonated 2-isocyano-2-tosylacetate (**24**). Reacting **24** with the nitroalkene **22** (RT, 2–4 days) resulted in the formation of the corresponding nitropyrrole via intermediate adduct **25**, ring closure, and $TolSO_2Li$ elimination. Unfortunately, only ethyl carbonochloridate

[2]2.0 eq nBuLi seems important to suppress cyclodimerization of TosMIC see [121] for reference.

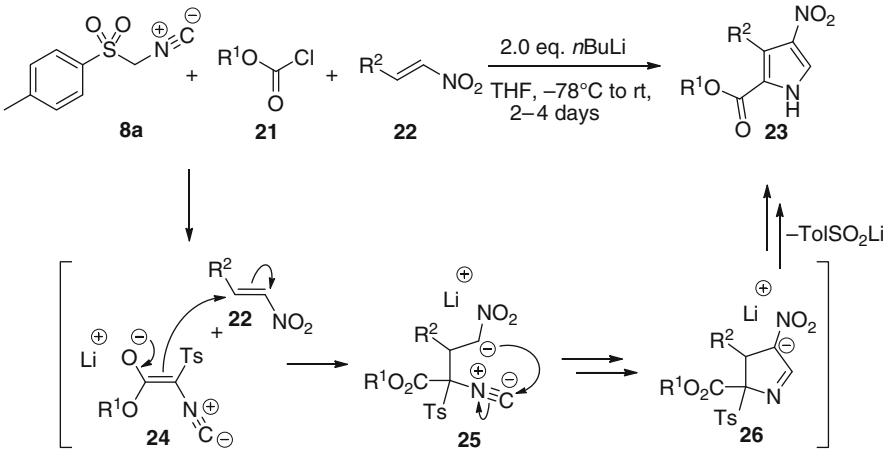


Fig. 10 MCR approach toward nitropyrroles (**23**)

(**21a**, R^1 = Et) and aromatic 2-nitrovinyl compounds (R^2 = Ar) were investigated; however, the corresponding nitropyrroles could be isolated in good yields (63–88%) using a polymer-assisted catch-and-release work-up.

4.5 2,4,5-Trisubstituted Oxazoles

The MCR toward 2,4,5-trisubstituted oxazoles (**27**) starting from α-isocyano amides (**2**), amines, and carbonyl components was first reported in 2001 by the research group of Zhu [138]. Since then, this MCR proved to be the basis of various multicomponent approaches toward very diverse heterocyclic scaffolds [138–148]. Initially, the reaction was well studied for the use of tertiary isocyano amides, where morpholine was typically chosen as the NR^2R^3 group, although other dialkylamino groups can be used as well. The mechanism of this MCR probably involves the attack of the terminal NC carbon atom at the (preformed) imine, leading to intermediate **29** followed by intramolecular ring closure and α-proton abstraction (or visa versa; see [149]). The R^3 substituent of the isocyanide can be varied from the electron-withdrawing Ph group to H and even the electron-donating groups like Me, Bn, and *i*Pr. Both aldehydes and ketones can be used as the carbonyl input. The 5-aminooxazole MCR is accessible for both primary and secondary amines, although in the case of primary amines the isolated yields are typically lower (40–75% compared to 51–96% for secondary amines). In contrast to most other MCR involving α-acidic isonitriles, the reaction can be accelerated by the presence of weak Brønsted acids like NH_4Cl, Py·HCl, or Et_3N·HCl. This can be explained by the faster formation of iminium ion **28** (with the use of secondary amines) or the activation of the aldimine (in case of primary amines), resulting in a

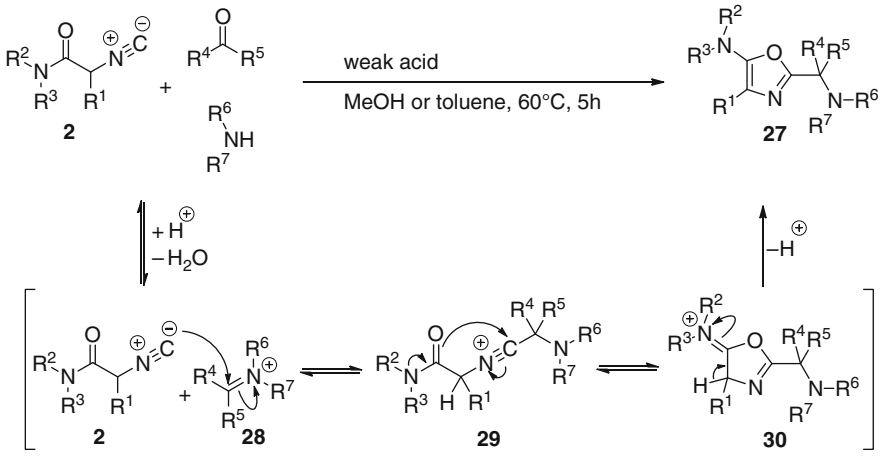


Fig. 11 The trisubstituted oxazole MCR

more facile attack of isonitrile **2**. Both toluene and MeOH were found to be excellent solvents and the substrates can be mixed in equimolar amounts to simplify the workup procedure.

Interestingly, when primary isocyano amides were used (**31**) under otherwise identical conditions, the corresponding oxazoles could not be obtained. Instead, a MCR toward *N*-(cyanomethyl)amides (**32**) was observed [150]. The unexpected formation of **32** could be rationalized by the attack of the isocyanide terminal C atom on the in situ-generated iminium ion (**28**) followed by cyclization and proton abstraction to form 5-iminooxazoline intermediate **33** (Fig. 12). Intermediate **33** could, in principle, undergo tautomerization to form the aromatic primary 5-aminooxazole, but instead, proton abstraction at the exocyclic imine nitrogen and subsequent ring opening occurs to give **32**.

Zhu and coworkers reported the first examples of the successful application of an isocyano ester in the MCR toward 2,4,5-trisubstituted oxazoles in 2007. Stirring the highly acidic methyl α-isocyano *para*-nitrophenyl acetate (**34a**, $R^1 = p\text{-}NO_2$) in the presence of an amine and carbonyl component gave 5-methoxyoxazole product **35** (Fig. 13) [36]. Again, a wide variety of aldehydes and amines could be used in this MCR, affording the corresponding oxazole (**35**, $R^1 = p\text{-}NO_2$) in moderate to excellent yield (23–97%). Reaction optimization by our research group extended the isocyano inputs in the MCR toward 5-methoxyoxazoles to less acidic α-aryl isocyano esters (**34b–f**) by switching to DMF as the solvent (Fig. 13) [151]. In addition, ketones proved to be successful entries and preformation of the imine was found to be unnecessary. Unfortunately, when the pK_a of the α-proton becomes too high (**34g**, $R^1 = o, p$-dimethoxyphenyl), no reaction is observed [151]. In addition, the MCR toward 5-methoxyoxazoles seems to be limited to the use of α-aryl

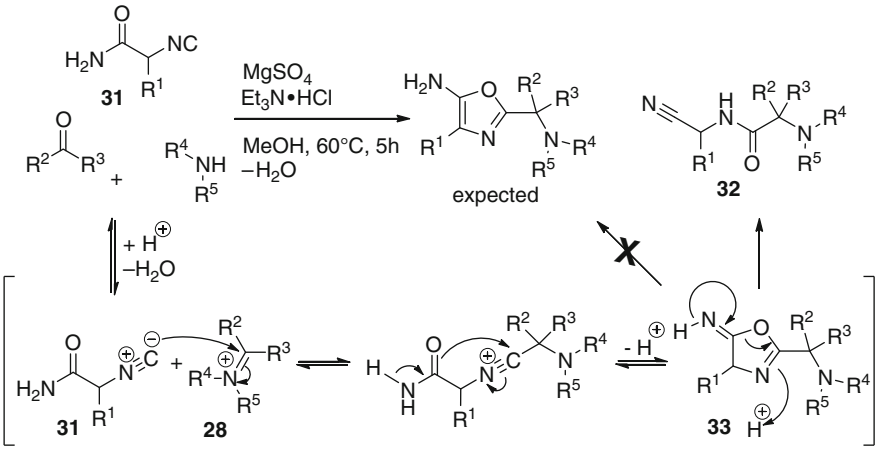
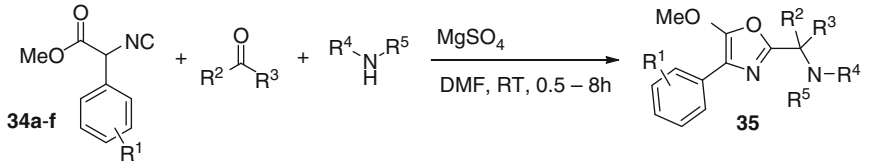


Fig. 12 Formation of *N*-(cyanomethyl)amides in the MCR between primary isocyano amides, aldehydes/ketones, and amines



34a: R^1 = *p*-NO_2, **34b**: R^1 = H, **34c**: R^1 = *o*-Cl, **34d**: R^1 = *m*-Cl, **34e**: R^1 = *p*-Cl, **34f**: R^1 = *p*-OMe

Fig. 13 Scope of isocyano esters in the MCR toward trisubstituted oxazoles

isocyanoesters, as the reaction of α-alkyl isocyanoesters, amines, and carbonyl components tends to yield the corresponding 2*H*-2-imidazolines (see below) [152].

4.5.1 Oxazole MCR Variations

In 2003, the research group of Ganem used the 5-aminooxazole MCR in their single reactant replacement (SRR) approach for developing variants of known MCRs (for an overview of strategies for innovation in multicomponent reactions see [153]). Substituting the amine input by a trialkylsilylchloride in the reaction of α,α-unsubstituted isocyanoamides (**36**) under $Zn(OTf)_2$ promotion led to the isolation of 2,5-disubstituted oxazole **37** (Fig. 14a) [143]. Increasing the dimensionality by addition of an acid chloride after 12 h even led to the development of a four-component approach toward 2,4,5-trisubstituted oxazoles **38** [144]. In addition, the MCR toward 2,5-disubstituted oxazoles **40** using TMSCl had previously been described using ethyl isocyanoacetate (**39**) by the same research group (Fig. 14b) [154].

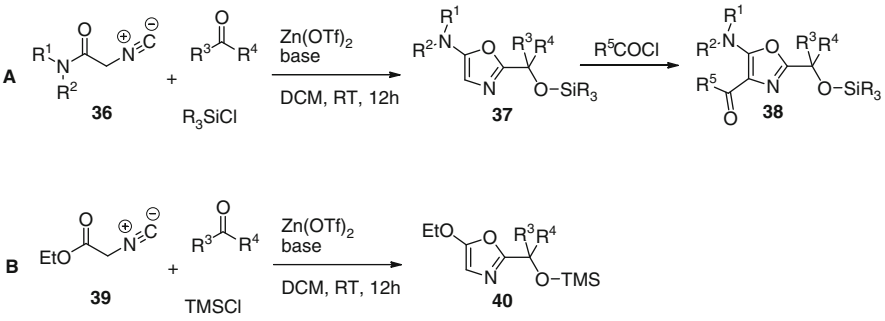


Fig. 14 Variations of the trisubstituted oxazole MCR using the single reactant replacement approach

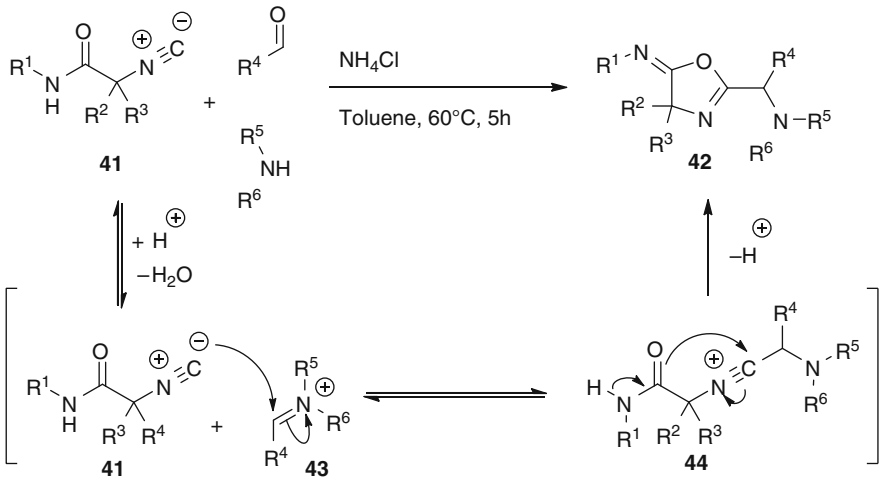


Fig. 15 Formation of 5-iminooxazolines (**42**) by the MCR between α,α-disubstituted isocyano amides (**41**), aldehydes, and amines

In 2007, Tron and Zhu reported the multicomponent synthesis of 5-iminooxazolines (**42**) starting from α,α-disubstituted secondary isocyano amides (**41**), amines, and carbonyl components (see Fig. 15) [155]. The reaction presumably follows a similar mechanism as in the 2,4,5-trisubstituted oxazole MCR (described in Fig. 11); however, because of the absence of α-protons at the isocyano amide **41**, the nonaromatized product is obtained. As in the 2,4,5-trisubstituted oxazole MCR, toluene was found to be the optimal solvent in combination with a weak Brønsted acid. The reaction was studied for a range of aldehydes and secondary amines. In addition, a variety of functionalities such as acetate, free hydroxyl group, carbamate, and esters are tolerated. Clean conversions were observed for this MCR as indicated by NMR analysis of the crude products (isolated yield 50–68%). The

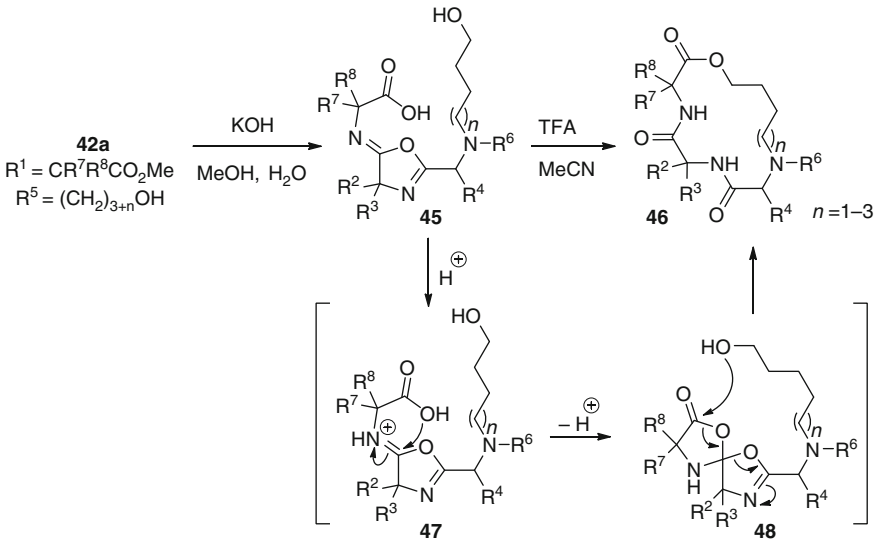


Fig. 16 Synthesis of macrocyclodepsipeptides from 5-imiooxazolines

moderate isolated yields compared to the conversion could be explained by partial degradation during purification. Unfortunately, the MCR seems to be limited to the use of secondary α,α-disubstituted α-isocyanoacetamides (R^2 and $R^3 \neq H$); only complex reaction mixtures were obtained with the use of α-monosubstituted isocyano amides.

With $R^1 = CR^7R^8CO_2Me$ and $R^5 = (CH_2)_{3+n}OH$, the obtained 5-iminooxazolines **42a** could be converted into macrocyclodepsipeptides of type **46** as shown in Fig. 16. Saponification of the ester with KOH in MeOH/H_2O followed by protonation of the exocyclic imine and attack of the neighboring carboxyl oxygen led to the formation of spirolactone **48**. Attack of the tethered OH and fragmentation generated the desired 14-, 15-, and 16-membered macrocycles in 27–54% yield [155].

4.5.2 Oxazole MCR + In Situ Tandem Processes

The structural diversity (and complexity) of the products obtained by the MCR between tertiary isocyano amides, aldehydes, and amines could be increased to various heterocyclic scaffolds by combining the initial 2,4,5-trisubstituted oxazole MCR with in situ intramolecular tandem processes (Fig. 17). Most tandem processes reported are based on the reactivity of the oxazole ring toward C=C or C≡C bonds in hetero Diels–Alder reactions followed by ring opening reactions generating the rather complex heterocyclic products with high degrees of variation.

For example, pyrrolo[3,4-*b*]pyridine-5-ones (**50**) could be obtained by a four-component tandem process using an acryloyl chloride derivative (**49**) as an

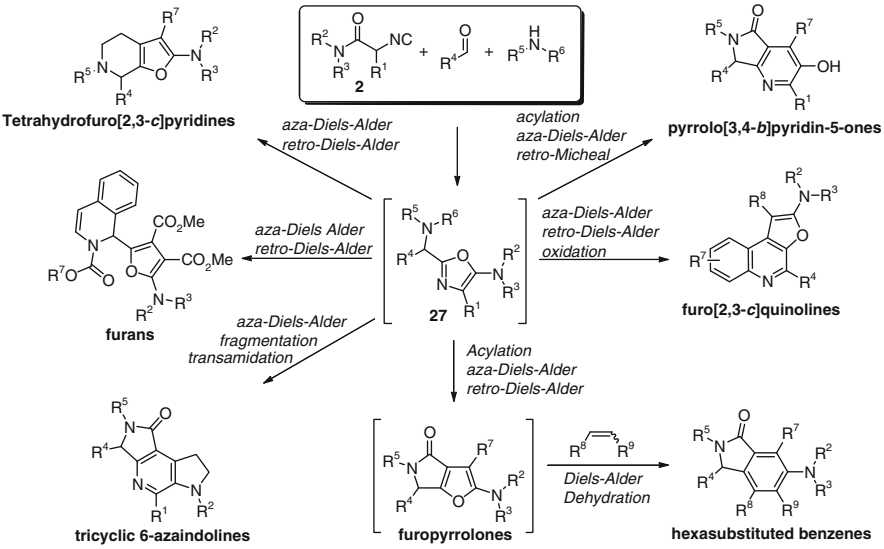


Fig. 17 Selected examples for scaffold diversity obtained by the trisubstituted oxazole MCR followed by intramolecular tandem processes

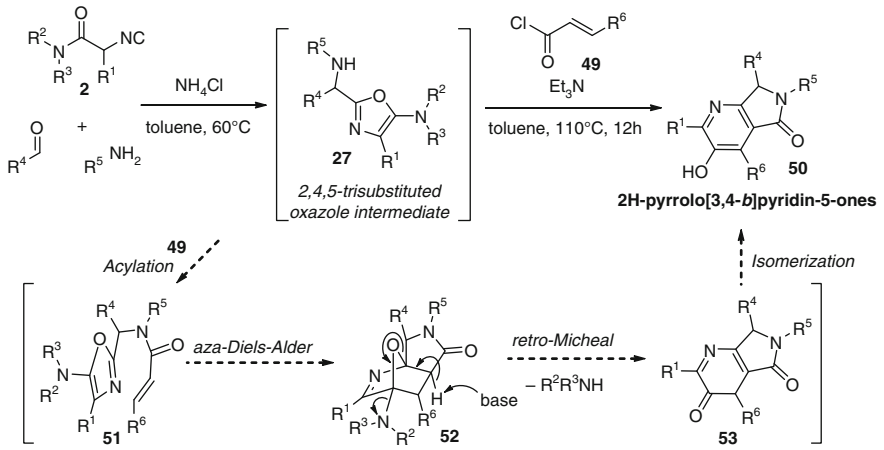


Fig. 18 Suggested reaction mechanism for the construction of pyrrolo[3,4-*b*]pyridine-5-ones (**50**) from the MCR between isocyano amides, aldehydes, amines, and acryloyl chloride derivatives

acylating agent. Preformation of an imine by stirring a primary amine and an aldehyde for 30 min followed by the addition of the isocyanide (**2**) generated the intermediate oxazole **27** upon heating at 60°C. When the initial MCR was finished, the acylating agent **49** was added at 0°C followed by heating at 110°C for 12 h, initially forming intermediate **51**, which subsequently undergoes an intramolecular *aza*-Diels–Alder reaction generating bicyclic **52** (Fig. 18). Proton abstraction at

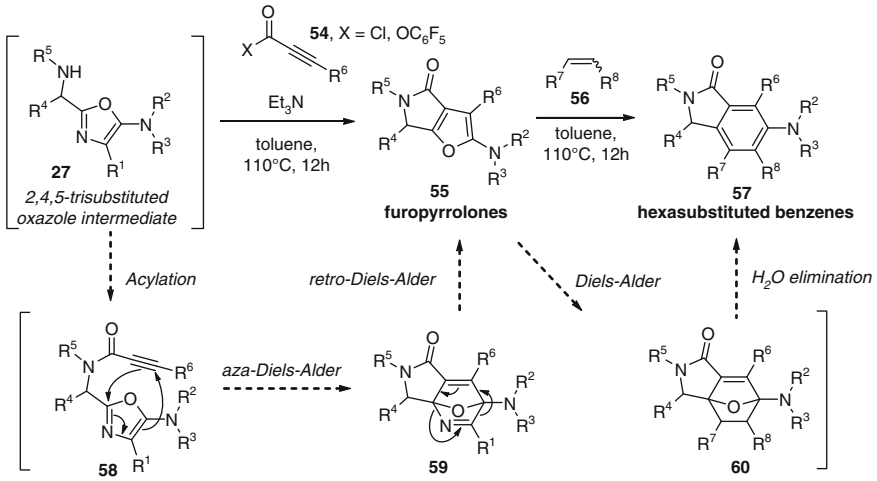


Fig. 19 Suggested reaction mechanism for the construction of furopyrrolones (**55**) and hexasubstituted benzenes (**57**) based on the trisubstituted oxazole MCR

intermediate **52** followed by ring opening and amine elimination (retro-Michael reaction) furnished intermediate **53**, which isomerizes to the corresponding pyrrolo [3,4-*b*]pyridine-5-one (**50**) [138, 140, 147].

When propiolyl chlorides (**54**, or pentafluorophenyl esters) are used as acylating agent under similar reaction conditions, furopyrrolones (**55**) are accessible (Fig. 19). Acylation of the intermediate oxazole **27** (see: Fig. 18) furnished **58**, which is able to undergo an *aza*-Diels–Alder reaction generating intermediate **59**. A retro-Diels–Alder reaction finally generates the furopyrrolone (**55**). Although the furopyrrolones obtained by this triple domino sequence can be isolated (one example **55a**: NR^2R^3 = morpholine, R^4 = *c*Hex, R^5 = *n*Bu, R^6 = Ph; >95%), a second domino sequence toward hexasubstituted benzene derivatives (**57**) could be initiated by the addition of an alkene (Diels–Alder reaction, dehydration). Because of the similar reaction conditions in the formation of **55** and **57**, a novel 5-CR toward hexasubstituted benzene derivatives **57** involving two consecutive domino processes was developed [142].

By the introduction of *aza*-dienophile at the isocyanoacetamide component **2**, 6-azaindolines (**61**) are accessible (Fig. 20) [156]. Preformation of the imine in toluene at room temperature for 1 h followed by the addition of highly functionalized isocyano amide **2** and heating at reflux temperature resulted in the formation of oxazole intermediate **27**. This is able to undergo the intramolecular *aza*-Diels–Alder reaction, generating *oxa*-bridged intermediate **63**. Subsequent (nitrogen-assisted) fragmentation yielded the corresponding 6-azaindolines **61**. When primary amines are used in combination with R^3 = CO_2Me, tricyclic 6-azaindolines (**62**) could be isolated due to a facile intramolecular transamidation under the reaction conditions used.

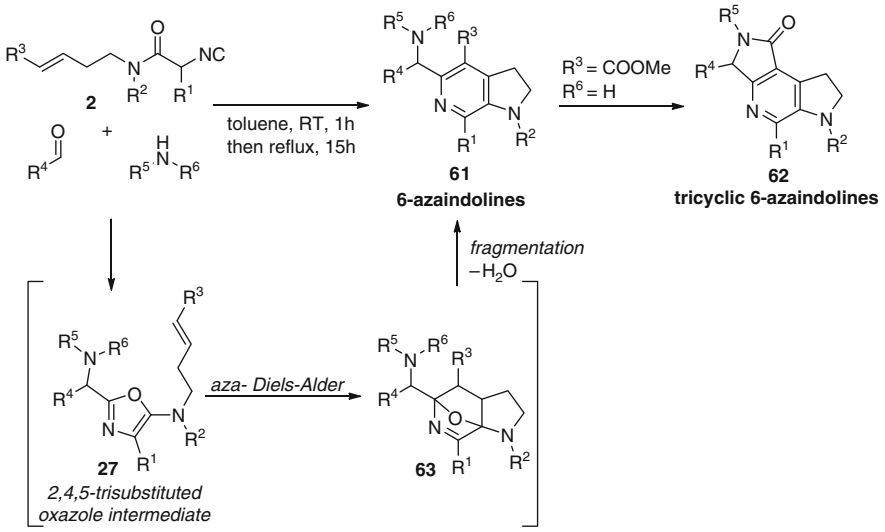


Fig. 20 Suggested reaction mechanism for the construction of (tricyclic) 6-azaindolines (**62**) based on the trisubstituted oxazole MCR

4.6 *2H*-2-Imidazoline MCR

In 2003, we reported a multicomponent approach toward highly substituted 2*H*-2-imidazolines (**65**) [157]. This 3CR is based on the reactivity of isocyano esters (**1**) toward imines as was studied in detail by Schöllkopf in the 1970s [76]. In our reaction, an amine and an aldehyde were stirred for 2 h in the presence of a drying agent (preformation of imine). Subsequent addition of the α-acidic isocyanide **64** resulted in the formation of the corresponding 2*H*-2-imidazolines (**65**) after 18 h in moderate to excellent yield. The mechanism for this MCR probably involves a Mannich-type addition of α-deprotonated isocyanide to (protonated) imine (**66**) followed by a ring closure and a 1,2-proton shift of intermediate **68** (Fig. 21). However, a concerted cycloaddition of **66** and deprotonated **64** to produce **65** cannot be excluded.

The reaction is reported to work well with methyl α-phenyl isocyanoacetate (**1**, R = Ph) and 9-fluoroenylisocyanide (**69**) in combination with a wide range of aldehydes and amines using DCM as the solvent [157]. Further reaction optimization [150, 151, 158, 159] indicated that ketones are reactive inputs as well, and preformation of the imine was not required. In addition, the three-component reaction can be performed in a wide range of solvents, and a wide range of functional groups in the inputs are tolerated (terminal alkene, free OH, esters, aliphatic isocyanides). In addition, the scope of compatible isocyanide inputs could be increased to *para*-nitrobenzylisonitrile (**70**) [158] and a wide range of

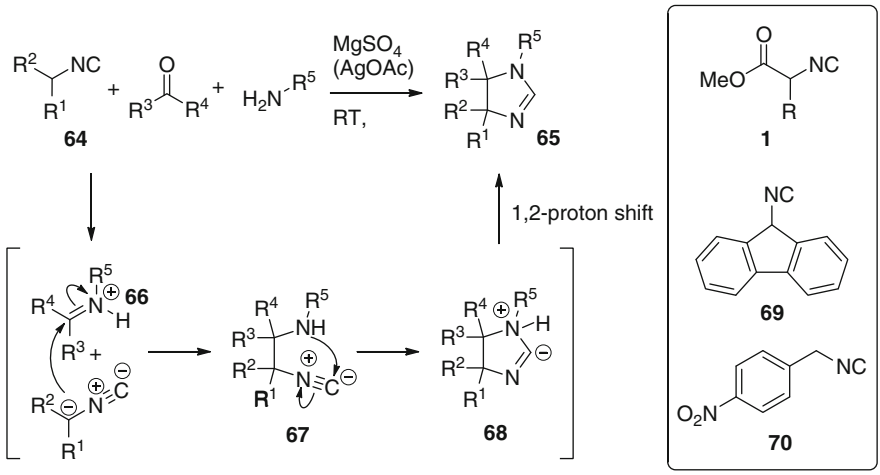


Fig. 21 Proposed reaction mechanism for the 2*H*-2-imidazoline MCR

other (less acidic) α-substituted isocyano acetates (**1**, R = H, Me, *i*Bu, *i*Pr) [159]. Silver(I) salts (AgOAc) were found to accelerate the reaction, probably by coordination of the terminal NC carbon atom to Ag^I, which increases the α-acidity and NC electrophilicity (Fig. 22). Remarkably, unlike most other reactions reported with α-acidic isonitriles, no additional base or acid is required for the three-component coupling to 2*H*-2-imidazolines **65**. Most likely, the intermediate imine is basic enough to deprotonate the isocyanide.

The scope of isocyanide inputs was further increased to tertiary isocyano amides (**2**) and primary isocyano amides (**31**, see Fig. 22). As discussed earlier, these isocyanide entries typically yield 2,4,5-trisubstituted oxazoles (**27**, Fig. 11) [138–148] and *N*-(cyanomethyl)amides (**32**, Fig. 12) [150], respectively. However, addition of only 2 mol% AgOAc (or CuI) in combination with the slow addition of the isocyanide to the imine gave the corresponding 2*H*-2-imidazoline (**65**) in moderate to very good yield (39–91%, Fig. 22). The increased formation of 2*H*-2-imidazoline under these reaction conditions can be explained by an increased concentration of the (silver-coordinated) isocyanide anion **71** (reactive species). In addition, AgOAc may block the oxazole (**27**) and *N*-(cyanomethyl)amide (**32**) formation by coordination of the isocyanide carbon to Ag^I, thus reducing its nucleophilicity. Unfortunately, all attempts in using α-alkyl-substituted isocyano amides (**2** or **31**, R^1 = alkyl) were unsuccessful, probably due to the increase in pK_a of the α-proton. However, by careful selection of the substrates and of the described experimental procedures, the MCR between α-acidic isocyano amides, aldehydes or ketones, and primary amines could be directed towards three alternative reaction paths, addressing considerable chemical diversity: At least four diversity points in three distinct scaffolds can be addressed.

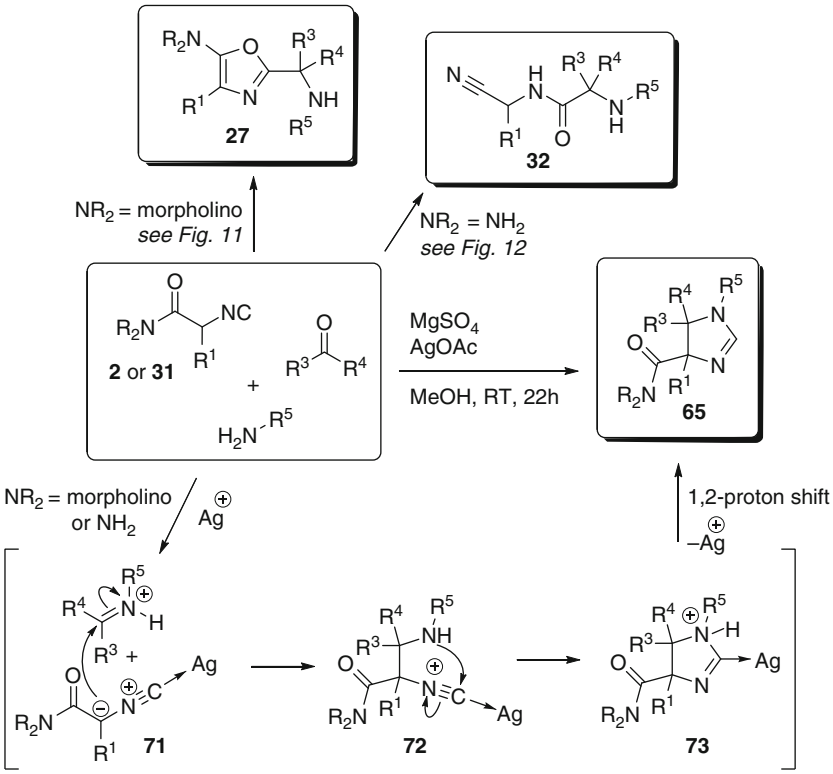


Fig. 22 Possible reaction paths for the reaction between α-acidic isocyano amides (**2** or **31**), primary amines, and carbonyl components, including the Ag^{I} catalyzed formation of 2*H*-2-imidazolines (**65**)

The MCR toward 2*H*-2-imidazolines (**65**) has found application in the construction of *N*-heterocyclic carbene (NHC) complexes (**74**). Alkylation of the sp^2 *N*-atom with an alkyl halide followed by abstraction of the proton at C2 with a strong base (NaH, KO*t*Bu) resulted in the formation of the free carbene species, which could be trapped and isolated as the corresponding metal complexes (Ir or Rh) [160]. The corresponding Ru-complexes were shown to be active and selective catalysts for the transfer hydrogenation of furfural to furfurol using *i*PrOH as hydrogen source [161].

Although the MCR affords highly substituted 2-imidazolines (**65**, R^1–R^5), variation at C2 is not possible. To overcome the limitation of substituent variation at C2, a versatile route towards C2-arylated 2-imidazolines (**75**) has been developed. Key steps involve oxidation at C2 and Liebeskind–Srogl cross-coupling of cyclic thioureas with boronic acids. The final products investigated contain Nutlin-like [162] backbones and could be prepared in good overall yields (23–35%). The high overall yields and the diversity of the products that could be obtained make this procedure amenable to library synthesis of potential p53-hdm2 interaction inhibitors [163, 164] (Fig. 23).

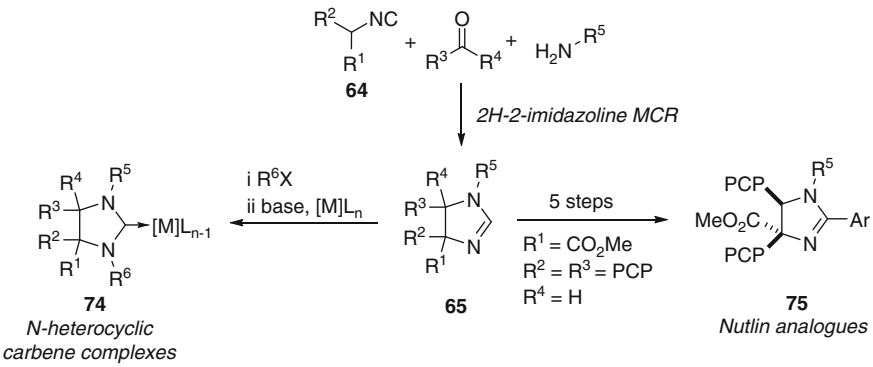


Fig. 23 Application of 2*H*-2-imidazoline MCR in the synthesis of *N*-heterocyclic carbene complexes (**74**) and Nutlin analogs (**75**)

4.6.1 2*H*-2-Imidazoline MCR in the Union of MCRs

Because of the high functional group tolerance and high conversions generally observed (>90%), the 2*H*-2-imidazoline MCR could be combined with other MCRs in the same pot, generating higher order MCRs (union of MCRs – combination of MCRs in a single pot performed either as a one-pot process (true novel MCR) or as a short sequence (tandem); see [165] and references cited therein. For the first examples of union of MCRs see [166, 167]). In addition, the broad solvent compatibility observed for the 2*H*-2-imidazoline MCR allows selection of the optimal solvent for the follow-up MCR. The most straightforward approach to such combinations of MCRs is the incorporation of a functional group in one of the inputs of the primary MCR that does not participate in the reaction, but does react as one of the components in the secondary MCR. For example, when an amino acid acts as amine input (R^5 = CHR^6CO_2H) in the 2*H*-2-imidazoline MCR, an imidazoline carboxylate (**65**, R^5 = $CHR^6CO_2^-$) is formed as intermediate under basic conditions, which can be used as carboxylic acid component in a subsequent Ugi 4-CR after protonation [168]. The united 2*H*-2-imidazoline ∪ Ugi products (**76**) generated by this formal 6CR could be isolated in 38–62%, which is excellent considering the number of bond formations (93% yield per bond formation). Moreover, this approach allows variation on no less than nine positions in a single reaction step (Fig. 24).

The same approach turned out to be successful using levulinic acid as carbonyl component, allowing the isolation of the corresponding intermediate 2*H*-2-imidazoline (**65**, R^3 = Me, R^4 = $(CH_2)_2CO_2H$) combined with Ugi 4CRs (**77**) or a Passerini 3CR (**78**) (32–58%). Introduction of an aliphatic isocyanide functional group by using a diisocyanide (R^2 = $(CH_2)_3NC$) allowed the union with Ugi, Passerini, and other IMCRs at the C4 position of the 2*H*-2-imidazoline (**79**–**82**, 41–78%). Beside the 2*H*-2-imidazolines (**65**) MCR, the *N*-(cyanomethyl)amide

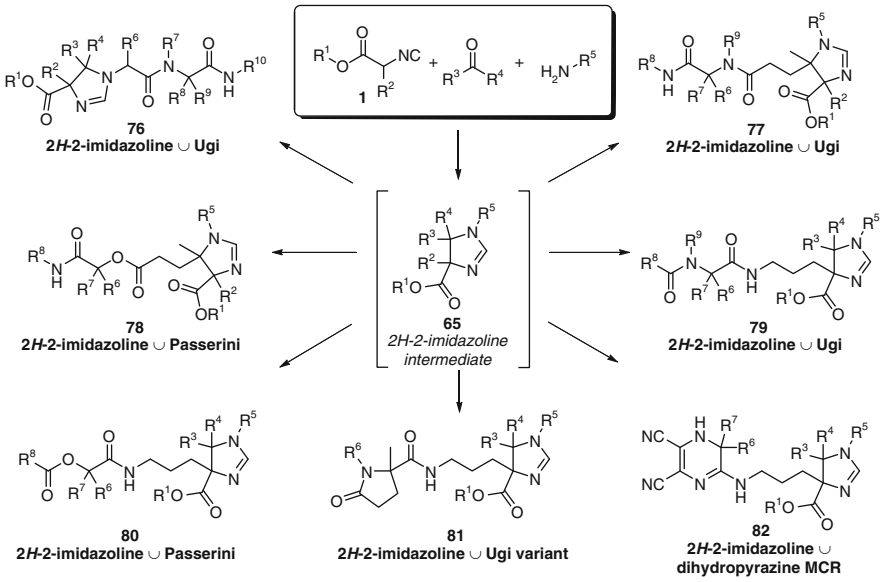


Fig. 24 Generation of higher order MCRs based on the 2*H*-2-imidazoline MCR

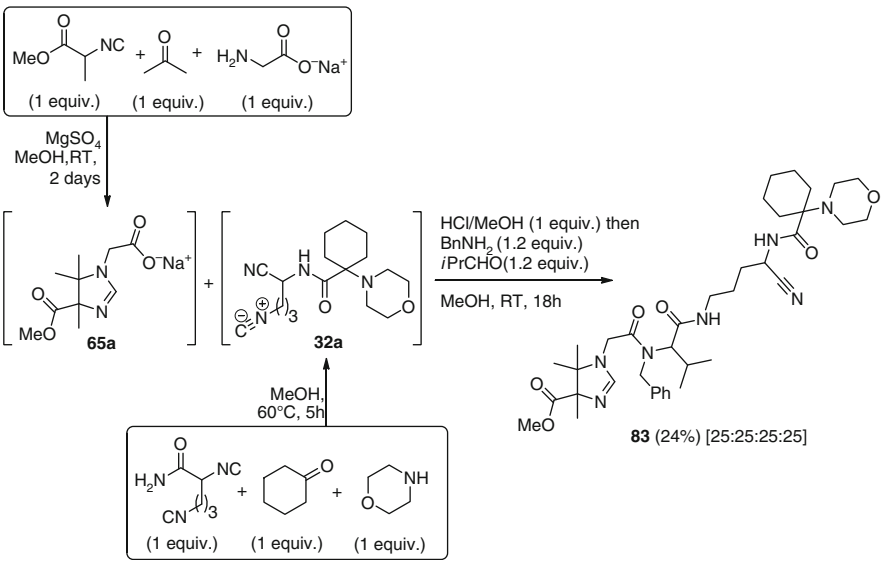


Fig. 25 One pot 8CR based on three sequential MCRs

(**32**) MCR also tolerates the aliphatic isocyanide functionality [150], thus allowing the union with various IMCRs. Finally, we developed the first example of a triple MCR process (8CR toward **83**) based on our 2*H*-2-imidazoline (**65**) and *N*-(cyanomethyl)amide (**32**) MCRs united with the Ugi-4CR (Fig. 25).

4.7 Dihydropyridone MCR

In 2006, our research group reported a novel MCR based on the reactivity of α-acidic isocyano esters (**1**) toward 1-azadienes (**84**) generated by the 3CR between phosphonates, nitriles, and aldehydes [169]. Remarkably, the dihydropyridone products (**85**) for this 4CR contained the intact isonitrile function at C3. The exceptional formation of the 3-isocyano dihydropyridone scaffold can be explained by the Michael-attack of the α-deprotonated isonitrile (**1**) to the (protonated) 1-azadiene (**84**), followed by lactamization via attack of the ester function by the intermediate enamine. Although in principle the isocyano functionality is not required for the formation of the dihydropyridone (**85**) scaffold, all attempts using differently functionalized esters (e.g., malonates, α-nitro, and α-cyano esters) gave lower yields of the dihydropyridone analogs [170] (Fig. 26).

The scope of the aldehyde inputs includes a wide range of (hetero)aromatic aldehydes as well as α,β-unsaturated aldehydes. With the use of aliphatic aldehydes, side products due to aldol condensations could be observed. Allowed α-substituents at the isocyano acetate (**1**) includes R^4 = Ph, H, Me, Et, Bn, *i*Bu, *i*Pr. The scope according to the nitrile input includes aromatic, heteroaromatic, and aliphatic nitriles. However, the use of primary aliphatic nitriles should be avoided.

Because of the retained isocyano functionality, the dihydropyridone MCR product **85** can be used in various follow-up (multicomponent) reactions. For example, the Passerini reaction between **85**, a carboxylic acid, and an aldehyde or ketone produces a series of dihydropyridone-based conformationally constrained depsipeptides **86** [171]. The subsequent Passerini reaction could also be performed in the same pot, resulting in a novel 6CR toward these complex products containing up to seven points of variation. Reaction of **85** with an aldehyde or ketone and amine component resulted in the isolation of dihydrooxazolopyridines (DHOPs, **87**) [172] via a similar approach as the 2,4,5-trisubstituted oxazole variant toward **42** reported by Tron and Zhu (Fig. 15) [155]. The corresponding DHOPs (**87**), which

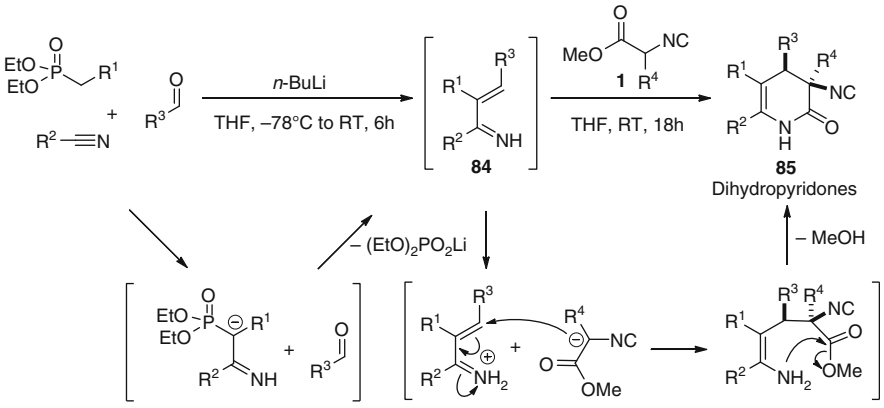


Fig. 26 Proposed reaction mechanism for the dihydropyridone 4-CR

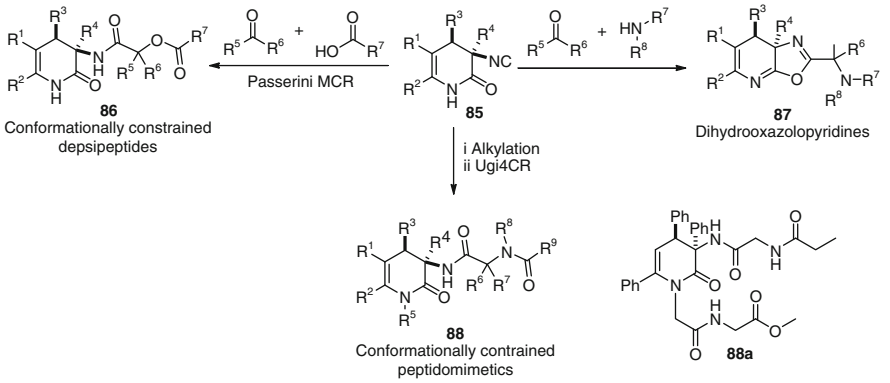


Fig. 27 Application of 3-isocyano dihydropyridones (**85**) in the multicomponent approaches toward conformationally constrained depsipeptides (**86**), dihydrooxazolopyridines (**87**), and conformationally constrained peptidomimetics (**88**)

represent a new synthetic scaffold, could be isolated in a good-to-excellent yield (62–100%) for a wide variety of reaction inputs. In addition, because of their structural similarities, DHOPs can be considered promising alternatives for the bioactive oxazolopyridines.

Unfortunately, direct Ugi reaction of **85** predominantly led to the formation of DHOPs (**87**) [172]. However, by applying a MCR-alkylation-MCR strategy, the Ugi products (**88**) could be isolated in high yields [173]. The obtained conformationally constrained peptidomimetics allow for unprecedented diversification and were ultimately evaluated for their turn-inducing properties, indicating an open turn structure for **88a** (Fig. 27).

5 Conclusion

The exceptional reactivity of isocyanides, as discussed here, is unrivaled by other functional groups and has led to many synthetically useful novel reactions. Especially, MCRs involving isocyanides as one of the inputs receive an ever-growing attention by the synthetic community. An appealing class of these versatile building blocks is the α-acidic isocyanides. Their use has led to a range of versatile IMCRs, as has become clear from this chapter. From a set of only three different types of α-acidic isocyanides, sometimes inspired by the early work of Schöllkopf and van Leusen, a wide range of novel reaction paths were discovered in the last decade. In this way a plethora of mainly heterocyclic scaffolds can be synthesized in a straightforward fashion. The IMCRs discussed are usually robust reactions that can be easily combined into very short reaction sequences with other complexity-generating reactions, such as cycloadditions or even additional MCRs, leading to

yet other classes of heterocyclic motifs. This offers exciting opportunities for library design of highly functionalized heterocyclic scaffolds employing diversity-oriented synthetic approaches. We envision that these MCRs employing α-acidic isocyanides will find widespread application in medicinal chemistry, in chemical biology as well as in catalysis.

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References

1. Dömling A, Ugi I (2000) Angew Chem 112:3300–3344
2. Hulme C, Gore V (2003) Curr Med Chem 10:51–80
3. Orru RVA, De Greef M (2003) Synthesis:1471–1499
4. Jacobi von Wangelin A, Neumann H, Gördes D, Klaus S, Strübing D, Beller M (2003) Chem Eur J 9:4286–4294
5. Nair V, Rajesh C, Vinod AU, Bindu S, Sreekanth AR, Mathen JS, Balagopal L (2003) Acc Chem Res 36:899–907
6. Zhu J (2003) Eur J Org Chem:1133–1144
7. Balme G, Bossharth E, Monteiro N (2003) Eur J Org Chem 4101–4111
8. Simon C, Constantieux T, Rodriguez J (2004) Eur J Org Chem:4957–4980
9. Ramón DJ, Yus M (2005) Angew Chem 117:1628–1661; (2005) Angew Chem Int Ed 44:1602–1634
10. Tempest P (2005) Curr Opin Drug Discov Devel 8:776–788
11. Dömling A (2006) Chem Rev 106:17–89
12. Godineau E, Landais Y (2009) Chem Eur J 15:3044–3055
13. Strecker A (1850) Liebigs Ann Chem 75:27
14. Strecker A (1850) Ann Chem Pharm 91:349
15. Hantzsch A (1882) Liebigs Ann Chem 215:1
16. Biginelli P (1891) Ber Dtsch Chem Ges 24:2962
17. Biginelli P (1893) Ber Dtsch Chem Ges 26:447
18. Mannich C, Krosche W (1912) Arch Pharm (Weinheim) 250:647
19. Passerini M (1922) Gazz Chim Ital 52:126–129
20. Passerini M (1922) Gazz Chim Ital 52:181–189
21. Ugi I, Meyr R (1958) Angew Chem 70:702–703
22. Ugi I, Meyr R, Steinbrückner C (1959) Angew Chem 71:386
23. Lieke W (1859) Liebigs Ann Chem 112:316
24. Ugi I, Betz W (1960) DE1177146; Chem Abstr 61:(14536e)
25. Beecham Group Ltd (1974) FR2260577; Chem Abstr 83:(206251)
26. van Leusen AM, Strating J (1970) Quart Rep Sulfur Chem 5:67
27. van Leusen AM, Boerma GJM, Helmholdt RB, Siderius H, Strating J (1972) Tetrahedron Lett 13:2367–2378
28. Schöllkopf U, Hoppe D, Jentsch R (1975) Chem Ber 108:1580–1592
29. Matsumoto K, Suzuki M, Yoneda N, Miyoshi M (1977) Synthesis:249–250
30. van Leusen AM, Bourma RJ, Possel O (1975) Tetrahedron Lett 16:3487–3488
31. Murakami M, Hasegawa N, Tomita I, Inouye M, Ito Y (1989) Tetrahedron Lett 30:1257–1260
32. Housseman C, Zhu J (2006) Synlett 11:1777–1779
33. Schöllkopf U, Hoppe D, Jentsch R (1971) Angew Chem 83:357–358; (1971) Angew Chem Int Ed Engl 10:331–332

34. Ito Y, Higuchi N, Murakami M (1988) Tetrahedron Lett 29:5151–5154
35. Ito Y, Sawamura M, Matsuoka M, Matsumoto Y, Hayashi T (1987) Tetrahedron Lett 28:4849–4852
36. Bonne D, Dekhane M, Zhu J (2007) Angew Chem Int Ed 46:2485–2488
37. van Leusen AM, Boerma GJM, Helmgoldt RB, Siderius H, Strating J (1972) Tetrahedron Lett 13:2367–2368
38. Matsumoto K, Suzuki M, Miyoshi M (1973) J Org Chem 38:2094–2096
39. Olijnsma T, Engberts JBFN, Strating J (1972) Recl Trav Chim Pays Bas 91:209
40. Hundscheid FJA, Tandon VK, Rouwette PHFM, van Leusen AM (1987) Tetrahedron 43:5073–5088
41. Barret AGM, Cramp SM, Hennessy AJ, Procopiou PA, Roberts RS (2001) Org Lett 3:271–274
42. Sisko J, Mellinger M, Sheldrake PW, Baine NH (1996) Tetrahedron Lett 37:8113–8116
43. Wright JJK, Cooper AB, McPhail AT, Merrill Y, Nagabhushan TL, Puar MS (1982) J Chem Soc Chem Commun 20:1188–1190
44. Urban R, Marquarding D, Seidel P, Ugi I, Weinelt A (1977) Chem Ber 110:2012–2015
45. Waki M, Meienhofer J (1977) J Org Chem 42:2019–2020
46. Kamer PCJ, Cleij MC, Nolte RJM, Harada T, Hezemans AMF, Drenth W (1988) J Am Chem Soc 110:1581–1587
47. Seebach D, Adam G, Gees T, Schiess M, Weigand W (1988) Chem Ber 121:507–518
48. Bowers MM, Carroll P, Joullie MM (1989) J Chem Soc Perkin Trans 1:857–865
49. Owens TD, Araldi G-L, Nutt RF, Semple JE (2001) Tetrahedron Lett 42:6271–6274
50. Wehner V, Stilz H-U, Osipov SN, Golubev AS, Sieler J, Burger K (2004) Tetrahedron 60:4295–4302
51. Horwell DC, Nichols PD, Roberts E (1994) Tetrahedron Lett 35:939–940
52. Obrecht R, Herrmann R, Ugi I (1985) Synthesis:400–402
53. Zhu J, Wu X, Danishefsky SJ (2009) Tetrahedron Lett 50:577–579
54. Pifferi G, LiBassi G, Broccali G (1976) Heterocycles 4:759–765
55. Skorna G, Ugi I (1977) Angew Chem 89:267–268; (1977) Angew Chem Int Ed Eng 16:259–260
56. van der Eijk JM, Nolte RJM, Richters VEM, Drenth W (1981) J Royal Netherlands Chem Soc 100:222–226
57. Nishimura S, Yasuda N, Sasaki H, Matsumoto Y, Kanimura T, Sakane K, Takaya T (1990) Bull Chem Soc Jpn 63:412–416
58. Ikota N (1990) Chem Pharm Bull 38:1601–1608
59. Creedon SM, Crowley HK, McCarthy DG (1998) J Chem Soc Perkin Trans 1 6:1015–1018
60. Banfi L, Guanti G, Riva R, Basso A, Calcagno E (2002) Tetrahedron Lett 43:4067–4070
61. de Witte PAJ, Castriciano M, Cornelissen JJLM, Scolaro LM, Nolte RJM, Rowan AE (2003) Chem Eur J 9:1775–1781
62. Zhao G, Bughin C, Bienayme H, Zhu J (2003) Synlett 8:1153–1154
63. Vriezema DM, Kros A, de Gelder R, Cornelissen JJLM, Rowan AE, Nolte RJM (2004) Macromolecules 37:4736–4739
64. Bughin C, Zhao G, Bienayme H, Zhu J (2006) Chem Eur J 12:1174–1184
65. Metselaar GA, Adams PJHM, Nolte RJM, Cornelissen JJLM, Rowan AE (2007) Chem Eur J 13:950–960
66. Schwartz E, Kitto HJ, de Gelder R, Nolte RJM, Rowan AE, Cornelissen JJLM (2007) J Mater Chem 17:1876–1884
67. Nunami K-I, Suzuki M, Hayashi K, Matsumoto K, Yoneda N, Takiguchi K (1985) Agric Biol Chem 49:3023–3028
68. Nunami K-I, Suzuki M, Matsumoto K, Yoneda N, Takiguchi K (1984) Agric Biol Chem 48:1073–1076
69. Takiguchi K, Yamada K, Suzuki M, Nunami K-I, Hayashi K, Matsumoto K (1989) Agr Biol Chem 53:77–82
70. Soloshonok VA, Hayashi T (1994) Tetrahedron Asymmetry 5:1091–1094

71. Beck B, Larbig G, Mejat B, Magnin-Lachaux M, Picard A, Herdtweck E, Dömling A (2003) Org Lett 5:1047–1050
72. van Leusen D, van Leusen AM (2001) Org React 57:417–679
73. Schöllkopf U (1977) Angew Chem 89:351–360; (1977) Angew Chem Int Ed Engl 16: 339–348
74. Seagusa T, Ito Y, Kinoshita H, Tomita S (1971) J Org Chem 36:3316–3323
75. Hoppe D, Schöllkopf U (1972) Liebigs Ann Chem:1–16
76. Meyer R, Schöllkopf U, Böhme P (1977) Liebigs Ann Chem:1183–1193
77. Hayashi T, Kishi E, Soloshonok VA, Uozumi Y (1996) Tetrahedron Lett 37:4969–4972
78. Lin Y-R, Zhou X-T, Dai L-X, Sun J (1997) J Org Chem 62:1799–1803
79. Benito-Garagorri D, Bocokíc V, Kirchner K (2006) Tetrahedron Lett 47:8641–8644
80. Meyer R, Schöllkopf U, Madawinata K, Stafforst D (1978) Liebigs Ann Chem:1982–1989
81. Suzuki M, Iwasaki T, Matsumoto K, Okumura K (1972) Syn Commun 2:237
82. Suzuki M, Iwasaki T, Miyoshi M, Okumura K, Matsumoto K (1973) J Org Chem 38:3571–3575
83. Matsumoto K, Suzuki M, Yoneda N, Miyoshi M (1976) Synthesis:805–807
84. Nunami K-I, Suzuki M, Matsumoto K, Miyoshi M, Yoneda N (1979) Chem Pharm Bull 27:1373–1377
85. Henneke K-W, Schöllkopf U, Neudecker T (1979) Liebigs Ann Chem:1370–1387
86. Gerecke M, Kyburz E, Borer R, Gassner W (1994) Heterocycles 39:693–722
87. Matecka D, Wong G, Gu Z-Q, Skolnick P, Rice KC (1995) Med Chem Res 5:63–76
88. Jacobsen EJ, Stelzer LS, TenBrink RE, Belonga KL, Carter DB, Im HK, Bin Im W, Sethy VH, Tang AH, VonVoigtlander PF, Petke JD, Zhong W-Z, Mickelson JW (1999) J Med Chem 42:1123–1144
89. Grigg R, Lansdell MI, Thornton-Pett M (1999) Tetrahedron 55:2025–2044
90. Kanazawa C, Kamijo S, Yamamoto Y (2006) J Am Chem Soc 128:10662–10663
91. Bonin M-A, Giguere D, Roy R (2007) Tetrahedron 63:4912–4917
92. Suzuki M, Moriya T, Matsumoto K, Miyoshi M (1982) Synthesis:874–875
93. Solomon DM, Rizvi RK, Kaminski JJ (1987) Heterocycles 26:651–674
94. Boros EE, Johns BA, Garvey EP, Koble CS, Miller WH (2006) Bioorg Med Chem Lett 16:5668–5672
95. Suzuki M, Miyoshi M, Matsumoto K (1974) J Org Chem 39:1980
96. Matsumoto K, Suzuki M, Ozaki Y, Miyoshi M (1976) Argic Biol Chem 40:2271
97. Sakai K, Suzuki M, Nunami K-I, Yoneda N, Onoda Y, Iwasawa Y (1980) Chem Pharm Bull 8:2384–2393
98. Barton DHR, Zard SZ (1985) J Chem Soc Chem Commun:1098–1100
99. Ono N, Kawamura H, Maruyama K (1989) Bull Chem Soc Jpn 62:3386–3388
100. Barton DHR, Kervagoret J, Zard SZ (1990) Tetrahedron 46:7587–7598
101. Lash TD, Bellettini JR, Bastian JA, Couch KB (1994) Synthesis:170–172
102. Ono N, Katayama H, Nisyiyama S, Ogawa T (1994) J Heterocycl Chem 31:707–710
103. Uno H, Sakamoto K, Tominaga T, Ono N (1994) Bull Chem Soc Jpn 67:1441–1448
104. Vicente MGH, Tome AC, Walter A, Cavaleiro JAS (1997) Tetrahedron Lett 38:3639–3642
105. Schmidt W, Monforts F-P (1997) Synlett 8:903–904
106. Abel Y, Haake E, Haake G, Schmidt W, Struve D, Walter A, Monforts F-P (1998) Helv Chim Acta 81:1978–1996
107. Bullington JL, Wolff RR, Jackson PF (2002) J Org Chem 67:9439–9442
108. Kamijo S, Kanazawa C, Yamamoto Y (2005) Tetrahedron Lett 46:2563–2566
109. Kamijo S, Kanazawa C, Yamamoto Y (2005) J Am Chem Soc 127:9260–9266
110. Larionov OV, de Meijere A (2005) Angew Chem 117:5809–5813; (2005) Angew Chem Int Ed Eng 44:5664–5667
111. Guo C, Xue M-X, Zhu M-K, Gong L-Z (2008) Angew Chem 120:3462–3465; (2008) Angew Chem Int Ed Eng 47:3414–3417
112. Tsunenishi Y, Ishida H, Itoh K, Ohno M (2000) Synlett:1318–1320

113. Schöllkopf U, Porsch P-H (1973) Chem Ber 106:3382–3390
114. Schöllkopf U, Hantke K (1973) Liebigs Ann Chem:1571–1582
115. Possel O, van Leusen AM (1977) Heterocycles 7:77–80
116. Horne DA, Yakushijin K, Buechi G (1994) Heterocycles 39:139–54
117. Hundscheid FJA, Tandon VK, Rouwette PHFM, van Leusen AM (1987) Recl Trav Chim Pays Bas 106:159–160
118. Atkins JM, Vedejs E (2005) Org Lett 7:3351–3354
119. van Leusen AM, Wildeman J, Oldenziel OT (1977) J Org Chem 42:1153–1159
120. van Leusen AM, Siderius H, Hoogenboom BE, van Leusen D (1972) Tetrahedron Lett 13:5337–5340
121. ten Have R, Leusink FR, van Leusen AM (1996) Synthesis:871–876
122. Beaza A, Mendiola J, Burgos C, Alvarez-Builla J, Vaquero JJ (2005) J Org Chem 70: 4879–4882
123. Hoppe I, Schöllkopf U (1976) Chem Ber 109:482–487
124. Ito Y, Sawamura M, Hamashima H, Emura T, Hayashi T (1989) Tetrahedron Lett 30: 4681–4684
125. Ozaki Y, Maeda S, Iwasaki T, Matsumoto K, Odawara A, Sasaki Y, Morita T (1983) Chem Pharm Bull 31:4417–4424
126. Coffin AR, Roussell MA, Tserlin E, Pelkey ET (2006) J Org Chem 71:6678–6681
127. Chupp JP, Leschinsky KL (1980) J Heterocycl Chem 17:705–709
128. Chupp JP, Leschinsky KL (1980) J Heterocycl Chem 17:711–715
129. Schöllkopf U, Hausberg H-H, Hoppe I, Segal M, Reiter U (1978) Angew Chem 90:136–138; (1978) Angew Chem Int Ed Eng 17:117–119
130. Schöllkopf U, Hausberg H-H, Segal M, Reiter U, Hoppe I, Saenger W, Lindner K (1981) Liebigs Ann Chem 3:439–458
131. Sisko J (1998) J Org Chem 63:4529–4531
132. Gracias V, Gasiecki AF, Djuric SW (2005) Org Lett 7:3183–3186
133. Lee JC, Laydon JT, McDonnell PC, Gallagher TF, Kumar S, Green D, McNulty D, Blumenthal MJ, Keys JR, Landvatter SW, Strickler JE, McLaughlin MM, Siemens IR, Fisher SM, Livi GP, White JR, Adams JL, Young PR (1994) Nature 372:739–746
134. Antuch W, Menon S, Chen Q-Z, Lu Y, Sakamuri S, Beck B, Schauer-Vukašinović V, Agarwal S, Hess S, Dömling A (2006) Bioorg Med Chem Lett 16:1740–1743
135. Neochoritis C, Stephanidou-Stephanatou J, Tsoleridis CA (2009) Synlett:302–305
136. Wu B, Wen J, Zhang J, Li J, Xiang Y-Z, Yu X-Q (2009) Synlett:500–504
137. Baxendale IR, Buckle CD, Ley SV, Tamborini L (2009) Synthesis:1485–1493
138. Sun X, Janvier P, Zhao G, Bienaymé H, Zhu J (2001) Org Lett 3:877–880
139. Lobrégat V, Alcaraz G, Bienaymé H, Vaultier M (2001) Chem Commun:817–818
140. Janvier P, Sun X, Bienaymé H, Zhu J (2002) J Am Chem Soc 124:2560–2567
141. Fayol A, Zhu J (2002) Angew Chem 114:3785–3787; (2002) Angew Chem Int Ed 41:3633–3635
142. Janvier P, Bienaymé H, Zhu J (2002) Angew Chem 114:4467–4470; (2002) Angew Chem Int Ed 41:4291–4294
143. Wang Q, Xia Q, Ganem B (2003) Tetrahedron Lett 44:6825–6827
144. Wang Q, Ganem B (2003) Tetrahedron Lett 44:6829–6832
145. Fayol A, Zhu J (2004) Org Lett 6:115–118
146. Cuny G, Gámez-Montano R, Zhu J (2004) Tetrahedron 60:4879–4885
147. Fayol A, Housseman C, Sun X, Janvier P, Bienaymé H, Zhu J (2005) Synthesis:161–165
148. Pirali T, Tron GC, Zhu J (2006) Org Lett 8:4145–4148
149. Mishchenco VV, Itov ZI, L'vova SD, Shostakovskaya GK, Gunar VI (1988) Phar Chem J 22:568–572
150. Elders N, Ruijter E, de Kanter FJJ, Janssen E, Lutz M, Spek AL, Orru RVA (2009) Chem Eur J 15:6096–6099
151. Elders N, Ruijter E, de Kanter FJJ, Groen MB, Orru RVA (2008) Chem Eur J 14:4961–4973

152. Elders N (2010) PhD Thesis, VU University, Amsterdam, the Netherlands. For details about the MCR toward 2*H*-2-imidazolines see: Sect. 4.6
153. Ganem B (2009) Acc Chem Res 42:463–471
154. Xia Q, Ganem B (2002) Org Lett 4:1631–1634
155. Pirali T, Tron GC, Masson G, Zhu J (2007) Org Lett 9:5275–5278
156. Fayol A, Zhu J (2005) Org Lett 7:239–242
157. Bon RS, Hong C, Bouma MJ, Schmitz RF, de Kanter FJJ, Lutz M, Spek AL, Orru RVA (2003) Org Lett 5:3759–3762
158. Bon RS, van Vliet B, Sprenkels NE, Schmitz RF, de Kanter FJJ, Stevens CV, Swart M, Bickelhaupt FM, Groen MB, Orru RVA (2005) J Org Chem 70:3542–3553
159. Elders N, Schmitz RF, de Kanter FJJ, Ruijter E, Groen MB, Orru RVA (2007) J Org Chem 72:6135–6142
160. Bon RS, de Kanter FJJ, Lutz M, Spek AL, Jahnke MC, Hahn FE, Groen MB, Orru RVA (2007) Organometallics 26:3639–3650
161. Strassberger Z, Mooijman M, Ruijter E, Alberts AH, de Graaff C, Orru RVA, Rothenberg G (2010) Appl Organometal Chem 24:142–146
162. Vassilev LT, Vu BT, Graves B, Carvajal D, Podlaski F, Filipovic Z, Kong N, Kammlott U, Lukacs C, Klein C, Fotouhi N, Liu EA (2004) Science 303:844–848
163. Bon RS, Sprenkels NE, Koningstein MM, Schmitz RF, de Kanter FJJ, Dömling A, Groen MB, Orru RVA (2008) Org Biomol Chem 6:130–137
164. Srivastava S, Beck B, Wang W, Czarna A, Holak TA, Dömling A (2009) J Comb Chem 11:631–639
165. Mironov MA (2006) QSAR Comb Sci 25:423–431, and references cited therein
166. Dömling A, Ugi I (1993) Angew Chem 105:634–635; (1993) Angew Chem Int Ed 32:563–564
167. Dömling A, Herdtweck E, Ugi I (1998) Act Chem Scan 52:107–113
168. Elders N, van der Born D, Hendrickx LJD, Timmer BJJ, Krause A, Janssen E, de Kanter FJJ, Ruijter E, Orru RVA (2009) Angew Chem 121:5970–5973; (2009) Angew Chem Int Ed 48:5856–5859
169. Paravidino M, Bon RS, Scheffelaar R, Vugts DJ, Znabet A, Schmitz RF, de Kanter FJJ, Lutz M, Spek AL, Groen MB, Orru RVA (2006) Org Lett 8:5369–5372
170. Scheffelaar R, Paravidino M, Znabet A, Schmitz RF, de Kanter FJJ, Lutz M, Spek AL, Fonseca Guerra C, Bickelhaupt FM, Groen MB, Ruijter E, Orru RVA (2010) J Org Chem 75: accepted
171. Paravidino M, Scheffelaar R, Schmitz RF, de Kanter FJJ, Groen MB, Ruijter E, Orru RVA (2007) J Org Chem 72:10239–10242
172. Scheffelaar R, Paravidino M, Muilwijk D, Lutz M, Spek AL, de Kanter FJJ, Orru RVA, Ruijter E (2009) Org Lett 11:125–128
173. Scheffelaar R, Klein Nijenhuis RA, Paravidino M, Lutz M, Spek AL, Ehlers AW, de Kanter FJJ, Groen MB, Orru RVA, Ruijter E (2009) J Org Chem 74:660–668

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Microreactor Technology as an Efficient Tool for Multicomponent Reactions

Ana Cukalovic, Jean-Christophe M.R. Monbaliu, and Christian V. Stevens

Abstract Multicomponent reactions are an important tool in organic synthesis as they often allow the circumvention of multistep procedures by combining three or more molecules into one structure in a single step. An additional asset of the approach is the significant increase of the combinatorial possibilities, since a modification of the final product is easily accomplished by implementing minor changes in the reaction setup; this obviously allows considerable savings in time and resources. These advantages are of particular interest in pharmaceutical research for the construction of libraries. In order to increase the sustainability of chemical processes, the field is intensively explored, and novel reactions are frequently reported.

Microreactor technology also offers a contemporary way of conducting chemical reactions in a more sustainable fashion due to the miniaturization and increased safety, and also in a technically improved manner due to intensified process efficiency. This relatively new technology is implemented in novel and improved applications and is getting more and more used in chemical research.

The combination of the benefits from the two approaches clearly presents an attractive reaction design, and this chapter presents an overview of the reported examples in which the microreactor technology and the multicomponent approach are combined, usually with dramatically improved results compared to those previously reported.

Keywords Continuous flow · Heterocycles · Microreactor · Multicomponent reactions · Sustainable processes

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Contents

Abbreviations

A-15	Amberlyst 15
A-21	Amberlyst 21
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
CFC	Convection-flow coil
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMF	Dimethylformamide
DPPA	Diphenylphosphoryl azide
ee	Enantiomeric excess
GC	Gas chromatography
HPLC	High pressure liquid chromatography/high performance liquid chromatography

i.d.	Internal diameter
MACOS	Microwave-assisted continuous flow organic synthesis
Me	Methyl
MNTS	*N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide
MR	Microreactor
MW	Microwave
PEEK	Polyether ether ketone
PFA	Poly(fluoroacetate)
PMP	*p*-Methoxy-phenyl
PS-BEMP	Polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
PSP	Polymer-supported tetra-*N*-alkylammonium perruthenate
PS-PIFA	Polymer-supported (ditrifluoroacetoxyiodo)benzene
PTFE	Polytetrafluoroethylene
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TMSCN	Trimethylsilyl cyanide
TOF-MS	Time-of-flight mass spectrometry
TTMSS	Tris(trimethylsilyl)silane
μSYNTAS	Miniaturised synthesis and total analysis system

1 Introduction

Multicomponent reactions are recognized as an important tool in organic synthesis. The benefits of the approach are obvious: when three or more molecules react to form a single compound, multistep procedures are avoided and combinatorial possibilities are built in a simple and elegant manner. The idea of multicomponent reactions is not new: Strecker, Hantzsch and Biginelli reactions were first reported in the nineteenth century, the Mannich reaction in 1912, the Passerini reaction in 1921, etc. [1–5]. All these reactions have been further modified and various adaptations are being reported over the years. Novel multicomponent reactions are also being reported frequently. Especially with the current trends in chemistry that stresses process efficiency and sustainability, multicomponent reactions are gaining a renewed significance and interest in research [6–9]. Probably the most important field for multicomponent reactions is the research in the pharmaceutical industry, where the number of combinatorial possibilities dramatically decreases the time needed for the production of libraries of biologically active chemical compounds.

Microreactor technology is a relatively young field: the first microreactor system was described in a German patent from 1986 [10]. A microreactor is generally defined as a device containing microstructured features, in which chemical reactions are performed in a continuous manner [11]. Microreactors offer a plethora of advantages over classical batch processes: miniaturization obviously leads to the use of smaller quantities of materials, providing economical and environmental benefits and easier control of the reactions' safety; flow conditions ensure good

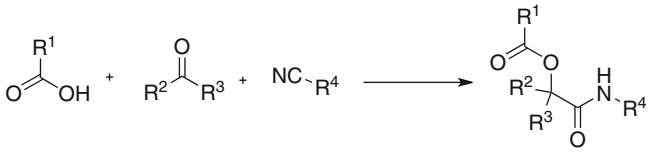
mixing of the reagents and strictly respected stoichiometry. Continuous processes furthermore allow faster processing of unstable intermediates and avoid serious drawbacks of the batch productions, such as, for example, delays due to reaction work-up. Another important convenience of the technology is the increased surface-to-volume ratio and the heat-exchange efficiency, which allows better thermal control of the reactions and makes microreactors suitable for exothermic reactions, sometimes even eliminating the need for external cooling and thus decreasing the overall process energy demands. Additionally, thanks to the enhanced temperature distribution, it is also possible to reduce the reaction time under carefully controlled conditions by increasing the temperature while avoiding the formation of side products. The main asset of microreactor technology adding an industrially important significance is its scalability: this is due to the favourable surface-to-volume ratio that reduces the number of steps needed in the transfer from lab to pilot and industrial scale (often mentioned "scale-out" instead of "scale-up"). Practically, the only serious drawback of the technology is the formation of solids during the reaction; insoluble particles can easily clog the fine routes stopping the flow and creating difficulties in conducting the reaction. Another problem can be the formation of gasses during the reaction, which can cause instability of the flow, thus demanding a strict control of the pressure in the device. However, when these risks are avoided or controlled, the microreactor technology is considered very advantageous for various applications in the fine chemical and the pharmaceutical industry [12, 13].

The combination of the two approaches that have obvious advantages therefore presents an attractive reaction design with added value in the inventions and optimizations of existing processes. We hereby give an overview of current achievements in this field. However, there is a rather limited number of published data on strictly defined multicomponent reactions in which all the reactants are added at once to the reaction mixture, due to the technical characteristics of the systems (e.g. number of inlets) or the possible complications due to side reactions; such reactions are conducted in a multistep mode or employ preformed intermediates. These reactions are also taken into account on the condition that the process is conducted continuously without purification of the intermediates and that the final product contains scaffolds originating from three or more starting molecules.

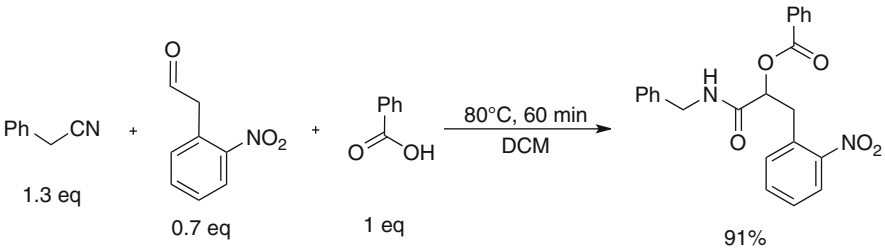
2 Multicomponent Reactions Under Microreactor Conditions (Sensu Stricto)

2.1 The Passerini Reaction

The manufacturer of the commercially available Syrris Africa system [14] reports on the optimization of several multicomponent reactions: Passerini, Biginelli and Ugi reaction. However, only the details of the three-component Passerini reaction were available [15].



Scheme 1 The Passerini reaction



Scheme 2 The Passerini reaction as performed at Syrris [15]

The Passerini reaction is a condensation between a carbonyl, a carboxylic acid and an isocyanide to form an α-acyloxycarboxamide (Scheme 1) [5].

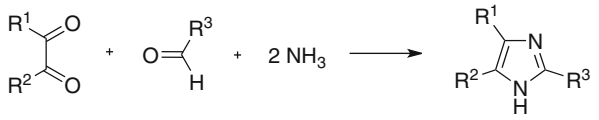
A significant improvement in the conduction of this reaction was reported under microflow conditions in comparison with batch mode. Batch conditions involved a reaction time of 60 h at room temperature to afford the final product in a 62% yield. Under optimized microreactor conditions, the online HPLC-determined yield was 91% in a 60 min reaction time (Scheme 2). Note that the microreactor setup allowed the reaction temperature to be higher than the atmospheric boiling point of the solvent.

2.2 *The Formation of Tetrasubstituted Imidazoles*

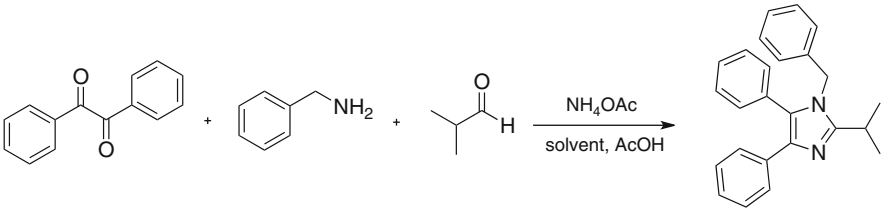
The imidazole ring is often found in biologically active molecules and is as such important in medicinal chemistry [16]. An interesting route for the production of substituted imidazoles is the Debus–Radziszewski reaction. This is a three-component reaction of a diketone, an amine and an aldehyde to form trisubstituted imidazoles (Scheme 3).

A modification of this reaction by Orru et al. [16] included an α-diketone, an amine and an aldehyde that react with ammonia to afford a tetrasubstituted imidazole (Scheme 4). Microwave heating was used to substantially decrease the reaction time.

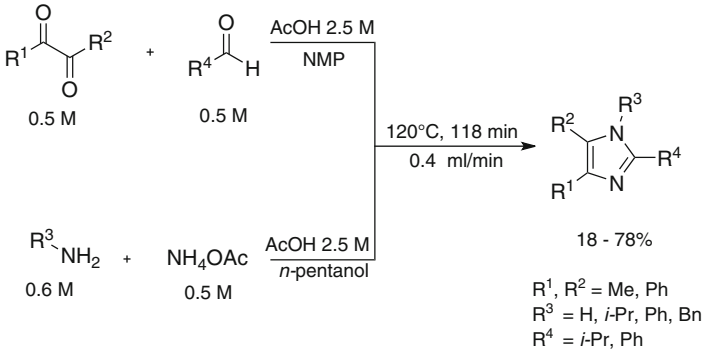
However, microwave-assisted reactions are not easy to scale-up to industrial dimensions. In the attempt to make this reaction more interesting for industrial applications, microreactor conditions were evaluated in a cooperation of the Stevens and the Orru research groups [17].



Scheme 3 The Debus–Radziszewski reaction



Scheme 4 Model reaction of the imidazole synthesis via the modified Radziszewski method to afford tetrasubstituted imidazoles [16]



Scheme 5 Modified Radziszewski reaction performed under microreactor conditions [17]

The microreactor system used was the commercial CYTOS College System [18]. The reactor is made of stainless steel, has 100 μm channels and 2 ml volume. It has two inlets operated by two piston pumps. An additional 45 ml residence time unit (RTU) is connected to the system after the reactor itself to increase the reaction time. The parts of the device are connected by polytetrafluoroethylene (PTFE) tubings.

Reagents were injected in pairs. After a series of trials with different flows, concentrations, solvents and temperatures, the reaction was optimized at 120°C and a 118 min residence time (Scheme 5).

Conversions were comparable to those previously reported in a batch mode with microwave heating [16] and the yields were in the range between 18 and 78%, with

productivities in the range of 5.5–40 g/day depending on the molar mass of the product. Purification of the final products by column chromatography was in some cases necessary due to the incomplete conversions and the formation of side products. However, it was shown that the technology is applicable to this reaction, in which the results are similar to those of reaction in batch using microwave heating.

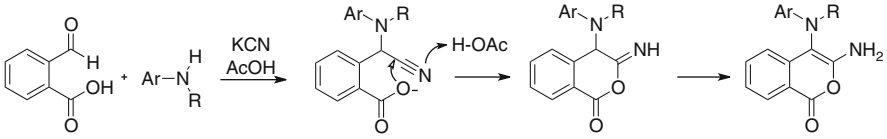
2.3 *Production of Isochromenones and Ring Closure to Isochromeno[3,4-d]imidazol-5-ones*

Opatz and Ferenc [19] produced a small library of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones from 2-formylbenzoic acid, potassium cyanide and a series of anilines. The reaction is based on a Strecker mechanism (Scheme 6).

These compounds have a possible biological activity as anti-cancer drugs due to their expected ability to form Watson–Crick-type base pairs with guanine [19] (Fig. 1).

The Stevens group [20] performed the reaction under microreaction conditions using the previously mentioned CYTOS College System [18]. The main problem with this setup is the formation of crystals (as the final products are crystalline) that leads to clogging of the system. This was circumvented by injection of a fluorinated inert solvent (Fluorinert FC-70) after the micromixing unit and before the RTU, which prevented the clogging and allowed the authors to collect the desired compounds easily by phase separation.

After the process optimisation (Scheme 7), the final results gave similar yields to the ones reported in batch trials [19]. The overall conclusion was positive as the continuous reaction procedure afforded more constant yields, a safer handling of



Scheme 6 Proposed mechanism for the formation of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones [19]

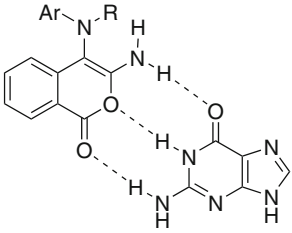
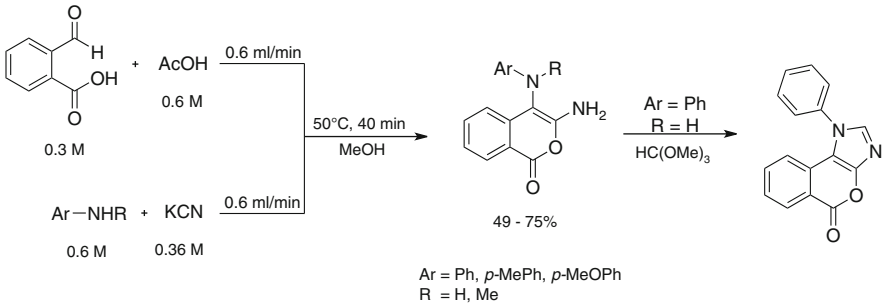


Fig. 1 Possible base pairing of isochromenone structures with guanine [19]



Scheme 7 Production of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones and subsequent ring closure to 1*H*-isochromeno[3,4-*d*]imidazol-5-ones [20, 21]

the HCN produced in the reaction and resulted in an easy scale-up, a common advantage of continuous flow microreactor setups.

In a further step, the authors performed a ring closure to the corresponding imidazole moiety affording isochromeno[3,4-*d*]imidazol-5-ones; it was not possible to afford the 1*H*-isochromeno[3,4-*d*]imidazol-5-ones directly from the 3-amino-4-(arylamino)-1*H*-isochromen-1-one precursors, but the reaction from purified isochromenone was successful with yields of up to 96% [21].

2.4 Tetrahydropyrazolo Quinolinones

A three-component reaction to form tetrahydropyrazolo[3,4-*b*]quinolin-5(6*H*)-ones by a reaction of dimedone (1,3-cyclohexanedione), 5-amino-3-methyl-1*H*-pyrazole and substituted benzaldehydes, carried out in batch, was recently reported [22–24]. Bremner and Organ [25] have performed this reaction in a microfluidic system under microwave heating (MACOS, microwave-assisted continuous flow organic synthesis). The system consisted of three capillary inlets (internal diameter 1.2 mm) fed by integrated syringe pumps, a stainless steel mixing chamber and a glass reaction capillary connected to an outlet via PTFE tubing (Fig. 2).

The system proved suitable containing microfluidic conversions over 90% obtained in a matter of seconds instead of previously reported prolonged refluxing in different solvents. Reactions performed in the absence of MW irradiation gave very low conversion with only traces of the products detected; the authors assumed that this is due to the absence of the turbulent flow induced by microwaves and the poorer mixing in the laminar flow in the tubings. Separate inlets optimized the system flexibility and the combinatorial efficiency. In all trials, the conversions were in the range of 91–100%, and after purification on column and recrystallization, the yields were 55–94%. Productivities are dependant on the molar mass of the product and are in the range of several hundreds of milligram per hour (determined on a half hour run of the system, Scheme 8).

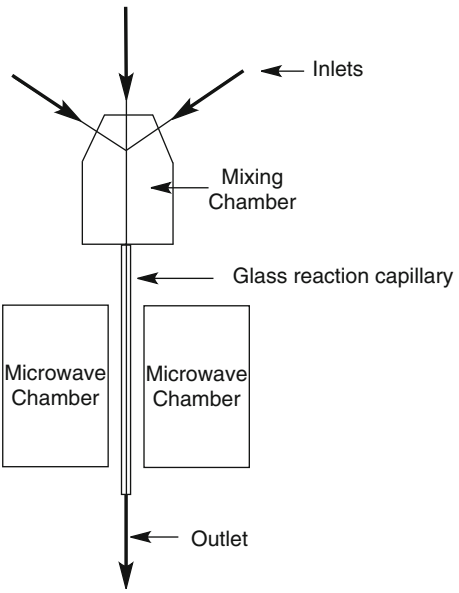
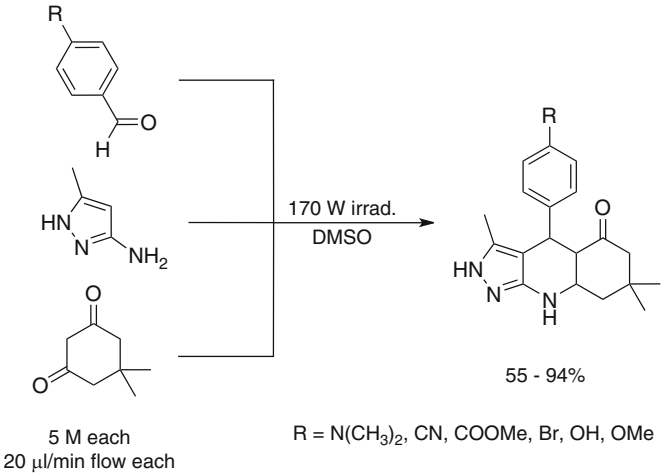
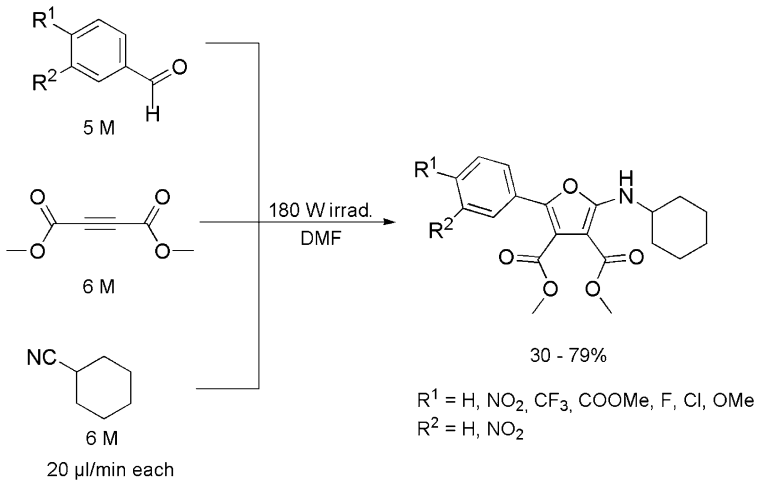


Fig. 2 A schematic view of MACOS setup [25]



Scheme 8 Microwave-assisted continuous flow process to form quinolinones [25]

The authors applied the similar methodology for a three-component reaction of dimethyl acetylenedicarboxylate, cyclohexyl isocyanide and several substituted benzaldehydes to obtain a small library of aminofurans (Scheme 9). Batch conversions reported in previous work required refluxing in benzene for 2–9 h [26] to achieve similar yields as reactions in dimethylformamide (DMF) under capillary flow using



Scheme 9 A three-component reaction to yield tetrasubstituted furans [25]

microwave irradiation in a matter of seconds [25]. Additional purification on column was performed after product collection.

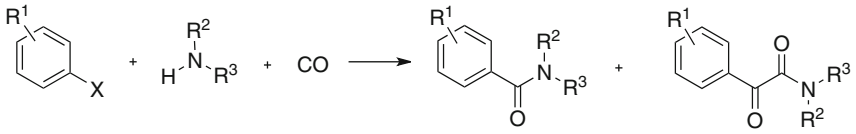
2.5 Carbonylation Reactions

Organocatalysed carbonylations of arylhalogenides are an interesting way of synthesizing carboxylic acids and their derivatives. They are usually carried out with the use of pressurized CO at elevated temperatures [27–29].

Pd-catalysed aminocarbonylations of arylhalogenides were performed by several research groups under microreactor conditions on various systems. The Long research group [30] used glass microplates of 5 × 5 cm with channel dimensions of 200 × 75 µm and system volumes of about 75 µl. The Jensen and the Buchwald research groups [31] used silicon/glass plate with nearly the same volume (78 µl). Both research groups noticed the formation of an α-ketoamide derivative and attributed the double carbonylation to the effect of the electron-rich substituents on the aromatic ring [30] and to the increased CO pressure [31] (Scheme 10).

A short comparison of the two reported procedures is presented in Table 1.

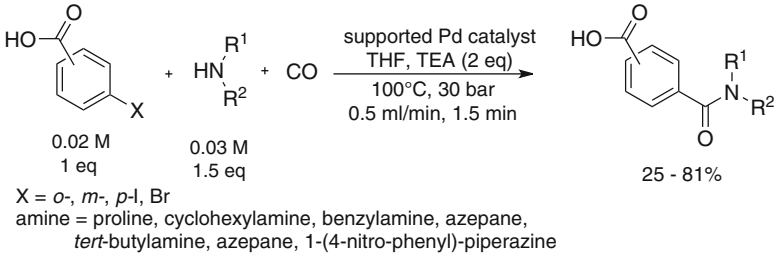
The Csajagi research group used a commercial X-Cube continuous flow reactor system [32] to perform similar reactions. The reactor is made of stainless steel, capable of reaching pressures of up to 150 bar, and equipped with preloaded catalyst cartridges. Monoamides of aryldicarboxylic acids are obtained in a reaction over a tetrakis(triphenylphosphine)palladium catalyst using *N*-methylpyrrolidone as base [33]. Terephtalic acid was reported as the byproduct, but not the α-ketoamide.



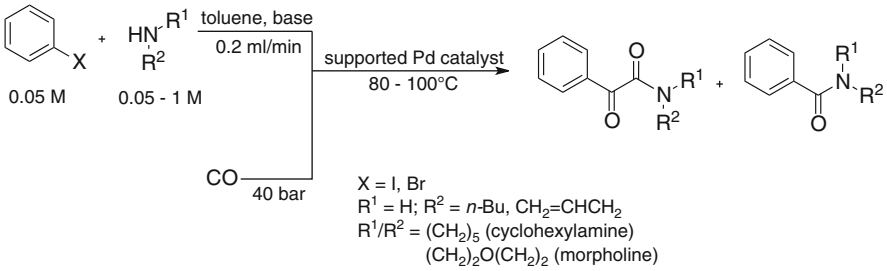
Scheme 10 Carbonylations of arylhalogenides [30, 31]

Table 1 Overview of aminocarbonylation reactions performed under microreaction conditions

Flow (µl/min)	Residence time (min)	CO input	T (°C)	R^1	R^2	R^3	X	Yield amide (%)	Yield α-ketoamide (%)	Source
5–20	<2	2 ml/min	80	H, N, OCH_3	Bn	H	I, Br	10–58	0–28	[30]
12	ca. 4	2.7–14.8 bar	109–160	CN, OMe	$(CH_2)_2O(CH_2)_2$ (morpholine)		I, Br	32–83	0–65	[31]



Scheme 11 The aminocarbonylation reaction performed in a microflow reactor [33]



Scheme 12 Carbonylation of iodobenzene and formation of side products [34]

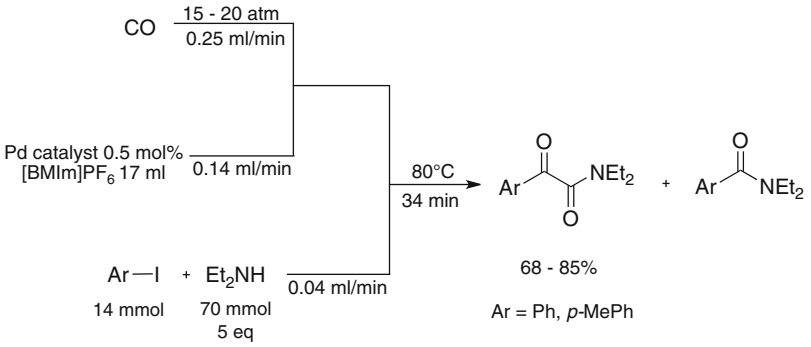
Flow conditions clearly proved superior to the batch conducted trials; the temperature and pressure conditions from the flow trials repeated in an autoclave even resulted in the lowest conversions and selectivities (84% vs. 52% in batch and 12% in autoclave, determined by the analysis of the reaction mixture, Scheme 11). The final yields were reported after purification by preparative HPLC.

In a later work by Skoda-Foldes et al. [34], the same microreactor X-Cube system [32] was employed to perform the double carbonylation of iodobenzene

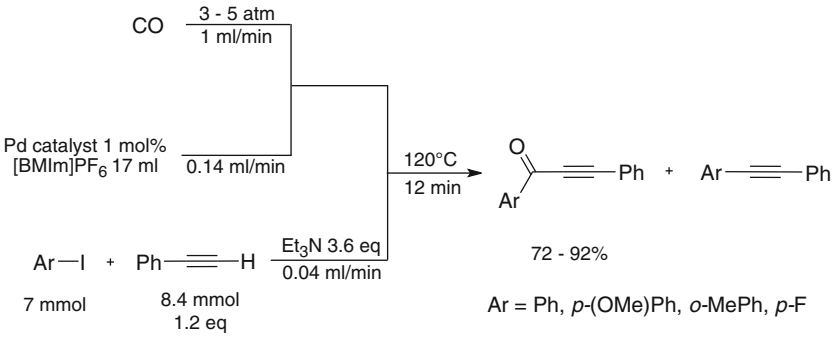
over the same $Pd(PPh_3)_4$ catalyst. After a series of 47 trials with various results, the optimum temperature was set at 80°C; at higher temperatures, the monocarbonylation reaction leading to the amide was favourized and the formation of side products was observed. Batch conditions led to lower conversions and higher formation of side products (Scheme 12).

Ruy et al. have performed a similar reaction under microreactor conditions in a multiphase solvent system containing an ionic liquid as the catalyst carrier and reaction promoter [35]. Their system consisted of two T-shaped micromixers (i.d. 1,000 and 400 μm) and a capillary stainless steel tube as an RTU (1,000 μm i.d. and 18 m length, giving a 14.1 ml volume), equipped with pumps and control valves. Under the optimized conditions, Pd-catalysed carbonylation of aromatic iodides in the presence of a secondary amine provided only the double carbonylated product, α-ketoamide, while the amide obtained by the single carbonylation was observed in high quantities only when the reaction was performed in batch (Scheme 13).

A palladium-catalysed carbonylative Sonogashira coupling was successfully carried out in the same setup [35]. Aryl iodides and phenylacetylene were submitted



Scheme 13 Pd-catalysed double carbonylation of aryl iodides [35]



Scheme 14 Pd-catalysed carbonylative Sonogashira coupling [35]

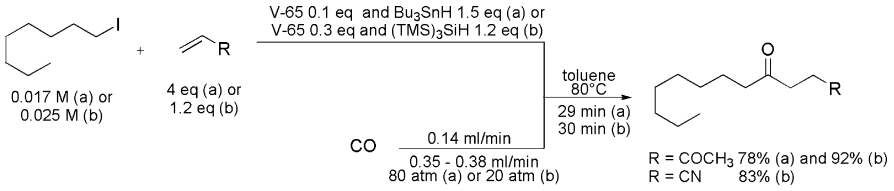
to the reaction with pressurized CO to give exclusively the carbonyl product, while on the contrary, reactions performed in batch generally led to the formation of the Sonogashira byproduct in significant amounts of 16–60% (Scheme 14).

The same research group has further performed radical carbonylation reactions on the same microreactor system [36]. First, alkyl halides were initiated and effectively reacted with pressurized carbon monoxide to form carbonyl compounds. The principle was subsequently successfully extrapolated to the multicomponent coupling reactions. 1-Iodooctane, carbon monoxide and methyl vinyl ketone were reacted in the presence of 2,2′-azobis(2,4-dimethylvaleronitrile) (V-65) as an initiator and tributyltin hydride or tris(trimethylsilyl)silane (TTMSS) as catalyst (Scheme 15).

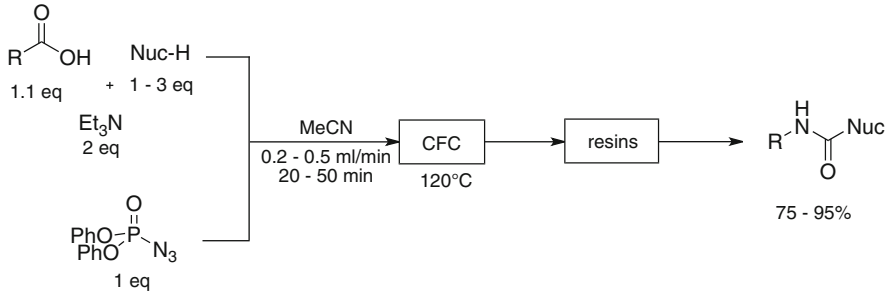
Reactions were conducted at 80°C and at different CO pressures with a reaction time of 29 to 30 minutes. Two different carbonyl compounds were produced by a three-component reaction setup. The yields were determined by GC analysis from the outlet flow.

2.6 Curtius Rearrangement Followed by Nucleophilic Protection

Curtius rearrangement is a well-known reaction of azides to form isocyanates [37]. It is taken into account in this overview, since in the example the azides are produced and reacted with a nucleophile in situ (in one flow), and thus the final product is composed from three starting components.



Scheme 15 A three-component condensation including a radical carbonylation [36]



Scheme 16 Curtius rearrangement as performed in the continuous flow [39]

On a commercially available Vapourtec R2+/R4 combination module [38], the Ley research group performed a Curtius rearrangement on a series of carboxylic acids capturing the isocyanates with suitable nucleophiles (Scheme 16) [39]. A similar reaction was performed earlier, with an intermediate separation of the reactants [40].

The microreactor system consists of a pumping module (R2+) and a four-channel heated component (R4). Two independently conducted flow streams are mixed in a T-piece and driven through a convection-flow coil (CFC, volume 10 ml) made of poly(fluoroacetate) (PFA). After the CFC, the flow is guided through Omnifit glass columns [41] packed with immobilized scavengers.

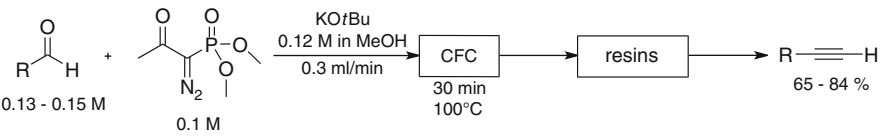
Diphenylphosphoryl azide (DPPA) was used as an azide source. The reaction was performed on a range of aromatic and aliphatic carboxylic acids. Acyl azides were formed quickly at room temperature; however, elevated temperatures were necessary for the rearrangement step. A variety of nucleophiles were successfully used to obtain a library of 29 products. Both one-flow and two-flow approaches were successful (all reactants injected via one or via two inlets). After the reaction, the resulting stream was purified by passage through columns containing a trimethylamine resin (Amberlyst 21) to remove the excess of the diphenylphosphonic acid formed in the activation step as well as the unreacted carboxylic acid, and a sulfonic acid resin (Amberlyst 15) to remove the triethylamine base from the reaction. After this step, the solvent was evaporated from the resulting flow, which was enough to obtain the products in sufficient purity (>90%) and in the yields of >75%.

Alternatively, microwave heating to 120°C was used for the synthesis of Boc-protected aniline because of the lower nucleophilicity of *tert*-butanol.

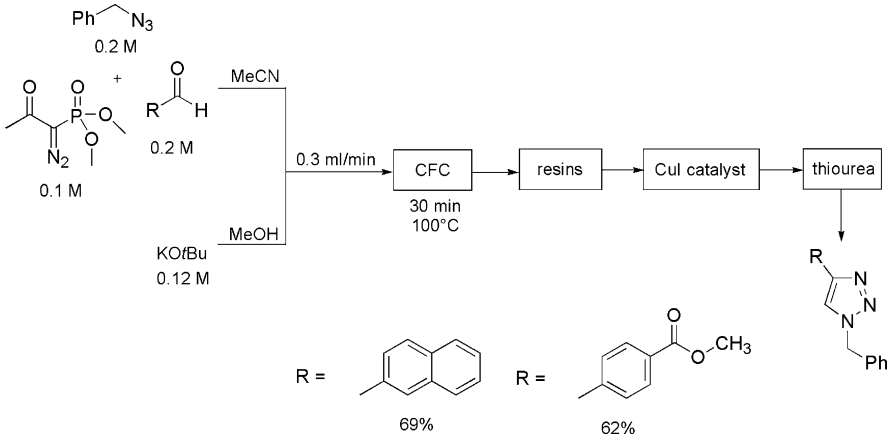
2.7 Formation of Triazoles Using the Bestmann–Ohira Reagent

In another series of experiments, the Ley research group [42] has used a Bestmann–Ohira reagent (dimethyl 1-diazo-2-oxopropylphosphonate [43]) to synthesize various alkynes and triazoles starting from aldehydes in the same Vapourtec system [38] combined with Omnifit glass columns [41].

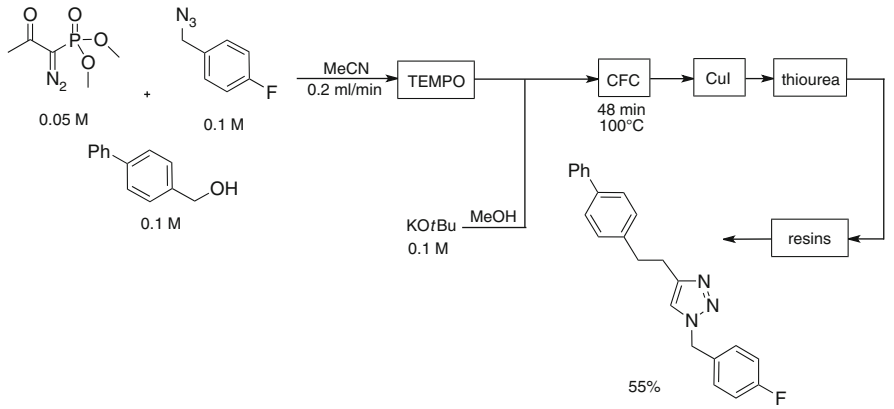
In the initial trials, a library of alkynes was synthesized from various aldehydes (Scheme 17). On the exit of the convection-flow coil, the flow was guided through a series of resin-filled glass cartridges to remove the side products and the unreacted materials and to afford the end stream with sufficient purity (>95%).



Scheme 17 Flow synthesis of terminal alkynes using the Bestmann–Ohira reagent [42]



Scheme 18 A three-component formation of triazoles from aldehydes [42]



Scheme 19 A three-step synthesis of triazole using Bestmann–Ohira reagent starting from an alcohol [42]

After the optimization of these conditions, by adding an azide to the input stream it was possible to synthesize a range of substituted triazoles in a heterogeneously catalysed three-component reaction (Scheme 18). After the CFC, the stream was passed through a column containing a resin-immobilized copper-based catalyst, which was used in a previous work by the same authors to successfully catalyze the formation of triazoles from alkynes and azides [44]. An immobilized thiourea-containing cartridge was subsequently used to remove any leached Cu catalyst. In a similar way as for the alkynes production, the series of resins was used to purify the product.

An alternative approach consisted of the use of an alcohol as aldehyde precursor since aldehydes are less stable (prone to overoxidation, polymerization or formation

of hydrates) and thus less suitable for this reaction. In this case, a polymer-supported TEMPO in a glass column was added in front of the rest of the columns containing resins and catalyst to selectively oxidize the alcohol to aldehyde. Similar flow conditions yielded the product in >95% purity after crystallization (Scheme 19).

This combined multicomponent multistep approach, including the elegantly solved issues of heterogeneous catalysis and product purification, thus proved successful on a small sample with the possibility of producing larger libraries.

2.8 The Mannich Reaction

The condensation between an aldehyde, an amine and an active methylene compound, named after Carl Mannich, was first published in 1912 [4]. The products of the reaction, α-amino ketones or Mannich bases are important compounds with numerous applications in the synthesis of pharmaceuticals and of natural products [7].

In 1994, Strauss et al. [45] reported a continuous flow microwave-assisted setup to perform a range of synthetic reactions (Fig. 3).

The system was composed from PTFE tubings with a 3 mm internal diameter, which allowed the use of a pressure of 1,400 kPa and a temperature of 200°C. The volume of the reaction coil alone was ca. 85 ml and of the whole system around 110 ml. In this system, the residence times were 1–2 min and flows of 15 ml/min were employed.

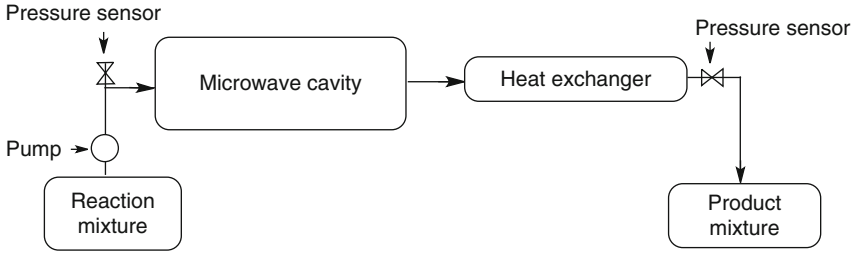
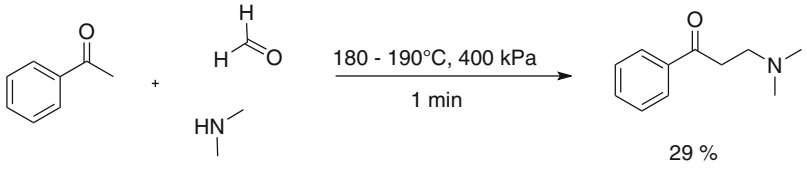


Fig. 3 A continuous-flow microwave-assisted setup [45]



Scheme 20 A microwave-assisted Mannich reaction performed in a continuous flow millireactor [45]

Various processes were tested, and among others, a Mannich-type reaction was performed (Scheme 20). The yield was modest but the reactor design was appealing and the methodology was further applied in the research group [46].

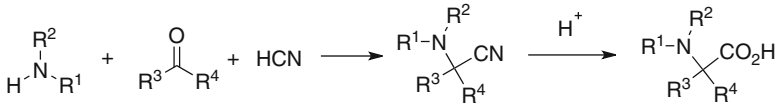
3 Multicomponent Multistep Reactions Performed in Microreactors

3.1 The Strecker Reaction

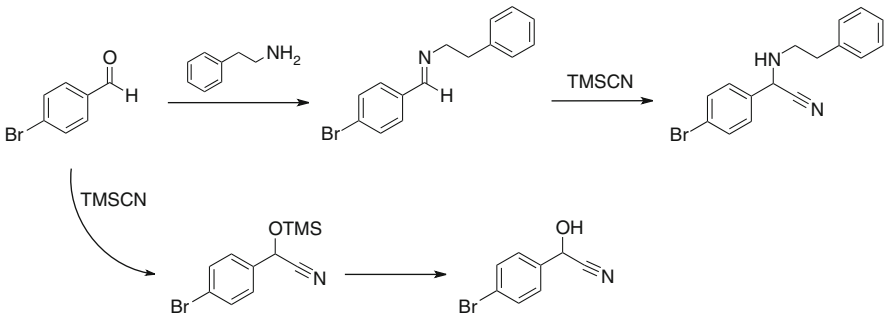
First published in 1850 [1], the Strecker reaction (Scheme 21) is a convenient tool for the synthesis of α-amino acids. Originally it was reported as a condensation of an aldehyde, ammonia and a cyanide source in buffered aqueous medium to form an α-amino nitrile, which is then hydrolysed to an α-amino acid [47, 48].

Alternatively, the nitriles can be further converted to a range of other molecules [49, 50]; yet, the synthesis of the α-amino acids (especially non-proteinogenic amino acids) remains the most important industrial application of this reaction because of its simplicity and the availability of the starting materials [47, 51].

Various adaptations of the original procedure have been reported over the years, with variations in catalysts and conditions [7, 8, 52]. However, most of these procedures still encounter a range of shortcomings: the need for elevated reaction temperatures, extended reaction times, expensive homogeneous catalysts or an excess of the cyanide source, variable yields and most notably competing cyanohydrin formation that can occur (Scheme 22) [48]. This problem is usually bypassed,



Scheme 21 The Strecker reaction



Scheme 22 The model Strecker condensation and the side reaction of cyanohydrin formation [48, 53]

also in industry, by the pre-formation of imines, thus by the indirect performance of the reaction [52]. However, this additionally complicates the process because the first step of the reaction, the imine formation, needs to be monitored and controlled. Because of the facile reaction control and modification of the conditions, microreactor technology offers a convenient solution to this problem.

Wiles and Watts [48, 53] have reported the use of a rather successful heterogenic catalytic system to carry out these reactions. They have tested a borosilicate glass microreactor (dimensions: 3.0 × 3.0 × 0.6 cm) consisting of two etched layers with two inlets, mixing channels, a larger etched region and the outlet. A solid-supported catalyst was dry-packed in this structure (Fig. 4).

In a first series of trials, trimethylsilyl cyanide (TMSCN) was used as the cyanide source and polymer-supported (ethylenediaminetetraacetic acid) ruthenium(III) chloride as the Lewis acid catalyst (Scheme 23). After the optimisation of the conditions on a model reaction, a small library of compounds was produced, proving the concept by obtaining 100% yields in 2.5 h reaction time. Using flow rates of

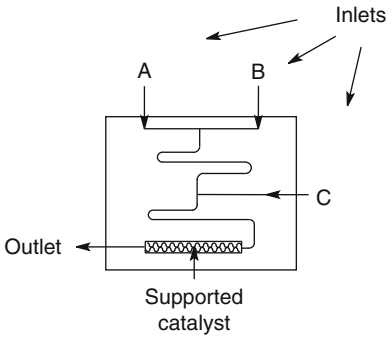
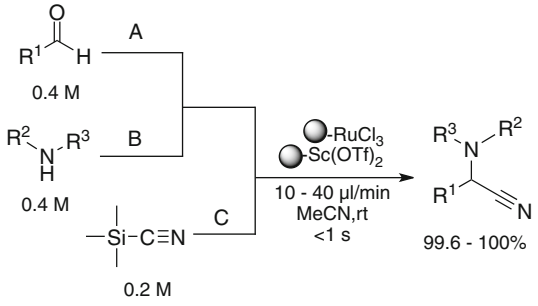


Fig. 4 The microreactor assembly for the Strecker reaction conducted under continuous flow [48, 53]



Scheme 23 The Strecker reaction as performed by Watts et al. [48, 53]

R^1 = Ph, di-*m*-OMePh, *p*-BrPh, *p*-ClPh, *p*-$COOCH_3$Ph
R^2 = $Ph(CH_2)_n$, n= 0 - 3
R^3 = H ; R^2/R^3 = $(CH_2)_4$ (proline)

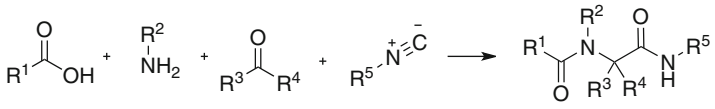
10 μl/min, the productivities were in the range of 17.2–19.7 mg/h. After solvent evaporation, no additional purification was needed. Reactions were conducted at room temperature since the initial heating to 40°C caused the leaching of Ru metal from the catalyst. Doubling the flow rate, the output (expressed in gram per hour) was increased by approximately 50%.

Alternatively, the authors have evaluated the polymer-bound scandium(III) bis (trifluoromethanesulfonate) as catalyst, and it proved to be slightly more active than the previous one. In a series of runs, the authors have re-evaluated the method and produced a library of 50 α-aminonitriles starting from aliphatic and aromatic aldehydes. In all runs, the reported yields were >99.6%.

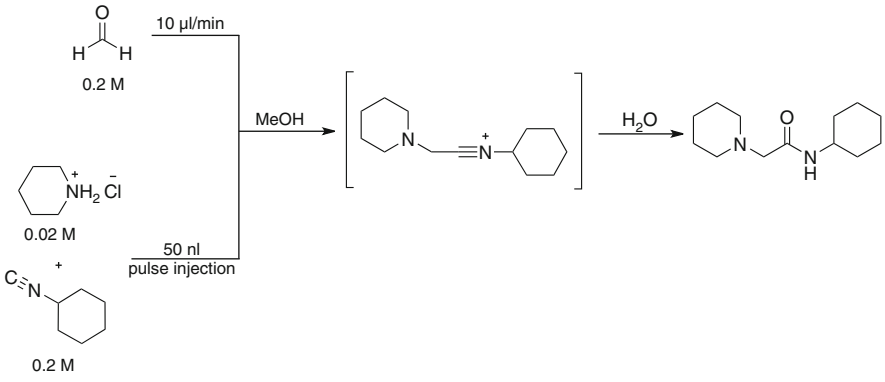
In this way, the authors have proven several significant advantages of the reactions performed in a microreactor: shorter reaction times, improved atom efficiency, excellent product yields and purities, efficient catalyst recycling and the increased safety of the reaction, thanks to the closed system which prevents the release of the cyanide.

3.2 *The Ugi Four-Component Condensation*

First reported in 1959 [54], this four-component reaction involves a carbonyl compound, an amine, an isocyanide and a carboxylic acid to form a diamide (Scheme 24).



Scheme 24 The four-component Ugi reaction



Scheme 25 Ugi reaction protocol applied in a μSYNTAS system [57]

Since its first introduction, the reaction proved useful for a number of applications, and a large number of variations have been reported; it is especially useful in medicinal chemistry for the synthesis of a range of active compounds [55].

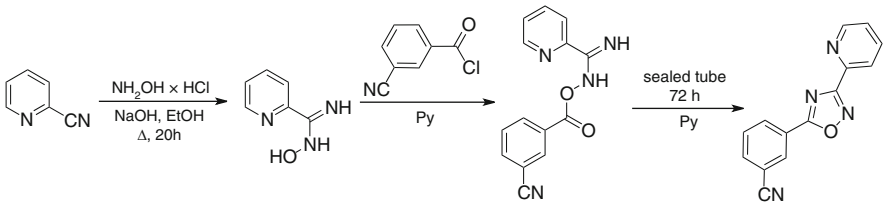
De Mello et al. have constructed a so-called μSYNTAS (miniaturized synthesis and total analysis system). The system was used to perform an Ugi-type reaction to form several α-aminoacetamides from amines, isocyanates and formaldehyde in the presence of water (Scheme 25) [56–58]. The reported system consists of a glass/silicon nanoreactor [59] in connection to a TOF-MS for the real-time online analysis of the reaction stream. Reactions were conducted in the 600 nl volume chip under continuous flow of 20–2 μl/min flow rate. Reduced flow rates resulted in increased outputs. The analyzed outlet flow showed high yields of the desired products with small quantities of starting materials and intermediates (no exact yields were reported).

The miniaturized conditions provided a suitable setting for this reaction, affording several important benefits. First, in microreactor environment this highly exothermic process demanded no additional cooling, whereas the reaction in batch needs to be conducted at 0°C. In addition to this, instant TOF-MS analysis proved the formation of the nitrilium cation intermediate, thus proving the reaction mechanism that was speculative until then. Another advantage of the reactor directly connected to the analyzer is the convenience and the speed of the reaction optimization.

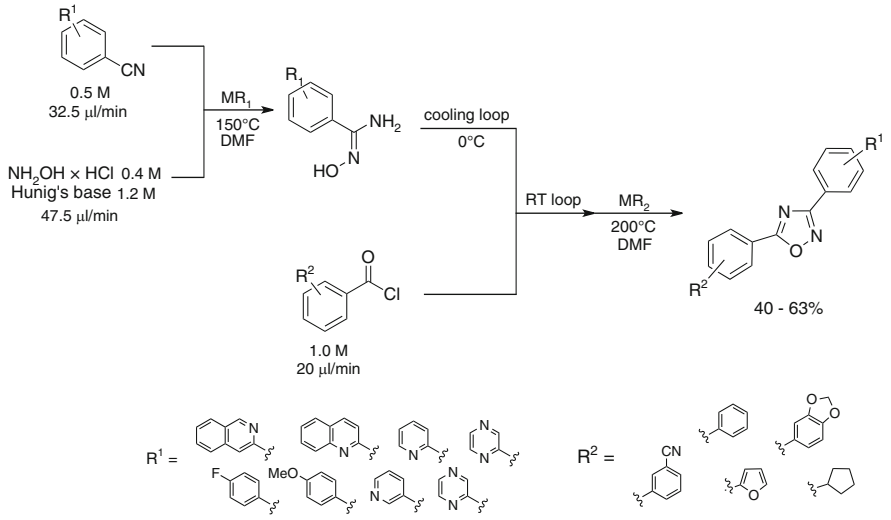
3.3 Trisubstituted Oxadiazoles

1,2,4-Oxadizole-containing structures are commonly found in biologically active molecules and are used in several drugs and drug precursors [60]. Typically, the production route leading to these scaffolds consists of two steps: in the first one, arylnitriles and hydroxylamine react to afford the corresponding amidoxime; in a second step, the amidoxime is cyclized using an acid chloride (Scheme 26) [61].

The final step poses difficulties to the process since it requires long reaction times and often needs to be performed in a sealed tube. Recently, improvements of the process were reported, including the use of microwaves [62]. However, microwaves-promoted reactions are not suitable for a convenient scale-up at the moment.



Scheme 26 Batch synthesis of disubstituted 1,2,4-oxadiazoles [61]



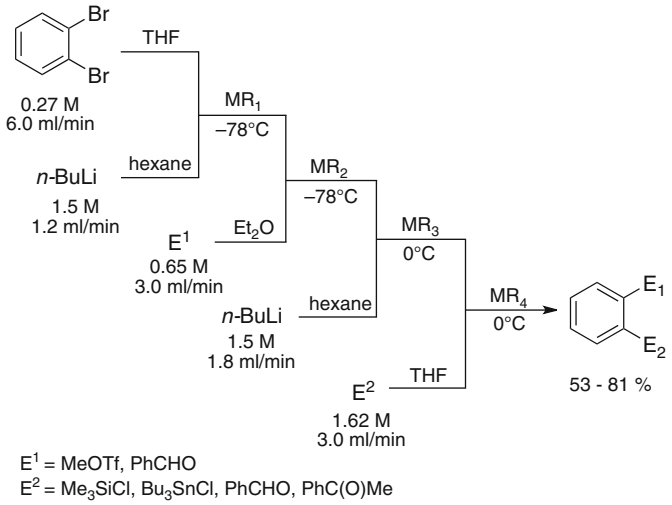
Scheme 27 The synthesis of disubstituted 1,2,4-oxadiazoles in a microreactor setup [60]

Cosford et al. [60] have used a commercial Syrris Africa system [14] to synthesize a library of 1,2,4-oxadiazoles (Scheme 27). By a multistep procedure using connected microreactors in a single sequence, the procedure was performed in an efficient way: the intermediate product purification was avoided and the reaction time was considerably reduced from several days to 30 min.

The steps were initially followed in order to optimize the conditions. In the preliminary experiments, the conversions to amidoximes (first step) were complete within 6 min at 150°C. The second step, cyclization to the final product, was finished after 10 min at 200°C and 7.5–9.0 bar. The stream of the intermediate amidoxime needed to be cooled before the reaction with the acid chloride, and this is achieved by introducing a cooling loop at 0°C.

This general procedure was applied to a variety of scaffolds to produce a small library of compounds. After the work-up and preparative HPLC, the final yields were in the range of 40–63%, which is comparable to the previously reported batch procedures. A typical 35 min run finally gave 0.5 mmol of the product that afforded 40–80 mg after the HPLC purification; this accounts to approximately 80–160 mg/h productivity.

A similar procedure was applied in the production of 3-(3-aryl-1,2,4-oxadiazol-5-yl)propanoic acids; succinic anhydride was used instead of the acid chloride and the yields of these reactions were similar to the previous trials (46–62%).



Scheme 28 Sequential reactions of *o*-dibromobenzene with two different electrophiles [63]

3.4 Electrophilic Substitution on Benzene Ring

Yoshida et al. [63] applied microreaction technology for the sequential synthesis and the disubstitution of *o*-bromophenyllithium (Scheme 28). Lithiation of *o*-dibromobenzene in batch leads to the formation of the highly reactive benzyne and to the further creation of various side products; thus this reaction needs to be conducted at −100°C and below to avoid this problem. This reaction was optimized under microreactor conditions for the production of *o*-bromophenyllithium and for its further reaction with methanol to determine the yield of bromobenzene. Microreactors were set up of stainless steel tubes with an internal diameter of 250–1,000 μm.

After the optimization of the conditions for the production of *o*-bromophenyllithium to −78°C with a 0.8 s residence time, the scope was extended to sequential Br–Li exchange of both bromine substituents on the benzene ring and the reaction with electrophiles to form *o*-disubstituted benzene rings. This was done in a four-step reaction in one flow using four-linked microreactors ($MR_{1–4}$). For the second lithiation, the temperature of 0°C was sufficient, which was expected since the aryllithium intermediate is more stable than *o*-bromophenyllithium.

In this way, the authors proved that microreactor technology is a useful tool in handling highly unstable intermediates in a way that is easy to control. The reactions were conducted using less harsh conditions (higher temperatures were possible due to the thermal efficiency of the system) and in short reaction times.

Further, the authors were able to perform similar reactions on *p*- and *m*-dibromobenzenes at 20°C, which is a significant improvement in comparison to batch mode conditions that demand temperatures below −48°C. They have applied the same four-membered system for sequential introduction of two lithium atoms to the

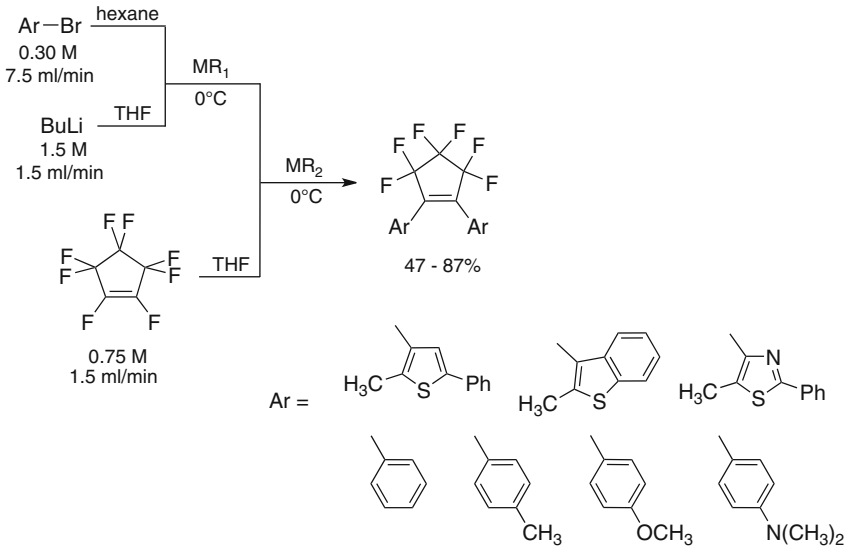
aromatic core and their substitution with a range of electrophiles, with yields similar to the previously reported *o*-disubstituted derivatives [64].

The same system is further applied to various dibromobiaryls and resulted in the successful production of unsymmetrically substituted biaryls [65].

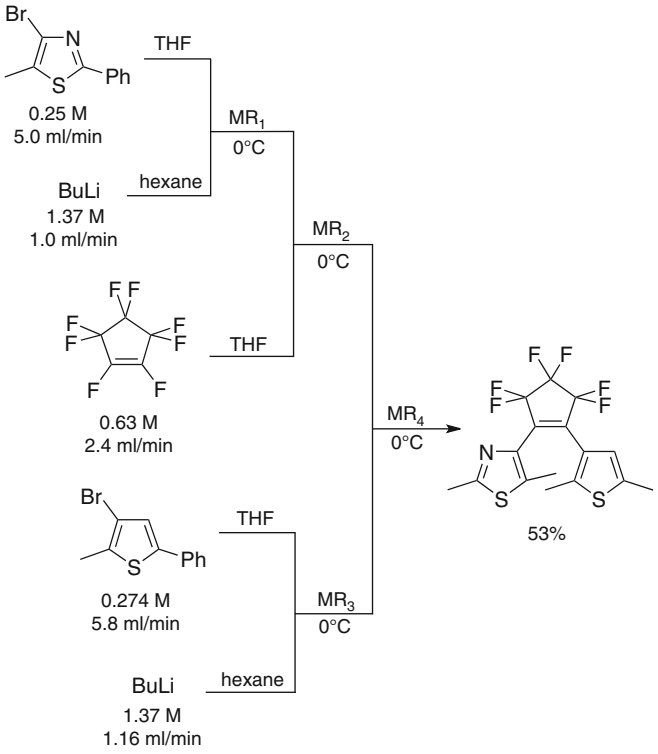
3.5 *Diarylethenes*

Following similar trials with the formation of diarylbenzenes [63–65], the same research group has reported a multistep synthesis of photochromic diarylethenes using a microflow system that contained two linked micromixers and microreactors (MR_{1-2}) [66]. Similarly to the previously reported linked microreactors, the reactors used in this setup were made of stainless steel tubes and T-shaped micromixers. Initial experiments were conducted in two steps in a continuous sequence to afford symmetrical octasubstitued diarylhexafluoro cyclopentene (Scheme 29).

Analogously to the previous work, a significant improvement was achieved using much shorter reaction times (seconds instead of hours) and less stringent conditions in comparison to the previously reported batch procedures: a temperature of 0°C was sufficient to perform the reaction successfully, while in batch a temperature of −78°C was necessary to avoid the formation of numerous side products. Also, the batch reaction demanded the intermediate isolation of the monosubstituted derivative before the second reaction with the aryllithium, as the main reaction product was the monosubstituted derivative, while under



Scheme 29 Initial trials affording symmetrical diarylethenes [66]



Scheme 30 Synthesis of an unsymmetrical diarylethene using a multistep microflow system [66]

microreactor conditions it was possible to perform the reaction in one step using two mole equivalents of an aryllithium (Scheme 30).

The reaction scope is further enlarged to unsymmetrically disubstituted derivatives. Using one mole equivalent of two different aryllithium precursors at a time in a sequence of four micromixers and microtube reactors ($MR_{1–4}$), it was possible to obtain an unsymmetrically disubstituted final diarylethene. The yield was determined after solvent evaporation and sample purification on the column.

3.6 Azo-Dyes

Azo-dyes are important in medicinal chemistry in the treatment of Crohn's disease and ulcerative colitis [67], and the Sudan series of azo-dyes are commonly used as microbial stains [68]. Diazonium salts are intermediates in the production route of these useful structures. Diazonium salts are instable and explosive, which imposes

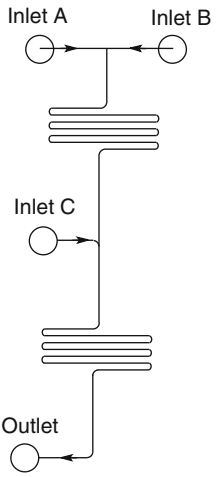
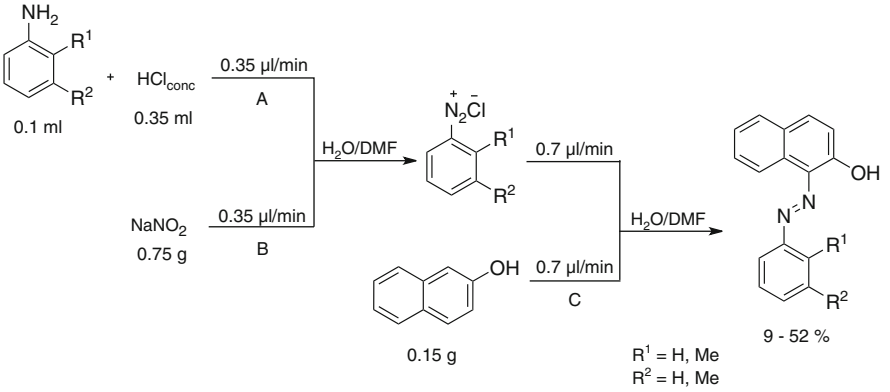


Fig. 5 A monolithic nanoreactor used for the production of azo-dyes [68]

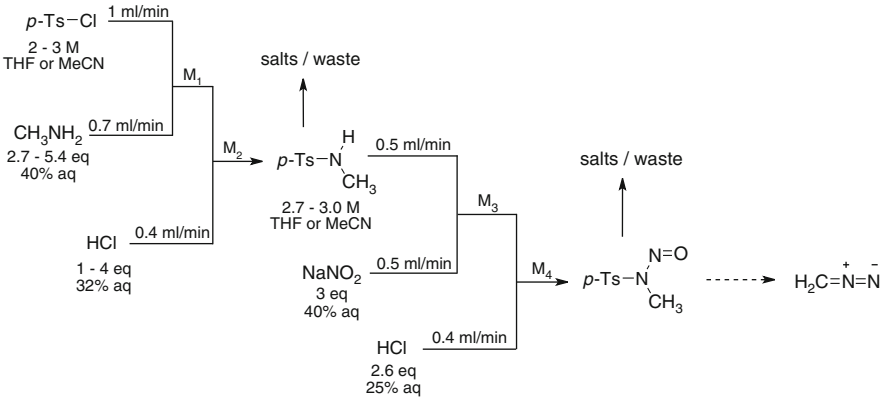


Scheme 31 The production of diazo compounds in a two-step continuous flow [68]

the need of high security levels in the industrial environments dealing with these processes. Microreactor technology offers a simple control of this hazard, thanks to the small scale and the flow conditions.

De Mello et al. [68] have produced several azo-dyes by the conversion of an aromatic amine to a diazonium salt and its reaction with β-naphtol in a monolithic nanoreactor (Fig. 5).

The reactor consisted of two inlets with a serpentine delay section and an additional inlet to perform the addition of the reagent in the second step. Channels were of 150 µm width and 50 µm depth. The amine and sodium nitrite solutions were injected separately at a rate of 3.5 µl/min, and β-naphtol was added via the third inlet at a flow rate of 7 µl/min (Scheme 31).



Scheme 32 Multistep synthesis of MNTS and the in situ liberation of diazomethane [70]

Reactions were conducted at room temperature. The monolithic design of the device led to the increased safety of the process. The authors assigned the variable yield of the reaction to the non-optimized conditions. However, they have proved the principle of conducting the reactions containing diazonium salts in a safe way at room temperature, which is not possible on macroscale and batch conditions.

3.7 N-*Methyl*-N-*Nitroso*-p-*Toluenesulfonamide*

N-Methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) is an important precursor for the production of diazomethane. Diazomethane is then further converted to a range of useful molecules in the pharmaceutical and fine chemical industry [69]. Production of MNTS is a highly exothermic process and includes the presence of the extremely toxic materials. Stark et al. [70] have explored the application of microreactor technology for the production of this industrially valuable material, assuming that due to the efficient heat exchange and the closed system, microflow conditions provide a safer environment for these hazards.

After initial batch optimization of the solvent, concentrations and molar quantities of the reagents, the transfer to a continuous setup was conducted. The microreactor was a commercially available glass unit from Little Things Factory GmbH [71], of dimensions 1.4 × 1.8 × 125 mm and of internal volume 0.12 ml, consisting of four layers with mixing elements distributed over the whole length. The glass units were combined with the PTFE capillaries connected to a PTFE micromixer to form a set up of four micromixers ($M_{1–4}$).

After the first step of the *N*-methyl-*p*-toluenesulfonamide production, the sulfonamide containing organic solvent stream is gravimetrically separated from the

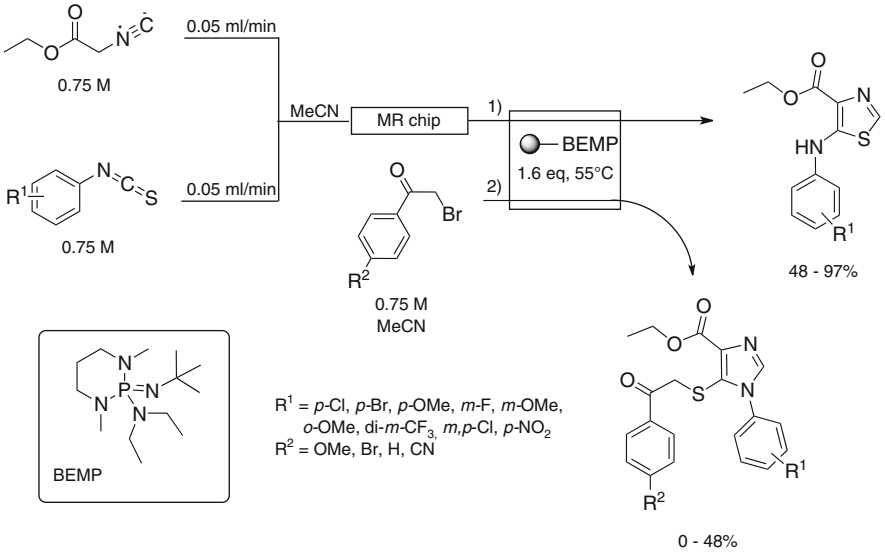
waste containing the water layer and is continuously fed without intermediate purification into mixer M_3 where it is submitted to nitrosation. Overall yields of the whole process are in the range of 70–80% (Scheme 32).

MNTS produced in this way is further converted to diazomethane in a microreactor setup as reported previously by the same research group [72].

3.8 *Trisubstituted Imidazoles by a Bifurcated Pathway to 5-Aminothiazoles*

A base-mediated condensation of an isocyanide and an isothiocyanate gives 4,5-disubstituted thiazoles, as first reported by Matsumoto et al. in 1982 [73]. In subsequent work by Solomon et al., a regioisomeric imidazole was observed as a side-product due to the flexibility of the route that allows facile introduction of a substituent on the exocyclic nitrogen atom [74]. Baxendale et al. [75] explored this reaction under microflow conditions (Scheme 33).

The system was assembled from HPLC pumps and a micromixer chip from Syrris [14] combined with Omnifit glass columns [41] containing polymer-supported catalysts, reagents or scavengers. The Vapourtec R4 module [38] was used to control the reaction temperature, and the progress of the reaction was followed by an online assembled UV-unit. In a typical procedure, ethyl isothiocyanate and 4-bromophenyl isothiocyanate in a MeCN solution were mixed in a chip and injected in a glass column containing a polystyrene-immobilized phosphazene base (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine,



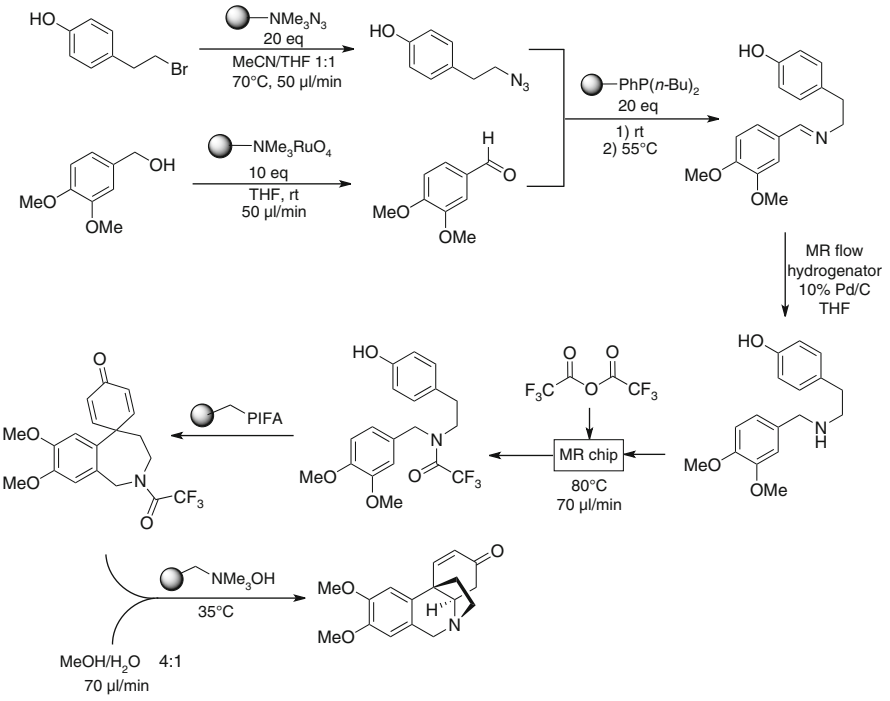
Scheme 33 Synthesis of 4,5-disubstituted imidazoles [75]

PS-BEMP). The reaction gave 4,5-disubsituted isothiazole in 58% yield. What was interesting was that an additional washing of the immobilized base with an electrophile (in a typical setup, 2,4′-dibromoacetophenone) gave the corresponding 1,4,5-trisubstituted imidazole in 38% yield and >95% purity. Additional efforts were done to produce only the imidazole structure by using the premixed electrophile and ethyl isothiocyanate, however, without success.

Technically, the 1,4,5-trisubstituted imidazoles are the side products of the above mentioned isothiazoles production. However, the results are reproducible (confirmed in a series of trials) and the reported bifurcation is an interesting method of extrapolating the microflow applications.

3.9 *Multistep Synthesis of Oxomaritidine*

The Ley research group [76] developed a flow process for the multistep synthesis of (±)-oxomaritidine, an alkaloid found in the *Amaryllidaceae* family, known to have antineoplastic activity (Scheme 34) [77, 78]. The route does not involve intermediate purification of the products, which is necessary in the previously reported

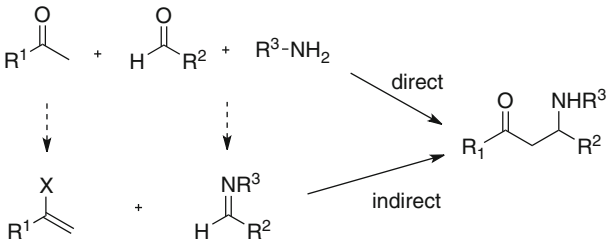


Scheme 34 A continuous flow synthesis of (±)-oxomaritidine [76]

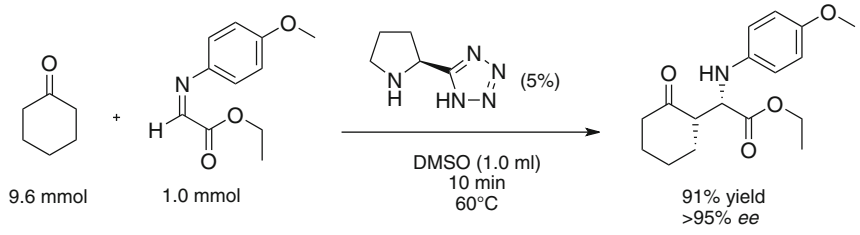
syntheses [79], and it also affords an important saving in time as it requires less than a day of operation as opposed to four days required for the multistep batch operations due to the necessary purification of intermediates.

The sequence includes several synthetic steps over polymer-supported catalysts in directly coupled commercially available Omnifit glass reaction columns [41] using a Syrris Africa microreactor system [14], Thales H-Cube flow hydrogenator [32] and a microfluidic chip. The process affords the alkaloid in 90% purity after solvent evaporation, but in a moderate 40% yield. After a closer investigation it was concluded that this is due to the poor yield of 50% in the phenolic oxidation step. On condition that this is resolved with the use of a more effective supported agent, the route would provide satisfactory yields and purities of the product.

The route is, however, important as it shows the possibility of passing from multistep sequences in batch that usually require intermediate isolation and purification in between steps to a continuous sequence using flow chemistry that produces the desired molecules requiring a minimum purification at the end and providing important savings in time and resources.



Scheme 35 Direct and indirect Mannich reaction [52]



Scheme 36 Mannich reaction as performed by Odedra and Seeberger [84]

4 Multicomponent Reactions Using Preformed Intermediates

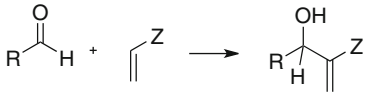
4.1 The Mannich Reaction

When performing a Mannich reaction in its initial three-component design, the selectivity is sometimes difficult to obtain due to the competition with the side processes, primarily the auto-aldol condensation [52, 80]. A common solution for this problem is the pre-formation of an imine or the enolate, or both and thus the sequential (indirect) performance of the reaction (Scheme 35) [52].

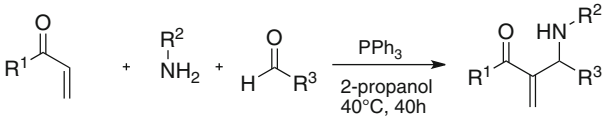
The problem of competitive reactions can also be overcome by the use of specific catalysts; proline and its derivatives proved to be effective and enantiomeric-specific organic catalysts [80–83].

Odedra and Seeberger [84] have successfully applied microreactor technology for the asymmetric aldol condensation between acetone and various aromatic aldehydes catalysed by a proline derivative, 5-(pyrrolidin-2-yl)tetrazole (Scheme 36). A glass microreactor with 1.0 ml capacity was used in these experiments. Proline-catalysed aldol condensation is generally a long reaction, taking up to several days, and requires heavy catalyst loading, up to 35% [82, 84]. Under microreactor conditions, the initial screening showed that it was possible to keep the yields while reducing the reaction time by increasing the temperature. Because of the better thermal profile of the microreactor, the enantiomeric purities of the products were retained as well. Reduced catalyst loading (5%) resulted in maintained yields and purities.

After the initially performed aldol condensations and the process optimisation, the scope of the reaction was further extended to an enantiomeric Mannich reaction. The authors started from *N*-PMP-protected α-imino ethyl glyoxylate and cyclohexanone in the presence of 5% catalyst loading. In 10 min at 60°C, the conversions were complete and the β-aminoketone was obtained in 91% yield and >95% *ee* after purification on column.



Scheme 37 The original Morita–Baylis–Hillman reaction [85, 86]



R^1 = Ts, Z, Boc
R^2 = Ph, *n*-Pr
R^3 = H, Me

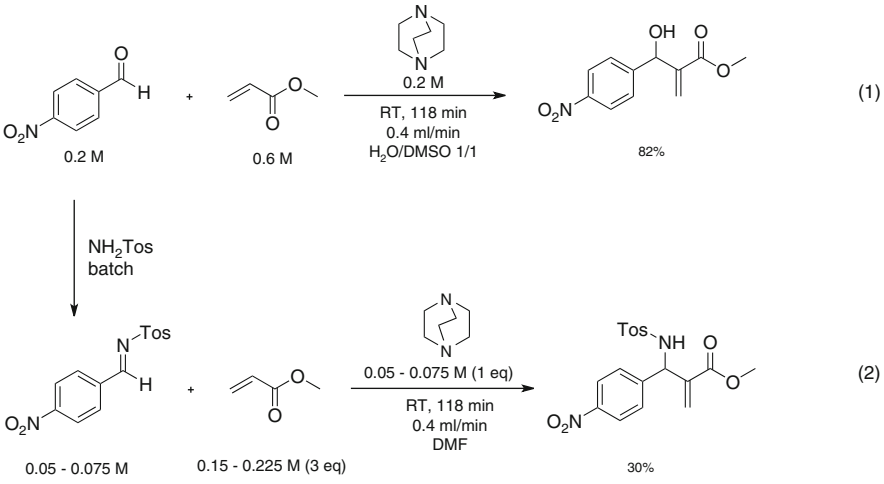
Scheme 38 The first reported three-component aza-Baylis–Hillman reaction [91]

4.2 Aza-Baylis–Hillman Reaction

The phosphine-catalysed reaction between an aldehyde and an acrylate yielding β-hydroxy-α-methylene structures was first described by Morita et al. in 1968 (Scheme 37) [85]. In 1972, Baylis and Hillman [86] used a tertiary amine as catalyst and improved the yield of this reaction.

The aldehyde can be replaced by an imine and the reaction is then called the aza-Baylis–Hillman reaction [87, 88]. β-Amino-α-methylene structures obtained in this way could further be converted to a range of biologically important molecules, such as β-amino acids [89]. First reaction of this kind was published in 1984 [90]. Tosylimines and ethylacrylate reacted in the presence of DABCO as catalyst to give β-aminoesters. First three-component aza-Baylis–Hillman reaction was published in 1989 by Bertenshaw and Kahn [91], with imine formation in situ from an aldehyde and an amine. In the presence of triphenylphosphine as catalyst, the reaction with methylacrylate led to the formation of the β-amino-α-methylene esters and ketones in good yields (Scheme 38).

The conversion rate in aza-Baylis–Hillman reactions is generally low, which leads to extended reaction times [87]. Heating is normally used to increase the reaction speed; however, it also promotes the formation of side products. Alternatively, microwave heating was successfully used as a way of promoting the reaction [92]. However, microwaves-promoted reactions are not easy to scale-up. Guided by this, the Stevens research group [89, 93] used the commercial CYTOS College System [18] to perform these reactions on a microscale in a continuous manner in order to improve the reaction rates and make it industrially more applicable.

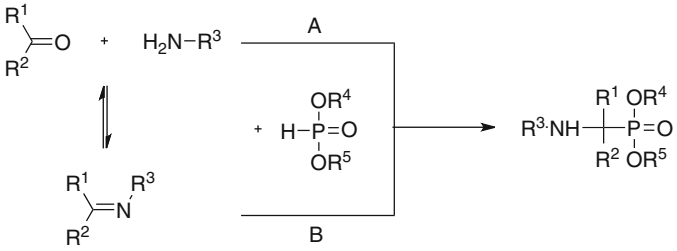


Scheme 39 Baylis–Hillman (1) and aza-Baylis–Hillman reaction (2) [89]

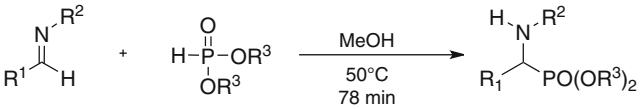
Initial experiments were performed with a Baylis–Hillman setup, with *p*-nitrobenzaldehyde and methyl acrylate, in the presence of DABCO as catalyst (Scheme 39). Optimized conditions with a 118 min residence time (30% faster than the required time under batch conditions) at room temperature and 0.4 ml/min flow resulted in encouraging conversions and yields (up to 93 and 82%, respectively).

The scope was then extrapolated to the two-step three-component aza-Baylis–Hillman setup to obtain β-amino-α-methylene structures. A two-step approach was chosen to avoid the competition between the aldehyde and the imine for the reaction with the enolate, that would lead to mixtures of Baylis–Hillman and aza-Baylis–Hillman adducts, that is β-hydroxy and β-amino esters [87].

Unfortunately, starting from the preformed imine and acrylate under conditions optimized for the Baylis–Hillman reaction, the authors could not reproduce the results from the Baylis–Hillman trials: they obtained only conversions up to 46% and yields of up to 30% (Scheme 39) [89].

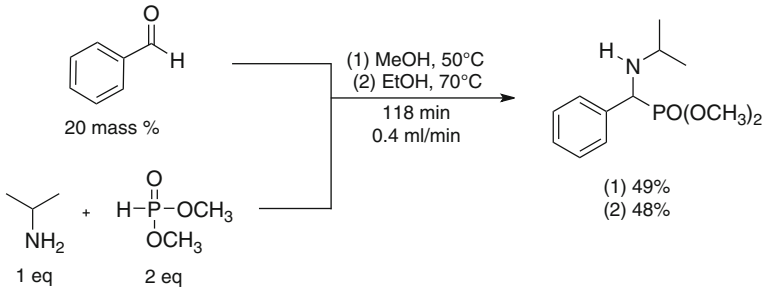


Scheme 40 Formation of α-aminophosphonates by a three-component (**a**) or a two-component (**b**) route [97]



R^1 = Ph, 2-phenylethenyl, *c*-Hex, *i*-Pr, 2-furyl
R^2 = *i*-Pr, allyl
R^3 = Me

Scheme 41 Synthesis of α-aminophosphonates [98]



Scheme 42 The three-component Kabachnik–Fields reaction in the microreactor setup [89]

4.3 α-Aminophosphonates

α-Aminophosphonates are an important class of organic compounds showing various pharmacological activities [7]. Several methods have been suggested for their production [7]. The classical method is a three-component reaction between a carbonyl compound, an amine and a dialkyl phosphite, usually known as the Kabachnik–Fields reaction. The reaction was independently reported in 1952 by both Kabachnik [94] and Fields [95]. An alternative method is the so-called Pudovik reaction, in which the corresponding imine reacts with a dialkylphosphite (Scheme 40) [96].

Lewis acids are usually used as catalysts for the Pudovik reaction [97]. On the contrary, the Stevens group [98] performed the reaction in a microreactor and proved that it can be successfully performed in the absence of any catalyst. The authors were guided by the reaction as reported by Fields in 1952 (performed in the absence of catalysts and also solvents), but certain modifications had to be applied to make the process suitable for continuous flow microreactor conditions, that is the use of methanol as a reaction promoting solvent.

The commercial CYTOS College System [18] was used in this work. The imine was preformed in batch. After the optimisation, similar yields in comparison to the batch conditions were obtained with productivities of 8.2–10.7 g/h (Scheme 41).

Using the optimized system for the two-component reaction, the same group [89] tested the three-component reaction, starting from an aldehyde, an amine and a phosphite (Scheme 42). An orthoester (trialkyl orthoformate, methyl or ethyl) was added to remove the formed water and to promote the imine formation, which was beneficial for the reaction; however, these trials afforded maximally 49% yield due to the low conversions and low selectivities towards the desired aminophosphonates.

5 Conclusion

The concept of multicomponent reactions performed under microreactor conditions presents a very promising direction in the exploration of novel production routes in

chemical research, especially in drug discovery. Multiple combinatorial possibilities and the ease of process control and optimization allow significant savings in time and materials. An overview of the current achievements in the combination of the two approaches, given in this chapter, confirms the expected benefits and the improvement of the chemical processes in a large majority of investigated applications. It has to be noted that this is a relatively new area of research, and thus the amount of published work is still limited; however, having in mind the advantageous possibilities of the technology and the intensive research focused on new application of microreactors in organic synthesis, an exponential increase in published work is expected in the very near future.

References

1. Strecker A (1850) Ueber die künstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper. Ann Chem Pharm 75(1):27–45
2. Hantzsch A (1882) Ueber die Synthese pyridinartiger Verbindungen aus Acetessigäther und Aldehydammoniak. Liebigs Ann Chem 215(1):1–82
3. Biginelli P (1893) Aldehyde-urea derivatives of aceto-and oxaloacetic acids. Gazz Chim Ital 23:360–413
4. Mannich C, Krösche W (1912) Ueber ein Kondensationsprodukt aus Formaldehyd, Ammoniak und Antipyrin. Arch Pharm 250(1):647–667
5. Passerini M, Simone L (1921) Sopra gli Isonitrili (I). Composto del p-Isonitrilazobenzolo con Acetone ed Acido Acetico. Gazz Chim Ital 51:126–129
6. Bienaymé H, Hulme C, Oddon G et al (2000) Maximizing synthetic efficiency: multi-component transformations lead the way. Chem Eur J 6(18):3321–3329
7. Syamala M (2005) A decade of advances in three-component reactions. A review. Org Prep Proced Int 37(2):103–171
8. Syamala M (2009) Recent progress in three-component reactions. An update. Org Prep Proced Int 41(1):1–68
9. Zhu J, Bienaymé H (eds) (2005) Multicomponent reactions. Wiley-VCH, Weinheim
10. Löhder W, Bergann L (1986) Akademie der Wissenschaften der DDR. DD 246, 257
11. Watts P, Wiles C (2007) Recent advances in synthetic micro reaction technology. Chem Commun 5:443–467
12. Roberge DM, Ducry L, Bieler N et al (2005) Microreactor technology: a revolution for the fine chemical and pharmaceutical industries? Chem Eng Technol 28(3):318–323
13. Roberge DM, Zimmermann B, Rainone F et al (2008) Microreactor technology and continuous processes in the fine chemical and pharmaceutical industry: is the revolution underway? Org Process Res Dev 12(5):905–910
14. www.syrris.com/. Accessed 14 Sept 2009
15. Syrris Ltd (2007) Africa application notes, reaction optimisation (1) http://www.johnmorris.com.au/inetstore/item/321431_opt7.pdf. Accessed 10 Sept 2009
16. Gelens E, De Kanter FJJ, Schmitz RF et al (2006) Efficient library synthesis of imidazoles using a multicomponent reaction and microwave irradiation. Mol Divers 10(1):17–22
17. Acke DRJ, Orru RVA, Stevens CV (2006) Continuous synthesis of tri- and tetrasubstituted imidazoles via a multicomponent reaction under microreactor conditions. QSAR Comb Sci 25(5–6):474–483
18. Schwalbe T, Golbig K, Hohmann M et al (2001) Miniaturized reaction apparatus. YMC Co Ltd, EP 1,123,734

19. Opatz T, Ferenc D (2005) Facile preparation of 3-amino-4-(arylamino)-1*H*-isochromen-1-ones by a new multicomponent reaction. Eur J Org Chem 5:817–821
20. Acke DRJ, Stevens CV (2007) A HCN-based reaction under microreactor conditions: industrially feasible and continuous synthesis of 3, 4-diamino-1H-isochromen-1-ones. Green Chem 9(4):386–390
21. Acke DRJ, Stevens CV, Roman BI (2008) Microreactor technology: continuous synthesis of 1H-isochromeno[3, 4-d]imidazol-5-ones. Org Process Res Dev 12(5):921–928
22. Quiroga J, Mejia D, Insuasty B et al (2001) Regioselective synthesis of 4, 7, 8, 9-tetrahydro-2H-pyrazolo[3, 4-b]-quinolin-5(6H)-ones. Mechanism and structural analysis. Tetrahedron 57(32):6947–6953
23. Lipson VV, Shirobokova MG, Shishkin OV et al (2006) Synthesis of partially hydrogenated pyrazolo[3, 4-b]quinolinones by condensation of 3-amino-5-methylpyrazole with aromatic aldehydes and dimedone. Russ J Org Chem 42(7):1015–1021
24. Jairo Q, Braulio I, Angelina H et al (1998) Synthesis of 4-aryl-4, 7, 8, 9-tetrahydro-6H-pyrazolo[3, 4-b]quinolin-5-ones. J Heterocycl Chem 35(3):575–578
25. Bremner WS, Organ MG (2007) Multicomponent reactions to form heterocycles by microwave-assisted continuous flow organic synthesis. J Comb Chem 9(1):14–16
26. Nair V, Vinod AU, Abhilash N et al (2003) Multicomponent reactions involving zwitterionic intermediates for the construction of heterocyclic systems: one pot synthesis of aminofurans and iminolactones. Tetrahedron 59(51):10279–10286
27. Skoda-Foldes R, Kollar L (2002) Synthetic applications of palladium catalysed carbonylation of organic halides. Curr Org Chem 6(12):1097–1119
28. Boyarskii VP (2008) Catalytic systems for carbonylation of aryl halides. Russ J Gen Chem 78(9):1742–1753
29. des Abbayes H, Salaun JY (2003) Double carbonylation and beyond: systems at work and their organometallic models. Dalton Trans 6:1041–1052
30. Miller PW, Long NJ, de Mello AJ et al (2006) Rapid formation of amides via carbonylative coupling reactions using a microfluidic device. Chem Commun 5:546–548
31. Murphy ER, Martinelli JR, Zaborenko N et al (2007) Accelerating reactions with microreactors at elevated temperatures and pressures: profiling aminocarbonylation reactions. Angew Chem Int Ed 46(10):1734–1737
32. www.thalesnano.com/#. Accessed 15 Sept 2009
33. Csajagi C, Borcsek B, Niesz K et al (2008) High-efficiency aminocarbonylation by introducing CO to a pressurized continuous flow reactor. Org Lett 10(8):1589–1592
34. Balogh J, Kuik Á, Ürge L et al (2009) Double carbonylation of iodobenzene in a microfluidics-based high throughput flow reactor. J Mol Catal A Chem 302(1–2):76–79
35. Rahman MT, Fukuyama T, Kamata N et al (2006) Low pressure Pd-catalyzed carbonylation in an ionic liquid using a multiphase microflow system. Chem Commun 21:2236–2238
36. Fukuyama T, Rahman T, Kamata N et al (2009) Radical carbonylations using a continuous microflow system. Beilstein J Org Chem 5 No. 34
37. Curtius T (1894) 20. Hydrazide und Azide organischer Säuren I. Abhandlung. J Prakt Chem 50(1):275–294
38. www.vapourtec.co.uk. Accessed 14 Sept 2009
39. Baumann M, Baxendale IR, Ley SV et al (2008) A modular flow reactor for performingCurtius rearrangements as a continuous flow process. Org Biomol Chem 6(9): 1577–1586
40. Sahoo HR, Kralj JG, Jensen KF (2007) Multistep continuous-flow microchemical synthesis involving multiple reactions and separations. Angew Chem Int Edit 46(30):5704–5708
41. www.kinesis.co.uk. Accessed 14 Sept 2009
42. Baxendale IR, Ley SV, Mansfield AC et al (2009) Multistep synthesis using modular flow reactors: Bestmann-Ohira reagent for the formation of alkynes and triazoles. Angew Chem Int Edit 48(22):4017–4021

43. Muller S, Liepold B, Roth GJ et al (1996) An improved one-pot procedure for the synthesis of alkynes from aldehydes. Synlett 6:521–522
44. Smith CJ, Iglesias-Siguenza FJ, Baxendale IR et al (2007) Flow and batch mode focused microwave synthesis of 5-amino-4-cyanopyrazoles and their further conversion to 4-amino-pyrazolopyrimidines. Org Biomol Chem 5(17):2758–2761
45. Cablewski T, Faux AF, Strauss CR (1994) Development and application of a continuous microwave reactor for organic synthesis. J Org Chem 59(12):3408–3412
46. Strauss CR (2009) A strategic, 'green' approach to organic chemistry with microwave assistance and predictive yield optimization as core, enabling technologies. Aust J Chem 62(1):3–15
47. Groger H (2003) Catalytic enantioselective Strecker reactions and analogous syntheses. Chem Rev 103(8):2795–2827
48. Wiles C, Watts P (2008) Evaluation of the heterogeneously catalyzed Strecker reaction conducted under continuous flow. Eur J Org Chem 33:5597–5613
49. Enders D, Shilvock JP (2000) Some recent applications of alpha-amino nitrile chemistry. Chem Soc Rev 29(5):359–373
50. Petasis N (2005) Multicomponent reactions with organoboron compounds. In: Zhu J, Bienaymé H (eds) Multicomponent reactions. Wiley-VCH, Weinheim, pp 199–223
51. Yet L (2001) Recent developments in catalytic asymmetric Strecker-type reactions. Angew Chem Int Edit 40(5):875–877
52. Seayad J, List B (2005) Catalytic asymmetric multicomponent reactions. In: Zhu J, Bienaymé H (eds) Multicomponent reactions. Wiley-VCH, Weinheim, pp 277–299
53. Wiles C, Watts P (2008) An integrated microreactor for the multicomponent synthesis of alpha-aminonitriles. Org Process Res Dev 12(5):1001–1006
54. Ugi I (1959) Versuche mit Isonitrilen. Angew Chem Int Edit 71(11):386–386
55. Hulme C (2005) Applications of multicomponent reactions in drug discovery – lead generation to process development. In: Zhu J, Bienaymé H (eds) Multicomponent reactions. Wiley-VCH, Weinheim, pp 311–341
56. Mitchell MC, Spikmans V, Bessoth F et al (2000) Towards organic synthesis in microfluidic devices: multicomponent reactions for the construction of compound libraries. In: van den Berg A, Olthuis W, Bergveld P (eds) Micro total analysis systems, proceedings of the μTAS 2000 symposium. Springer, Netherlands, pp 463–466
57. Mitchell MC, Spikmans V, de Mello AJ (2001) Microchip-based synthesis and analysis: control of multicomponent reaction products and intermediates. Analyst 126(1):24–27
58. Mitchell MC, Spikmans V, Manz A et al (2001) Microchip-based synthesis and total analysis systems (μSYNTAS): chemical microprocessing for generation and analysis of compound libraries. J Chem Soc Perkin Trans 1(5):514–518
59. Bessoth FG, deMello AJ, Manz A (1999) Microstructure for efficient continuous flow mixing. Anal Commun 36(6):213–215
60. Grant D, Dahl R, Cosford NDP (2008) Rapid multistep synthesis of 1, 2, 4-oxadiazoles in a single continuous microreactor sequence. J Org Chem 73(18):7219–7223
61. Slassi A, Van Wagenen B, Stormann TM et al (2002) Heteropolycyclic compounds and their use as metabotropic glutamate receptor antagonists. NPS Pharmaceuticals, Inc. WO/2002/068417
62. Adib M, Jahromi AH, Tavoosi N et al (2006) Microwave-assisted efficient, one-pot, three-component synthesis of 3, 5-disubstituted 1, 2, 4-oxadiazoles under solvent-free conditions. Tetrahedron Lett 47(17):2965–2967
63. Usutani H, Tomida Y, Nagaki A et al (2007) Generation and reactions of *o*-bromophenyllithium without benzyne formation using a microreactor. J Am Chem Soc 129(11):3046–3047
64. Nagaki A, Tomida Y, Usutani H et al (2007) Integrated micro flow synthesis based on sequential Br-Li exchange reactions of *p*-, *m*-, and *o*-dibromobenzenes. Chem Asian J 2(12):1513–1523

65. Nagaki A, Takabayashi N, Tomida Y et al (2009) Synthesis of unsymmetrically substituted biaryls via sequential lithiation of dibromobiaryls using integrated microflow systems. Beilstein J Org Chem 5:11
66. Ushiogi Y, Hase T, Iinuma Y et al (2007) Synthesis of photochromic diarylethenes using a microflow system. Chem Commun 28:2947–2949
67. Peppercorn MA (1984) Sulfasalazine – pharmacology, clinical use, toxicity, and related new drug development. Ann Intern Med 101(3):377–386
68. Wootton RCR, Fortt R, de Mello AJ (2002) On-chip generation and reaction of unstable intermediates-monolithic nanoreactors for diazonium chemistry: azo dyes. Lab Chip 2(1):5–7
69. McKervey MA, Miel H, Hodgson A (2008) Diazocarbonyls: versatile intermediates in chemical synthesis. SP2 7(9) http://www.almacgroup.com/papers/Papers/Diazocarbonyls%2024Oct2008.pdf. Accessed 17 Sept 2009
70. Struempel M, Ondruschka B, Stark A (2009) Continuous production of the diazomethane precursor N-methyl-N-nitroso-*p*-toluenesulfonamide: batch optimization and transfer into a microreactor setup. Org Process Res Dev 13(5):1014–1021
71. http://www.ltf-gmbh.de. Accessed 22 Sept 2009
72. Struempel M, Ondruschka B, Daute R et al (2008) Making diazomethane accessible for R&D and industry: generation and direct conversion in a continuous micro-reactor set-up. Green Chem 10(1):41–43
73. Suzuki M, Moriya T, Matsumoto K et al (1982) Synthesis of amino-acids and related compounds. 25. A new convenient synthesis of 5-amino-1, 3-thiazole-4-carboxylic acids. Synthesis 10:874–875
74. Solomon DM, Rizvi RK, Kaminski JJ (1987) Observations on the reactions of isocyanoacetate esters with isothiocyanates and isocyanates. Heterocycles 26(3):651–674
75. Baxendale IR, Ley SV, Smith CD et al (2008) A bifurcated pathway to thiazoles and imidazoles using a modular flow microreactor. J Comb Chem 10(6):851–857
76. Baxendale IR, Deeley J, Griffiths-Jones CM et al (2006) A flow process for the multi-step synthesis of the alkaloid natural product oxomaritidine: a new paradigm for molecular assembly. Chem Commun 24:2566–2568
77. Weniger B, Italiano L, Beck JP et al (1995) Cytotoxic activity of *Amaryllidaceae* alkaloids. Planta Med 61(1):77–79
78. Herrera MR, Machocho AK, Brun R et al (2001) Crinane and lycorane type alkaloids from *Zephyranthes citrina*. Planta Med 67(2):191–193
79. Ley SV, Schucht O, Thomas AW et al (1999) Synthesis of the alkaloids (+/-)-oxomaritidine and (+/-)-epimaritidine using an orchestrated multi-step sequence of polymer supported reagents. J Chem Soc Perkin Trans 1(10):1251–1252
80. Cordova A (2004) The direct catalytic asymmetric cross-Mannich reaction: a highly enantioselective route to 3-amino alcohols and alpha-amino acid derivatives. Chem Eur J 10 (8):1987–1997
81. Cordova A, Notz W, Zhong GF et al (2002) A highly enantioselective amino acid-catalyzed route to functionalized alpha-amino acids. J Am Chem Soc 124(9):1842–1843
82. List B (2000) The direct catalytic asymmetric three-component Mannich reaction. J Am Chem Soc 122(38):9336–9337
83. Notz W, Tanaka F, Barbas CF (2004) Enamine-based organocatalysis with proline and diamines: the development of direct catalytic asymmetric aldol, Mannich, Michael, and Diels-Alder reactions. Acc Chem Res 37(8):580–591
84. Odedra A, Seeberger PH (2009) 5-(Pyrrolidin-2yl)tetrazole-catalyzed aldol and Mannich reactions: acceleration and lower catalyst loading in a continuous-flow reactor. Angew Chem Int Edit 48(15):2699–2702
85. Morita K, Suzuki Z, Hirose H (1968) A tertiary phosphine-catalyzed reaction of acrylic compounds with aldehydes. Bull Chem Soc Jpn 41(11):2815–2815
86. Baylis AB, Hillman MED (1972) Acrylic compounds. Celanese Corp. DE 2155113
87. Declerck V, Martinez J, Lamaty F (2009) Aza-Baylis-Hillman reaction. Chem Rev 109(1):1–48

88. Shi Y-L, Shi M (2007) Aza-Baylis-Hillman reactions and their synthetic applications. Eur J Org Chem 18:2905–2916
89. Acke D (2007) Evaluation of microreactor technology for multicomponent reactions. PhD thesis. Organic Chemistry Department, Faculty of Bioscience Engineering, Ghent University, Belgium
90. Perlmutter P, Teo CC (1984) A simple synthesis of 2-methylidene-3-aminopropanoates. Tetrahedron Lett 25(51):5951–5952
91. Bertenshaw S, Kahn M (1989) Phosphine mediated synthesis of 2-methylidene-3-amino esters and ketones. Tetrahedron Lett 30(21):2731–2732
92. Ribiere P, Yadav-Bhatnagar N, Martinez J et al (2004) Microwave-assisted aza-Baylis-Hillman reaction preparation of poly(ethylene glycol) supported alpha-methylene-beta-aminoester. QSAR Comb Sci 23(10):911–914
93. Acke DRJ, Stevens CV (2006) Study of the Baylis-Hillman reaction in a microreactor environment: first continuous production of Baylis-Hillman adducts. Org Process Res Dev 10(3):417–422
94. Kabachnik MI, Medved TY (1952) New synthesis of aminophosphonic acids. Dokl Akad Nauk SSSR 83:689–692
95. Fields EK (1952) The synthesis of esters of substituted amino phosphonic acids. J Am Chem Soc 74(6):1528–1531
96. Pudovik AN (1952) Addition of dialkyl phosphites to imines. New method of synthesis of esters of amino phosphonic acids. Dokl Akad Nauk SSSR 83:865–868
97. Zefirov NS, Matveeva ED (2008) Catalytic Kabachnik-Fields reaction: new horizons for old reaction. ARKIVOC i:1–17
98. Van Meenen E, Moonen K, Acke D et al (2006) Straightforward continuous synthesis of alpha-aminophosphonates under microreactor conditions. ARKIVOC i:31–45

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Cyclic Peptidomimetics and Pseudopeptides from Multicomponent Reactions

Ludger A. Wessjohann, Cristiano R.B. Rhoden, Daniel G. Rivera, and Otilie Eichler Vercillo

Abstract Multicomponent reactions (MCRs) that provide in the final product amides are suitable to produce peptides and peptide-like moieties. The Passerini and Staudinger reactions provide one amide bond, and the Ugi-four-component reaction generates two amides from three or even four (or more) components, respectively. The Ugi-reaction thus is most important to produce peptides and peptoids while the Passerini reaction is useful to generate depsipeptoid moieties. In order to produce cyclic peptides and pseudopeptides, the linear peptidic MCR products have to be cyclized, usually with the help of bifunctional or activatable building blocks. Orthogonal but cyclizable secondary functionalities that need no protection in isonitrile MCRs commonly include alkenes (for ring closing metathesis), azide/alkyne (for Huisgen click reactions) or dienes and enoates (Diels-Alder) etc. If MCR-reactive groups are to be used also for the cyclisation, monoprotected bifunctional building blocks are used and deprotected after the MCR, e.g. for Ugi reactions as Ugi-Deprotection-Cyclisation (UDC). Alternatively one of the former building blocks or functional groups generated by the MCR can be activated. Most commonly these are activated amides (from so-called convertible isonitriles) which can be used e.g. for Ugi-Activation-Cyclisation (UAC) protocols, or most recently for a simultaneous use of both strategies Ugi-Deprotection/Activation-Cyclisation (UDAC). These methods mostly lead to small, medicinally relevant peptide turn mimics. In an opposing strategy, the MCR is rather used as ring-closing reaction,

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thereby introducing a (di-)peptide moiety. Most recently these processes have been combined to use MCRs for both, linear precursor synthesis and cyclisation. These multiple MCR approaches allow the most efficient and versatile one pot synthesis of macrocyclic pseudopeptides known to date.

Keywords Cyclopeptides · Depsipeptides · Peptoids · Macrocycles · Diketopiperazines · Benzodiazepines · Ugi-reaction · Polycyclic compounds · Orthogonal reactivity · Sequential reactions · Iteration · Bifunctional building blocks · Medium sized rings · Beta-turn motif

Contents

1 Cyclic Peptides

Cyclic peptides are important biologically active compounds that combine peptide properties with conformational bias and often improved serum stability and membrane penetration [1–3]. Depsipeptides are similar compounds, but they contain as part of their backbone one or more hydroxylated amino acid residues that add ester or lactone moieties to the peptide (Fig. 1) [4–6]. Cyclo- and

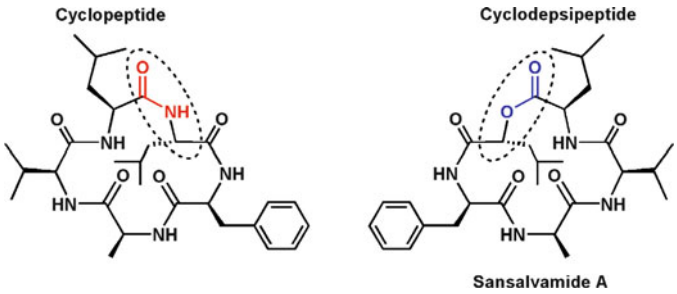


Fig. 1 Sansalvamide A and peptide analog *(left)*

depsipeptides have been found in many natural environments and are widely investigated for therapeutic uses. Their flexible or rigid scaffold (e.g., macromolecular receptors or β-turn mimics), bioavailability (e.g., membrane permeability) [7, 8], and protease stability can be tuned by substitution, *N*-alkylation (e.g., peptoids), or other modifications leading to pseudopeptides, natural or artificial. Crucial, however, is cyclization to avoid the linear peptides N and C termini [9–11]. Details can be found in [1–11].

The widespread occurrence of cyclic peptides and depsipeptides in natura makes the research on the development of rapid and efficient approaches for their generation mandatory. The rational design of synthetic cyclic peptide analogs, focused on biological activities that imitate natural structural motifs (turns, helices, etc.), can help to increase their native properties and to adapted them for human applications, for example, in medicine [12–14].

One way to gain fast access to complex structures are multicomponent reactions (MCRs), of which especially the isocyanide-based MCRs are suitable to introduce peptidic elements, as the isonitrile usually ends up as an amide after the reaction is complete. Here the Ugi-4 component reaction (Ugi-4CR) is the most suitable one as it introduces two amide bonds to form an *N*-alkylated dipeptide usually (Fig. 2). The Passerini-3CR produces a typical element of depsipeptides with ester and amide in succession, and the Staudinger-3CR results in β-lactams. The biggest unsolved problem in all these MCRs is, however, that it is still close to impossible to obtain products with defined stereochemistry. On the other hand, this resistance, particularly of the Ugi-reaction, to render diastereo- and enantioselective processes allows the easy and unbiased synthesis of libraries with all stereoisomers present, usually in close to equal amounts.

The combination of pept(o)id-introducing MCRs with subsequent and efficient post-condensation transformations, especially ring-closing protocols, is an efficient concept to produce (cyclic) pseudopeptides. The most important versions make use of protected or convertible functional building blocks to allow later condensation, specially cyclization. Most relevant are Ugi–deprotection–cyclization (UDC), Ugi–activation–cyclization (UAC), and the Ugi–deprotection–activation–cyclization (UDAC), which take advantage of the diverse functionalities incorporated into the previously synthesized MCR-adduct as bi- or polyfunctional building block (Fig. 3) [15, 16].

Of course, such deprotection/activation and cyclization protocols are conceptually not limited to Ugi-MCRs, but these are the most suitable ones toward (pseudo) peptide moieties as pointed out earlier (Figs. 2 and 3). The ring-forming steps following the MCR can lead either to small rings, usually five- to seven-membered ring heterocycles, or in recent time increasingly also to medium-sized or macrocyclic rings. A wide variety of reactions including condensations, ring-closing metathesis (RCM), cycloadditions, peptide and aryl couplings, amidations, intramolecular SNAr reactions, nucleophilic substitutions, and macrolactonization have been combined with MCRs. They provide a plethora of peptidomimetic or pseudo-peptidic cyclic scaffolds relevant in medicinal chemistry and biology. The ring-closing reaction itself may, finally, be an MCR too.

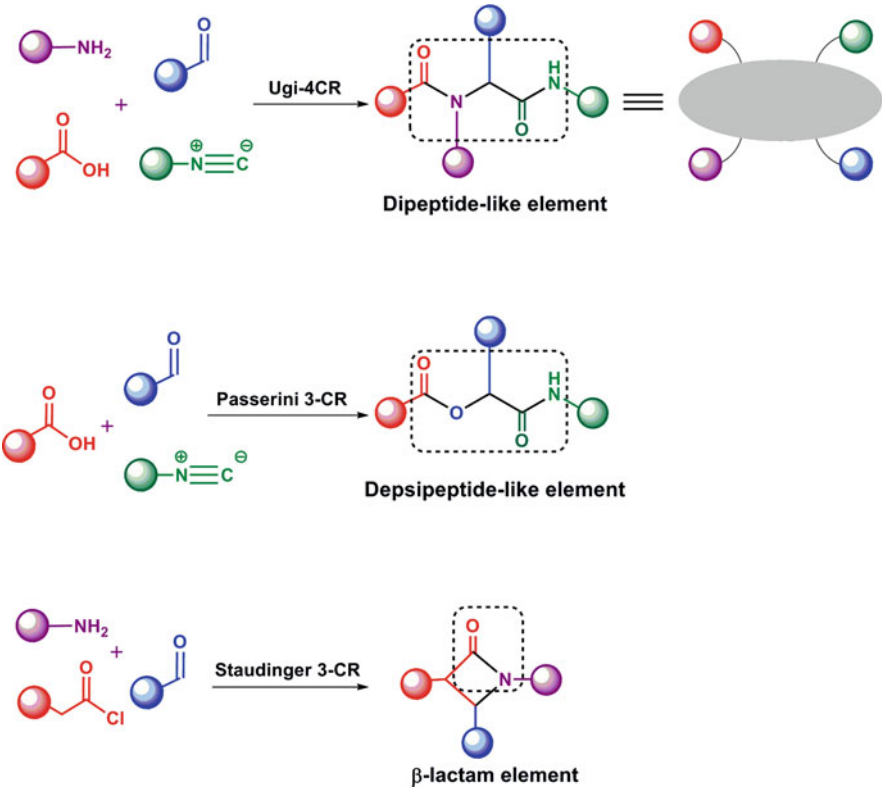


Fig. 2 Selected multicomponent reactions (MCRs) producing peptidic substructures, with the Ugi-4 component reaction (Ugi-4CR) as most commonly used one

This review will focus on the use of MCR approaches to cyclic peptides, cyclic peptidomimetics, or cyclic pseudopeptides, including small or medium-sized heterocycles as mimics of peptide motifs and macrocycles with amino acid or peptide moieties.

2 Cyclic Peptides and Their Mimetics from MCR/Cyclization Strategies

2.1 Diketopiperazines

Diketopiperazines (DKPs) are the smallest naturally occurring cyclic peptides. They are folded head-to-tail and conformationally constrained by a six-membered ring with the side chains orientated in a spatially defined manner. The DKP core

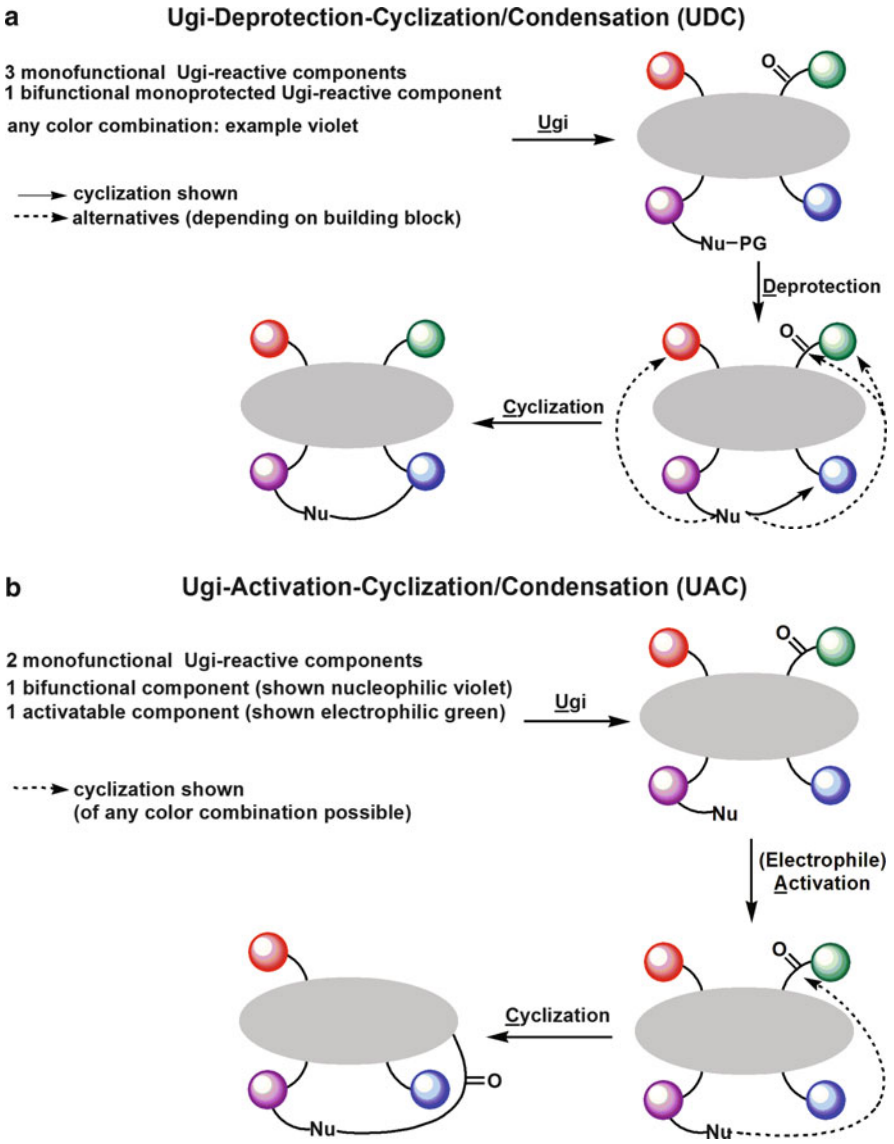


Fig. 3 (continued)

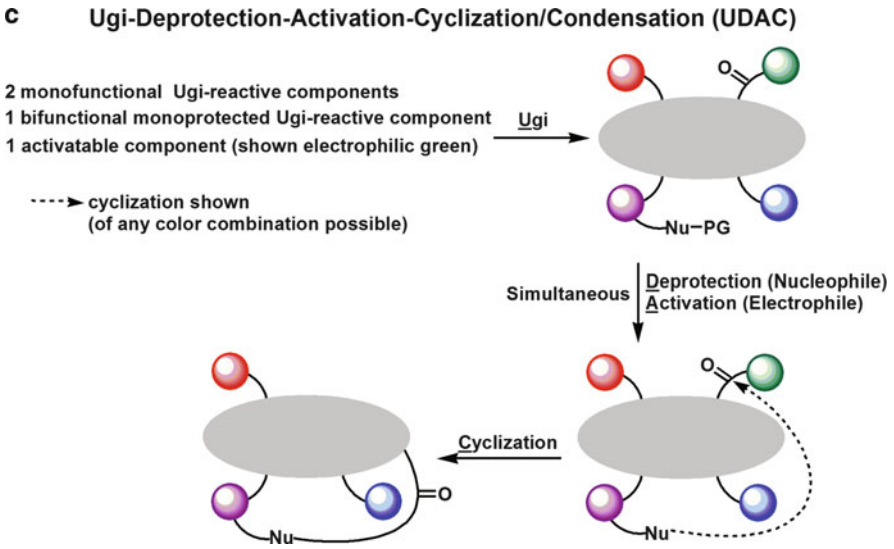


Fig. 3 The three most common modes to activate linear Ugi-products for cyclization, especially if the cyclization involves Ugi-reactive groups (e.g., acid, oxo-compound, or amine). Activation is mostly achieved with convertible isonitriles, i.e., activated amides (see text). Other MCRs follow similar concepts. With orthogonal second functionalities for cyclizations such deprotection and/or activation is not required (see below, e.g., RCM or cycloadditions)

shares three different isomers distinguished by the position of the oxo groups in the piperazine-backbone (Fig. 4).

DKPs possess properties that are useful for medicinal chemistry, such as resistance to proteolysis, mimicry of peptidic pharmacophoric groups, and conformational rigidity (for reviews and books see [17–19]). They can form hydrogen bonds as donor or acceptor. DKPs have been employed as selective colagenase-1 inhibitors, bradykinin antagonists [20], opioid receptor agonists and antagonists [21], antifungal [22, 23] and antibacterial agents [24, 25], inhibitors of mammalian DNA topoisomerase I, and suppressors of tumor cell growth [26]. They are not only potent and selective ligands for a wide variety of further biological targets [27–30], but, like asparagines, are also the source of the bitter taste in some foods such as coffee, beer, cacao, and chocolate [31, 32]. Furthermore, DKPs often possess favorable pharmacological parameters and are amenable to combinatorial synthesis.

One of the pioneer works in the synthesis of DKPs through MCRs was reported by Hulme and coworkers in a three-step solution phase protocol based on UDC [33, 34]. They have obtained a series of different DKPs by reacting Armstrong's convertible isocyanide with aldehydes, *N*-Boc-protected amino acids as bifunctional acid component containing a protected internal amino nucleophile, and amines in methanol at room temperature. After Ugi-reaction, the isonitrile-derived amide is activated with acid (UAC) and allows cyclization to the DKP with the

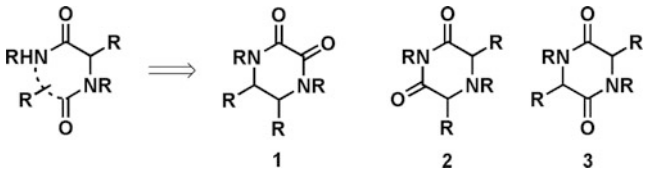
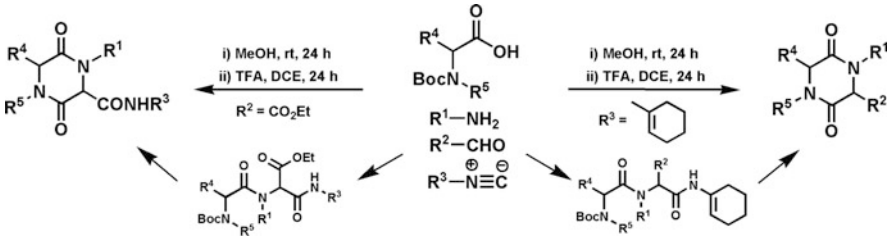
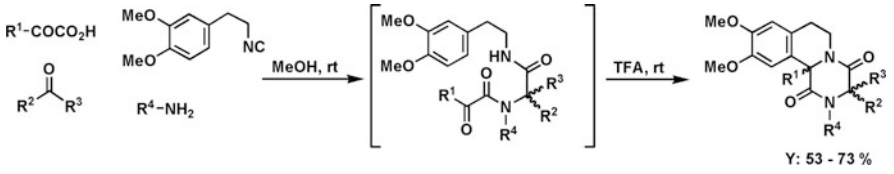


Fig. 4 Diketopiperazine structural isomers. Isomer **3** is the most relevant natural cyclodipeptide



Scheme 1 Multistep Ugi/De-Boc/cyclization (UDC)



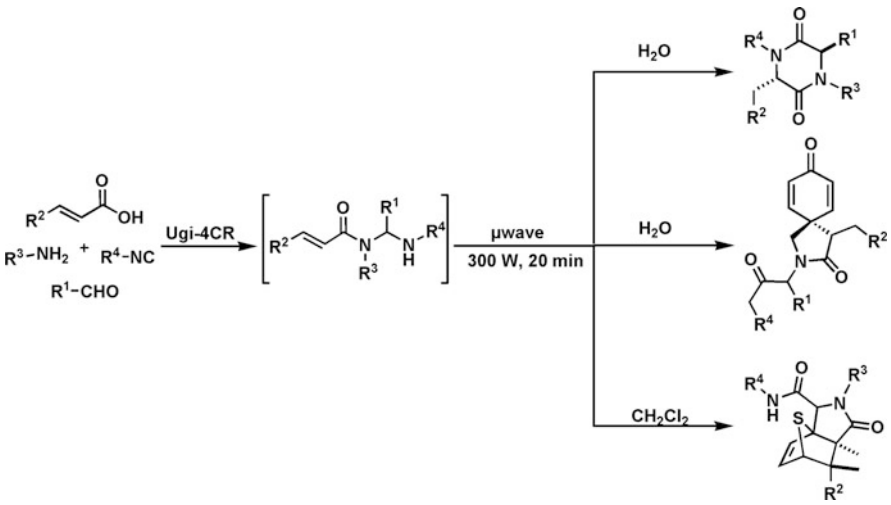
Scheme 2 El Kaims synthesis of DKPs using an Ugi/Pictet–Spengler combination

liberated amino function. In a variation, they have used ethyl glyoxylate as a bifunctional carbonyl component affording the *N*-Boc-protected Ugi-adduct. Subsequent deprotection with TFA furnished the desired DKP in yields of 63–95% (Scheme 1). In this case, the glyoxylate ester acts as the electrophilic carbonyl for cyclization.

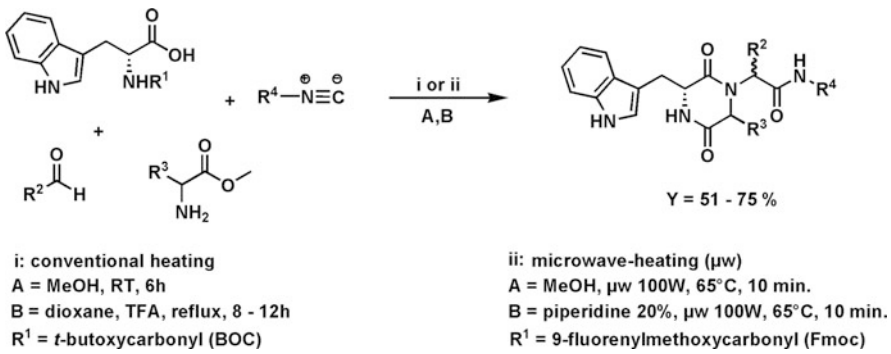
Recently, new strategies and improvements to the already known and previously reviewed articles appeared [17–19]. In this section, a small update on MCRs leading to DKPs and related compounds is given.

El Kaim and coworkers introduced a new variation for the formation of polycyclic DKPs via Ugi/Pictet–Spengler multicomponent combination [35]. The reaction of homoveratryl isocyanide with different aldehydes, amines, and α-keto acids leads to the expected Ugi-adducts, which are not isolated. Addition of trifluoroacetic acid promotes a cyclodehydratation affording the tricyclic DKPs (Scheme 2).

Andreana and Santra have investigated the influence of the solvent on the generation of molecular diversity arising from a set of MCR substrates under microwave irradiation [36]. They have found that by using water as solvent, both 2,5-DKPs and 2-azaspiro[4.5]deca-6,9-diene-3,8-diones were obtained through aza-Michael reaction and 5-*exo* Michael cyclization, respectively. Nevertheless,



Scheme 3 Effect of the solvent in a Ugi-4CR

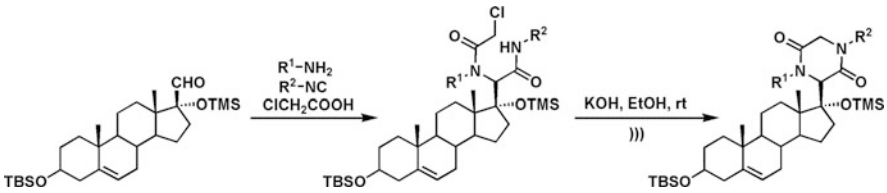


Scheme 4 Tryptophane derived diketopiperazines by microwave vs. conventional heating

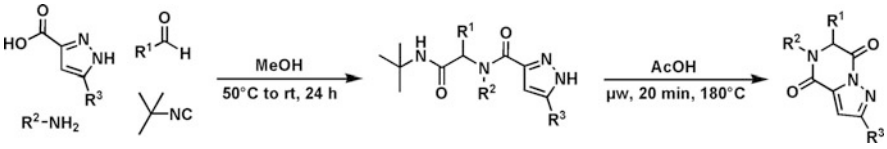
when dichloromethane was employed, an intramolecular Diels–Alder reaction took over, affording a tricyclic lactam instead (Scheme 3).

Wessjohann's group reported a one-pot synthesis of tryptophane DKPs [37]. This combination of two biologically highly active moieties was achieved in a one-pot variation of the UDC protocol (Scheme 4). It was shown that, assisted by microwave irradiation, the reaction times can be reduced significantly and that the formation of DKPs occurs even without the necessity to activate the ester. By employing microwave (dielectric) heating, the reaction times were reduced substantially.

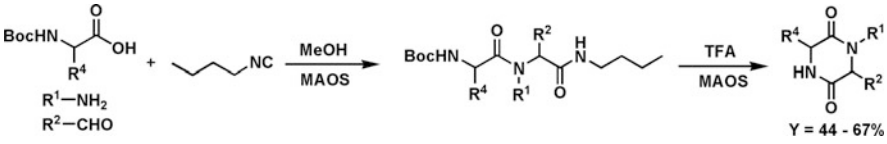
The synthesis of steroidal 2,5-DKPs was reported by Bruttomesso and coworkers in a two-step-based strategy from a steroidal carboxaldehyde and chloroacetic acid in combination with several amines and isocyanides by employing Ugi-4CR [38].



Scheme 5 Steroidal DKP synthesis



Scheme 6 DKP synthesis by UAC with *tert*-butyl isocyanide as convertible reagent. The amide is activated by acid and microwave heating



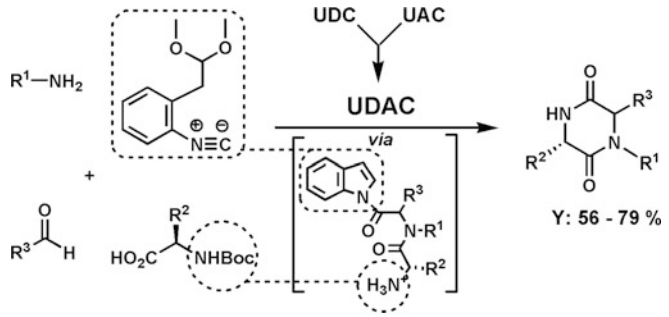
Scheme 7 Hulmes UDC approach to DKPs with common isonitriles. The intermediate amide is activated as leaving group by acid and microwave (MAOS) heating

The *N*-substituted steroidal DKPs were obtained under ultrasound irradiation in the presence of KOH with high stereoselectivity (Scheme 5).

Krasavin et al. described the synthesis of dihydropyrazol pyrazine diones via Ugi-4CR, employing *tert*-butyl isocyanide as a convertible reagent [102]. The authors reported that, under microwave irradiation, the *tert*-butyl isocyanide behaves similar to Armstrong's isocyanide, furnishing the DKPs in good yields. It is noteworthy that the low priced isonitrile applied may be helpful for developing large-scale syntheses in the future (Scheme 6).

A similar approach was recently reported by Hulme and coworkers. They published an Ugi-reaction-based DKP synthesis that does not require special isonitriles but uses simple linear ones like *N*-butyl isocyanide. The corresponding Amide-Ugi-products usually do not cyclize well, but under microwave conditions, good yields were obtained (Scheme 7) [39].

Recently, a combination of the UAC and UDC protocols was reported by Wessjohann's group [40]. In this work, the acid-activated, well-behaved 1-isocyano-2-(2,2-dimethoxyethyl)-benzene was employed as convertible isocyanide in an Ugi-4CR [41]. The advantage of this one-pot procedure is the in situ deprotection of the *N*-protected amino acid along with the simultaneous activation of the isonitrile-born carboxylate, enabling the nucleophilic attack of the free amine



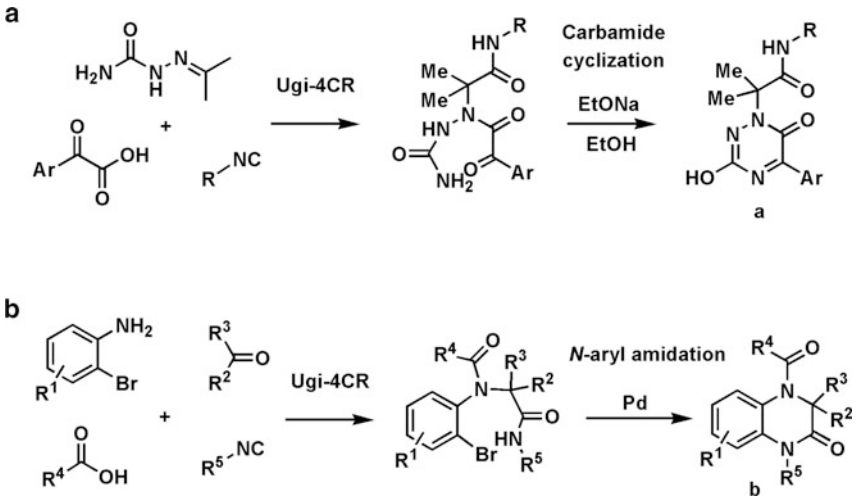
Scheme 8 Diketopiperazines by UDAC procedure. The simultaneous deprotection of BOC to liberate the amino nucleophile, and active amide (acylindole) formation is achieved with mild acid only

to the carbonyl moiety to afford the desired peptide–peptoid diketoperazines (Scheme 8).

2.2 *Further Six-Membered and Seven-Membered Ring Heterocycle Mimics of Peptide-Turn Motifs*

In addition to the many MCR-based methodologies available for DKPs, versatile procedures for other types of pseudo-peptidic six-membered cyclic ring scaffolds of interest for drug-discovery research have been reported recently. Among the peptidomimetics currently available, peptide isosteres such as ureidopeptides and azapeptides have found therapeutic applications [42–45]. Although these linear oligomeric backbones are mostly obtained by procedures not including MCRs, there are promising possibilities for the MCR/cyclization strategy. They can become an important alternative for small heterocyclic mimics of peptide-turn motifs. The groups of Marcaccini and Torroba reported an interesting sequential approach towards 6-oxo-[1,2,4]-triazines, a new type of dipeptidyl urea scaffold [46]. As shown in scheme 9, the procedure comprises the realization of a 3-CR (similar as an Ugi-4CR) incorporating phenylglyoxalic acid and, for the first time in Ugi-like reactions, semicarbazones as the imino-component. Cyclization was achieved by treatment of the linear MCR product with sodium ethoxide in ethanol. A new class of pseudo-peptidic 1,2,4-triazines **9a** was obtained in 40–70% overall yield.

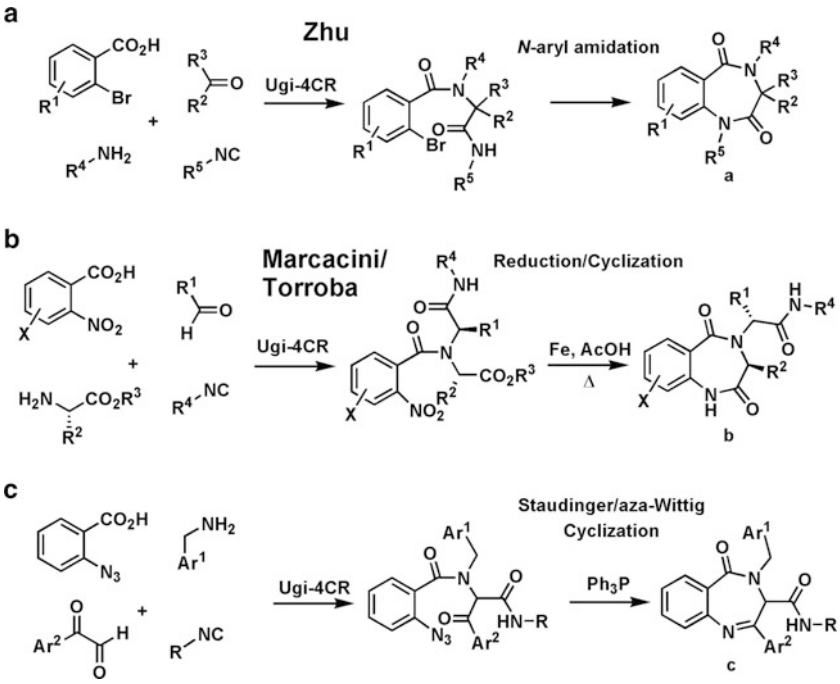
An alternative six-membered ring dipeptidyl platform is the one featuring the 4-acyl-quinoxaline-2-one skeleton accessible by a sequential Ugi-4CR/*N*-arylamidation process [47]. Again, improvements of this Ugi-4CR/Buchwald–Hartwig strategy were achieved by utilizing microwave heating for the ring-forming *N*-arylamidation step. As depicted in scheme 9, the use of 2-bromoanilines as the amino component in the Ugi-4CR followed by intramolecular amidation furnished the desired 4-acyl-quinoxaline-2-ones **9b** in 25–50% yield. As demonstrated by the



Scheme 9 Ugi-4CR + cyclization approaches to six-membered pseudo-peptidic scaffolds

authors, this strategy enables the rapid access to a wide variety of pharmaceutically relevant scaffolds by simply tuning the nature of the Ugi component located in *ortho*-position to the halogen. Accordingly, not only quinoxaline-2-ones but also indol-2-ones [48, 49] and the very important benzodiazepine-2-ones are readily available by this Ugi-4CR/ Buchwald–Hartwig strategy (Scheme 9b). Benzodiazepines will be discussed in more detail in the following.

Benzodiazepines comprise a family of small peptide mimics with a wide variety of pharmaceutical and biological applications [103, 104, 105]. These privileged scaffolds are known to exhibit good drug-like properties and have been recognized as relative potent small-molecule inhibitors of protein–protein interactions [50–54]. It has been proposed that the ability of benzodiazepines either to act as selective protein ligands or to disrupt protein–protein interactions derives from their capacity of mimicking different types of β-turn motifs [55–58]. Several Ugi-4CR/cyclization approaches have been reported over the last two decades to provide benzodiazepine platforms with potential pharmaceutical applications. Among these appear the classical UDC strategy both in solution and on solid-phase, the use of convertible isocyanides as carboxy-activator for the ring-forming step and the versatile Ugi-4CR/S_NAr strategy, which have been systematically reviewed elsewhere [15, 16]. In the following we will focus on illustrating the most recent MCR-based procedures towards these seven-membered pseudo peptides and β-turn mimics. The first example shows the general strategy introduced by Zhu and co-workers, which makes use of 2-bromobenzoic acid in the Ugi-4CR with the subsequent *N*-arylamidation protocol to furnish 3-substituted benzodiazepine-2,5-diones **10a** in 25–50% yield (Scheme 10a) [47]. The groups of Marcaccini and Torroba have implemented alternative I-MCR/post-condensation cyclization protocols to access benzodiazepines encompassing diverse substitution patterns [59–61]. Their recent



Scheme 10 Recent UAC approaches to benzodiazepine scaffolds as mimics of β-turn peptide motifs

approaches rest on the use of an initial Ugi-4CR that incorporates benzoic acids that are *ortho*-substituted with an amino precursor group (e.g., nitro as shown in Scheme 10b). If another component bears an additional electrophilic or oxo-function at a suitable distance, this enables the spontaneous cyclization after liberation or generation of the amino group. Scheme 10b and c show two variations of this protocol by utilizing 2-nitro- and 2-azido-benzoic acids along with another bifunctional reagent that takes part in the subsequent ring-forming step. The resulting benzodiazepine skeletons **10b** and **c** are obtained in good yields of 48–99% and exhibit different substitution patterns, depending on the choice of the bifunctional reagents employed. Interestingly, it was demonstrated that the 3-carboxamide-benzodiazepines **c** superimpose quite well in both solid state and solution with varied types of β-turn motifs, thereby illustrating the potential of this MCR-based approach to access rigid scaffold mimics of small peptide motifs.

Some related cyclic scaffolds, such as the azepines, were obtained by Ugi-4CR/RCM combinations (Fig. 5a) [61], and fused benzodiazepine/triazole frameworks were derived from sequential Ugi-4CR/alkyne–azide dipolar cycloaddition (Fig. 5b) [62]. Both are considered as interesting β-turn mimics. Similarly, bicyclic systems featuring fused DKP rings (Fig. 5c) have been reported to mimic the ten-membered pseudo-cycle of type I β-turns [63, 64].

3 Medium-Sized Cyclic Peptidomimetics

Several groups tried to access medium-sized rings (ca. 8–12 membered) with peptide-like moieties. Most prominent is the I-MCR/RCM strategy [15, 16]. As shown in Scheme 11. 12-Membered cyclic peptidomimetics were reported by Oikawa and co-workers who used initial Ugi-4CRs performed in excellent yields, followed by functionalization of the resulting Ugi-platform to introduce the desired alkene functionalities [65]. RCM with the second generation Hoveyda–Grubbs

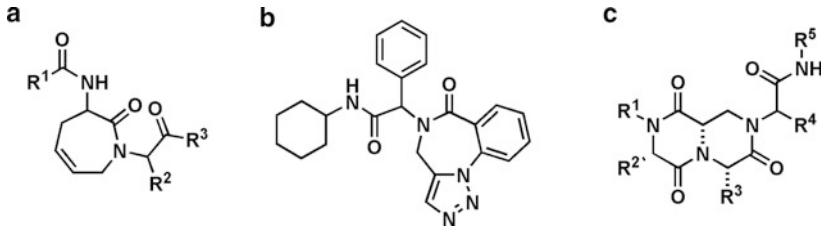
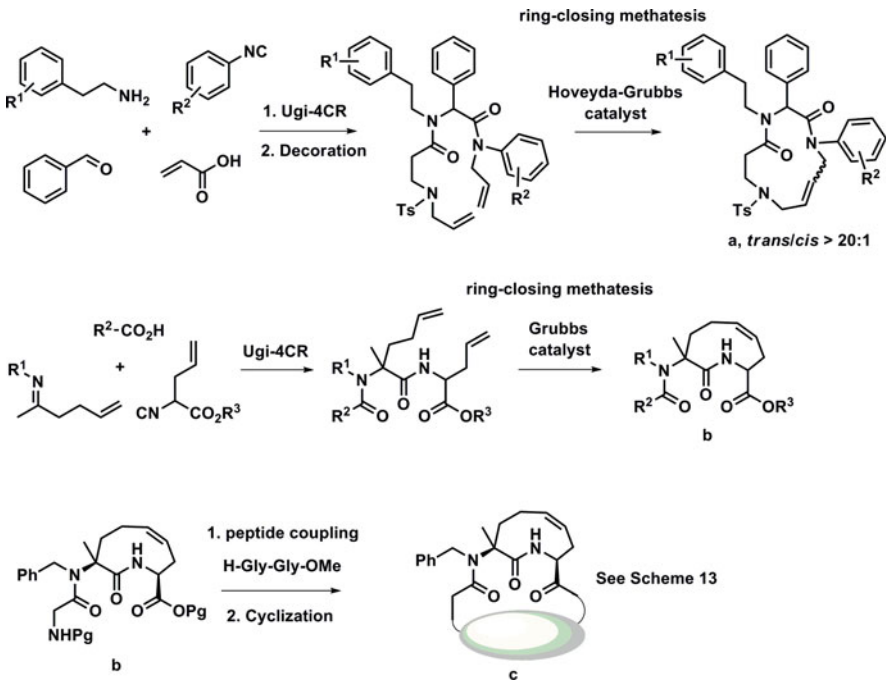


Fig. 5 Selected further six- and seven-membered peptidomimetic heterocycles by Ugi-4CR + cyclization



Scheme 11 Synthesis of conformationally restricted cyclopeptides and cyclic peptidomimetics by the Ugi4CR/RCM strategy

catalyst furnished the desired cyclic structures **11a**, with the *trans*-double bond isomer as the major compound. The group of Banfi and Riva achieved a remarkable result by implementing this versatile protocol to provide one of the few available entries for a nine-membered cyclopeptide-like compound **b** [66]. The scope of this approach lies in the possibility to produce short peptide stretches with restricted conformational freedom. Such elements were incorporated into macrobicyclic architectures [67]. Scheme 11 highlights the ready access to conformationally restricted pentapeptide **c** by a sequence of the Ugi-4CR/RCM protocol as the key step. Accordingly, a short *N*-alkylated dipeptide moiety of the macrocyclic peptide appears incorporated into an unsaturated nine-membered cyclolactam skeleton, produced as diastereomeric mixture. Interestingly, only peptide **b** with *cis* configuration at the attachment points was capable to cyclize in good yield, a feature that confirms the strong conformational restriction introduced to the system by the formation of the medium-sized ring. Structural studies suggested the superposition of this pre-organized cyclic scaffold with type II turns, an important feature regarding pharmaceutical applications. An extension of this strategy was proven to be suitable to provide biologically active cyclopeptides containing the RGD tripeptide sequence [67]. Cyclic peptidomimetics including this motif with defined conformation are strong ligands of $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrins, proteins involved in important processes such as tumor-induced angiogenesis [68]. Banfi et al. employed their strategy to produce a cyclopentapeptide as selective ligand of $\alpha_V\beta_5$, that unfortunately displayed a lower potency then some previously introduced peptidomimetics [106].

4 Macrocyclic Peptidomimetics and Pseudopeptides

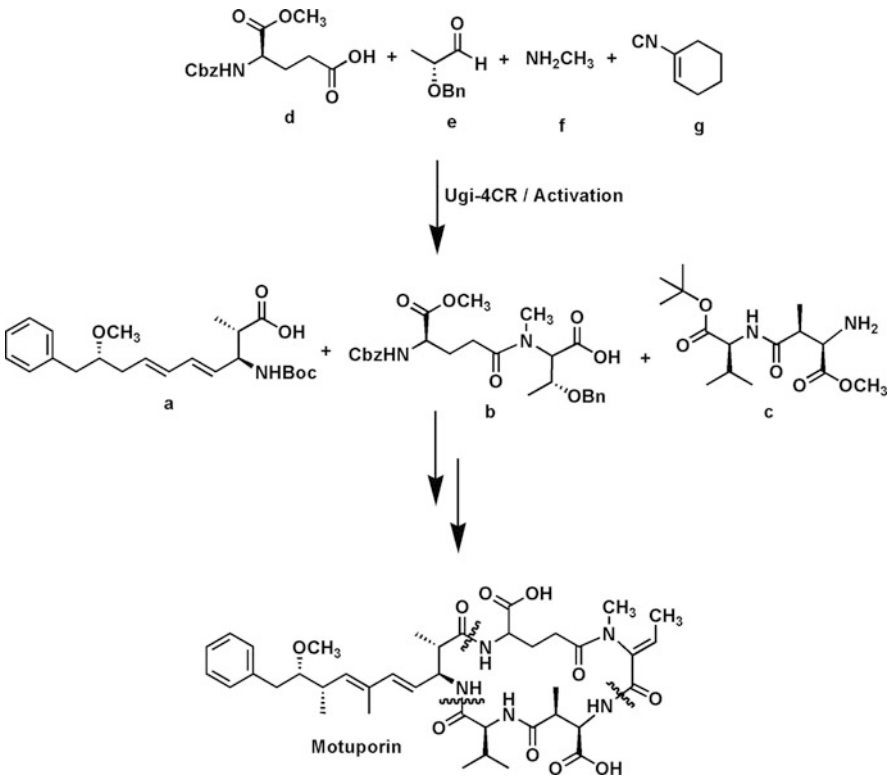
Macrocycles, especially cyclopeptide-like ones, can be considered as privileged molecules in medicinal chemistry because they can combine flexibility and conformational bias. This allows them structural adaptations for binding as ligands to proteins, as hosts to internal guests, or for a chimaric behavior improving cell penetration [5]. At the same time, they can have an improved overall energy term while binding compared to their linear counterparts, as the latter usually need more folding energy to achieve a binding conformation. This renders macrocycles perfectly suitable for applications in (organo)catalytic, supramolecular, or biological chemistry. In the latter case, they usually show improved metabolic stability too, lacking a terminal group commonly required for efficient catabolic processes (e.g., by exo-proteases or beta-oxidation routes). Their potential biological and chemical success is not only based on their intrinsic features, but also on the chemists capability to devise efficient strategies toward their synthesis. Here MCR strategies are likely to play a dominant role in the future. There are two main routes to achieve macrocycles that include MCRs. The first one is to synthesize the linear precursor by MCRs and later cyclize them by regular cyclization methods such as macrolactonization, macrolactamization, or ring-closing metathesis [69]. The still less

common way is to obtain a linear precursor by other methods and later cyclize it using a MCR [70]. Included in this route is the possibility to construct the linear precursor and cyclize the compound both with MCRs [70, 71].

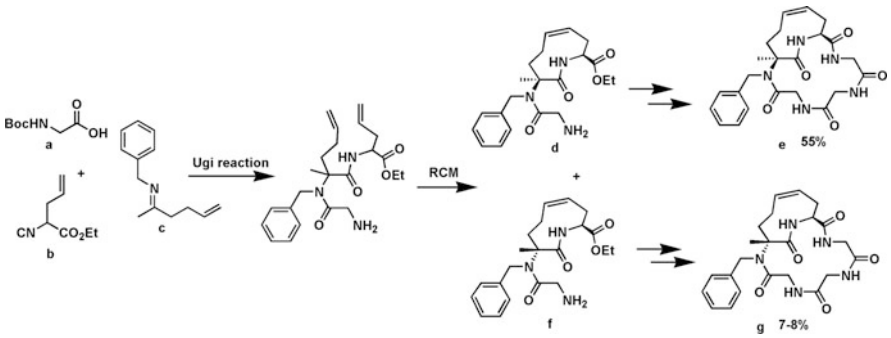
4.1 MCR-Precursor + Macrocyclization

Armstrong and coworker reported the synthesis of Motuporin (Scheme 12) [72], where a MCR was employed in the preparation of a linear precursor. Ugi-4CR was used to achieve fragment **12b** that was coupled with fragments **a** and **c** to give a linear precursor that was cyclized with the peptide condensation reagent HATU to yield Motuporin. The coupling of functionalized acid **d**, aldehyde **e**, methylamine **f,** and cyclohexenylisocyanide (Armstrong's convertible isocyanide **g**) gave a cyclohexenamide that was converted to compound **b** after hydrolysis with HCl.

Riva and coworkers obtained conformationally restricted cyclic peptidomimetics **13a** and **b** by a tandem Ugi-4CR/RCM procedure as reported before (Scheme 13). The initial *N*-alkylated dipeptide moiety was formed in the Ugi reaction of *N*-Boc



Scheme 12 Motuporin synthesis with an MCR-derived central building block



Scheme 13 Cyclic peptidomimetics by Ugi-4CR and RCM

glycines **13a**, isocyanide **13b,** and imine **13c**, which after the RCM reaction rendered the functionalized nine-membered lactam as a diasteromeric mixture. This latter mixture was coupled to diglycine methyl ester, followed by removal of the protecting groups and final peptide coupling with HATU to furnish the cyclic peptidomimetics. Of the two diastereomers **d** and **f**, only **d** with a *cis* configuration at the ring junctions was capable to cyclize in good yield to **13e**.

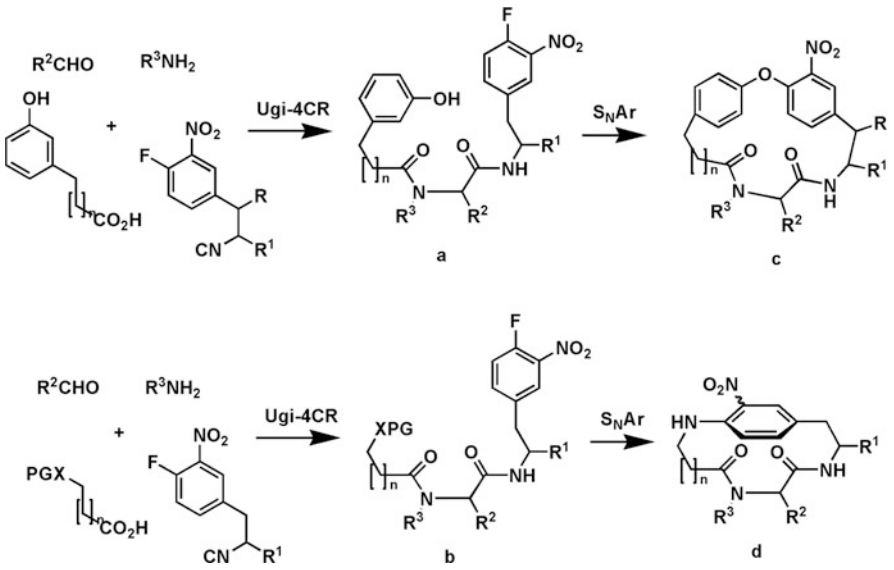
The Joullie, Zhu, and Wessjohann groups reported the synthesis of different *N*-alkyl ansa-cyclopeptides and the corresponding ansa-cyclopeptoids. These are inspired by natural cyclopeptide alkaloids. The first approaches to combine the Ugi reaction with a macrocyclization toward cyclopeptide alkaloids was done by Joullie and coworkers [73–75].

In more recent works, Zhu and coworkers synthesized a variety of *para*-cyclophanes and biarylether containing macrocycles (**14c** and **d**) using a reaction sequence consisting of an Ugi reaction followed by an intramolecular S_NAr cyclization (Scheme 14) [76–78]. Many linear precursors (**14a** and **b**) were achieved with the Ugi reaction by employing varied primary amines. This synthetic planning allowed the introduction of four points of diversity within the resulting scaffolds, thus producing a small library of cyclopeptoids.

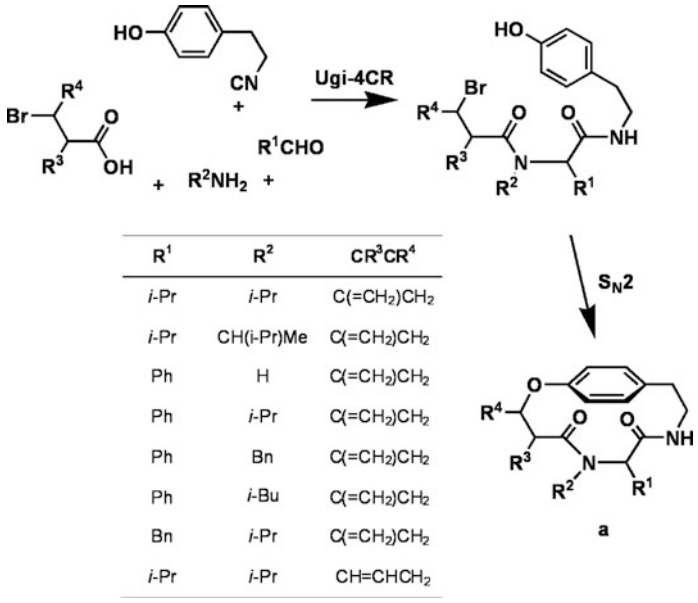
A similar type of compounds, without the nitro group, was achieved by Wessjohann and coworkers (Scheme 15) [79]. Their approach also uses the Ugi reaction to build the linear peptoid intermediates, but a nucleophilic substitution is employed for the ring closure, which is a difficult task with a strained phenolate. A small library of macrocycles with general formula **15a** was prepared, including also some 15-membered ansa-cycles (not shown).

Dömling and coworkers described the synthesis of natural product-inspired macrocycles using a Passerini reaction with two bifunctional starting materials containing terminal alkenes (**a** and **c**, Scheme 16) [80]. The resulting linear precursor **d** was cyclized by RCM. With access to a diversity of olefin-bearing isocyanides and carboxylic acids, this strategy was used for the syntheses of macrocycles **h** and **k** with a peptide (mimicking) moiety.

Dipolar cycloadditions are among the most efficient and amenable transformations to produce macrocycles via MCR/cyclization strategies. The functionalities



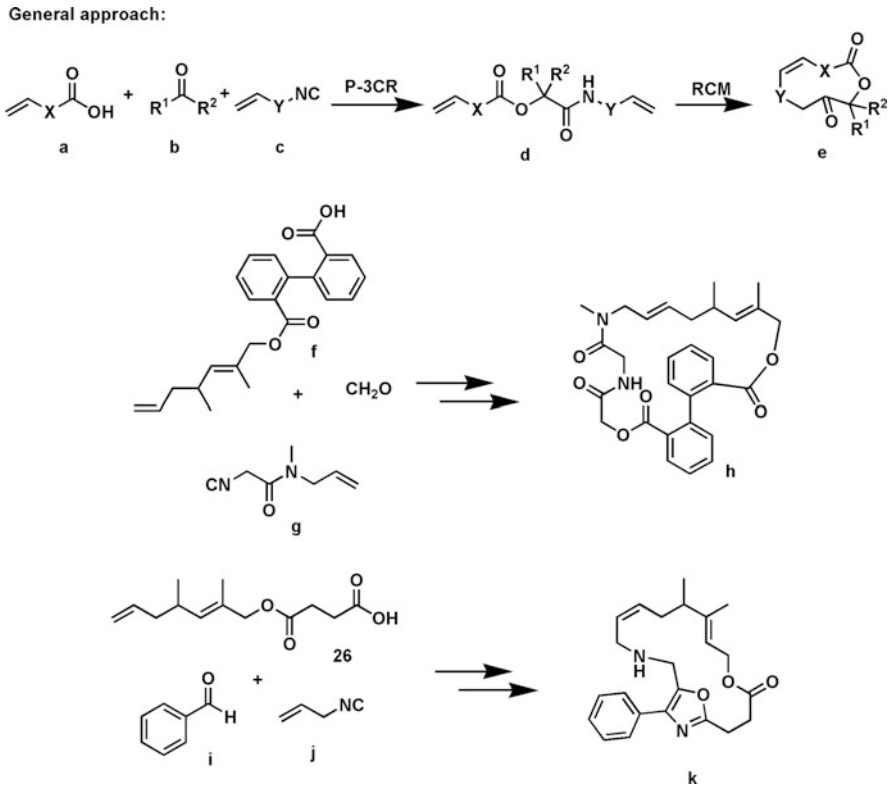
Scheme 14 Biarylether containing macrocycles and *p*-cyclophanes



R^1	R^2	CR^3CR^4
i-Pr	*i*-Pr	C(=CH_2)CH_2
i-Pr	CH(i-Pr)Me	C(=CH_2)CH_2
Ph	H	C(=CH_2)CH_2
Ph	*i*-Pr	C(=CH_2)CH_2
Ph	Bn	C(=CH_2)CH_2
Ph	*i*-Bu	C(=CH_2)CH_2
Bn	*i*-Pr	C(=CH_2)CH_2
i-Pr	*i*-Pr	CH=$CHCH_2$

Scheme 15 Mimics of natural cyclopeptide alkaloids by Ugi-4CR + S_N2 cyclization

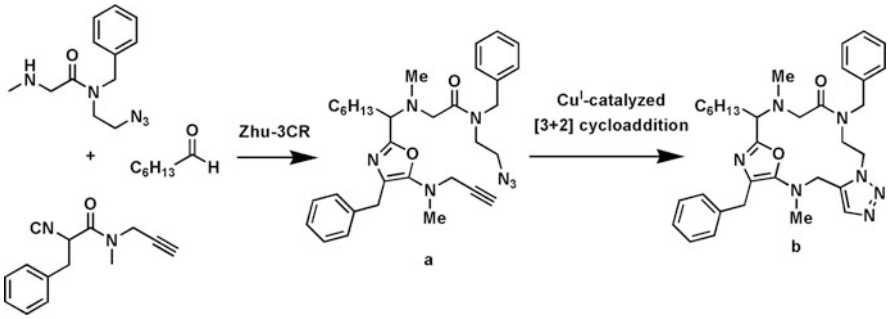
required for a successful intramolecular post-condensation cycloaddition are completely orthogonal to most MCR-type functionalities. As previously mentioned, this concept was originally described to furnish fused benzodiazepine/triazole



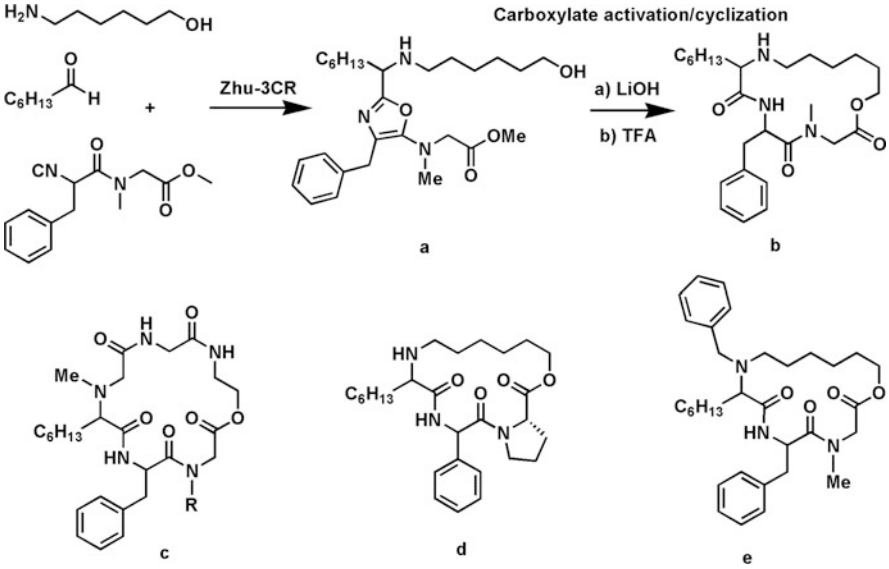
Scheme 16 Passerini-3CR and RCM approach toward macrocycles

frameworks derived from a sequential Ugi-4CR/alkyne–azide dipolar cycloaddition [61], and recently it has been applied to afford macrocycles, including both oxazole and triazole moieties within large rings [81]. The approach towards this class of natural product-like macrocycles involves an initial α-isocyano acetamide-based three-component reaction (Zhu-3CR) to produce oxazole moieties in excellent yields [82, 83]. By an appropriate selection of bifunctional building blocks including azide and alkyne functionalities, a sequence encompassing the MCR followed by a copper-catalyzed intramolecular [3 + 2] dipolar cycloaddition (the Huisgen-type click reaction) was successfully implemented to afford cyclic pseudopeptides endowed with oxazole/triazole macrocyclic cavities (Scheme 17). One straightforward variation rests on functionalizing the isocyano-acetamide component with an alkyne group and the amino component with an azido group. The resulting Zhu-3CR product leads to cyclic peptidomimetics of type **17b** after Cu-activation. The same approach also enables the use of bifunctional oxo-components containing either azido or alkyne group, as well as an easy tuning of the functionality incorporated into the bifunctional amino or isocyano-acetamide components.

Scheme 18 shows a remarkable approach towards cyclodepsipeptides that includes Zhu-3CR as the key step of a tandem deprotection/cyclization strategy



Scheme 17 Synthesis of cyclic peptidomimetics by sequential Zhu-3CR/azide-alkyne dipolar cycloaddition strategy



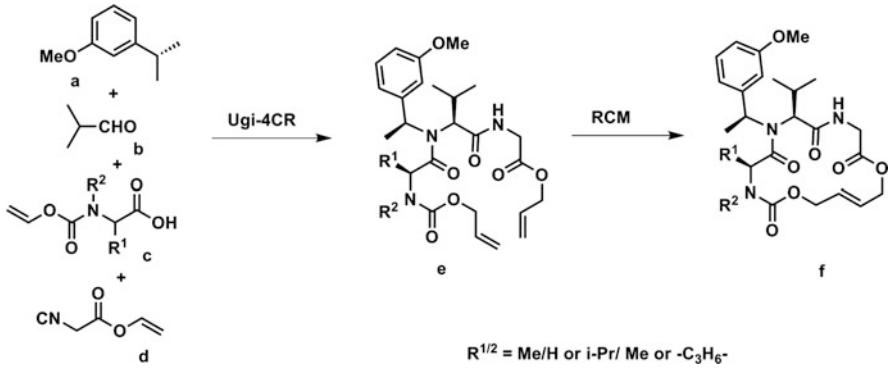
Scheme 18 Synthesis of cyclodepsipeptides by a domino MCR/deprotection/activation/cyclization strategy

[84]. The method is based on the use of 5-amino-oxazoles [81] of type **18a** as key intermediates, which upon consecutive treatment with base and acid allows a "guided" macrolactonization. Again the use of a bifunctional building block enables a later cyclization of a (linear) precursor to be cyclized after deprotection (cf. UDC-protocols) to give macrocycle **18b** in good yield and without the need of an external carboxylate activator. The overall sequential process starts by converting the oxazole-containing structure **a** into the lithium salt, followed by protonation of the oxazole by treatment with TFA. This activates the neighboring carboxylate, presumably by trapping it into an intermediate spirolactone moiety. Final nucleophilic attack of the internal alcohol leads to cyclodepsipeptides. This strategy

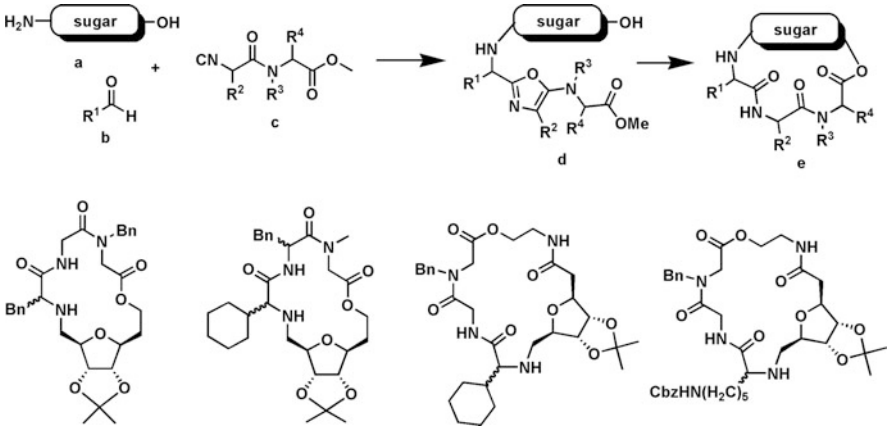
was later employed to construct a parallel library of cyclodepsipeptides of type **18c**, **d**, and **e** [85].

Kazmaier and coworker described a simple approach to several cyclic peptidomimetics containing a *N*-alkylated amino acid via Ugi reaction and a RCM (Scheme 19) [86, 87]. *N*-terminally protected Aloc amino acids **c** and allyl isocyanides **d** were used in an Ugi-4CR to give the linear precursors **e** in good yields (72–96%); these were cyclized to the macrocycles **f** by a subsequent RCM.

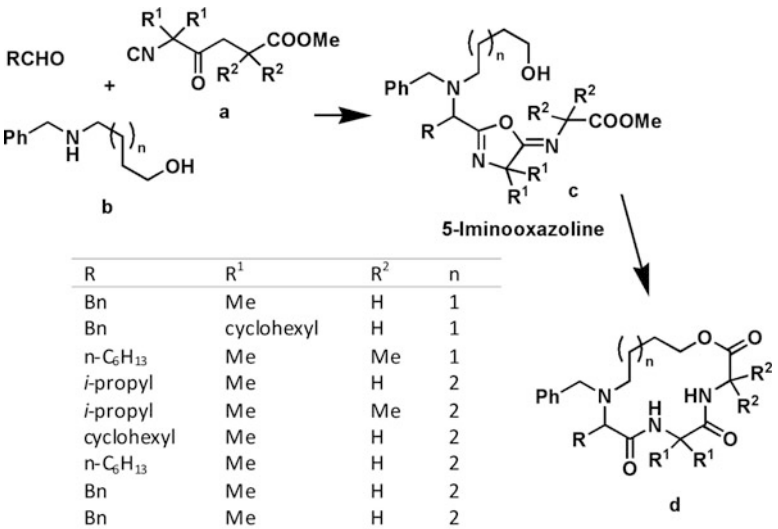
A rapid synthesis of cyclodepsipeptides containing sugar moieties was reported by Zhu and coworkers (Scheme 20) [88]. A three-component reaction of a sugar amino acid derivative **20a**, an aldehyde **b,** and a dipeptide isocyanide **c**, followed by saponification and trifluoroacetic acid-promoted macrocyclization was employed to afford the cyclic amino sugar cyclopeptides **d**. This approach allows to systematically modify the amino acids and the carbohydrate residue, as well as the size of the macrocycle. Again, the only reagents used to mediate the formation of the



Scheme 19 The Kazmaier approach to cyclic peptidomimetics



Scheme 20 Cyclodepsipeptides containing sugar amino acids



R	R^1	R^2	n
Bn	Me	H	1
Bn	cyclohexyl	H	1
n-C_6H_{13}	Me	Me	1
i-propyl	Me	H	2
i-propyl	Me	Me	2
cyclohexyl	Me	H	2
n-C_6H_{13}	Me	H	2
Bn	Me	H	2
Bn	Me	H	2
n-C_6H_{13}	cyclohexyl	H	2

Scheme 21 Macrocyclodepsipeptides from 5-iminooxazolines formed by MCR

macrocycles are trifluoroacetic acid and lithium hydroxide. None of the fancy condensation reagents usually applied for macrocyclization was required.

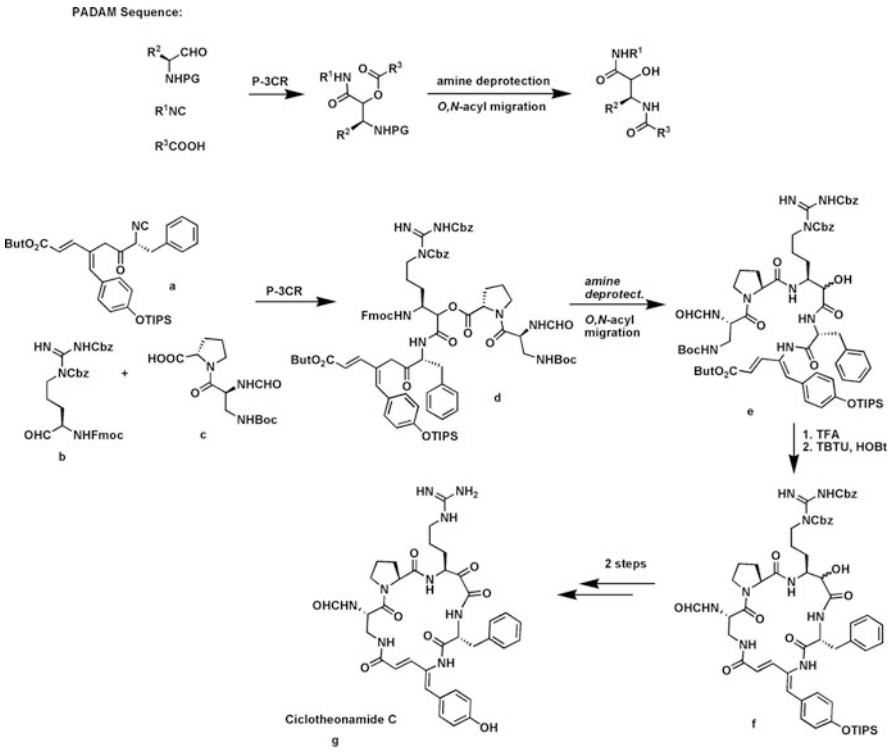
Zhu's group also developed an ammonium chloride-promoted three-component synthesis of 5-iminooxazole and subsequent transformation to a macrocyclodepsipeptide [89]. In this approach, a three-component reaction of an α,α-disubstituted α-isocyanoacetamide **21a**, an aldehyde, and an amino alcohol **b** afforded the 5-iminooxazole **c**, which was cyclized after saponification under acidic conditions to furnish the macrocyclodepsipetides **d** (Scheme 21).

More recently, Aitken and coworkers described a short and convergent formal total synthesis of cyclotheonamide C using a process that involves a Passerini reaction, amine deprotection, and an acyl migration (PADAM sequence, Scheme 22) [90]. The key linear pentapeptide **22e** is obtained by a Passerini reaction of isocyanide **a**, Fmoc-amino aldehyde **b**, and Boc-dipeptide acid **e** followed by Fmoc removal and consequently *O*,*N*-acyl migration [91]. The macrocyclization was achieved with TBTU and HOBt after Boc and *t*Bu removal in good yield (52%) to furnish intermediate **f**.

4.2 Linear (Pseudo) Peptides + MCR-Cyclization

There are only a few records of macrocycle synthesis where the linear precursor was cyclized by a MCR. The first one to observe an MCR-macrocyclization by coincidence were Failli et al. who tried to couple oligoglycines [92].

Wessjohann and coworkers described the design and synthesis of cyclic RGD pentapeptoids and related derivates by consecutive Ugi reactions (Scheme 23) [93].

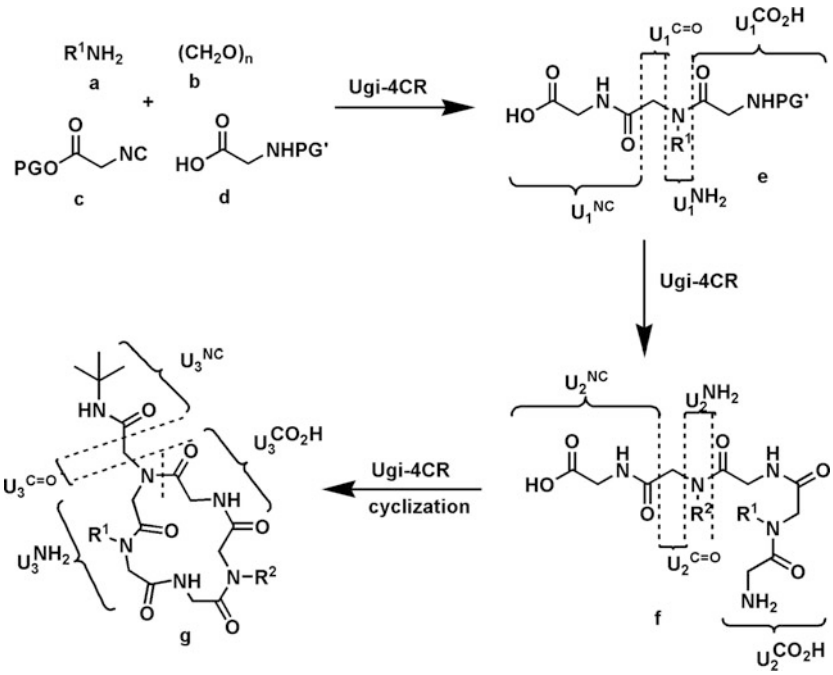


Scheme 22 Formal synthesis of cyclotheonamide C using the PADAM-sequence (Passerini-3CR/amine-deprotection/acyl-migration)

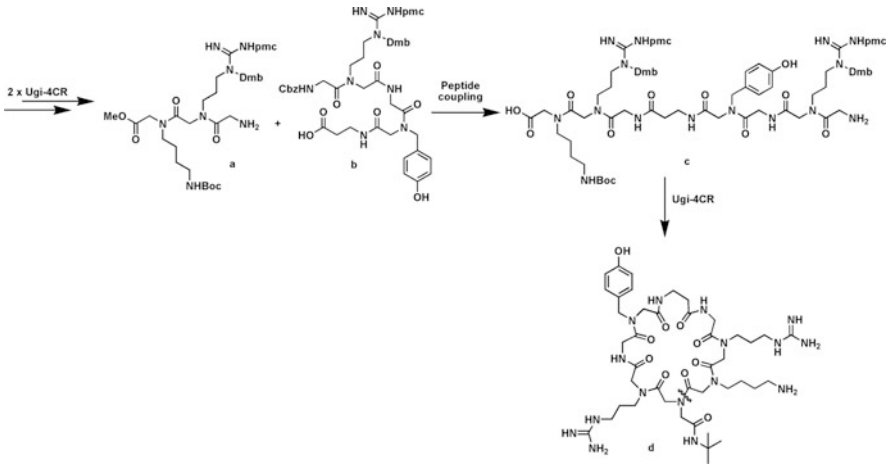
The cyclic pentapeptoid skeleton **23a** was assembled after three consecutive U-4CRs, two of them to prepare the linear precursor **b** and the final one for the ring closure. The approach has been shown to be straightforward and opens the possibility for a combinatorial strategy toward a wide range of cyclic oligopeptoids. This was the first report where the peptoid backbone and the macrocycle closure were performed by consecutively employing MCRs.

The same approach was recently used for the synthesis of a cyclopeptoid as potential inhibitor of the Tat/TAR complex of the HIV-1 virus (Scheme 24) [94, 95]. Two Ugi reactions were used to prepare fragment **b** that was coupled to fragment **a** to afford linear precursor **c**. The macrocyclic peptidomimetic **d** was obtained after cyclization employing Ugi reaction of amino acid **c** with paraformaldehyde and *t*-butyl isocyanide.

Another approach to cyclize macrocycles employing MCRs is the multiple multicomponent macrocyclization including bifunctional building blocks (MiB). This synthetic strategy, developed in the Wessjohann group, proved suitable for the one-pot diversity-oriented synthesis of varied macrocycles (Scheme 25) [71, 96, 107]. Toward pseudopeptides, the MiB-approach using Ugi-4CR is the most suitable one, but also Passerini- and Staudinger-3CR–MiBs provide (depsi)

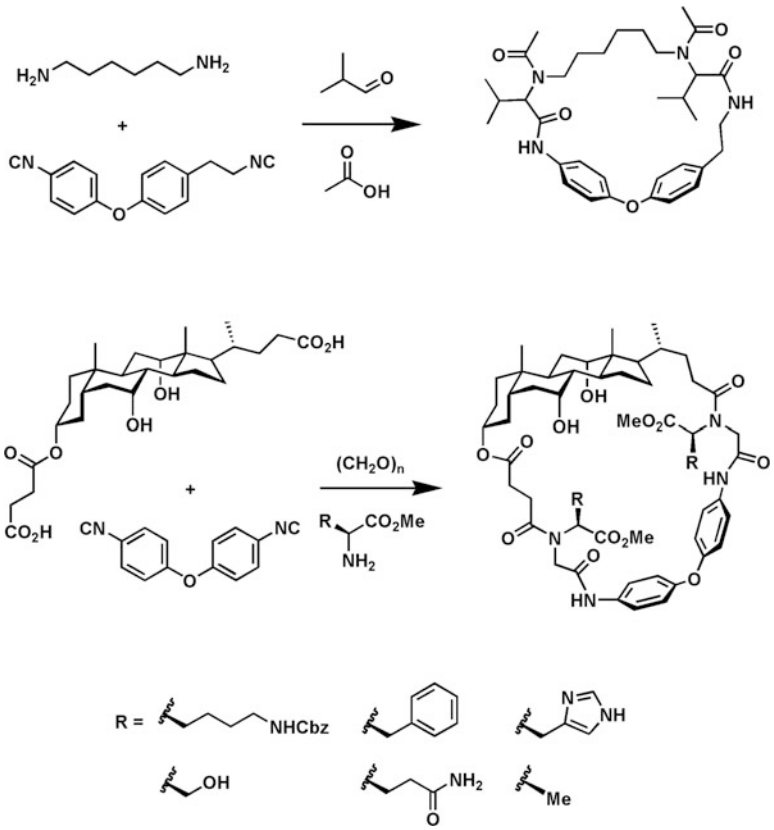


Scheme 23 Consecutive and cyclative U-4CRs in the synthesis of cyclic RGD pentapeptoids

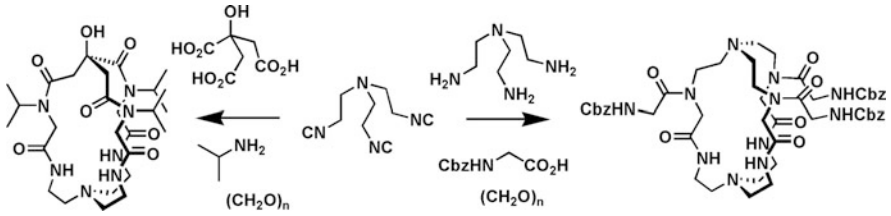


Scheme 24 Consecutive U-4CRs for the synthesis of a macrocyclic octapeptoid

peptidic elements within macrocycles [97]. In this concept, macrocyclization is achieved by combining two (or more) Ugi reactions with at least two bifunctional building blocks, whereby both functionalities are unprotected Ugi-reactive groups (e.g., a bis-isonitrile or an amino acid). The methodology is very



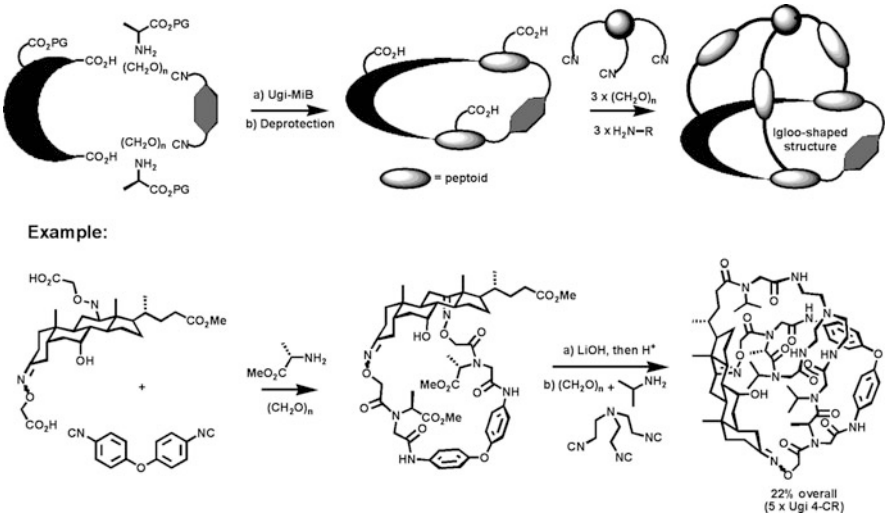
Scheme 25 Ugi-MiBs approach toward macrocycles



Scheme 26 Macrobicycles synthesized by the MiB strategy

straightforward, versatile, and generates libraries of macrocyclic pseudo peptides with unprecedent functional and skeletal diversity. For example, natural product-inspired biaryl ether-cyclopeptoid macrocycles were obtained by this methodology [98, 99].

The same strategy can be used with polyfunctional building blocks, and a variety of peptoid-based cryptands, cages, and cryptophanes was synthesized (Scheme 26) [100].



Scheme 27 Igloo-shaped tetramacrocyclic pseudopeptides with 20 amide bonds in a defined three-dimensional arrangement synthesized by the MiBs strategy in one-pot

These complex macrobicycles were assembled by the incorporation of eight more building blocks, forming 12–24 new bonds in a one-pot reaction. The more complex three-dimensional multi-macrocyclic pseudopeptides like the igloos might in principle be considered mimics of internally disulfide bridged crumpled proteins like the knottins (Scheme 27) [101].

References

1. Davies JS (2003) J Pept Sci 9:471–501
2. Wessjohann LA, Ruijter E, Rivera DG, Brandt W (2005) Mol Divers 9:171–186
3. Lambert JN, Mitchell JP, Roberts KD (2001) J Chem Soc Perkin Trans 1 471–484
4. Gulevich AV, Shpilevaya IV, Nenajdenko VG (2009) Eur J Org Chem 22:3801–3808
5. Brandt W, Haupt VJ, Wessjohann LA (2010) Cheminformatic analysis of biologically active macrocycles, Curr Top Med Chem, in print
6. Wessjohann LA, Andrade CKZ, Vercillo OE, Rivera DG (2007) In: Attanasi OA, Spinelli D (eds) Targets in heterocyclic systems: chemistry and properties. Royal Society of Chemistry, Cambridge, pp 24–53
7. Adessi C, Soto C (2002) Curr Med Chem 9:963
8. Arbor S, Kao J, Wu Y, Marshall GR (2008) Biopolymers 3:384–393
9. Xiao Q, Pei D (2007) J Med Chem 50:3132–3137
10. Rezai T, Bock JE, Zhou MV, Kalyanaraman C, Lockey RS, Jacobson MP (2006) J Am Chem Soc 128:14073–14080
11. Kessler H (1982) Angew Chem Int Ed Engl 21:512–523
12. Wipf P (1995) Chem Rev 95:2115–2134
13. Hamada Y, Shioiri T (2005) Chem Rev 105:4441–4482

14. Pomilio AB, Battista ME, Vitale AA (2006) Curr Org Chem 10:2075–2121
15. Marcaccini S, Torroba T (2005) In: Zhu J, Bienaymé H (eds) Multicomponent reactions. Wiley, Weinheim, pp 33–75, Chapter 2 (cf. also other chapters of this book)
16. Dömling A (2006) Chem Rev 106:17–89
17. Fischer PM (2003) J Pept Sci 9:9–35
18. Dinsmore CJ, Beshore DC (2002) Tetrahedron 58:3297–3312
19. Martins MB, Carvalho I (2007) Tetrahedron 63:9923–9932
20. Szardenings AK, Antonenko V, Campbell DA, De Francisco N, Ida S, Shi L, Sharkov N, Tien D, Wang Y, Navre M (1999) J Med Chem 42:1348–1357
21. Bryant SD, Balboni G, Guerrini R, Salvadori S, Tomatis R, Lazarus LH (1997) Biol Chem 378:107–114
22. Houston DR, Synstad B, Eijsink VGH, Stark MJR, Eggleston IM, van Aalten MF (2004) J Med Chem 47:5713–5720
23. Byun H-G, Zhang H, Mochizuki M, Adachi K, Shizuri Y, Lee W-J, Kim S-K (2003) J Antibiot 56:102–106
24. Fdhila F, Vázquez V, Sánchez JL, Riguera R (2003) J Nat Prod 66:1299–1301
25. Abraham W-R (2005) Drug Des Rev 2:13
26. Funabashi Y, Horiguchi T, Iinum S, Tanida S, Harada S (1994) J Antibiot 47:1202–1218
27. Gellerman G, Hazan E, Kovaliov M, Albeck A, Shatzmiler S (2009) Tetrahedron 65: 1389–1396
28. Cain JP, Mayorov AV, Hruby V (2006) J Bioorg Med Chem Lett 16:5462–5467
29. Pedro B, Mamedova L, Jacobson KA (2005) Org Biomol Chem 3:2016–2025
30. Souers AJ, Ellman JA (2001) Tetrahedron 57:7431–7448
31. Jainta M, Nieger M, Bräse S (2008) Eur J Org Chem 5418
32. Stark T, Hofmann T (2005) J Agric Food Chem 53:7222–7231
33. Hulme C, Cherrier M-P (1999) Tetrahedron Lett 40:5295–5299
34. Hulme C, Morrissette MM, Volz FA, Burns CJ (1998) Tetrahedron Lett 39:1113–1116
35. El Kaim L, Gageat M, Gaultier L, Grimaud L (2007) Synlett 56:500–502
36. Santra S, Andreana P (2007) Org Lett 9:5035–5038
37. Rhoden CRB, Westerman B, Wessjohann LA (2008) Synthesis 2077–2082
38. Bruttomesso AC, Eiras J, Ramírez JA, Galagovsky LR (2009) Tetrahedron Lett 50: 4022–4024
39. Hulme C, Chappeta S, Dietrich J (2009) Tetrahedron Lett 50:4054–4057
40. Rhoden CRB, Rivera DG, Kreye O, Bauer AK, Westermann B, Wessjohann LA (2009) J Comb Chem 11:1078–1082
41. Kreye O, Westermann B, Wessjohann LA (2007) Synlett 3188–3192
42. Venkatesan N, Kim BH (2002) Curr Med Chem 9:2243–2270
43. Myers AC, Kowalski JA, Lipton MA (2004) Bioorg Med Chem Lett 14:5219–5222
44. Zega A (2005) Curr Med Chem 12:589–597
45. Piliero PJ (2004) Drugs Today 40:901–912
46. Sañudo M, Marcaccini S, Basurto SJ, Torroba T (2006) J Org Chem 71:4578–4584
47. Cuny G, Bois-Choussy M, Zhu J (2004) J Am Chem Soc 126:14474–14484
48. Bonnaterre F, Bois-Choussy M, Zhu J (2006) Org Lett 8:4351–4354
49. Kalinski C, Umkehrer M, Ross G, Kolb J, Burdack C, Hiller W (2006) Tetrahedron Lett 47:3423–3426
50. Horton DA, Bourne GT, Smythe ML (2003) Chem Rev 103:893–930
51. Herpin TF, Van Kirk KG, Salvino JM, Yu ST, Labaudinière RF (2000) J Comb Chem 2:513–521
52. Carlier PR, Zhao H, MacQuarrie-Hunter SL, De Guzman JC, Hsu DC (2006) J Am Chem Soc 128:15215–15220
53. Joseph CG, Wilson KR, Wood MS, Sorenson NB, Phan DV, Xiang Z, Witek RM, Haskell-Luevano C (2008) J Med Chem 51:1423–1431
54. Ramajayam R, Girdhar R, Yadav MR (2007) Mini Rev Med Chem 7:793–812

55. Butini S, Gabellieri E, Huleatt PB, Campiani G, Franceschini S, Brindisi M, Ros S, Coccone SS, Fiorini I, Novellino E, Giorgi G, Gemma S (2008) J Org Chem 73:8458–8468
56. Blakeney JS, Reid RC, Le GT, Fairlie DP (2007) Chem Rev 107:2960–3041
57. Butler MS (2005) Nat Prod Rep 22:162–195
58. Evans BE, Bock MG, Rittle KE, DiPardo RM, Whitter WL, Veber DF, Anderson PS, Freidinger RM (1986) Proc Natl Acad Sci USA 83:4918–4922
59. Faggi C, Marcaccini S, Pepino R, Pozo MC (2002) Synthesis 2756–2760
60. Marcaccini S, Miliciani M, Pepino R (2005) Tetrahedron Lett 46:711–713
61. Sañudo M, García-Valverde M, Marcaccini S, Delgado JJ, Rojo J, Torroba T (2009) J Org Chem 74:2189–2192
62. Akritopoulou-Zanze I, Gracias V, Djuric SW (2004) Tetrahedron Lett 45:8439–8441
63. Golebiowski A, Jozwik J, Klopfenstein R, Colson A, Grieb AL, Russell AF, Rastogi VL, Diven CF, Portlock D, Chen J (2002) J Comb Chem 4:584–590
64. Golebiowski A, Klopfenstein R, Shao X, Chen JJ, Colson A-O, Grieb AL, Russell AF (2000) Org Lett 2:2615–2617
65. Oikawa M, Naito S, Sasaki M (2006) Tetrahedron Lett 47:4763–4767
66. Banfi L, Basso A, Guanti G, Riva R (2003) Tetrahedron Lett 44:7655–7658
67. Dietrich SA, Banfi L, Basso A, Damonte G, Guanti G, Riva R (2005) Org Biomol Chem 3:97–106
68. Dechantsreiter MA, Planker E, Matha B, Lohof E, Hoelzemann G, Jonczyk A, Goodman SL, Kessler H (1999) J Med Chem 42:3033–3040
69. Wessjohann LA, Ruijter E (2005) Top Curr Chem 243:137–184
70. Wessjohann LA, Ruijter E (2005) Mol Divers 9:159–169
71. Wessjohann LA, Rivera DG, Vercillo OE (2009) Chem Rev 109:796–814
72. Bauer SM, Armstrong RW (1999) J Am Chem Soc 121:6355–6366
73. Bowers MM, Carroll P, Joullié MM (1989) J Chem Soc Perkin Trans 1, 857–865
74. Joullié MM, Nutt RF (1985) In: Pelletier SW (ed) Alkaloids: chemical and biological perspectives, vol 3. Wiley, New York, 3:113pp
75. Gournelis DC, Laskaris GG, Verpoorte R (1997) Nat Prod Rep 14:75–82
76. Cristau P, Vors J-P, Zhu J (2001) Org Lett 3:4079–4082
77. Cristau P, Vors J-P, Zhu J (2003) Tetrahedron 59:7859–7870
78. Cristau P, Vors J-P, Zhu J (2006) QSAR Comb Sci 25:519–526
79. De Greef M, Abeln S, Belkasmi K, Dömling A, Orru RVA, Wessjohann LA (2006) Synthesis 3997–4004
80. Beck B, Larbig G, Mejat B, Magnin-Lachaux M, Picard A, Herdtweck E, Dömling A (2003) Org Lett 5:1047–1050
81. Pirali T, Tron GC, Zhu J (2006) Org Lett 8:4145–4148
82. Sun X, Janvier P, Zhao G, Bienaymé H, Zhu J (2001) Org Lett 3:877–880
83. Janvier P, Sun X, Bienaymé H, Zhu J (2002) J Am Chem Soc 124:2560–2567
84. Zhao G, Sun X, Bienaymé H, Zhu J (2001) J Am Chem Soc 123:6700–6701
85. Bughin C, Zhao G, Bienaymé H, Zhu J (2006) Chem Eur J 12:1174–1184
86. Hebach C, Kazmaier U (2003) Chem Comm 5:596–597
87. Kazmaier U, Hebach C, Watzke A, Maier S, Mues H, Huch V (2005) Org Biomol Chem 3:136–145
88. Bughin G, Masson G, Zhu J (2007) J Org Chem 72:1826–1829
89. Pirali T, Tron GC, Masson G, Zhu J (2007) Org Lett 9:5275–5278
90. Faure S, Hjelmgaard T, Roche SP, Aitken DJ (2009) Org Lett 11:1167–1170
91. Owens TD, Araldi GL, Nutt RF, Semple JE (2001) Tetrahedron Lett 42:6271–6274
92. Failli A, Immer H, Götz MD (1979) Can J Chem 57:3257–3261
93. Vercillo OE, Andrade CKZ, Wessjohann LA (2008) Org Lett 10:205–208
94. Vercillo OE, Andrade CKZ, Wessjohann LA. Unpublished
95. Vercillo OE (2007) Ugi reaction on the cyclopeptoids construction: Synthesis of a potencial inhibitor of Tat/TAR complex of HIV-1 virus. PhD thesis, Universidade de Brasília, Brasil

96. Wessjohann LA, Rivera DG, Coll F (2006) J Org Chem 71:7521–7526
97. Leon F, Rivera DG, Wessjohann LA (2008) J Org Chem 73:7162–7167
98. Michalik D, Schaks A, Wessjohann LA (2007) Eur J Org Chem 149–157
99. Westermann B, Michalik D, Schaks A, Kreye O, Wagner C, Merzweiler K, Wessjohann LA (2007) Heterocycles 73:863–872
100. Rivera DG, Wessjohann LA (2006) J Am Chem Soc 128:7122–7123
101. Rivera DG, Wessjohann LA (2009) J Am Chem Soc 131:3721–3723
102. Nikulinkov M, Tsirulnikov S, Kysil V, Ivachtchenko A, Krasavin M (2009) Synlett 260–262
103. Da Settimo F, Taliani S, Trincavelli ML, Montali M, Martini C (2007) Curr Med Chem 14:2680–2701
104. Whiting PJ (2006) Curr Opin Pharmacol 6:24–29
105. Atack JR (2005) Expert Opin Investig Drugs 14:601–618
106. Banfi L, Basso A, Damonte G, De Pellegrini F, Galatini A, Guanti G, Monfardini I, Riva R, Scapolla C (2007) Bioorg Med Chem Lett 17:1341–1345
107. Wessjohann LA, Voigt B, Rivera DG (2005) Angew Chem Int Ed 44:4785–4790

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β-Diketo Building Blocks for MCRs-Based Syntheses of Heterocycles

Maria del Mar Sanchez Duque, Christophe Allais, Nicolas Isambert, Thierry Constantieux, and Jean Rodriguez

Abstract In the context of sustainable chemistry, because of economic and ecological increasing pressure, domino multicomponent reactions (MCRs) constitute a central academic and industrial investigation domain in diversity-oriented synthesis of functionalized heterocycles. Although isocyanide-based MCRs generally predominate nowadays, the use of 1,3-dicarbonyls as substrates, proposed as early as 1882 by Hantzsch, proved to be highly efficient, but have been relatively unexplored until recently. In the last few years, such transformations received a growing attention as new useful methodologies valuable for the selective direct access to highly functionalized small organic molecules of primary synthetic and biological value. This review focuses on the more significant recent developments on the use of β-diketo building blocks for MCRs published in the last 5 years.

Keywords 1,3-Dicarbonyls, Biginelli reaction, Hantzsch reaction, Heterocyclic chemistry, Knoevenagel condensation, Mannich reaction, Michael addition, Multicomponent reactions

Contents

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Abbreviations

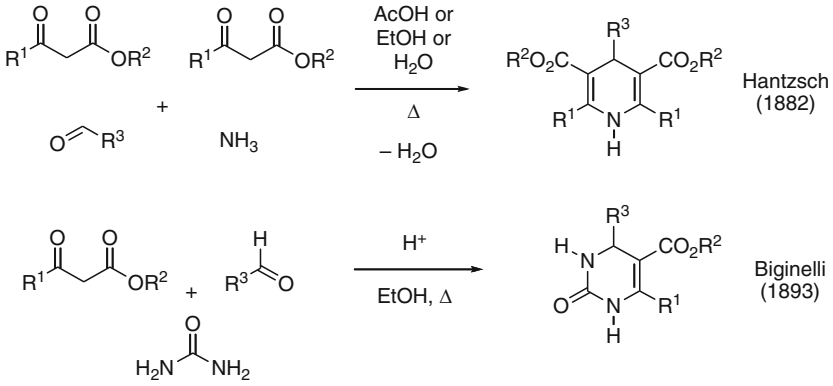
aemim	Aminoethyl methylimidazolium
BDMS	Bromodimethylsulfonium bromide
bmim	Butyl methylimidazolium
CAN	Cerium(IV) ammonium nitrate
cat	Catalyst
DABCO	Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DHP	Dihydropyridine
DHPM	Dihydropyrimidinone
DMF	Dimethylformamide
ee	Enantiomeric excess
HPLC	High performance liquid chromatography
IBX	2-Iodoxybenzoic acid
L*	Ligand
LUMO	Lowest unoccupied molecular orbital
MARDi	Michael addition-Aldolisation-Retro-Dieckmann
MCR	Multicomponent reaction
MS	Molecular sieves
MW	Microwave
PFO	Perfluorooctanoate
p-TSA	*Para*-toluenesulfonic acid
RCM	Ring closing metathesis

rt	Room temperature
TBAF	Tetrabutylammonium fluoride
TEBA	Triethylbenzylammonium chloride
THF	Tetrahydrofurane
TMAH	Tetramethylammonium hydroxide
TMSCl	Trimethylsilyl chloride
Yb	Ytterbium

1 General Introduction

The development of rapid and selective synthetic routes toward focused libraries of functionalized heterocyclic building blocks is of great importance to both medicinal and organic chemists, and still constitutes a challenge from academic and industrial points of view. In modern organic chemistry, because of economic and ecological increasing pressure, investigations are now directed to the discovery of methods that largely take into account the criterion of sustainable chemistry [1]. In this context, multicomponent reactions (MCRs) [2] involving domino processes [3], combining at least three different substrates in a one-pot operation, have emerged as powerful tools and complementary substrate-directed synthetic alternatives to other well-known methods [4–7]. Moreover, these transformations combine classical concerns such as efficiency, selectivity, molecular complexity and diversity [8, 9], with current preoccupations such as atom- and step-economy [10–12], and environmentally benign reactions, thus approaching quite closely the concept of an ideal synthesis [13]. Since the first MCR reported by Strecker in 1850, this concept has been extensively explored, and isocyanides became one of the most popular reactant, especially as a key component in the well-known Passerini and Ugi reactions [14, 15]. However, one of the first substrate classes involved in a MCR was that of β-ketoesters, with Hantzsch's dihydropyridines (DHPs) and Biginelli's dihydropyrimidinones (DHPMs) synthesis appearing as early as 1882 and 1893, respectively (Scheme 1).

In 2004, we reported an overview of the high synthetic potential of MCRs involving the specific reactivity of easily accessible 1,3-dicarbonyl derivatives [16]. In the last few years, such transformations received a growing worldwide attention because of their ability to selectively furnish a direct access to highly functionalized small organic molecules of primary synthetic and biological value. In this review, on the basis of selected examples, we focus only on the recent developments of β-diketo building blocks-based MCRs published in the last 5 years. In each chapter, examples are organized with respect to the nature of both the reaction and the heterocyclic ring formed during the process. The discussion is limited to the use of organocatalysts or Lewis acid catalysts, thus no transformations involving the utilization of transition-metal catalysts will be presented.



Scheme 1 Hantzsch's dihydropyridines and Biginelli's dihydropyrimidinones synthesis

2 Hantzsch Heterocyclic Synthesis

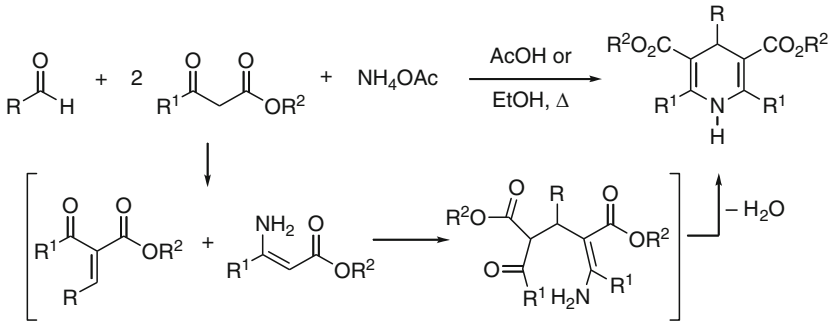
2.1 The Hantzsch Reaction

2.1.1 Synthesis of 1,4-Dihydropyridines

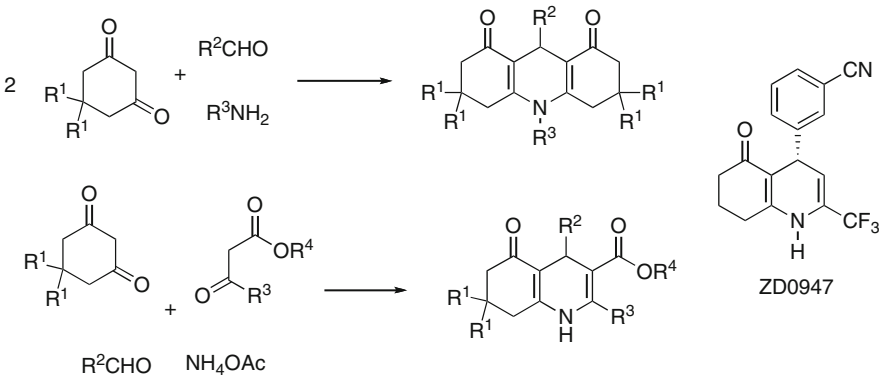
1,4-DHPs and their derivatives are important classes of bioactive molecules in the pharmaceutical field [17] and constitute also interesting biomimetic reducing agents [18, 19]. 1,4-DHPs are generally synthesized using the four-component Hantzsch reaction, which involves the one-pot cyclocondensation of an aldehyde, two equivalents of a β-ketoester and ammonia, or a synthetic equivalent (Scheme 2). The reaction proceeds through the condensation of in situ formed alkylidene malonate and enaminoester derivatives, followed by a cyclodehydration affording the symmetric heterocycles.

Cyclic 1,3-diketones can also participate in this MCR. Thus, utilization of two equivalents of 1,3-cyclohexanedione or dimedone instead of β-ketoesters led to hydrogenated acridine derivatives. However, when only one equivalent of cyclic 1,3-dicarbonyl is used in combination with one equivalent of β-ketoester, unsymmetric 1,4-DHPs may be obtained (Scheme 3). For example, this reaction was applied to the synthesis of ZD0947, a potassium channel opener [20].

Over the years, the great biological importance of these various symmetric or unsymmetric 1,4-DHPs has prompted the development of new improved methodologies for their synthesis. According to the original procedure described by Arthur Hantzsch in 1882, the reaction is conducted either in acetic acid or in refluxing alcohols for long reaction times, but these rather harsh conditions typically lead to low yields. Aiming at developing more efficient and environmentally benign Hantzsch reactions, some procedures involving different activating modes such as microwave irradiations [21, 22], ultrasonic irradiations [23, 24], or even use of solar



Scheme 2 General scheme of the Hantzsch's 1,4-DHPs synthesis

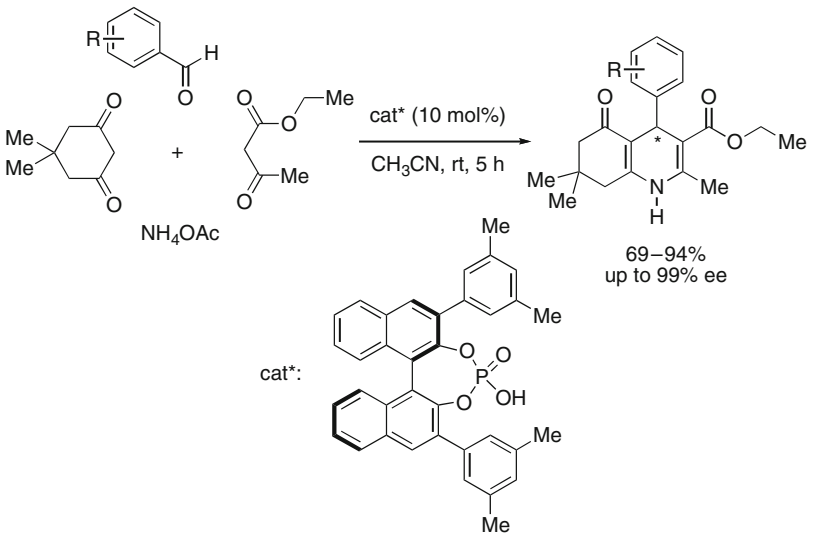


Scheme 3 Acridines and unsymmetric 1,4-DHPs via Hantzsch reaction

energy as a free energy source [25] have been reported. Conventional organic solvents have also been replaced by water [26] or reusable fluoroalcohols [27]. One example of the synthesis of polyhydroquinolines was also described under solvent-free conditions on grinding [28]. Alternatively, task-specific ionic liquids were used as soluble support on which the β-ketoesters were bounded [29].

The standard Hantzsch procedure does not involve the use of additive or reagent, but to improve reaction time and yield, the use of a large variety of catalysts has been developed, which makes possible to operate at room temperature in some cases. In the last few years, particular efforts have been devoted to the utilization of low cost, nontoxic, environmentally benign and reusable catalysts [22, 29–40].

The initial harsh conditions have made the development of an asymmetric route a challenge. Very recently, an organocatalyzed version of this reaction was reported with good yields and excellent enantiomeric excesses (ee's). Thus, the enantioselective synthesis of polyhydroquinolines was achieved in the presence of a catalytic



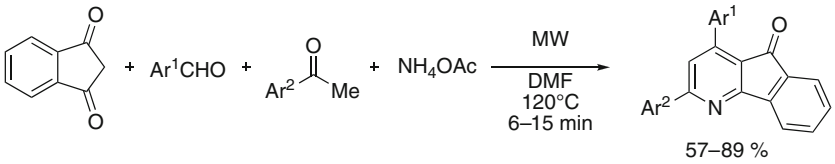
Scheme 4 Enantioselective four-component Hantzsch reaction

amount of a BINOL-phosphoric acid derivative, at room temperature, with ee's up to 99% (Scheme 4) [41]. These products are not only DHPs of medicinal interest, but also interesting reagents for enantioselective hydrogenation reactions [42–44]. It is important to note that only aromatic aldehydes gave enantioenriched products. Reactions with alkyl aldehydes proceeded in good yields but no enantioselectivity was observed. In these cases, the size of the appended functionality appeared to dictate the outcome.

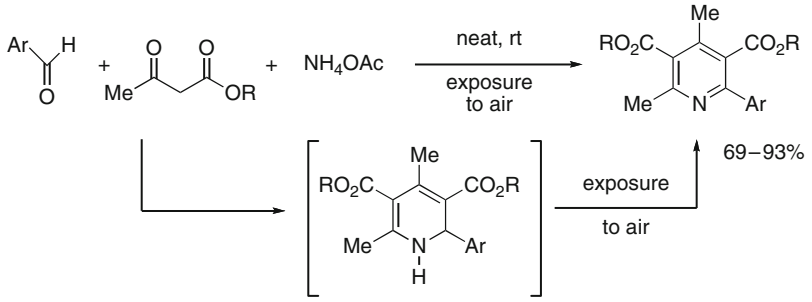
2.1.2 Synthesis of Pyridines

The oxidation of 1,4-DHP into pyridines was easily performed using well-known oxidative reagents [45, 46]. The oxidizing agent can be directly introduced into the reaction media after formation of the 1,4-DHP for a one-pot sequence [34, 47]. However, there are two recent examples for the direct synthesis of pyridines involving an in situ spontaneous oxidation. Indeed, the sequence involving 1,3-indanedione, aromatic aldehydes, ammonium acetate, and acetophenones in the place of 1,3-dicarbonyl in dimethylformamide (DMF) under microwave irradiations is of particular interest (Scheme 5) [48]. This methodology allowed the high yielding formation of various aryl-substituted 4-azafluorenones, which are common skeletons in natural products and molecules of pharmacological interest.

More recently, Shen et al. reported on a green and efficient three-component one-pot synthesis of 2-aryl-pyridines with the same starting materials as the Hanztsch reaction, under solvent-, catalyst-, and heat-free conditions. This methodology does



Scheme 5 Microwave-assisted four-component synthesis of 4-azafluorenone derivatives



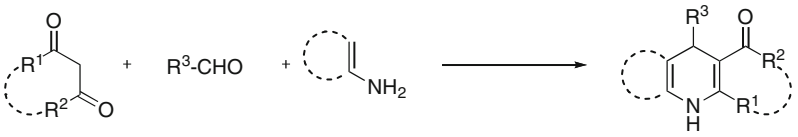
Scheme 6 Three-component synthesis of pyridines upon exposure to air

not require the use of any additional oxidant; the initially formed 1,2-DHP intermediates being in situ oxidized by air (Scheme 6) [49].

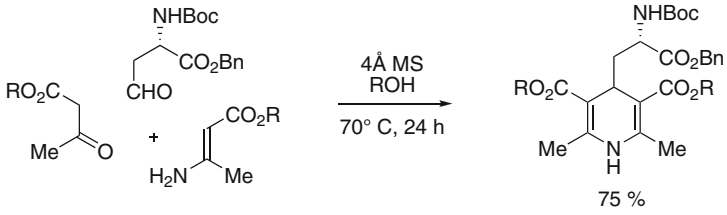
2.2 *Modified Hantzsch Reaction*

In classical Hantzsch procedure, an enaminocarbonyl is formed in situ by condensation of ammonia source onto the 1,3-dicarbonyl substrate. But many groups have used a three-component modified-Hantzsch protocol in which the preformed enamine is introduced as a partner. Thus, utilization of cyclic or acyclic 1,3-dicarbonyl compounds, aldehydes, and acyclic or cyclic enamines has been reported, leading regioselectively to diversely substituted 1,4-DHP derivatives (Scheme 7). The sequence involving such starting materials was performed in numerous efficient systems, and more particularly in the following: (1) microwave-assisted reaction in acetic acid [50], DMF [51], or an acetic acid/DMF system [52]; (2) sonification in ethylene glycol [53]; and (3) use of ionic liquids such as [bmim]BF_4 [54].

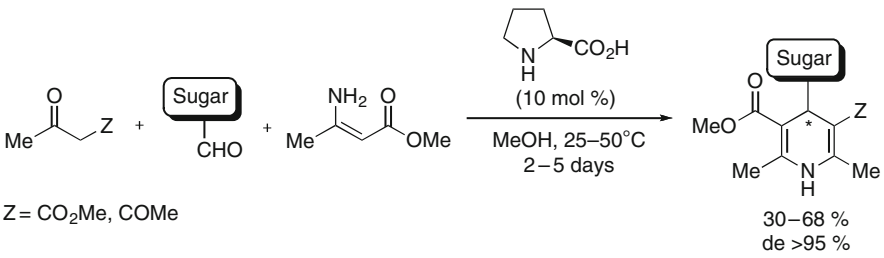
Dondoni and co-workers have successfully extended this strategy to form functionalized 1,4-dihydropyridinylalanines using either aldehydes or β-ketoesters derived from amino acids and sugar derivatives (Scheme 8) [55]. More recently, the same group reported the first organocatalyzed version of this Hantzsch-like reaction using *C*-glycosyl aldehydes [56]. This L-proline-catalyzed three-component process occurred with high diastereoselectivity to furnish symmetrically and



Scheme 7 Synthesis of 1,4-dihydropyridine derivatives by the three-component Hantzsch-like reaction



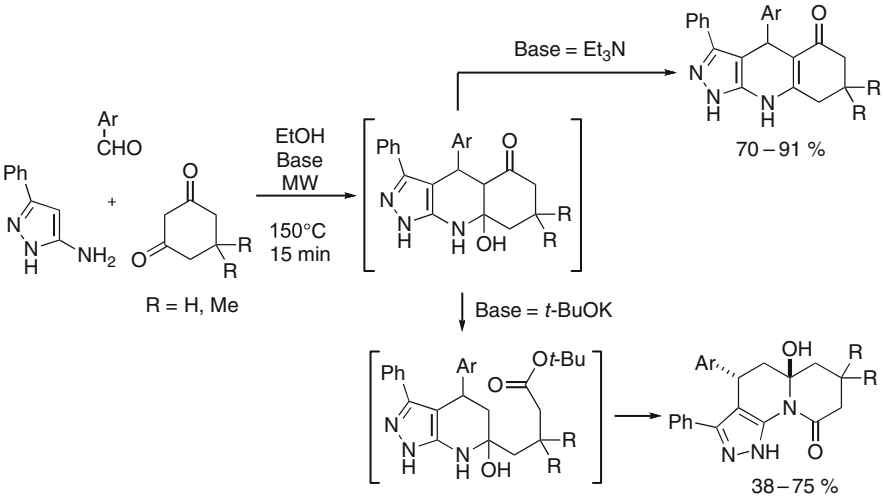
Scheme 8 Synthesis of 1,4-dihydropyridinylalanines



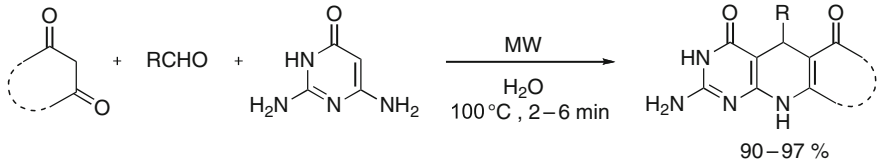
Scheme 9 First organocatalyzed asymmetric three-component variant of Hantzsch reaction

unsymmetrically substituted DHP *C*-glycoconjugates of great biological interest (Scheme 9).

This modified-Hantzsch approach has recently been exploited for the syntheses of pyrazoloquinolinones [57], pyrazoloquinolizinones [58], and dihydropyridopyrimidinones [59]. In the first two cases, Kappe's group showed that a mixture of dimedone, aminopyrazole, and aromatic aldehydes in ethanol could regio- and chemoselectively conduce to these fused heterocyclic skeletons depending on the base employed under microwave irradiations (Scheme 10). The relative basicity and the nucleophilicity of the base is crucial. Thus, with triethylamine, the reaction occurred probably via a Knoevenagel/Michael addition/cyclodehydration sequence. But when a strong bulky base such as potassium *tert*-butoxide was used, the reaction proceeded apparently through a ring-opening step followed by an intramolecular transamidation leading to angular fused systems.



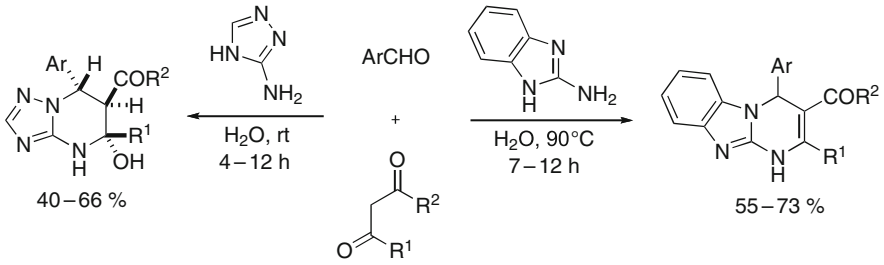
Scheme 10 Regio- and chemoselective access to tricyclic heterocycles



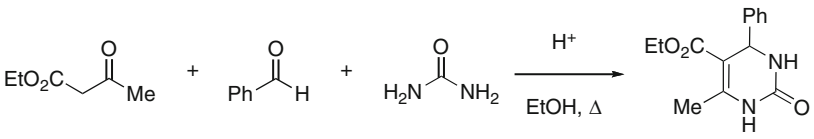
Scheme 11 Ecocompatible three-component synthesis of dihydropyridopyrimidinone derivatives

Dealing with the synthesis of dihydropyridopyrimidinones, the procedure was quite similar to the precedent, involving 2,6-diaminopyrimidin-4(3*H*)-one as enaminocarbonyl partner, various 1,3-dicarbonyl derivatives, and either aliphatic or aromatic aldehydes in water under microwave irradiations (Scheme 11). Interestingly, the guanidine system was unreactive, and a library of tri- and tetracyclic dihydropyridopyrimidinone derivatives was chemoselectively synthesized in high yields and short reaction times from this environmentally friendly procedure.

Finally, when the enamine partner is replaced by a guanidine system, the modified MCR evolves through a Knoevenagel-aza-Michael sequence, leading to nitrogen-containing polyheterocycles of biological interest. This is the case with both 3-amino-1,2,4-triazole and 2-aminobenzimidazole combined with aromatic aldehydes and 1,3-dicarbonyl substrates (Scheme 12) [60]. The environmentally benign catalyst-free reaction was performed either in water at room temperature with 3-amino-1,2,4-triazole to furnish the corresponding hemi-aminal or upon heating at 90°C with 2-aminobenzimidazole, leading to the corresponding dehydrated tricyclic ring systems.



Scheme 12 Synthesis of nitrogen-containing bi- and tricyclic heterocycles by a Knoevenagel-aza-Michael sequence



Scheme 13 General scheme of the Biginelli reaction

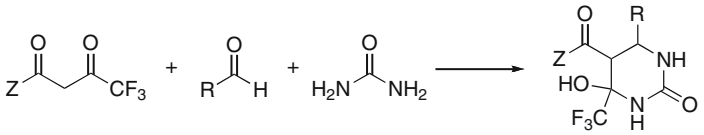
3 Biginelli Heterocyclic Synthesis

3.1 The Biginelli Reaction

The Biginelli reaction, discovered by Pietro Biginelli in 1893, is a multicomponent reaction allowing the synthesis of DHPMs by reacting urea, a dicarbonyl derivative, and an aldehydic component (Scheme 13). As described in the initial work, this reaction requires harsh conditions, that is, use of protic or Lewis acids and generally high temperatures. An increased interest has been shown during the past few years; the main goal of recent investigations aims at performing the MCR under milder conditions, increasing the yields and opening the scope of the different partners. An abundant literature covers all these aspects including a recent compilation of catalytic systems [61], which we will complete here with some recent selected examples. Concerning the mechanistic aspects, the key *N*-acyliminium intermediate identified by Kappe in 1997 has been recently confirmed by combined experimental and theoretical data [62].

3.1.1 Synthesis of Hydropyrimidinone Derivatives

As summarized recently [61], a large scope of Brønsted and Lewis acids catalyze this multicomponent reaction to promote the DHPM formation. The heterocyclic Biginelli scaffold has also been obtained under eco-friendly conditions, as illustrated



Scheme 14 Three-component synthesis of hexahydropyrimidine derivatives

Table 1 Conditions for the three-component synthesis of hexahydropyrimidine derivatives

Z	Catalyst	Solvent	Conditions	Yield	Ref.
OEt	$BnEt_3N^+$, Cl^-	None	100°C, 2 h	65–70%	[70]
OEt	SmI_2	None	100°C	71%	[80]
OEt	None	None	MW irradiation	78–85%	[82]
CF_3	[bmim]BF_4	None	100–125°C, 6 h	34–92%	[68]
OEt, Me, Ar, CF_3	TMSCl	DMF	rt, 24–48 h	69–85%	[83]
		DMF	reflux, 30 min	80–87%	[84]

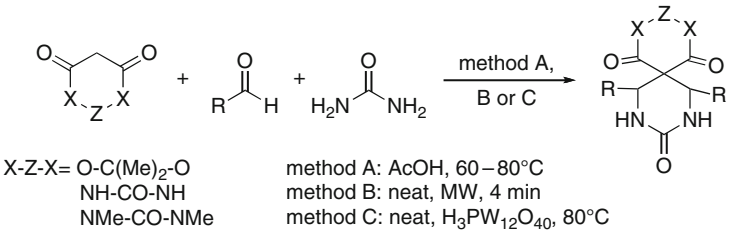
by the use of water [63] or ionic liquids [64–71] as solvent. Alternatively, the reaction may be conducted under solvent-free conditions [72, 73] or under microwave irradiation [74, 75]. Finally, among other activating catalysts, Baker's yeast [76], iodine [77], Zeolite [78], and ion exchange resin [79] may be outlined.

It is interesting to note that when the dicarbonyl partner is a trifluoromethylketone derivative, the dehydration is not observed and the corresponding hexahydropyrimidines are obtained in good yields [70, 80–82], regardless of the reaction conditions involving various catalytic systems, different medium, and thermal activation modes (Scheme 14 and Table 1). The different observations based on the isolation of these hydroxylated products allowed to corroborate the acyliminium ion mechanism [62].

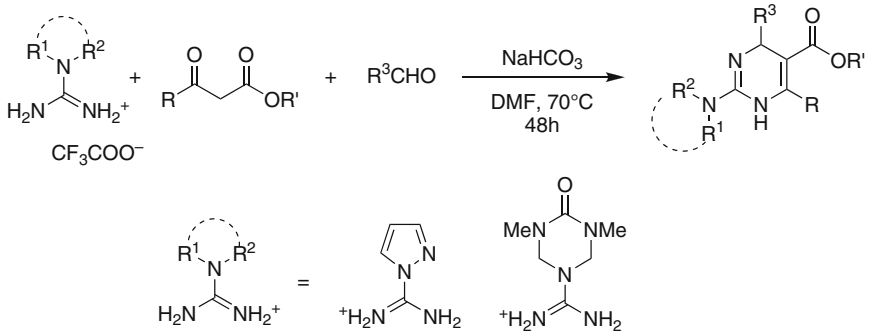
When the 1,3-dicarbonyl substrate reacts twice via its activated methylene due to the presence of heteroatoms blocking the enolization process on other positions, spiranic systems are formed in the presence of two equivalents of aldehyde and an equivalent of urea (Scheme 15) [85]. The reaction can be promoted either in acetic acid as solvent or neat under microwave irradiations or in the presence of $H_3PW_{12}O_{40}$ as catalyst. Finally, this technique for generating spiroheterocyclic products has been transferred to solid-supported methodology by immobilizing the 1,3-dicarbonyl partner onto a resin [86].

3.1.2 Synthesis of Cyclic Guanidine Derivatives

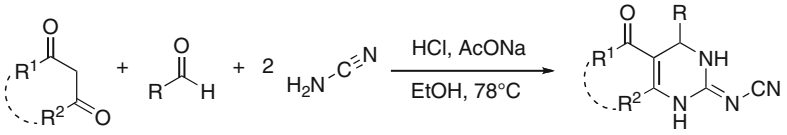
Guanidine moiety is a very important functional group with interesting biological and synthetic properties that are also found in several natural products (saxitoxin, tetrodotoxin, or batzelladine F). An interesting approach to cyclic guanidines was proposed by Overman et al. using guanylating agents instead of ureas in a Biginelli-type multicomponent reaction (Scheme 16) [87]. Pyrazole carboxamidines and triazone-protected guanidines proved to be efficient substrates in the presence of



Scheme 15 Three-component synthesis of spiroheterocyclic Biginelli's products



Scheme 16 Multicomponent synthesis of cyclic guanidine derivatives



Scheme 17 Synthesis of 4-aryl-2-cyanoimino-3,4-dihydro-1H-pyrimidine derivatives

$NaHCO_3$, leading to the expected 2-aminopyrimidines in moderate to good yields (43–91%).

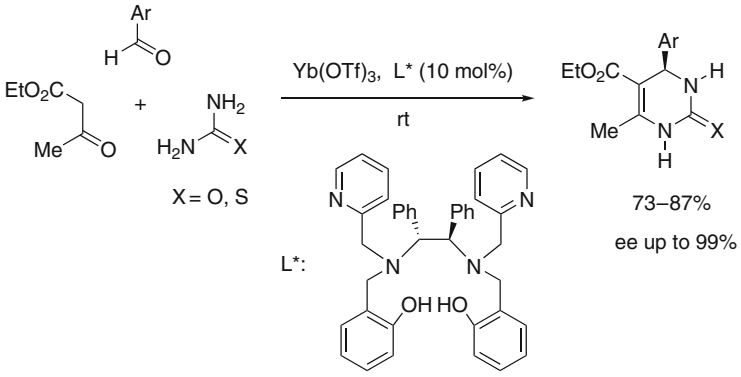
In the same context, successful utilization of cyanamide allowed the incorporation of the cyanoimino moiety of potential pharmacological properties (Scheme 17) [88]. In this case, the in situ hydrolysis of cyanamide into urea constitutes the corner stone of this four-component Biginelli-like reaction.

3.2 The Asymmetric Biginelli Reaction

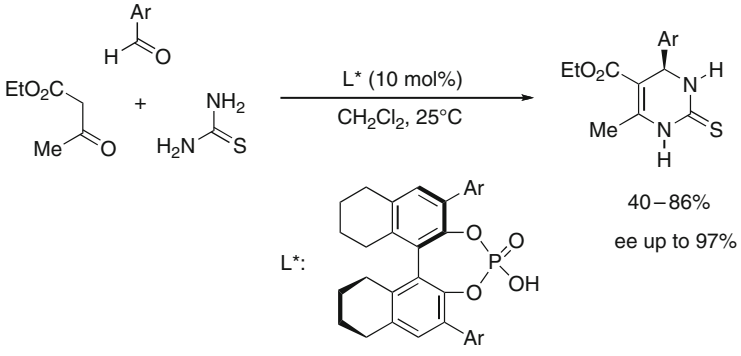
DHPMs obtained through a Biginelli reaction contain a stereogenic center, and the absolute configuration has a considerable influence on the biological activity. Indeed, the two individual enantiomers may perform different or even opposite

activities [89, 90]. Thus, the development of representative methods to approach enantiomerically enriched DHPMs is a task of primary importance [91]. Initially, chemical resolutions [92] and enzymatic strategies [93] were the methods of choice. Attempted synthesis of optically active DHPMs were also conducted through auxiliary-assisted asymmetric synthesis, using chiral starting materials such as *C*-glycosyl aldehydes [94] or (−)-menthol-derived acetoacetate [93]. A few years later, significant advances were made in the synthesis of optically active DHPMs with the use of catalytic amounts of chiral metal complexes. In 2005, Zhu and co-workers described a highly enantioselective multicomponent Biginelli reaction using a recyclable Yb triflate coordinated with a novel chiral hexadentate ligand bearing tertiary amine, phenol, and pyridine functional groups (Scheme 18) [95]. The products were obtained in high yields with enantiomeric excesses up to 99%.

Finally, a highly efficient organocatalytic asymmetric approach was described by Gong et al. in 2006, using chiral phosphoric acids as catalysts. These results opened a window for the development of new optically active DHPMs synthesis (Scheme 19) [96, 97]. More recently, chiral organocatalysts such as *Cinchona*



Scheme 18 Chiral ytterbium triflate-catalyzed enantioselective Biginelli reaction



Scheme 19 Chiral phosphoric acid organocatalyzed Biginelli reaction

alkaloids [98] or substituted tetrazoles [99] have also found interesting applications in asymmetric Biginelli transformations.

4 MCRs Based on the Mannich Reaction

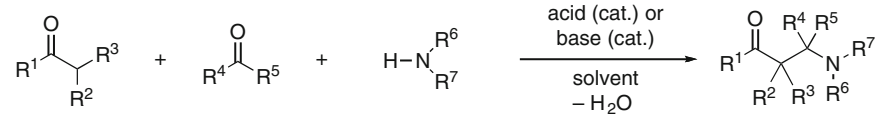
4.1 The Mannich Reaction

The Mannich reaction consists on the condensation of a CH-activated compound with a primary or a secondary amine and a non-enolizable aldehyde or ketone to afford β-aminocarbonyl derivatives known as Mannich bases (Scheme 20). This sequence is of great use for the construction of heterocyclic targets, as illustrated for example by the Robinson-Schöpf synthesis of tropinone in 1937 or by the preparation of some azabicyclo[3.3.1]nonanones or pyranocoumarine derivatives (Fig. 1) [100]. In the following, representative recent examples of the formation of five- to seven-membered ring heterocycles will be presented.

4.2 Five-Membered Heterocycles

4.2.1 Pyrrolidine Derivatives

The three-component reaction of sodium ethyl oxalacetate with ammonia or primary amines with an aromatic aldehyde in ethanol or acetic acid results in the



R^1= H, alkyl, aryl, OR
$R^{2–3}$= H, alkyl, aryl
$R^{4–5}$= H, alkyl, aryl
R^6= H, alkyl, OH, NH_2
R^7= H, alkyl
solvent= ROH, H_2O, AcOH

Scheme 20 General scheme of the Mannich reaction

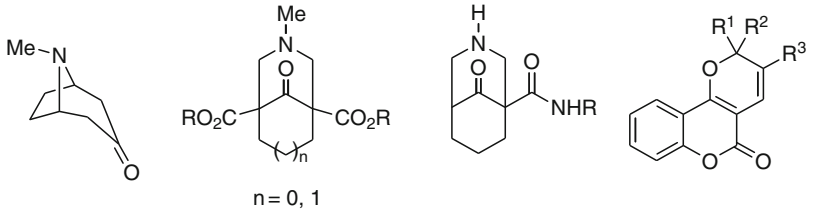
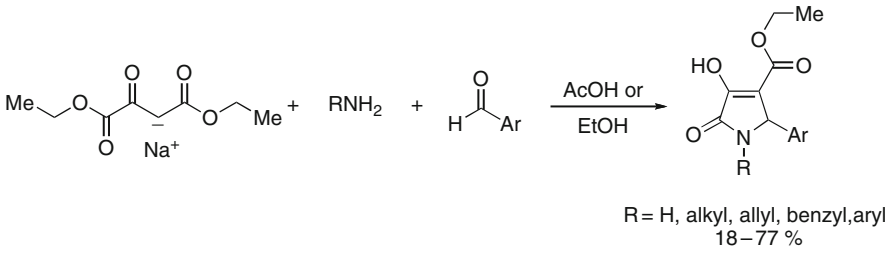
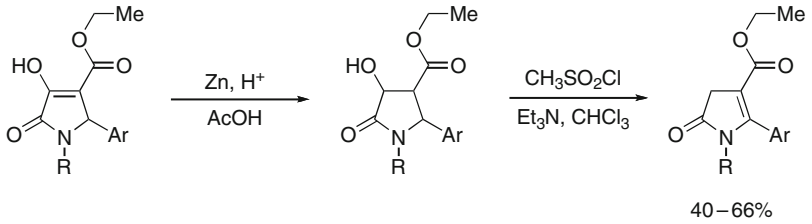


Fig. 1 Examples of (poly)heterocycles available through Mannich condensations



Scheme 21 Three-component synthesis of 2,3-dioxopyrrolidine derivatives

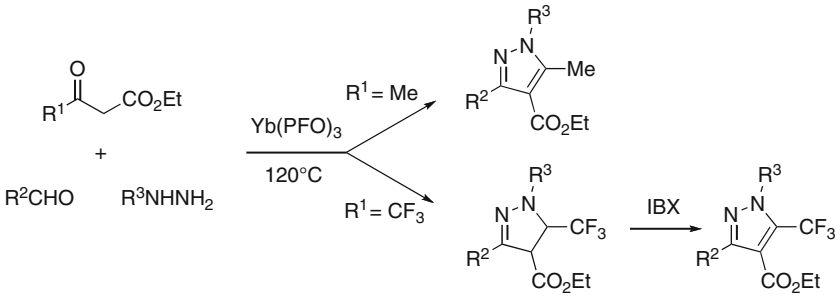


Scheme 22 Synthesis of 2-oxo-5-(hetero)arylpyrroles from 2,3-dioxopyrrolidines

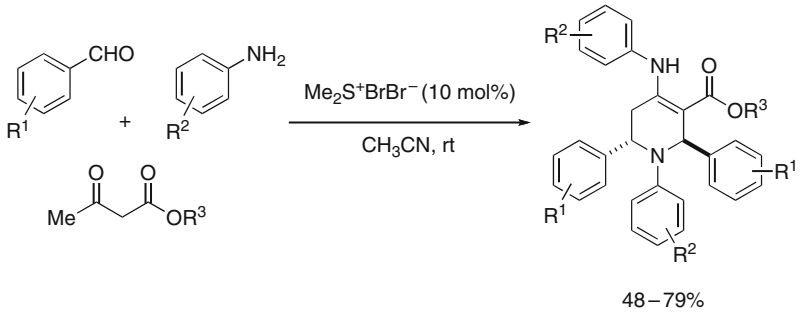
formation of 2,3-dioxopyrrolidine derivatives (Scheme 21) [101]. These compounds can easily be converted into the corresponding 2-oxopyrroles through consecutive reduction of the enol, mesylation of the secondary alcohol, and elimination with concomitant isomerization of the double bond (Scheme 22). This methodology allowed the preparation of a small library of original 2-oxo-5-(hetero)-arylpyrroles, compounds of which the various synthetic and biological potentialities have been largely investigated.

4.2.2 Pyrazole Derivatives

Substituted pyrazole derivatives have attracted much attention due to their biological activities, making these products increasingly important agricultural chemicals and pharmaceutical agents. Among the different methods reported for the synthesis of fully substituted pyrazoles, the most general and applicable one consists on the cyclization of 1,3-diketones with substituted hydrazines. However, this methodology suffers from poor regioselectivity when unsymmetrical 1,3-diketones are employed. To circumvent this drawback, an efficient and selective three-component alternative has been proposed with the development of an ytterbium perfluorooctanoate-catalyzed coupling of aldehydes, phenylhydrazine, and 1,3-dicarbonyl compounds under solvent-free conditions (Scheme 23) [102]. The catalyst is not only highly efficient and easy to prepare, but also recyclable for



Scheme 23 [$Yb(PFO)_3$]-catalyzed three-component synthesis of fully substituted pyrazoles



Scheme 24 BDMS-catalyzed multicomponent access to functionalized piperidines

subsequent runs. The methodology has been successfully extended to the synthesis of trifluoromethyl-containing pyrazoles starting from ethyl trifluoroacetoacetate, but it is noteworthy to highlight that in this case the three-component reaction stopped at the formation of the corresponding pyrazolines, and a subsequent oxidation with IBX was necessary to obtain the desired pyrazoles [103].

4.3 Six-Membered Heterocycles

4.3.1 Piperidine Derivatives

A vast array of piperidine containing cores, both natural and synthetic, are of biological and medicinal interest. These heterocyclic scaffolds have been the subjects of considerable synthetic efforts, especially for the construction of optically active compounds. In this context, Khan et al. reported a catalytic bromodimethylsulfonium bromide (BDMS) three-component reaction of 1,3-dicarbonyls with aromatic aldehydes and aromatic amines for a facile access to highly functionalized piperidines (Scheme 24) [104]. This strategy is an interesting illustration of

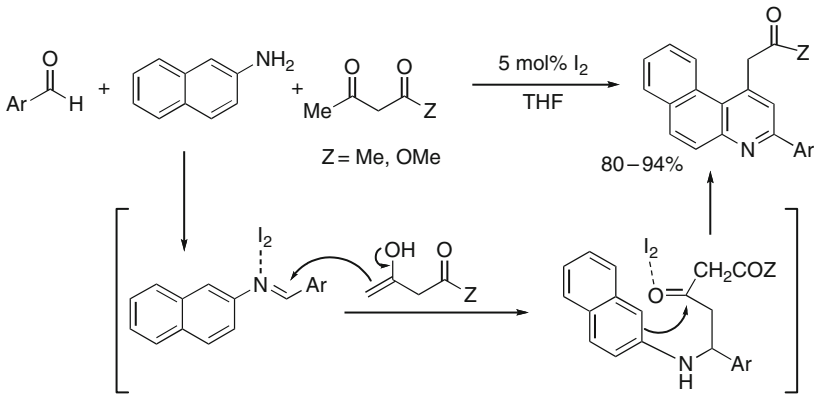
quite rarely exploited potentialities of β-ketoesters to react both at α- and γ-positions with electrophiles for C–C bond formations [105].

4.3.2 Quinoline Derivatives

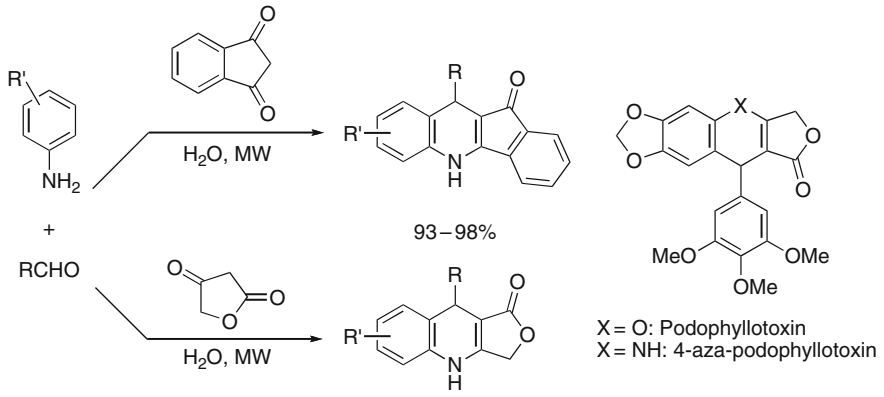
In view of the importance of benzoquinoline and its derivatives in various fields of chemistry, biology, and pharmacology, many efforts have been devoted to their synthesis. A highly selective and operational simple procedure was reported on the basis of a three-component reaction of arylaldehydes, 2-amino-naphtalene, and either ketones or β-ketoesters, using 5 mol% of iodine acting as a mild Lewis acid catalyst (Scheme 25) [106]. Iodine is involved not only in the first step of the sequence as activator of the Schiff base during the Mannich reaction, but also as a promoter of an intramolecular Friedel-Craft cyclization leading, after dehydration, to a dihydroquinoline derivative. The latter compound is oxidized in situ by air, giving the aromatized benzo[*f*]quinoline.

Partially hydrogenated quinoline cores are also present in some important bioactive compounds. For example, the 4-aza-analogs of Podophyllotoxin, a plant lignan that inhibits microtubule assembly, revealed to be more potent and less toxic anticancer agents. In 2006, Ji's group reported a green multicomponent approach to a new series of these derivatives, consisting of the reaction of either tetronic acid or 1,3-indanedione with various aldehydes and substituted anilines in water under microwave irradiation conditions (Scheme 26) [107]. For this efficient and eco-friendly transformation, the authors proposed a mechanism quite similar to the one that was postulated for the synthesis of tetrahydroquinolines in the precedent section.

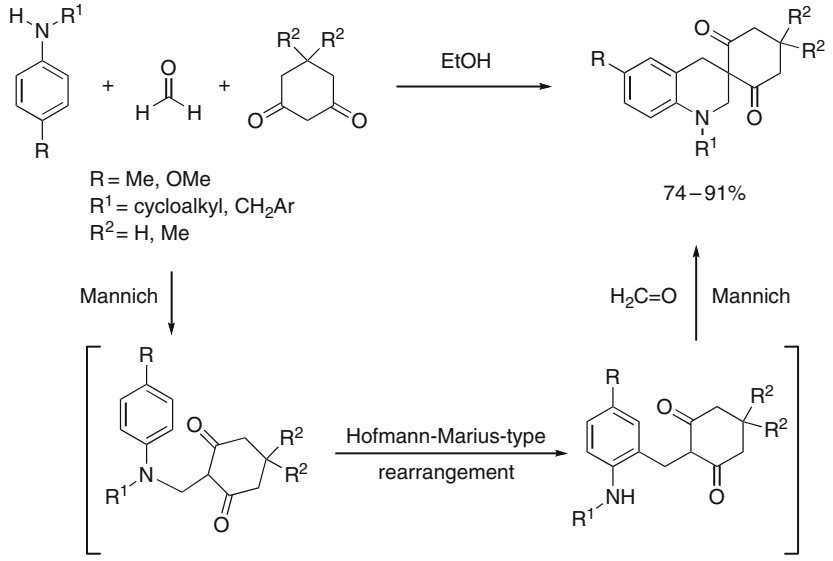
Finally, the tetrahydroquinoline subunit is present in various natural alkaloids and synthetic pharmaceuticals [108], and the development of methods for the preparation of products containing this skeleton has been the subject of intense



Scheme 25 I_2-catalyzed three-component synthesis of benzo[*f*]quinoline derivatives



Scheme 26 Multicomponent synthesis of 4-aza-podophyllotoxin derivatives



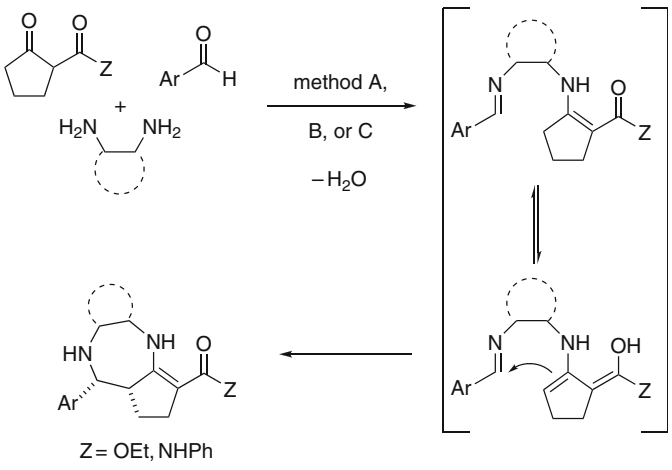
Scheme 27 Multicomponent synthesis of 3-spirosubstituted-1,2,3,4-tetrahydroquinolines

investigations. Although access to two- and four-substituted tetrahydroquinolines is well-documented in the literature [109, 110], the synthesis of three-substituted derivatives remains a challenge. In this context, Kadutskii reported a three-component reaction of cyclic β-diketones, formaldehyde, and substituted anilines, leading efficiently to 3-spirosubstituted 1,2,3,4-tetrahydroquinolines (Scheme 27) [111]. From a mechanistic point of view, the Mannich base, formed by the reaction of β-diketone with amine and formaldehyde, undergoes a rearrangement leading to the formation of an aminodiketone. Finally, an intramolecular Mannich reaction takes place, giving the final tricyclic product in good yields.

4.4 Seven-Membered Heterocycles

4.4.1 1,4-Diazepane Derivatives

Seven-membered ring systems with 1,4-diazepane skeleton are scaffolds of high biological interest. Kita's team and our own group reported independently, but quite at the same time, a one-pot access to these heterocycles by a cyclodehydrative three-component reaction of 1,3-dicarbonyls with aromatic aldehydes and 1,2-diamines. The reaction involves the formation of an intermediate with imine and enamino ester functionalities, which then evolves to the final product via an intramolecular Mannich-type condensation. The latter step of the sequence corresponds to a γ-functionalization of the starting 1,3-dicarbonyl (Scheme 28). The reaction may be conducted either in refluxing 1,2-dichlorethane in the presence of *para*-toluene sulfonic acid (method A) [112] or 4 Å molecular sieves (method B) [113] as catalyst or under solvent- and catalyst-free conditions (method C) [114]. The latter conditions were particularly efficient when β-ketoamides were used as substrates. It is noteworthy that 1,2-phenylenediamine was not effective in this multicomponent reaction, but the access to the corresponding 1,5-benzodiazepine derivatives were made possible by the development of a sequential one-pot protocol involving the preliminary acid-catalyzed formation of an enamino ester from the 1,2-diamine and a 1,3-dicarbonyl [115].



Scheme 28 Three-component synthesis of 1,4-diazepane derivatives

5 MCRs Based on the Knoevenagel Reaction

5.1 The Knoevenagel Reaction

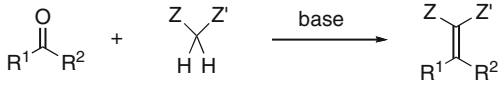
The Knoevenagel reaction consists in the condensation of aldehydes or ketones with active methylene compounds usually performed in the presence of a weakly basic amine (Scheme 29) [116]. It is well-known that aldehydes are much more reactive than ketones, and active methylene substrates employed are essentially those bearing two electron-withdrawing groups. Among them, 1,3-dicarbonyl derivatives are particularly common substrates, and substances such as malonates, acetoacetates, acyclic and cyclic 1,3-diketones, Meldrum's acid, barbituric acids, quinines, or 4-hydroxycoumarins are frequently involved. If Z and Z′ groups are different, the Knoevenagel adduct can be obtained as a mixture of isomers, but the reaction is thermodynamically controlled and the major product is usually the more stable one.

Thanks to its mild reaction conditions, its simplicity, and the availability of the substrates, the Knoevenagel condensation became a more and more attractive synthetic method. Water being the only by-product, this methodology is an environmentally friendly procedure, which has been combined with other classical methods resulting in some very efficient Knoevenagel-initiated multicomponent sequences. Indeed, Knoevenagel products are highly reactive compounds because of their low-energy LUMOs, and so they can act either as Michael acceptors or as Diels–Alder heterodienes. By this way, five- and six-membered heterocyclic rings can be formed, resulting in a considerable gain of molecular complexity in a single operation as illustrated in the following paragraphs.

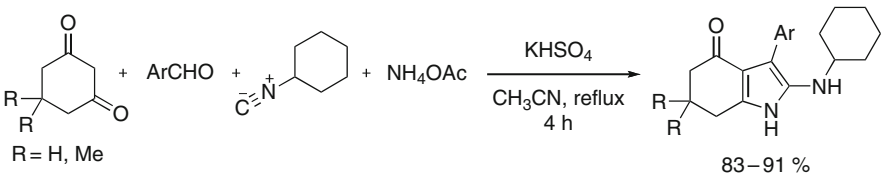
5.2 Five-Membered Heterocycles

5.2.1 Synthesis of Dihydroindolone Derivatives

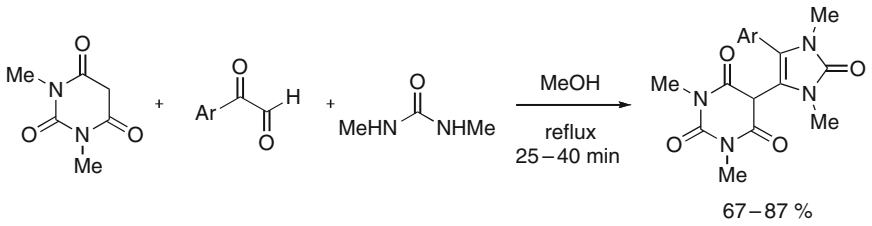
Indole derivatives such as dihydroindolone are scaffolds of potentially biological interest. Thus, the development of such functionalized skeletons has been approached by a MCR involving cyclic 1,3-diketones, cyclohexyl isocyanide, aromatic aldehydes, and ammonium acetate in the presence of catalytic amount of $KHSO_4$ in refluxing acetonitrile (Scheme 30) [117]. In this strategy, the imine derived from the Knoevenagel adduct reacts with cyclohexyl isocyanide to give the



Scheme 29 General scheme of the Knoevenagel condensation



Scheme 30 Four-component synthesis of dihydroindolone derivatives



Scheme 31 Catalyst-free three-component synthesis of functionalized imidazolones

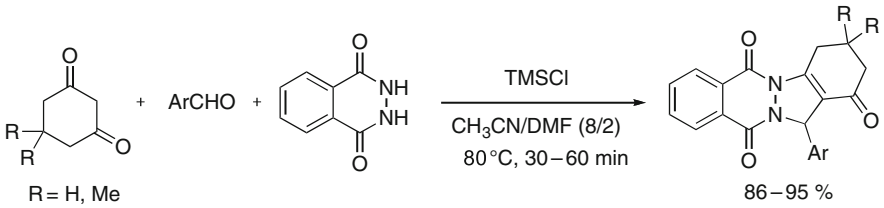
desired product after tautomerization. The study of this methodology was limited to the use of aromatic aldehydes and no other isocyanides were tested.

5.2.2 Synthesis of Imidazolone Derivatives

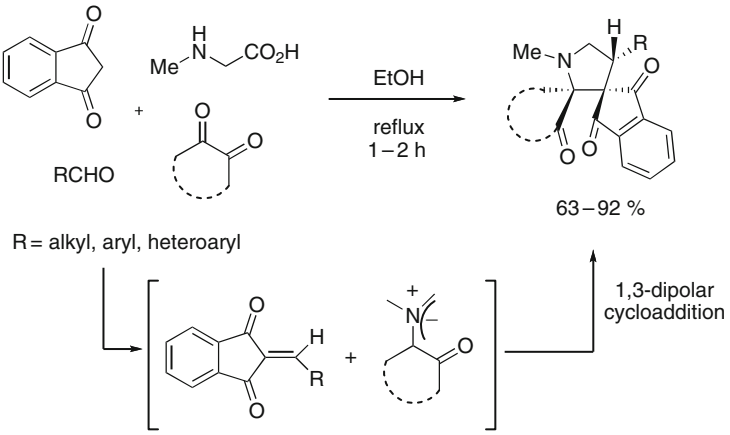
It is well-known that nitrogen-containing compounds such as pyrimidines and imidazole derivatives are of widespread interest in pharmacology. Thus, a catalyst-free three-component transformation combining both heterocycles was developed involving 1,3-dimethylbarbituric acid, arylglyoxals, and dimethylurea in methanol heated at reflux to furnish imidazolylpyrimidinone scaffolds (Scheme 31) [118]. Mechanistic investigations were in accordance with a Knoevenagel-initiated process followed by an aza-Michael addition of urea moiety and cyclodehydration.

5.2.3 Synthesis of Dihydropyrazole Derivatives

Dihydropyrazole derivatives containing phthalazide nucleus showed in the past some interesting pharmacological and biological properties, and high-throughput synthetic methods were logically developed. Among them, the three-component condensation of phthalazide with cyclohexane-1,3-dione derivatives and aromatic aldehydes in CH_3CN/DMF media in the presence of trimethylsilyl chloride led to a tetracyclic indazolophtalazide-triones library (Scheme 32) [119]. The silicon-based catalyst is not only highly efficient but also environmentally benign and not



Scheme 32 TMSCl-catalyzed three-component route to indazolophthalazide-trione derivatives



Scheme 33 Four-component synthesis of functionalized bispiropyrrolidines

expensive. In the proposed mechanism, TMSCl played a Lewis acid role, which activated aromatic aldehyde and catalyzed the formation of the Knoevenagel adduct. Then, subsequent aza-Michael addition of phthalazide moiety followed by cyclodehydration gave the desired products.

5.2.4 Synthesis of Bispiropyrrolidine Derivatives

Knoevenagel reaction has also been combined with 1,3-dipolar cycloaddition to allow the formation of challenging bispiropyrrolidine derivatives. A mixture of 1,3-indanedione, an aldehyde, sarcosine, and a cyclic 1,2-dione was heated in refluxing ethanol without any catalyst to give bispiropyrrolidine derivatives as a single diastereomer (Scheme 33) [120]. This highly regio- and stereoselective four-component Knoevenagel–Huisgen cycloaddition sequence is of great interest for the synthesis of such spiropyrrolidines, which are potential antileukemic and anticonvulsant agents possessing antiviral properties. A reasonable mechanism involved a twofold role of sarcosine, which acted both as an efficient catalyst for the Knoevenagel

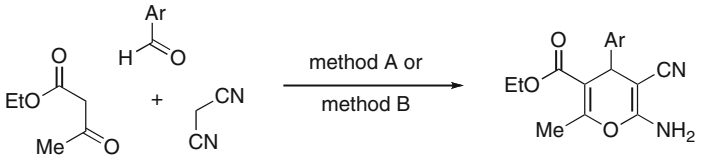
condensation and as a key partner with isatin or acenaphtylene-1,2-dione for in situ formation of the dipolarophile. It was noteworthy that employed aldehydes were either aliphatic, heteroaromatic, or aromatic ones, and in the latter case, there was no electronic effect of the substituent on the reaction yields.

5.3 *Six-Membered Heterocycles*

5.3.1 Synthesis of Pyran Derivatives

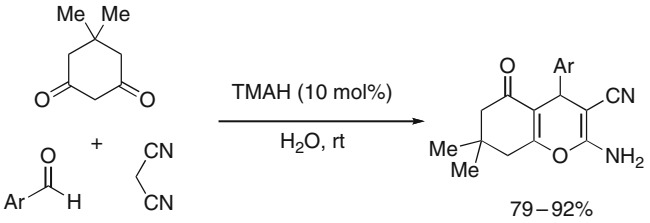
4*H*-Pyran and its derivatives are heterocycles of primary interest owing to their biological and pharmaceutical activities. The reaction of arylidenemalononitriles with activated acyclic methylene compounds in the presence of organic bases allows the formation of 5-substituted-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans, which have found important applications in the treatment of neuro degenerative diseases. A three-component version of this reaction has been studied in the last few years; the arylidenemalonotrile being generated in situ via a Knoevenagel reaction between malononitrile and an aromatic aldehyde. In this context, and with the aim to develop environmentally friendly methodologies, Peng and Song conducted this MCR in a mixture of catalytically active ionic liquid and water (Scheme 34, method A) [121], and Lingaiah and co-workers reported the use of a heterogeneous strong basic Mg/La mixed oxide catalyst in methanol (Scheme 34, method B) [122]. Compared to the utilization of more classical solvents and organic bases, these strategies combine advantages in efficiency such as shorter reaction times and higher yields, with ecological advantages in terms of recovery and reusability of the catalyst.

This approach has been extended to cyclic 1,3-dicarbonyls for the synthesis of tetrahydrobenzopyrane derivatives, also known as tetrahydrochromenes, which have attracted much attention due to their wide range of biological properties. Thus, a mixture of an aromatic aldehyde, dimedone, and malonitrile in aqueous media catalyzed either by (*S*)-proline [123] or tetramethylammonium hydroxide (TMAH) [124] gave the bicyclic heterocycle in excellent yields (Scheme 35).

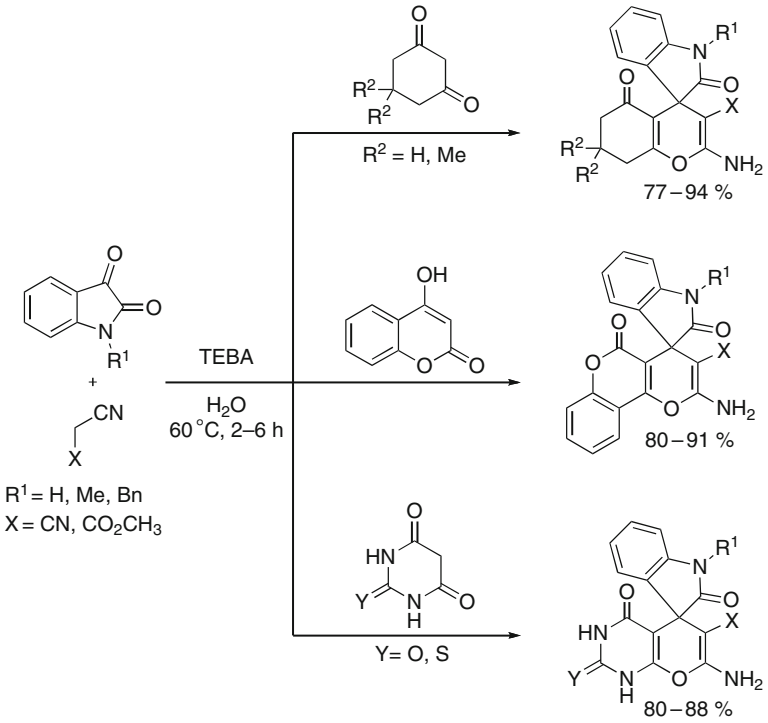


method A: [2-aemim]PF_6, H_2O, MW, 100 °C 81–83%
method B: Mg/La mixed oxide, MeOH, 65 °C 35–92%

Scheme 34 Green methodologies for the three-component synthesis of 4*H*-pyran derivatives

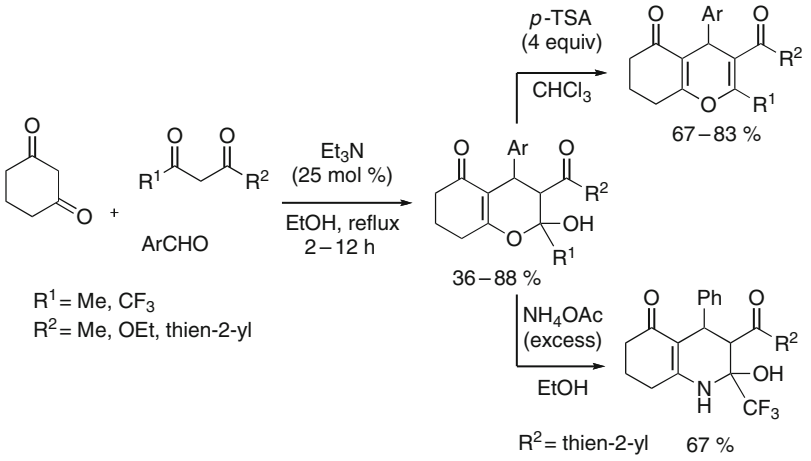


Scheme 35 TMAH-catalyzed multicomponent synthesis of tetrahydrochromenes



Scheme 36 Three-component synthesis of spirooxindole-containing tetrahydrochromene derivatives

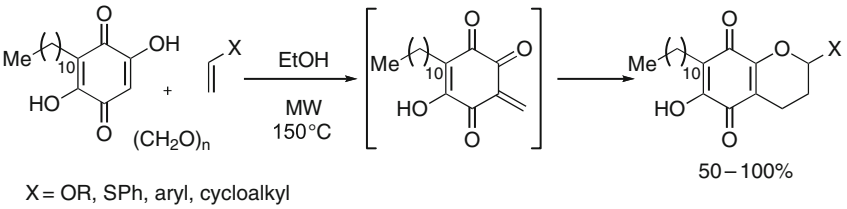
Interestingly enough, a closely related protocol was successfully proposed for the synthesis of spirooxindoles-containing tetrahydrochromene skeletons when aromatic aldehydes were switched for isatin derivatives. This high-yielded reaction was performed with dimedone, 4-hydroxycoumarin, or barbituric acids in water using triethylbenzylammonium chloride (TEBA) as catalyst (Scheme 36) [125]. A Knoevenagel condensation occurred first between isatin and malonitrile derivative, followed by Michael addition of 1,3-dicarbonyl substrates and cyclization to the cyano moiety.



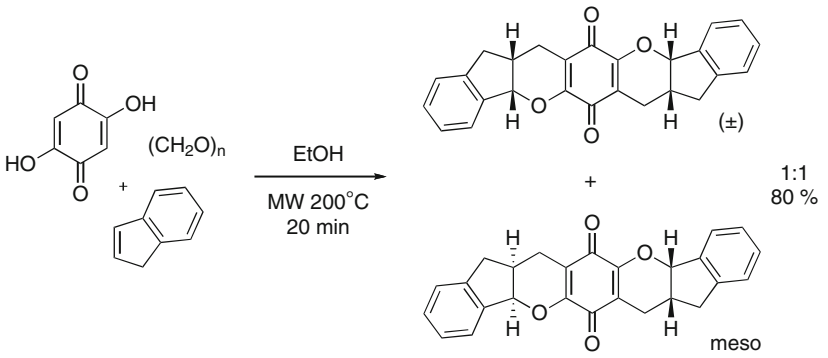
Scheme 37 Three-component synthesis and reactivity of hemi-ketal tetrahydrochromene derivatives

Alternatively, under specific conditions, using an aromatic aldehyde and two different 1,3-dicarbonyl substrates in ethanol with catalytic amount of triethylamine, the dehydration step did not occur and challenging cyclic hemi-ketals were isolated in moderate to good yields (Scheme 37) [126]. Even if the reaction can be performed with various amine catalysts, the best results were obtained with triethylamine and further chemical transformations were made, leading to dehydrated compounds (i.e., tetrahydrochromenes) or hexahydroquinolinone derivatives upon treatment with *p*-TSA or NH_4OAc, respectively. In this paper, there was no discussion about the diastereoselectivity and no mechanistic investigations were proposed to determine which Knoevenagel adduct was involved in the reaction. It was also noteworthy that aliphatic aldehydes as well as *ortho*-substituted arylaldehydes were unreactive under these conditions.

An interesting entry to functionalized dihydropyrans has been intensively studied by Tietze in the 1990s using a three-component domino-Knoevenagel Hetero-Diels–Alder sequence. The overall transformation involves the transient formation of an activated heterodienophile by condensation of simple aldehydes with 1,3-dicarbonyls such as barbituric acids [127], Meldrum's acid [128], or activated carbonyls. In situ cycloaddition with electron-rich alkenes furnished the expected functionalized dihydropyrans. Two recent examples concern the reactivity of 1,4-benzoquinones and pyrazolones as 1,3-dicarbonyl equivalents under microwave irradiation. In the first case, a new three-component catalyst-free efficient one-pot transformation was proposed for the synthesis of pyrano-1,4-benzoquinone scaffolds [129]. In this synthetic method, 2,5-dihydroxy-3-undecyl-1,4-benzoquinone, paraformaldehyde, and alkenes were suspended in ethanol and placed under microwave irradiations to lead regioselectively the corresponding pyrano-1,4-benzoquinone derivatives (Scheme 38). The total regioselectivity was



Scheme 38 Three-component synthesis of pyrano-1,4-benzoquinone derivatives

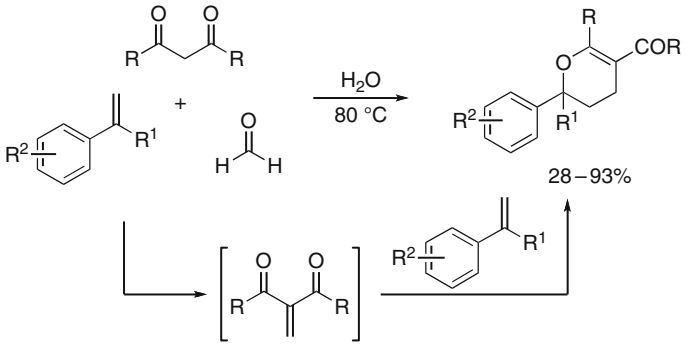


Scheme 39 Example of heptacyclic bis-pyrano-1,4-benzoquinone derivative

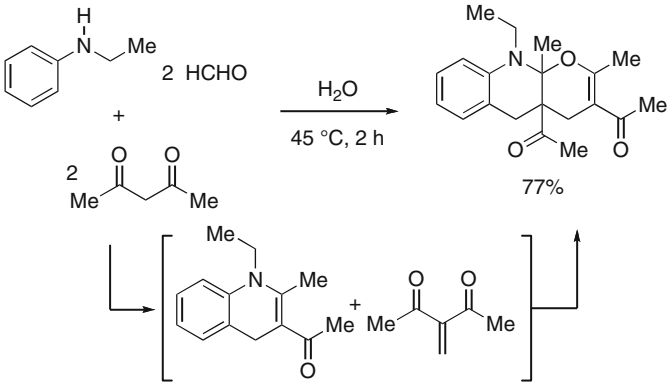
explained by the fact that the in situ formed electron-poor heterodiene is more reactive in the inverse electron demand Hetero-Diels–Alder reaction.

This sequence has been successfully extended to the regioselective multicomponent construction of bis- pyrano-1,4-benzoquinone derivatives when unsubstituted 2,5-dihydroxy-1,4-benzoquinone is used (Scheme 39) [130]. Depending on the alkene moiety, the reaction yielded only the linear tri-, penta-, or heptacyclic product in a 1:1 diasteromeric ratio, as illustrated with indene.

More recently, a catalyst-free aqueous version of this strategy was proposed with simple acyclic 1,3-dicarbonyls, formaldehyde, and styrene or anilines derivatives (Scheme 40) [131]. In the first case (Scheme 40), the very reactive 2-methylene-1,3-dicarbonyl intermediate reacts smoothly at 80°C with a variety of substituted styrenes to give the corresponding dihydropyrans in moderate to good yields. Remarkably, when styrenes were replaced by *N*-ethylaniline, a novel five-component reaction involving twofold excess of both formaldehyde and 1,3-dicarbonyl selectively occurred (Scheme 41). The result is the formation of complex fused pyranoquinolines following a Friedel-Craft alkylation – dehydration sequence to furnish the quinoline nucleus, which suffers the Hetero-Diels–Alder cyclization in synthetically useful yields.



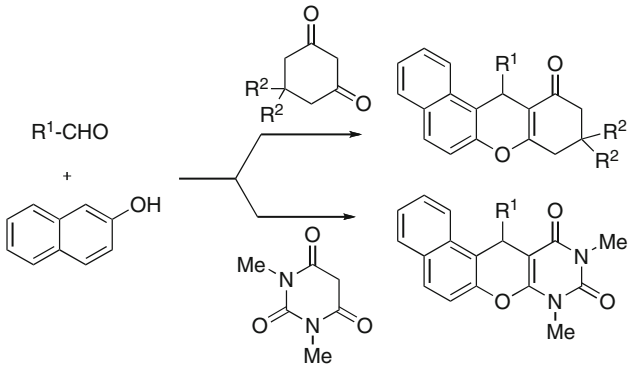
Scheme 40 Multicomponent synthesis of dihydropyrans from substituted styrene



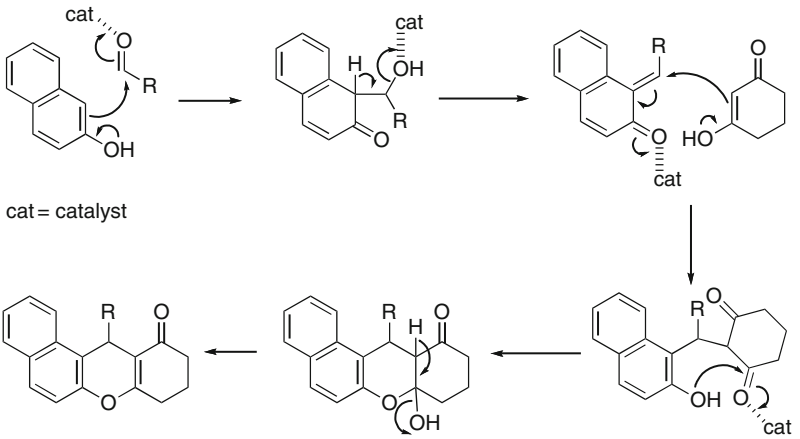
Scheme 41 Catalyst-free aqueous MCR from formaldehyde,1,3-dicarbonyl and aniline derivative

5.3.2 Synthesis of Tetrahydrobenzoxanthenone Derivatives

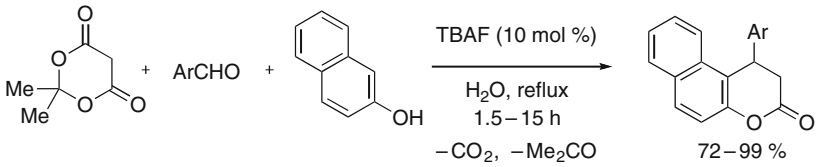
A Knoevenagel-type-initiated multicomponent process was described for the synthesis of benzoxanthene derivatives, which are important biologically active heterocycles, by mixing β-naphtol, an aromatic or aliphatic aldehyde, and a 1,3-dicarbonyl substrate (Scheme 42). Several groups related various Lewis acid systems such as (1) solvent-free with indium(III) chloride or phosphorus pentoxide as catalyst [132]; (2) tetrabutyl ammonium fluoride in water [133]; (3) *para*-toluene sulfonic acid in ionic liquid [bmim]BF_4 [134]; (4) solvent-free with iodine [135]; (5) sodium hydrogenosulfate on silica gel in dichloromethane [136]. From a mechanistic point of view, instead of the regular Knoevenagel adduct, all these authors are in accordance to propose the in situ regioselective formation of an ortho-quinone methide on electron-rich C-1 position of β-naphtol as first step of the sequence. This intermediate could then undergo a Michael addition followed by a cyclodehydration (Scheme 43).



Scheme 42 General scheme of the three-component synthesis of tetrahydrobenzoxanthenone derivatives



Scheme 43 Proposed mechanism for the synthesis of tetrahydrobenzoxanthenone derivatives



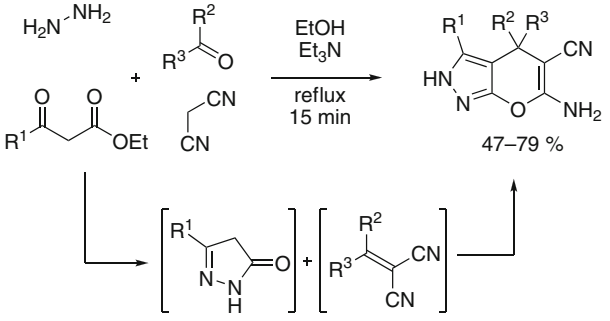
Scheme 44 Three-component synthesis of chromenone derivatives from Meldrum's acid

As demonstrated by Gao and co-workers [133], this methodology was applied to the synthesis of chromenone scaffolds when Meldrum's acid was used as 1,3-dicarbonyl partner (Scheme 44). The reaction evolves via an intramolecular

nucleophilic substitution with concomitant decarboxylation and loss of acetone. In this interesting process, Meldrum's acid may be regarded as a ketene equivalent involved in a formal [4+2] heterocyclization. It was noteworthy that the use of TBAF in water gave the expected product in excellent yields and the catalyst could be recycled four times with no loss of efficiency.

5.3.3 Synthesis of Dihydropyranopyrazole Derivatives

Although polyheterocycles can be obtained from well-chosen starting materials, a Knoevenagel-based reaction was recently reported for the simultaneous construction of two different fused heterocycles from acyclic precursors. In fact, a four-component Knoevenagel–Michael addition-cyclization sequence has been studied for the synthesis of dihydropyranopyrazole derivatives from hydrazine hydrate, a malonitrile, a β-ketoester, and an aldehyde or a ketone. The reaction was described under catalyst- and solvent-free conditions [137] and using piperidine in ultrapure aqueous media [138], both at room temperature (Scheme 45). But this methodology was intensively developed by Shestopalov and co-workers since they used a wide range of aldehydes, ketones, and β-ketoesters to form a series of these fused heterocyclic skeletons, even if substituted hydrazines were unreactive in this protocol [139]. Use of ketones led to spiro-compounds, and interestingly enough, when a bulky aromatic aldehyde such as 2-methoxynaphtaldehyde was used, two atropoisomers were isolated in a 2:1 ratio (Fig. 2).



Scheme 45 Four-component synthesis of highly substituted dihydropyranopyrazole derivatives

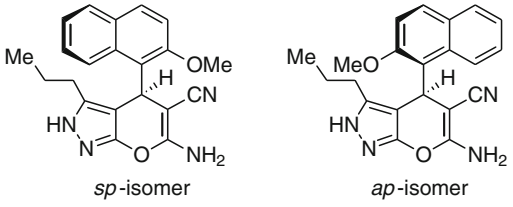
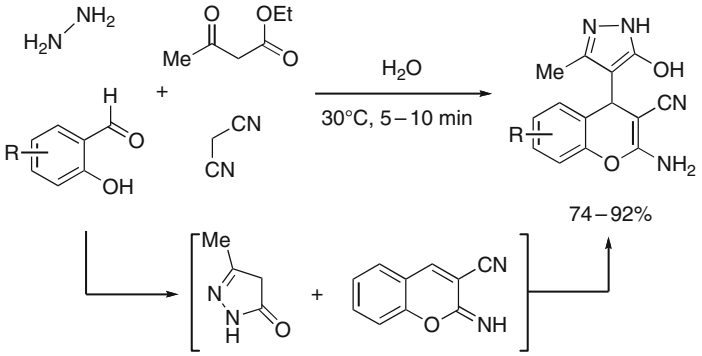


Fig. 2 Atropoisomers formed from 2-methoxynaphtaldehyde



Scheme 46 Multicomponent synthesis of aminochromenes

More recently, an adaptation of this four-component transformation in water was proposed as a green combinatorial synthesis of novel aminochromenes derivatives bearing an hydroxymethyl pyrazole functional group in the four-position, instead of a fused skeleton. In this unexpected transformation, 2-hydroxybenzaldhyde plays a crucial role by reacting selectively with malonitrile to form the chromene intermediate (Scheme 46) [140].

6 MCRs Based on the Michael Reaction

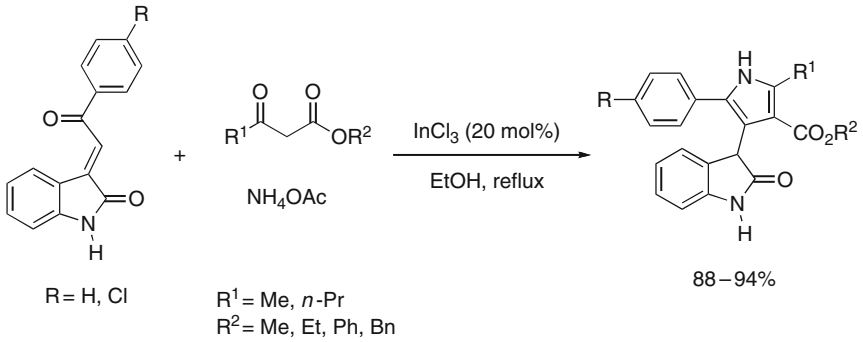
6.1 The Michael Addition

In its original form, the Michael addition consisted on the addition of diethyl malonate across the double bond of ethyl cinnamate in the presence of sodium ethoxide to afford a substituted pentanedioic acid ester. Currently, all reactions that involve a 1,4-addition of stabilized carbon nucleophiles to activated π-systems are known as Michael additions. Among the various reactants, enolates derived from β-dicarbonyl compounds are substrates of choice due to their easy deprotonation under mild conditions. Recently, Michael addition-based MCRs emerged as highly potential methodologies for the synthesis of polysubstituted heterocycles in the five- to seven-membered series.

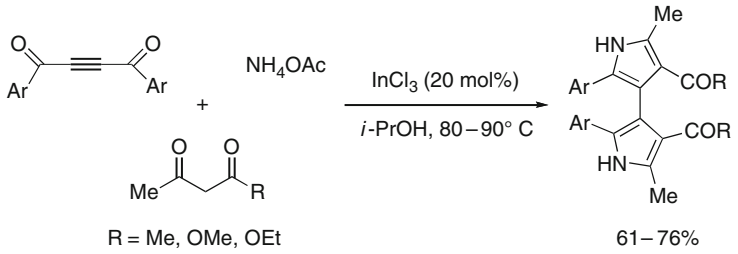
6.2 Five-Membered Heterocycles

6.2.1 Synthesis of Pyrrole Derivatives

The development of new and simple methods for the synthesis of diversely polysubstituted pyrroles from readily available building blocks still remains an open



Scheme 47 $InCl_3$-catalyzed three-component synthesis of 2-pyrrolo-3′-yloxindoles

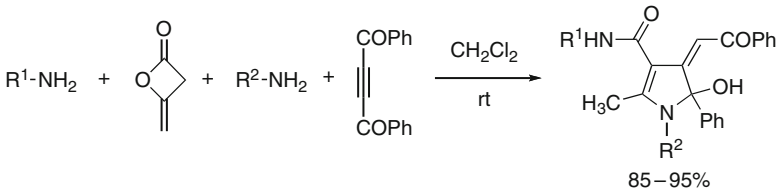


Scheme 48 Lewis acid-catalyzed three-component synthesis of 3,3′-bipyrroles

area of investigations for organic chemists. In this context, Perumal's group reported an $InCl_3$-catalyzed MCR of 3-phenacylideneoxindole with ammonium acetate and various β-ketoesters for the efficient synthesis of 2-pyrrolo-3′-yloxindoles (Scheme 47) [141]. This sequence involves the Michael addition of the enol form of the 1,3-dicarbonyl onto the 3-phenacylideneoxindole affording a 1,4-dicarbonyl intermediate, which then undergoes a Paal–Knorr condensation with ammonium acetate.

In recent years, polypyrroles have been extensively studied as organic materials with particularly good conducting properties. Bipyrroles are not only known for their physical properties, but also for their broad range of biological activities. The Indian group of Jaisankar recently reported a very efficient chiral route to 3,3′-bipyrroles via a Lewis acid-catalyzed three-component double Michael addition sequence between diaroyl acetylenes, ammonium acetate, and appropriate 1,3-dicarbonyls (Scheme 48) [142]. Reaction of diaroyl acetylenes with one equivalent of the 1,3-dicarbonyl derivative and ammonium acetate resulted in the formation of the first pyrrole unit, which underwent a second Michael addition and nitrogen insertion for the bipyrrole formation. The atropoisomers were separated on a chiral column and fully characterized.

Many natural products contain a pyrrole subunit as the basic core. Of particular interest is the remarkable diversity of biological activity associated to the



Scheme 49 Four-component synthesis of 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives

3,4-disubstituted 1*H*-pyrrole scaffold. From a synthetic point of view, pyrroles substituted in positions 3 and 4 are difficult to prepare, most of the reactivity being concentrated at the α-position of the pyrrole. As an interesting alternative to multistep approaches, Alizadeh et al. developed a four-component route to 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives, involving the reaction between two primary amines and diketene in the presence of dibenzoylacetylene (Scheme 49). The reaction was conducted under neutral conditions at room temperature for 6 h to afford the desired products with high yields ranging from 85 to 95% [143].

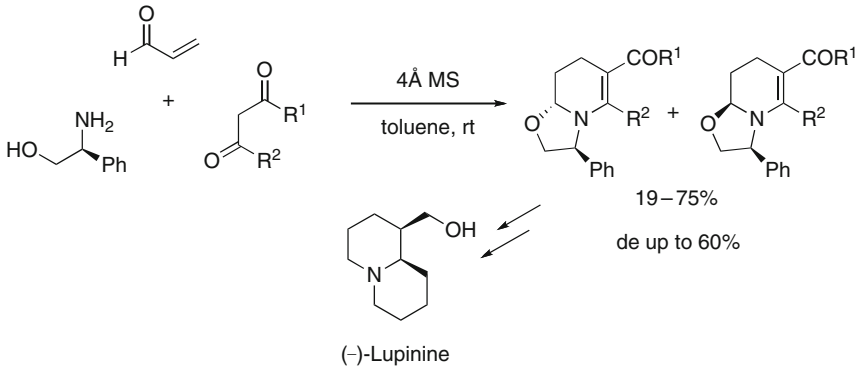
6.3 Six-Membered Heterocycles

Pyridine and its partially or totally unsaturated derivatives such as tetrahydropyridines, DHPs, and piperidines are ubiquitous cores found in numerous natural product skeletons and in synthetic compounds of primary interest for synthetic chemistry, agrochemistry, or pharmacology. Among the various methodologies available for the synthesis of these compounds, multicomponent approaches have attracted much attention in the last few years. Most of these sequences are initiated by a Michael addition.

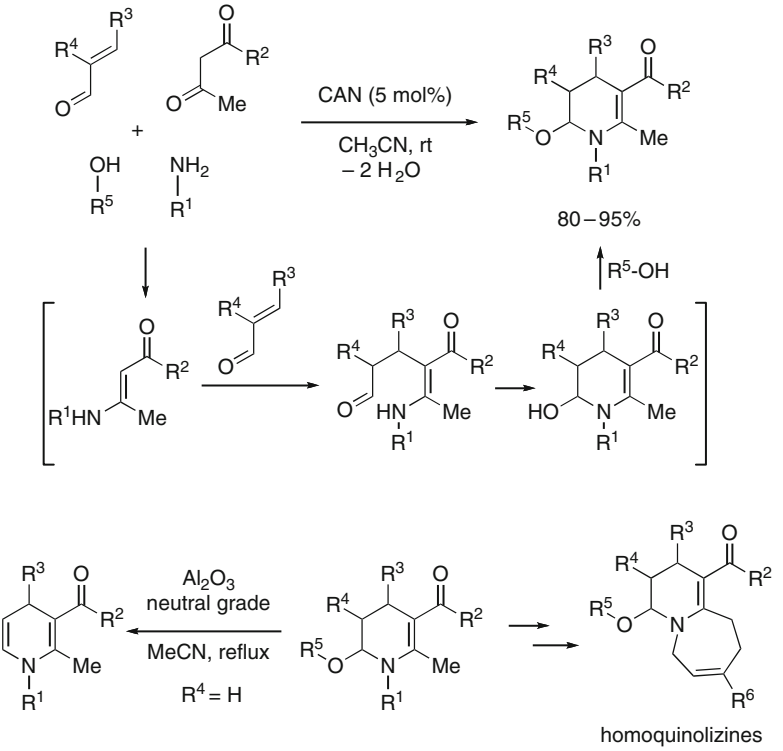
6.3.1 Synthesis of Tetrahydropyridines

In 2008, Lhommet and co-workers, by extrapolation of a previously described polycyclic version [144], proposed the three-component condensation of acrolein, (*S*)-2-phenylglycinol, and various acyclic 1,3-dicarbonyls in toluene in the presence of 4 Å molecular sieves for the preparation of chiral, bicyclic functionalized tetrahydropyridines (Scheme 50) [145]. These heterocycles may be used as chiral building blocks for the synthesis of alkaloids, as illustrated by the total enantioselective synthesis of (−)-lupinine in five steps and 29% overall yield.

More recently, Menendez et al. reported a closely related four-component access to tetrahydropyridines, the amino alcohol being replaced by a primary amine and an alcohol. Thus, the cerium(IV) ammonium nitrate (CAN)-catalyzed reaction between primary aliphatic amines, 1,3-dicarbonyls, α,β-unsaturated aldehydes, and alcohols resulted in the formation of 6-alkoxy-2-methyl-1,4,5,6-tetrahydropyridines with



Scheme 50 Three-component synthesis of chiral, bicyclic functionalized tetrahydropyridines



Scheme 51 CAN-catalyzed four-component synthesis of tetrahydropyridine derivatives

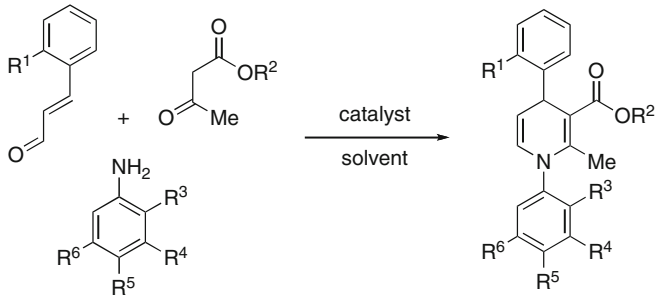
high yields (Scheme 51) [146]. From a mechanistic point of view, a Michael addition occurs between the enamino ester derived from the 1,3-dicarbonyl and the unsaturated aldehyde, followed by an intramolecular cyclization leading to a

2-hydroxytetrahydropyridine derivative. The latter compound is finally transformed into the observed product by nucleophilic displacement of the hydroxy group by the alcohol. These products were then easily converted into homoquinolizine derivatives in only two steps. Finally, the same group also demonstrated that these 2-alkoxytetrahydropyridine derivatives, by treatment with neutral alumina suspended in refluxing acetonitrile, afforded 1,4-DHPs in excellent yields [147].

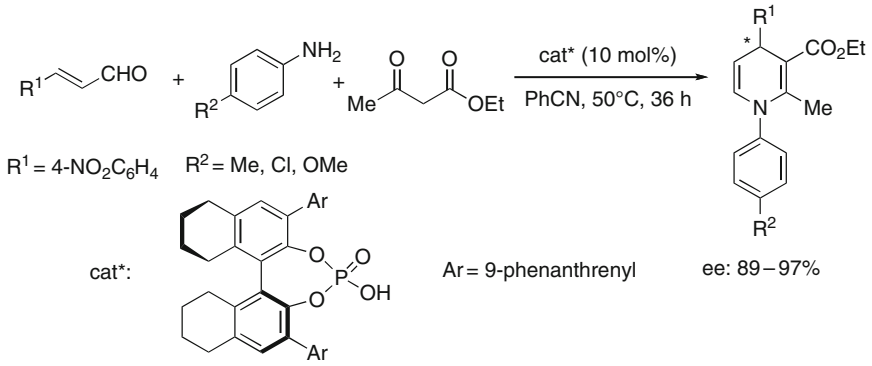
6.3.2 Synthesis of 1,4-Dihydropyridines

As previously reported in Sect. 2, the best known procedure for the synthesis of 1,4-DHPs is the classical Hantzsch synthesis or its variants. However, these well-established multicomponent transformations do not allow the preparation of some important biologically active derivatives such as C_5–C_6-unsubstituted 1,4-DHPs, for example. To circumvent these drawbacks, the three-component Michael addition-based reaction between α,β-unsaturated aldehydes, substituted anilines, and β-ketoesters (Scheme 52) has been developed and studied by several groups. Thus, the group of Menendez reported that the reaction may be conducted under mild conditions, using CAN as catalyst in water [148]. More recently, a solvent-free variant of this MCR involving small molecules such as amino acids or cinchona alkaloids as organocatalysts was also proposed [149]. Some heterogeneous catalysts such as sulfonic acid functionalized silica [150] or nanocrystalline copper(II) oxide [151] are also efficient, offering the advantage of being recycled and reused several times.

Recently, an asymmetric version of this reaction has been reported by Gong and co-workers, allowing an efficient access to highly enantiomerically enriched 4-aryl-substituted 1,4-DHPs [152]. Thus, the use of chiral phosphoric acids as catalysts allowed the preparation of the desired products with enantiomeric excesses up to 97% (Scheme 53). To illustrate the importance of this asymmetric cyclization reaction, the authors developed the synthesis of some optically active heterocycles



Scheme 52 Michael-addition-based MCR for the synthesis of C_5–C_6-unsubstituted 1,4-dihydropyridines



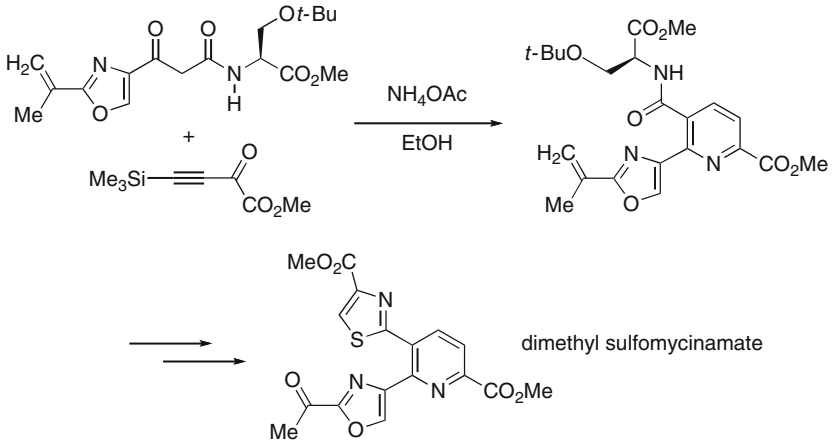
Scheme 53 Organocatalyzed synthesis of enantiomerically enriched 1,4-dihydropyridines

from the resulting chiral DHPs through 1,3-dipolar cycloaddition and subsequent diastereoselective reduction.

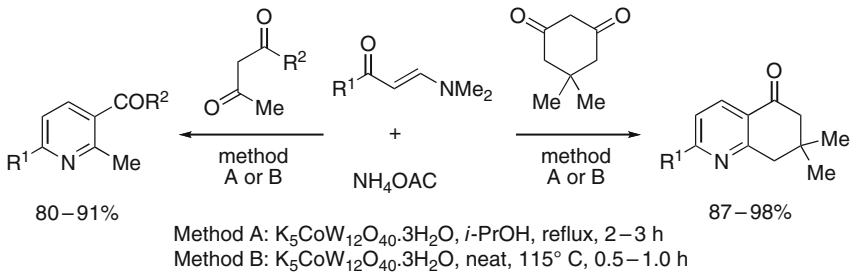
6.3.3 Synthesis of Pyridine Derivatives

Functionalized pyridines are one of the most important nitrogen heterocycles found in numerous natural products and synthetic pharmaceutical agents. Thus, the synthesis of highly substituted and specifically functionalized members of this heterocyclic family is a continuing challenge in modern organic chemistry. Back in 1957, Bohlmann and Rahtz reported the preparation of polysubstituted pyridines by a two-step sequence consisting in a Michael addition of an enaminoester onto an alkynone to give an enaminodienone intermediate that is subsequently cyclodehydrated to the final product. The group of Bagley intensively revisited this transformation and proposed a more direct and efficient approach towards pyridines based on the three-component condensation of a 1,3-dicarbonyl, an alkynone, and an ammonium acetate, the so-called three-component Bohlmann–Rahtz reaction. In 2005, they illustrated the potentialities of this methodology with the synthesis of dimethyl sulfomycinamate (Scheme 54) [153]. More recently, similar three-component approach has been developed by Gree and co-workers starting from optically active propargylic fluorides for the synthesis of chiral pyridines with a fluor atom in the benzylic position [154].

Another example of a MCR-based strategy for the synthesis of pyridines was reported by Kantevari et al. in 2007. Thus, the three-component condensation of enaminones, 1,3-dicarbonyls, and ammonium acetate in the presence of a catalytic amount of a tangstocobaltate salt as heterogeneous catalyst, either in refluxing solvent or under solvent-free conditions, allowed the regioselective formation of 2,3,6-trisubstituted pyridines and 2,7,7-trisubstituted tetrahydroquinolin-5-ones (Scheme 55) [155]. This methodology combines shorter reaction times and



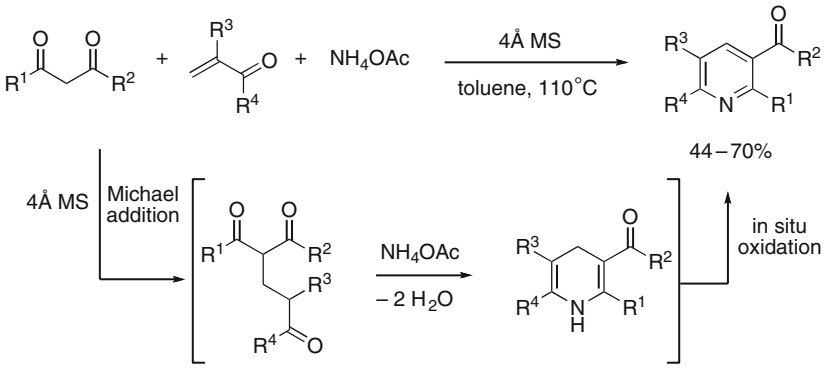
Scheme 54 Application of the three-component Bohlmann–Rahtz reaction to the synthesis of dimethyl sulfomycinamate



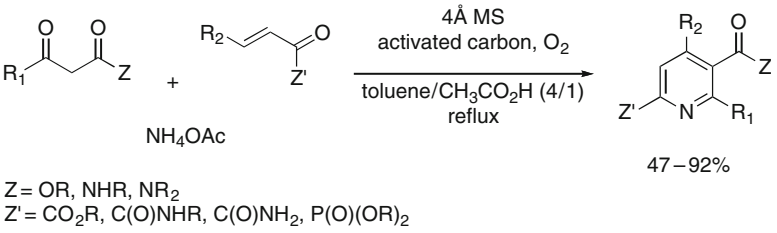
Scheme 55 Multicomponent synthesis of substituted pyridines and tetrahydroquinolinones

practical work-up procedure with respect to more classical procedures. Moreover, the catalyst exhibited remarkable reusable activity.

Our own group is also involved in the development of domino multicomponent reactions for the synthesis of heterocycles of both pharmacologic and synthetic interest [156]. In particular, we recently reported a totally regioselective and metal-free Michael addition-initiated three-component substrate directed route to polysubstituted pyridines from 1,3-dicarbonyls. Thus, the direct condensation of 1,3-diketones, β-ketoesters, or β-ketoamides with α,β-unsaturated aldehydes or ketones with a synthetic equivalent of ammonia, under heterogeneous catalysis by 4 Å molecular sieves, provided the desired heterocycles after in situ oxidation (Scheme 56) [157]. A mechanistic study demonstrated that the first step of the sequence was a molecular sieves-promoted Michael addition between the 1,3-dicarbonyl and the α,β-unsaturated carbonyl compound. The corresponding 1,5-dicarbonyl adduct then reacts with the ammonia source leading to a DHP derivative, which is spontaneously converted to the aromatized product.



Scheme 56 Regioselective 4 Å MS-promoted three-component synthesis of pyridines

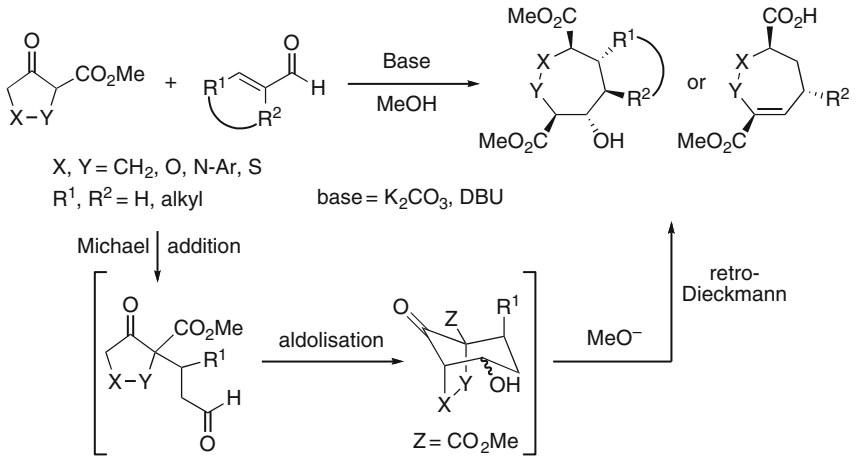


Scheme 57 Use of α-ketocarbonyls in the multicomponent synthesis of 2,4-disubstituted pyridines

However, this methodology was limited to the use of β-unsubstituted aldehydes and ketones, probably because of the reversibility of the Michael addition with hindered substrates, preventing any access to four-substituted pyridines and limiting the functional diversity at the strategic two-position. These major drawbacks were circumvented by the use of activated Michael acceptors such as β,γ-unsaturated-α-keto carbonyls [158]. Under optimized heterogeneous oxidative conditions, we managed to obtain the corresponding 2,4-disubstituted pyridines with good to excellent yields (Scheme 57) [159].

6.4 Seven-Membered Heterocycles

Heterocyclic seven-membered ring systems are present in various natural and synthetic bioactive compounds and pharmaceuticals. Therefore, the development of new approaches to these heterocycles with total regio- and stereocontrol is of great importance to both medicinal and synthetic chemists, and still constitutes an exciting synthetic challenge. For this purpose, we recently invented a base-induced

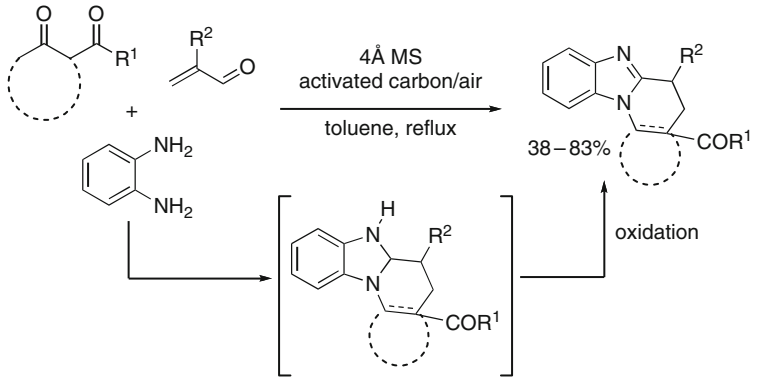


Scheme 58 General scheme for the MARDi cascade

anionic domino three-component transformation of 1,3-dicarbonyls, named the MARDi cascade, for the stereoselective construction of heterocyclic seven-membered ring in the aza-, oxa-, and thia-series (Scheme 58) [160–162]. This reaction is based on a Michael addition-Aldolisation-Retro-Dieckmann sequence involving the solvent as a third component and constitutes a formal two-carbon ring expansion of heterocyclic cyclopentanones. This methodology allows the formation of diversely substituted and functionalized seven-membered heterocycles, with the control of up to five newly created stereocenters. Moreover, the products are obtained under user and environmentally friendly conditions from easily available substrates.

6.5 Polycyclic Heterocycles

In the course of our studies on Michael addition-initiated MCRs, we developed a three-component domino reaction between 1,3-dicarbonyls, α,β-unsaturated aldehydes or ketones, and nucleophilic (hetero)functionalized primary amines, providing a one-pot access to polyheterocyclic compounds of both synthetic and biological interest. This molecular sieves-promoted sequence allows the direct formation of two fused rings and evolves through an intramolecular trapping of an in situ formed ene-iminium intermediate as the key step. As a first illustration of the potentialities of this methodology, we described the synthesis of original and highly functionalized pyrido[1,2-a]benzimidazoles from various cyclic and acyclic β-ketoesters (Scheme 59) [163]. The domino sequence afforded an aminal intermediate, which was in situ oxidized by air in the presence of activated carbon. The two heterogeneous catalysts were then eliminated by simple filtration. Therefore, this



Scheme 59 Multicomponent synthesis of [1,2-a]-fused benzimidazoles

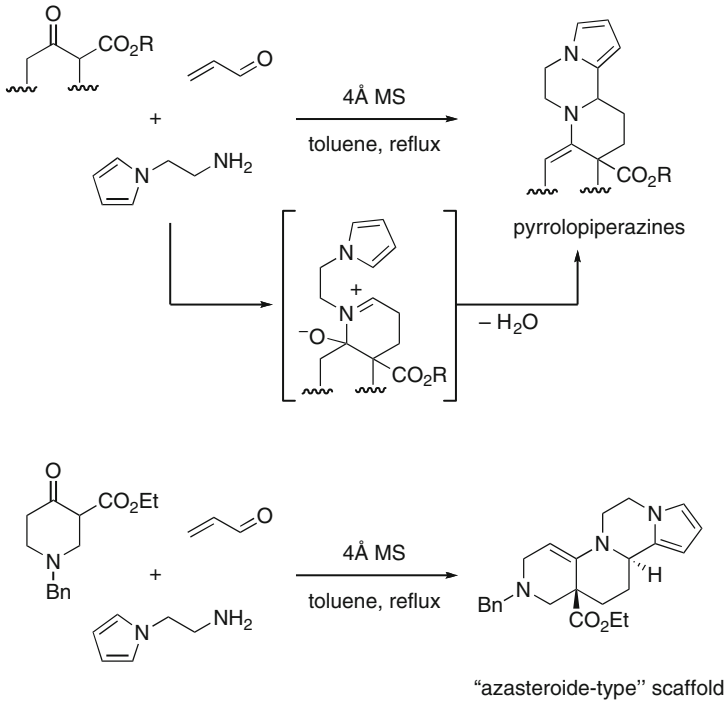
economical and environmentally friendly approach was a good alternative to previously reported multistep metal-catalyzed reactions for the synthesis of [1,2-a]-fused benzimidazoles.

Heterocycles with a 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine core are also available through this multicomponent reaction. Compounds with a related structure are of high interest either for synthetic applications or for biological purposes. For the first time we were able to propose a one-pot access to pyrrolopiperazine and azasteroide-type scaffolds, illustrating the potential of this ecocompatible sequence to create molecular complexity and diversity from simple and readily available substrates (Scheme 60) [164]. In this case, the primary amine partner bears a pyrrole nucleophile, which neutralizes the transient iminium intermediate to form a new C–C bond via an intramolecular Pictet–Spengler-type cyclization.

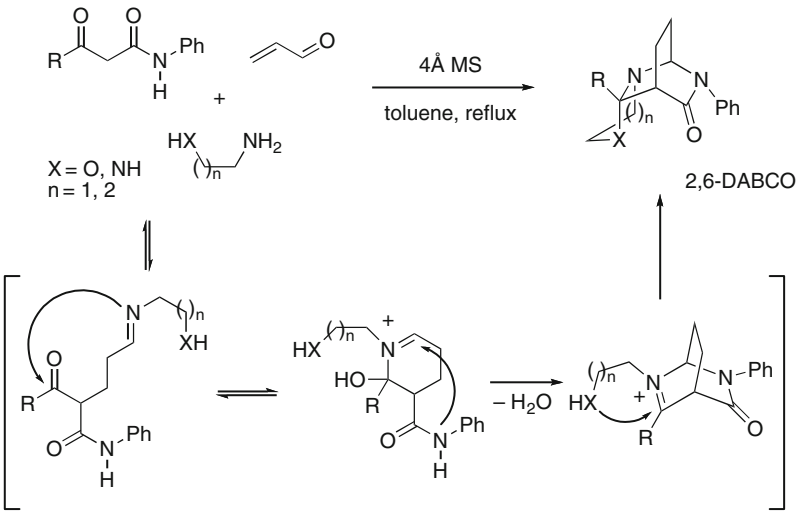
Finally, the highest level of complexity for this three-component reaction was reached when β-ketoamides were used as substrates. We demonstrated that these particular 1,3-dicarbonyls could be involved not only as substrates but also as nucleophilic partners through the highly diastereoselective synthesis of scaffolds containing an original 2,6-diazabicyclo[2.2.2]octane skeleton (2,6-DABCO) [165]. In this transformation, two different iminium intermediates were successively generated and trapped by two different nucleophiles, one being the substrate itself and the other one resulting from the heterofunctionalization of the amine partner (Scheme 61).

7 Miscellaneous

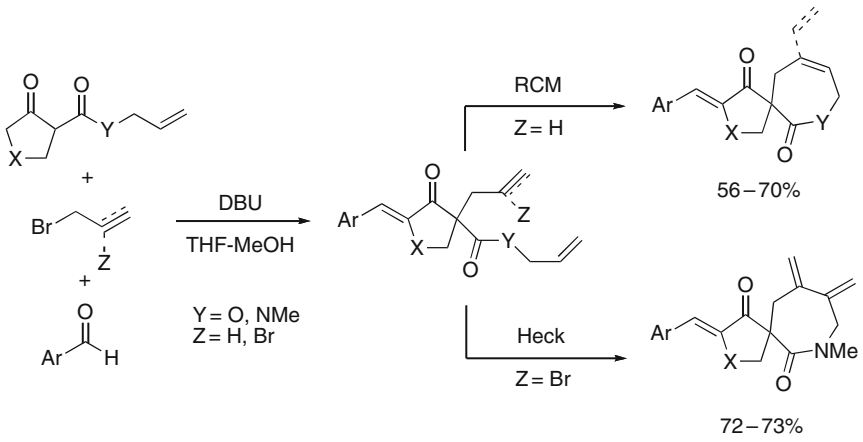
As part of our efforts to develop new efficient one-pot methodologies to access novel heterocyclic structures, we also reported an efficient synthesis of spiro[4,6]-lactones and lactames by sequential multicomponent reaction/metal-catalyzed carbocyclizations from simple five-membered cyclic β-ketoesters and β-ketoamides,



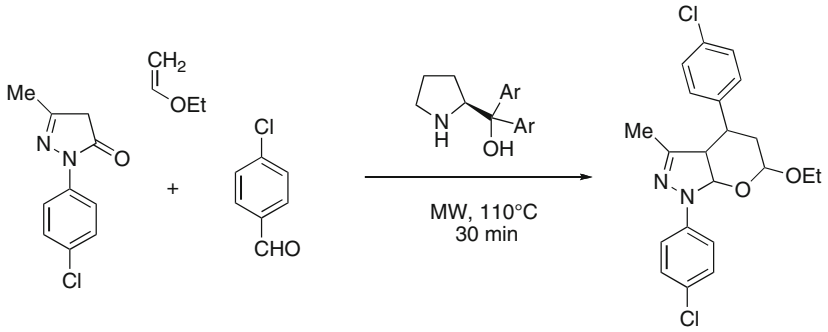
Scheme 60 Three-component synthesis of polycyclic pyrrolopiperazine scaffolds



Scheme 61 Three-component synthesis of 2,6-DABCO skeletons



Scheme 62 Sequential multicomponent α,γ-difunctionalization of 1,3-dicarbonyl/metal-catalyzed carbocyclization for the synthesis of spiro[4,6]-lactones and lactames

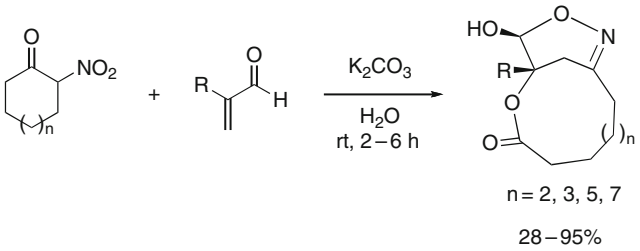


Scheme 63 Three-component synthesis of 2,3-dihydropyran[2,3-*c*]pyrazoles

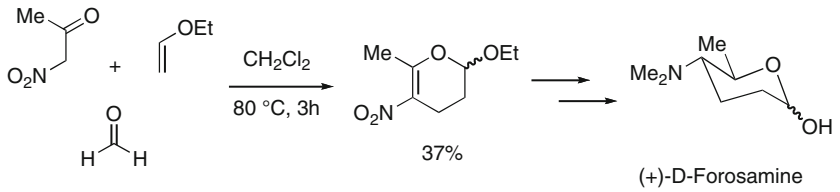
respectively [166]. Thus, the combination of the three-component α,γ-difunctionalization of 1,3-cyclodicarbonyl compounds with either diene- and enyne-ring closing methatesis (RCM), or palladium-catalyzed Heck carbocyclizations, afforded an easy and modular entry to original functionalized spiroheterocycles with good yields over the two steps (Scheme 62).

Alternatively to the direct use of 1,3-dicarbonyls, pyrazol-2-ones, which constitute masked 1,3-dicarbonyls, have been involved in a microwave-assisted organocatalytic MCR with aromatic aldehydes and ethyl vinyl ether leading to 2,3-dihydropyran[2,3-*c*]pyrazoles (Scheme 63) [167].

Finally, other α-activated carbonyl compounds such as α-nitroketones have been used successfully in very interesting and novel MCRs. Our group proposed an unprecedented reactivity of α-nitroalkanones towards two-substituted acroleins under aqueous conditions, with participation of water as third component [168].



Scheme 64 MCRs from α-nitroketones: synthesis of bicyclic macrolactones



Scheme 65 Synthesis of (+)D-forosamine

This three-component sequence led to the one-pot synthesis of hitherto unknown functionalized bridged bicyclic lactones containing 10-, 11-, 13-, and 15-membered rings, with a high stereocontrol of the two newly created adjacent stereogenic centers (Scheme 64). One of the key steps of this one-pot process consists of the fragmentation of the initial Michael adduct through a retro-Claisen-type reaction, initiated by water. It is interesting to note that such new heterocyclic structures can be considered as lactones derived from a tertiary alcohol, which are difficult to make by other methods.

More recently, Tietze's group adapted the well-known domino Knoevenagel-Hetero-Diels–Alder MCR to the efficient synthesis of the deoxyaminosugar (+)-D-Forosamine starting from nitroacetone, aqueous formaline, and ethyl vinyl ether (Scheme 65) [169]. The expected racemic dihydropyran was obtained in 37% yield and further transformed to the optically pure product in eight steps in chiral resolution with chiral HPLC.

8 Conclusion

This selection of diverse MCRs developed in the last 5 years clearly illustrates the high synthetic potential of 1,3-dicarbonyl derivatives in heterocyclic chemistry. These very easily accessible and versatile substrates can be accommodated in many original synthetic pathways. Therefore, they have found numerous applications, especially for the synthesis of complex heterocyclic structures, allowing the facile

and selective construction of highly functionalized small organic molecules of high synthetic and biological value. Further developments of the specific reactivity of 1,3-dicarbonyls in MCRs will constitute a challenging investigation area, which could be complementary to the utilization of isonitriles.

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References

1. For a special issue in green chemistry (2007) see: Chem Rev 107:2167–2820
2. Zhu J, Bienaime H (2005) Multicomponent reactions. Wiley-VCH, Weinheim
3. Tietze LF, Brasche G, Gericke KM (2006) Domino reactions in organic synthesis. Wiley-VCH, Weinheim
4. Orru RVA, de Greef M (2003) Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. Synthesis 10:1471–1499
5. Ramon DJ, Yus M (2005) Asymmetric multicomponent reactions (AMCRs): the new frontier. Angew Chem Int Ed 44:1602–1634
6. Guillena G, Ramon DJ, Yus M (2007) Organocatalytic enantioselective multicomponent reactions (OEMCRs). Tetrahedron-Asymmetry 18:693–700
7. Padwa A, Bur SK (2007) The domino way to heterocycles. Tetrahedron 63:5341–5378
8. Vugts DJ, Koningstein MM, Schmitz RF, de Kanter FJJ, Groen MB, Orru RVA (2006) Multicomponent synthesis of dihydropyrimidines and thiazines. Chem Eur J 12:7178–7189
9. Nielsen TE, Schreiber SL (2008) Diversity-oriented synthesis – towards the optimal screening collection: a synthesis strategy. Angew Chem Int Ed 47:48–56
10. Trost BM (2002) On inventing reactions for atom economy. Acc Chem Res 35:695–705
11. Wender PA, Baryza JL, Brenner SE, Clarke MO, Gamber CG, Horan JC, Jessop TC, Kan C, Pattabiraman K, Williams TJ (2003) Inspirations from nature. New reactions, therapeutic leads, and drug delivery systems. Pure Appl Chem 75:143–155
12. Wender PA, Gamber GG, Hubbard RD, Pham SM, Zhang L (2005) Inspirations from nature. New reactions, therapeutic leads, and drug delivery systems. J Am Chem Soc 127:2836–2837
13. Wender PA, Handy ST, Wright DL (1997) Towards the ideal synthesis. Chem Ind 765–768
14. Zhu JP (2003) Recent developments in the isonitrile-based multicomponent synthesis of heterocycles. Eur J Org Chem 1133–1144
15. Domling A (2006) Recent developments in isocyanide-based multicomponent reactions in applied chemistry. Chem Rev 106:17–89
16. Simon C, Constantieux T, Rodriguez J (2004) Utilisation of 1,3-dicarbonyl derivatives in multicomponent reactions. Eur J Org Chem 4957–4980
17. Reddy GM, Shiradkar M, Chakravarthy AK (2007) Chemical and pharmacological significance of 1,4-dihydropyridines. Curr Org Chem 11:847–852
18. Murakami Y, Kikuchi J, Hisaeda Y, Hayashida O (1996) Artificial enzymes. Chem Rev 96:721–758
19. Sambongi Y, Nitta H, Ichihashi K, Futai M, Ueda I (2002) A novel water-soluble Hantzsch 1,4-dihydropyridine compound that functions in biological processes through NADH regeneration. J Org Chem 67:3499–3501

20. Moseley JD (2005) Alternative esters in the synthesis of ZD0947. Tetrahedron Lett 46:3179–3181
21. Mobinikhaledi A, Foroughifar N, Fard MAB, Moghanian H, Ebrahimi S, Kalhor M (2009) Efficient one-pot synthesis of polyhydroquinoline derivatives using silica sulfuric acid as a heterogeneous and reusable catalyst under conventional heating and energy-saving microwave irradiation. Synth Commun 39:1166–1174
22. Sapkal SB, Shelke KF, Shingate BB, Shingare MS (2009) Nickel nanoparticle-catalyzed facile and efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation under solvent-free conditions. Tetrahedron Lett 50:1754–1756
23. Kumar A, Maurya RA (2008) Efficient synthesis of Hantzsch esters and polyhydroquinoline derivatives in aqueous micelles. Synlett 883–885
24. Wang SX, Li ZY, Zhang JC, Li JT (2008) The solvent-free synthesis of 1,4-dihydropyridines under ultrasound irradiation without catalyst. Ultrason Sonochem 15:677–680
25. Mekheimer RA, Hameed AA, Sadek KU (2008) Solar thermochemical reactions: four-component synthesis of polyhydroquinoline derivatives induced by solar thermal energy. Green Chem 10:592–593
26. Bandgar BP, More PE, Kamble VT, Totre JV (2008) Synthesis of polyhydroquinoline derivatives under aqueous media. Arkivoc 1–8
27. Heydari A, Khaksar S, Tajbakhsh M, Bijanzadeh HR (2009) One-step, synthesis of Hantzsch esters and polyhydroquinoline derivatives in fluoro alcohols. J Fluor Chem 130:609–614
28. Kumar S, Sharma P, Kapoor KK, Hundal MS (2008) An efficient, catalyst- and solvent-free, four-component, and one-pot synthesis of polyhydroquinolines on grinding. Tetrahedron 64:536–542
29. Legeay JC, Goujon JY, Eynde JJV, Toupet L, Bazureau JP (2006) Liquid-phase synthesis of polyhydroquinoline using task-specific ionic liquid technology. J Comb Chem 8:829–833
30. Wang LM, Sheng J, Zhang L, Han JW, Fan ZY, Tian H, Qian CT (2005) Facile Yb(OTf)(3) promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction. Tetrahedron 61:1539–1543
31. Nagarapu L, Kumari MD, Kumari NV, Kantevari S (2007) MCM-41 catalyzed rapid and efficient one-pot synthesis of polyhydroquinolines via the Hantzsch reaction under solvent-free conditions. Catal Commun 8:1871–1875
32. Kumar A, Maurya RA (2007) Bakers' yeast catalyzed synthesis of polyhydroquinoline derivatives via an unsymmetrical Hantzsch reaction. Tetrahedron Lett 48:3887–3890
33. Kumar A, Maurya RA (2007) Synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction using organocatalysts. Tetrahedron 63:1946–1952
34. Das Sharma S, Hazarika P, Konwar D (2008) A simple, green and one-pot four-component synthesis of 1,4-dihydropyridines and their aromatization. Catal Commun 9:709–714
35. Debache A, Boulcina R, Belfaitah A, Rhouati S, Carboni B (2008) One-pot synthesis of 1,4-dihydropyridines via a phenylboronic acid catalyzed Hantzsch three-component reaction. Synlett 509–512
36. Cherkupally SR, Mekala R (2008) P-TSA catalyzed facile and efficient synthesis of polyhydroquinoline derivatives through Hantzsch multi-component condensation. Chem Pharm Bull 56:1002–1004
37. Akbari JD, Tala SD, Dhaduk MF, Joshi HS (2008) Molecular iodine-catalyzed one-pot synthesis of some new Hantzsch 1,4-dihydropyridines at ambient temperature. Arkivoc 126–U21
38. Sabitha G, Arundhathi K, Sudhakar K, Sastry BS, Yadav JS (2009) CeCl3 center dot 7H2O-Catalyzed one-pot synthesis of Hantzsch 1,4-dihydropyridines at room temperature. Synth Commun 39:2843–2851
39. Suresh KD, Sandhu JS (2009) New efficient protocol for the production of Hantzsch 1,4-dihydropyridines using RuCl3. Synth Commun 39:1957–1965
40. Debache A, Ghalem W, Boulcina R, Belfaitah A, Rhouati S, Carboni B (2009) An efficient one-step synthesis of 1,4-dihydropyridines via a triphenylphosphine-catalyzed three-component Hantzsch reaction under mild conditions. Tetrahedron Lett 50:5248–5250

41. Evans CG, Gestwicki JE (2009) Enantioselective organocatalytic Hantzsch synthesis of polyhydroquinolines. Org Lett 11:2957–2959
42. Martin NJA, Cheng X, List B (2008) Organocatalytic asymmetric transferhydrogenation of beta-nitroacrylates: accessing beta(2)-amino acids. J Am Chem Soc 130:13862–13863
43. Simon L, Goodman JM (2008) Theoretical study of the mechanism of Hantzsch ester hydrogenation of imines catalyzed by chiral BINOL-phosphoric acids. J Am Chem Soc 130:8741–8747
44. Franke PT, Johansen RL, Bertelsen S, Jorgensen KA (2008) Organocatalytic enantioselective one-pot synthesis and application of substituted 1,4-dihydropyridines – Hantzsch ester analogues. Chem Asian J 3:216–224
45. Heravi MM, Behbahani FK, Oskooie HA, Shoar RH (2005) Catalytic aromatization of Hantzsch 1,4-dihydropyridines by ferric perchlorate in acetic acid. Tetrahedron Lett 46:2775–2777
46. Yadav JS, Reddy BVS, Basak AK, Baishya G, Narsaiah AV (2006) Iodoxybenzoic acid (IBX): an efficient and novel oxidizing agent for the aromatization of 1,4-dihydropyridines. Synthesis 451–454
47. Xia JJ, Wang GW (2005) One-pot synthesis and aromatization of 1,4-dihydropyridines in refluxing water. Synthesis 2379–2383
48. Tu SJ, Jiang B, Jia RH, Zhang JY, Zhang Y (2007) An efficient and expeditious microwave-assisted synthesis of 4-azafluorenones via a multi-component reaction. Tetrahedron Lett 48:1369–1374
49. Shen L, Cao S, Wu JJ, Zhang J, Li H, Liu NJ, Qian XH (2009) A revisit to the Hantzsch reaction: unexpected products beyond 1,4-dihydropyridines. Green Chem 11:1414–1420
50. Tu SJ, Wu SS, Yan S, Hao WJ, Zhang XH, Cao XD, Han ZG, Jiang B, Shi F, Xia M, Zhou JF (2009) Design and microwave-assisted synthesis of naphtho 2,3-f quinoline derivatives and their luminescent properties. J Comb Chem 11:239–242
51. Shi F, Yan S, Zhou DX, Tu SJ, Zou X, Hao WJ, Zhang XH, Han ZG, Wu SS, Cao XD (2009) A facile and efficient synthesis of novel pyrimido 5,4-b 4,7 phenanthroline-9,11 (7H, 8H, 10H, 12H)-dione derivatives via microwave-assisted multicomponent reactions. J Heterocycl Chem 46:563–566
52. Wang XH, Hao WJ, Tu SJ, Zhang XH, Cao XD, Yan S, Wu SS, Han ZG, Shi F (2009) Microwave-assisted multicomponent reaction for the synthesis of new and significative bisfunctional compounds containing two furo 3,4-b quinoline and acridinedione skeletons. J Heterocycl Chem 46:742–747
53. Tu SJ, Cao LJ, Zhang Y, Shao QQ, Zhou DX, Li CM (2008) An efficient synthesis of pyrido 2,3-d pyrimidine derivatives and related compounds under ultrasound irradiation without catalyst. Ultrason Sonochem 15:217–221
54. Wang XS, Zhang MM, Jiang H, Shi DQ, Tu SJ, Wei XY, Zong ZM (2006) An improved and benign synthesis of 9,10-diarylacridine-1,8-dione and indenoquinoline derivatives from 3-anilino-5,5-dimethylcyclohex-2-enones, benzaldehydes, and 1,3-dicarbonyl compounds in an ionic liquid medium. Synthesis 4187–4199
55. Dondoni A, Massi A, Aldhoun M (2007) Hantzsch-type three-component approach to a new family of carbon-linked glycosyl amino acids. synthesis of C-glycosylmethyl pyridylalanines. J Org Chem 72:7677–7687
56. Ducatti DRB, Massi A, Noseda MD, Duarte MER, Dondoni A (2009) Dihydropyridine C-glycoconjugates by organocatalytic Hantzsch cyclocondensation. Stereoselective synthesis of alpha-threofuranose C-nucleoside enantiomers. Org Biomol Chem 7:1980–1986
57. Muravyova EA, Shishkina SV, Musatov VI, Knyazeva IV, Shishkin OV, Desenko SM, Chebanov VA (2009) Chemoselectivity of multicomponent condensations of barbituric acids, 5-aminopyrazoles, and aldehydes. Synthesis 1375–1385
58. Chebanov VA, Saraev VE, Desenko SM, Chernenko VN, Knyazeva IV, Groth U, Glasnov TN, Kappe CO (2008) Tuning of chemo- and regioselectivities in multicomponent condensations of 5-aminopyrazoles, dimedone, and aldehydes. J Org Chem 73:5110–5118

59. Tu SJ, Zhang Y, Jiang H, Jiang B, Zhang JY, Jia RH, Shi F (2007) A simple synthesis of furo 3′,4′: 5,6 pyrido 2,3-d pyrimidine derivatives through multicomponent reactions in water. Eur J Org Chem 1522–1528
60. Shaabani A, Rahmati A, Rezayan AH, Darvishi M, Badri Z, Sarvari A (2007) Clean synthesis in water: Uncatalyzed three-component condensation reaction of 3-amino-1,2,4-triazole or 2-aminobenzimidazole with aldehyde in the presence of activated CH-Acids. QSAR Comb Sci 26:973–979
61. Kolosov MA, Orlov VD, Beloborodov DA, Dotsenko VV (2009) A chemical placebo: NaCl as an effective, cheapest, non-acidic and greener catalyst for Biginelli-type 3,4-dihydropyrimidin-2(1H)-ones (-thiones) synthesis. Mol Divers 13:5–25
62. De Souza R, da Penha ET, Milagre HMS, Garden SJ, Esteves PM, Eberlin MN, Antunes OAC (2009) The three-component Biginelli reaction: a combined experimental and theoretical mechanistic investigation. Chem Eur J 15:9799–9804
63. Sabitha G, Reddy KB, Yadav JS, Shailaja D, Sivudu KS (2005) Ceria/vinylpyridine polymer nanocomposite: an ecofriendly catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones. Tetrahedron Lett 46:8221–8224
64. Shaabani A, Rahmati A (2005) Ionic liquid promoted efficient synthesis of 3,4-dihydropyrimidin-2-(1H)-ones. Catal Lett 100:177–179
65. Dabiri M, Salehi P, Baghbanzadeh M, Shakouri M, Otokesh S, Ekrami T, Doosti R (2007) Efficient and eco-friendly synthesis of dihydropyrimidinones, bis(indolyl) methanes, and N-alkyl and N-arylimides in ionic liquids. J Iran Chem Soc 4:393–401
66. Legeay JC, Eynde JJV, Bazureau JP (2008) Ionic liquid phase organic synthesis (IoLiPOS) methodology applied to the preparation of new 3,4-dihydropyrimidine-2(1H)-ones bearing bioisostere group in N-3 position. Tetrahedron 64:5328–5335
67. Gui JZ, Liu D, Wang C, Lu F, Lian JZ, Jiang H, Sun ZL (2009) One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Catalyzed by Acidic Ionic Liquids Under Solvent-Free Conditions. Synth Commun 39:3436–3443
68. Putilova ES, Troitskii NA, Zlotin SG, Khudina OG, Burgart YV, Saloutin VI, Chupakhin ON (2006) One-step solvent-free synthesis of fluoroalkyl-substituted 4-hydroxy-2-oxo(thioxo) hexahydropyrimidines in the presence of 1-butyl-3-methylimidazolium tetrafluoroborate. Russ J Org Chem 42:1392–1395
69. Ming L, Guo WS, Wen LR, Li YF, Yang HZ (2006) One-pot synthesis of Biginelli and Hantzsch products catalyzed by non-toxic ionic liquid (BMImSac) and structural determination of two products. J Mol Catal A: Chem 258:133–138
70. Bose DS, Sudharshan M, Chavhan SW (2005) New protocol for Biginelli reaction-a practical synthesis of monastrol. Arkivoc 228–236
71. Dong F, Jun L, Xinli Z, Zhiwen Y, Zuliang L (2007) One-pot green procedure for Biginelli reaction catalyzed by novel task-specific room-temperature ionic liquids. J Mol Catal A: Chem 274:208–211
72. Comas H, Buisson DA, Najman R, Kozielski F, Rousseau B, Lopez R (2009) Synthesis of 5-Acyl-3,4-dihydropyrimidine-2-thiones via solvent-free, solution-phase and solid-phase Biginelli procedures. Synlett 1737–1740
73. Bahrami K, Khodaei MM, Farrokhi A (2009) Highly efficient solvent-free synthesis of dihydropyrimidinones catalyzed by zinc oxide. Synth Commun 39:1801–1808
74. Gross GA, Wurziger H, Schober A (2006) Solid-phase synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2(1H)-one-5-carboxylic acid amide derivatives: a Biginelli three-component-condensation protocol based on immobilized beta-ketoamides. J Comb Chem 8:153–155
75. Desai B, Dallinger D, Kappe CO (2006) Microwave-assisted solution phase synthesis of dihydropyrimidine C5 amides and esters. Tetrahedron 62:4651–4664
76. Kumar A, Maurya RA (2007) An efficient bakers' yeast catalyzed synthesis of 3,4-dihydropyrimidin-2-(1H)-ones. Tetrahedron Lett 48:4569–4571
77. Zalavadiya P, Tala S, Akbari J, Joshi H (2009) Multi-component synthesis of dihydropyrimidines by iodine catalyst at ambient temperature and in-vitro anti mycobacterial activity. Arch Pharm 342:469–475

78. Hegedus A, Hell Z, Vigh I (2006) Convenient one-pot heterogeneous catalytic method for the preparation of 3,4-dihydropyrimidin-2(1H)-ones. Synth Commun 36:129–136
79. Joseph JK, Jain SL, Sain B (2006) Ion exchange resins as recyclable and heterogeneous solid acid catalysts for the Biginelli condensation: an improved protocol for the synthesis of 3,4-dihydropyrimidin-2-ones. J Mol Catal A: Chem 247:99–102
80. Han XY, Xu F, Luo YQ, Shen Q (2005) An efficient one-pot synthesis of dihydropyrimidinones by a samarium diiodide catalyzed Biginelli reaction under solvent-free conditions. Eur J Org Chem 1500–1503
81. Putilova ES, Troitskii NA, Zlotin SG (2005) Reaction of aromatic aldehydes with beta-dicarbonyl compounds in a catalytic system: piperidinium acetate – 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid. Russ Chem Bull 54:1233–1238
82. Khunt RC, Akbari JD, Manvar AT, Tala SD, Dhaduk MF, Joshi HS, Shah A (2008) Green chemistry approach to synthesis of some new trifluoromethyl containing tetrahydropyrimidines under solvent-free conditions. Arkivoc 277–U8
83. Ryabukhin SV, Plaskon AS, Ostapchuk EN, Volochnyuk DM, Shishkin OV, Tolmachev AA (2008) CF3-substituted 1,3-dicarbonyl compounds in the Biginelli reaction promoted by chlorotrimethylsilane. J Fluor Chem 129:625–631
84. Azizian J, Mirza B, Mojtahedi MM, Abaee MS, Sargordan M (2008) Biginelli reaction for synthesis of novel trifluoromethyl derivatives of bis(tetrahydropyrimidinone)benzenes. J Fluor Chem 129:1083–1089
85. Amini MM, Shaabani A, Bazgir A (2006) Tangstophosphoric acid (H3PW12O40): an efficient and eco-friendly catalyst for the one-pot synthesis of dihydropyrimidin-2(1H)-ones. Catal Commun 7:843–847
86. Byk G, Kabha E (2006) A solid-supported stereoselective multicomponent reaction: One-pot generation of three asymmetric carbons. Synlett 747–748
87. Nilsson BL, Overman LE (2006) Concise synthesis of guanidine-containing heterocycles using the Biginelli reaction. J Org Chem 71:7706–7714
88. Hulme R, Zamora ODP, Mota EJ, Pasten MA, Contreras-Rojas R, Miranda R, Valencia-Hernandez I, Correa-Basurto J, Trujillo-Ferrara J, Delgado F (2008) Cyanamide: a convenient building block to synthesize 4-aryl-2-cyanoimino-3,4-dihydro-1H-pyrimidine systems via a multicomponent reaction. Tetrahedron 64:3372–3380
89. Kappe CO (2000) Biologically active dihydropyrimidones of the Biginelli-type – a literature survey. Eur J Med Chem 35:1043–1052
90. Kappe CO (2003) The generation of dihydropyrimidine libraries utilizing Biginelli multicomponent chemistry. QSAR Comb Sci 22:630–645
91. Gong LZ, Chen XH, Xu XY (2007) Asymmetric organocatalytic biginelli reactions: a new approach to quickly access optically active 3,4-dihydropyrimidin-2-(1H)-ones. Chem Eur J 13:8920–8926
92. Kappe CO, Uray G, Roschger P, Lindner W, Kratky C, Keller W (1992) Synthesis and reactions of Biginelli compounds. 5. Facile preparation and resolution of a stable 5-dihydropyrimidinecarboxylic acid. Tetrahedron 48:5473–5480
93. Schnell B, Strauss UT, Verdino P, Faber K, Kappe CO (2000) Synthesis of enantiomerically pure 4-aryl-3,4-dihydro-pyrimidin-2(1H)-ones via enzymatic resolution: preparation of the antihypertensive agent (R)-SQ 32926. Tetrahedron Asymmetry 11:1449–1453
94. Dondoni A, Massi A (2006) Design and synthesis of new classes of Heterocyclic C-glycoconjugates and carbon-linked sugar and heterocyclic amino acids by asymmetric multicomponent reactions (AMCRs). Acc Chem Res 39:451–463
95. Huang YJ, Yang FY, Zhu CJ (2005) Highly enantioseletive biginelli reaction using a new chiral ytterbium catalyst: Asymmetric synthesis of dihydropyrimidines. J Am Chem Soc 127:16386–16387
96. Chen XH, Xu XY, Liu H, Cun LF, Gong LZ (2006) Highly enantioselective organocatalytic Biginelli reaction. J Am Chem Soc 128:14802–14803

97. Li N, Chen XH, Song J, Luo SW, Fan W, Gong LZ (2009) Highly enantioselective organocatalytic Biginelli and Biginelli-like condensations: reversal of the stereochemistry by tuning the 3,3′-disubstituents of phosphoric acids. J Am Chem Soc 131:15301–15310
98. Goss JM, Schaus SE (2008) Enantioselective synthesis of SNAP-7941: chiral dihydropyrimidone inhibitor of MCH1-R. J Org Chem 73:7651–7656
99. Wu YY, Chai Z, Liu XY, Zhao G, Wang SW (2009) Synthesis of substituted 5-(Pyrrolidin-2-yl) tetrazoles and their application in the asymmetric Biginelli reaction. Eur J Org Chem 904–911.
100. Jeyaraman R, Avila S (1981) Chemistry of 3-azabicyclo 3.3.1 nonanes. Chem Rev 81:149–174
101. Metten B, Kostermans M, Van Baelen G, Smet M, Dehaen W (2006) Synthesis of 5-aryl-2-oxopyrrole derivatives as synthons for highly substituted pyrroles. Tetrahedron 62:6018–6028
102. Shen L, Cao S, Liu NJ, Wu JJ, Zhu LJ, Qian XH (2008) Ytterbium(III) perfluorooctanoate catalyzed one-pot, three-component synthesis of fully substituted pyrazoles under solvent-free conditions. Synlett 1341–1344
103. Shen L, Zhang J, Cao S, Yu JL, Liu NJ, Wu JJ, Qian XH (2008) One-pot synthesis of trifluoromethyl-containing pyrazoles via sequential Yb(PFO)(3)-catalyzed three-component reaction and IBX-mediated oxidation. Synlett 3058–3062
104. Khan AT, Parvin T, Choudhury LH (2008) Effects of Substituents in the beta-Position of 1,3-dicarbonyl compounds in bromodimethylsulfonium bromide-catalyzed multicomponent reactions: a facile access to functionalized piperidines. J Org Chem 73:8398–8402
105. Habib-Zahmani H, Hacini S, Charonnet E, Rodriguez J (2002) A new multicomponent domino transformation of 1,3-dicarbonyl compounds: one-pot regio-, chemo- and stereoselective access to valuable alpha,gamma-difunctionalized alpha-ketoesters and amides. Synlett 1827–1830
106. Wang XS, Li Q, Wu JR, Li YL, Yao CS, Tu SJ (2008) An efficient and highly selective method for the synthesis of 3-arylbenzoquinoline derivatives catalyzed by iodine via three-component reactions. Synthesis 1902–1910
107. Tu SJ, Zhang Y, Zhang JY, Jiang B, Jia RH, Zhang JP, Ji SJ (2006) A simple procedure for the synthesis of 4-aza-podophyllotoxin derivatives in water under microwave irradiation conditions. Synlett 2785–2790
108. Wender PA, Zercher CK, Beckham S, Haubold EM (1993) A photochemically triggered DNA-cleaving agent – synthesis, mechanistic and DNA cleavage studies on a new analog of the antitumor antibiotic dynemicin. J Org Chem 58:5867–5869
109. Ori M, Toda N, Takami K, Tago K, Kogen H (2005) Stereospecific synthesis of 2,2,3-trisubstituted tetrahydroquinolines: application to the total syntheses of benzastatin E and natural virantmycin. Tetrahedron 61:2075–2104
110. Zhang W, Guo YP, Liu ZG, Jin XL, Yang L, Liu ZL (2005) Photochemically catalyzed Diels-Alder reaction of arylimines with N-vinylpyrrolidinone and N-vinylcarbazole by 2,4,6-triphenylpyrylium salt: synthesis of 4-heterocycle-substituted tetrahydroquinoline derivatives. Tetrahedron 61:1325–1333
111. Kadutskii AP, Kozlov NG (2006) A novel three-component reaction of anilines, formaldehyde and beta-diketones: simple synthesis of 3-spirosubstituted 1,2,3,4-tetrahydroquinolines. Synlett 3349–3351
112. Fujioka H, Murai K, Kubo O, Ohba Y, Kita Y (2007) New three-component reaction: novel formation of a seven-membered ring by the unexpected reaction at the gamma-position of the beta-keto ester. Org Lett 9:1687–1690
113. Sotoca E, Allais C, Constantieux T, Rodriguez J (2009) User-friendly stereoselective one-pot access to 1,4-diazepane derivatives by a cyclodehydrative three-component reaction with 1,3-dicarbonyls. Org Biomol Chem 7:1911–1920
114. Sotoca E, Constantieux T, Rodriguez J (2008) Solvent- and catalyst-free three-component reaction with beta-ketoamides for the stereoselective one-pot access to 1,4-diazepines. Synlett 1313–1316

115. Murai K, Nakatani R, Kita Y, Fujioka H (2008) One-pot three-component reaction providing 1,5-benzodiazepine derivatives. Tetrahedron 64:11034–11040
116. Tietze LF (1990) Domino-reactions – the tandem-Knoevenagel-hetero-Diels-Alder reaction and its application in natural product synthesis. J Heterocycl Chem 27:47–69
117. Heravi MM, Baghernejad B, Oskooie HA, Hekmatshoar R (2008) A novel and facile synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1H-indole-4(5H)-ones via a one-pot multi-component reaction. Tetrahedron Lett 49:6101–6103
118. Gozalishvili LL, Beryozkina TV, Omelchenko IV, Zubatyuk RI, Shishkin OV, Kolos NN (2008) A rapid and facile synthesis of new spiropyrimidines from 5-(2-arylethylidene-2-oxo)-1,3-dimethylpyrimidine-2,4,6-triones. Tetrahedron 64:8759–8765
119. Nagarapu L, Bantu R, Mereyala HB (2009) TMSCl-mediated one-pot, three-component synthesis of 2H-indazolo 2, 1-b phthalazine-triones. J Heterocycl Chem 46:728–731
120. Li M, Yang WL, Wen LR, Li FQ (2008) A first resource-efficient and highly flexible procedure for a four-component synthesis of dispiropyrrolidines. Eur J Org Chem 2751–2758
121. Peng YQ, Song GH (2007) Amino-functionalized ionic liquid as catalytically active solvent for microwave-assisted synthesis of 4H-pyrans. Catal Commun 8:111–114
122. Babu NS, Pasha N, Rao KTV, Prasad PSS, Lingalah N (2008) A heterogeneous strong basic Mg/La mixed oxide catalyst for efficient synthesis of polyfunctionalized pyrans. Tetrahedron Lett 49:2730–2733
123. Balalaie S, Bararjanian M, Amani AM, Movassagh B (2006) (S)-Proline as a neutral and efficient catalyst for the one-pot synthesis of tetrahydrobenzo b pyran derivatives in aqueous media. Synlett 263–266
124. Balalaie S, Sheikh-Ahmadi M, Bararjanian M (2007) Tetra-methyl ammonium hydroxide: an efficient and versatile catalyst for the one-pot synthesis of tetrahydrobenzo b pyran derivatives in aqueous media. Catal Commun 8:1724–1728
125. Zhu SL, Ji SJ, Zhang Y (2007) A simple and clean procedure for three-component synthesis of spirooxindoles in aqueous medium. Tetrahedron 63:9365–9372
126. Song SD, Song LP, Dai BF, Yi H, Jin GF, Zhu SZ, Shao M (2008) A convenient one-pot synthesis of 2-(trifluoromethyl)-3,4,7,8-tetrahydro-2H-chromen-5(6H)-one derivatives and their further transformations. Tetrahedron 64:5728–5735
127. Prajapati D, Gohain M (2006) An efficient synthesis of novel pyrano 2,3-d - and furopyrano 2,3-d pyrimidines via indium-catalyzed multi-component domino reaction. Beilstein J Org Chem 2. Doi:10.1186/1860-5397-2-11
128. Gerencser J, Dorman G, Darvas F (2006) Meldrum's acid in multicomponent reactions: applications to combinatorial and diversity-oriented synthesis. QSAR Comb Sci 25:439–448
129. Jimenez-Alonso S, Chavez H, Estevez-Braun A, Ravelo AG, Feresin G, Tapia A (2008) An efficient synthesis of embelin derivatives through domino Knoevenagel hetero Diels-Alder reactions under microwave irradiation. Tetrahedron 64:8938–8942
130. Jimenez-Alonso S, Estevez-Braun A, Ravelo AG, Zarate R, Lopez M (2007) Double domino Knoevenagel hetero Diels-Alder strategy towards bis-pyrano-1,4-benzoquinones. Tetrahedron 63:3066–3074
131. Gu Y, De Sousa R, Frapper P, Bachmann C, Barrault J, Jérôme F (2009) Catalyst-free aqueous multicomponent domino reaction from formaldehyde and 1,3-dicarbonyls derivatives. Green Chem 11:1968–1972
132. Nandi GC, Samai S, Kumar R, Singh MS (2009) An efficient one-pot synthesis of tetrahydrobenzo a xanthene-11-one and diazabenzo a anthracene-9,11-dione derivatives under solvent free condition. Tetrahedron 65:7129–7134
133. Gao SJ, Tsai CH, Yao CF (2009) A simple and green approach for the synthesis of tetrahydrobenzo a xanthen-11-one derivatives using tetrabutyl ammonium fluoride in water. Synlett 949–954
134. Khurana JM, Magoo D (2009) pTSA-catalyzed one-pot synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo a xanthen-11-ones in ionic liquid and neat conditions. Tetrahedron Lett 50:4777–4780

135. Wang RZ, Zhang LF, Cui ZS (2009) Iodine-catalyzed synthesis of 12-aryl-8,9,10,12-tetrahydro-benzo a xanthen-11-one derivatives via multicomponent reaction. Synth Commun 39:2101–2107
136. Das B, Laxminarayana K, Krishnaiah M, Srinivas Y (2007) An efficient and convenient protocol for the synthesis of novel 12-aryl- or 12-alkyl-8,9,10,12-tetrahydrobenzo a xanthen-11-one derivatives. Synlett 3107–3112
137. Nagarajan AS, Reddy BSR (2009) Synthesis of substituted pyranopyrazoles under neat conditions via a multicomponent reaction. Synlett 2002–2004
138. Vasuki G, Kumaravel K (2008) Rapid four-component reactions in water: synthesis of pyranopyrazoles. Tetrahedron Lett 49:5636–5638
139. Litvinov YM, Shestopalov AA, Rodinovskaya LA, Shestopalov AM (2009) New convenient four-component synthesis of 6-amino-2,4-dihydropyrano 2,3-c pyrazol-5-carbonitriles and one-pot synthesis of 6′-aminospiro (3H)-indol-3,4′-pyrano 2,3-c pyrazol -(1H)-2-on-5′-carbonitriles. J Comb Chem 11:914–919
140. Kumaravel K, Vasuki G (2009) Four-component catalyst-free reaction in water: combinatorial library synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromene-3-carbonitrile derivatives. Green Chem 11:1945–1947
141. Shanthi G, Perumal PT (2009) InCl3-catalyzed efficient one-pot synthesis of 2-pyrrolo-3 '-yloxindoles. Tetrahedron Lett 50:3959–3962
142. Dey S, Pal C, Nandi D, Giri VS, Zaidlewicz M, Krzeminski M, Smentek L, Hess BA, Gawronski J, Kwit M, Babu NJ, Nangia A, Jaisankar P (2008) Lewis acid-catalyzed one-pot, three-component route to chiral 3,3′-bipyrroles. Org Lett 10:1373–1376
143. Alizadeh A, Rezvanian A, Zhu LG (2008) One-pot synthesis of 4,5-dihydro-1H-pyrrol-3-carboxamide derivatives via a four-component reaction. Tetrahedron 64:351–355
144. Simon C, Peyronel JF, Rodriguez J (2001) A new multicomponent domino reaction of 1,3-dicarbonyl compounds: One-pot access to polycyclic N/O-, N/S-, and N/N-aminals. Org Lett 3:2145–2148
145. Noel R, Fargeau-Bellassoued MC, Vanucci-Bacque C, Lhommet G (2008) Convenient one-pot synthesis of chiral tetrahydropyridines via a multicomponent reaction. Synthesis 1948–1954
146. Sridharan V, Maiti S, Menendez JC (2009) A very efficient cerium(IV) ammonium nitrate catalyzed, four-component synthesis of tetrahydropyridines and its application in the concise generation of functionalized homoquinolizine frameworks. Chem Eur J 15:4565–4572
147. Maiti S, Menendez JC (2009) A mild protocol for the efficient synthesis of 5,6-unsubstituted 1,4-dihydropyridines. Synlett 2249–2252
148. Sridharan V, Perumal PT, Avendano C, Menendez JC (2007) A new three-component domino synthesis of 1,4-dihydropyridines. Tetrahedron 63:4407–4413
149. Kumar A, Maurya RA (2008) Organocatalysed three-component domino synthesis of 1,4-dihydropyridines under solvent free conditions. Tetrahedron 64:3477–3482
150. Das B, Suneel K, Venkateswarlu K, Ravikanth B (2008) Sulfonic acid functionalized silica: an efficient heterogeneous catalyst for a three-component synthesis of 1,4-dihydropyridines under solvent-free conditions. Chem Pharm Bull 56:366–368
151. Kantam ML, Ramani T, Chakrapani L, Choudary BM (2009) Synthesis of 1,4-dihydropyridine derivatives using nanocrystalline copper(II) oxide catalyst. Catal Commun 10:370–372
152. Jiang J, Yu J, Sun XX, Rao QQ, Gong LZ (2008) Organocatalytic asymmetric three-component cyclization of cinnamaldehydes and primary amines with 1,3-dicarbonyl compounds: straightforward access to enantiomerically enriched dihydropyridines. Angew Chem Int Ed 47:2458–2462
153. Bagley MC, Chapaneri K, Dale JW, Xiong X, Bower J (2005) One-pot multistep Bohlmann-Rahtz heteroannulation reactions: synthesis of dimethyl sulfomycinamate. J Org Chem 70:1389–1399
154. Blayo AL, Le Meur S, Gree D, Gree R (2008) New enantioselective synthesis of monofluorinated pyridines designed for the preparation of chemical libraries. Adv Synth Cat 350:471–476

155. Kantevari S, Chary MV, Vuppalapati SVN (2007) A highly efficient regioselective one-pot synthesis of 2,3,6-trisubstituted pyridines and 2,7,7-trisubstituted tetrahydroquinolin-5-ones using K5CoW12O40 center dot 3H(2)O as a heterogeneous recyclable catalyst. Tetrahedron 63:13024–13031
156. Lieby-Muller F, Simon C, Constantieux T, Rodriguez J (2006) Current developments in Michael addition-based multicomponent domino reactions involving 1,3-dicarbonyls and derivatives. QSAR Comb Sci 25:432–438
157. Lieby-Muller F, Allais C, Constantieux T, Rodriguez J (2008) Metal-free Michael addition initiated multicomponent oxidative cyclodehydration route to polysubstituted pyridines from 1,3-dicarbonyls. Chem Commun 4207–4209
158. Allais C, Constantieux T, Rodriguez J (2009) Highly Efficient Synthesis of trans-beta, gamma-Unsaturated alpha-Keto Amides. Synthesis 2523–2530
159. Allais C, Constantieux T, Rodriguez J (2009) Use of β, γ-unsaturated α-ketocarbonyls for a totally regioselective oxidative multicomponent synthesis of polyfunctionalized pyridines. Chem Eur J 15:12945–12948
160. Coquerel Y, Bensa D, Moret V, Rodriguez J (2006) Synthetic studies on the MARDi cascade: stereoselective preparation of sulfonyl-substituted seven-membered rings. Synlett 2751–2754
161. Coquerel Y, Bensa D, Doutheau A, Rodriguez J (2006) Synthetic studies on the MARDi cascade: stereoselective synthesis of heterocyclic seven-membered rings. Org Lett 8:4819–4822
162. Coquerel Y, Filippini MH, Bensa D, Rodriguez J (2008) The MARDi cascade: a Michael-initiated domino-multicomponent approach for the stereoselective synthesis of seven-membered rings. Chem Eur J 14:3078–3092
163. Lieby-Muller F, Simon C, Imhof K, Constantieux T, Rodriguez J (2006) A multicomponent domino reaction and in situ aerobic oxidation sequence for the first one-pot synthesis of polycyclic benzimidazoles from 1,3-dicarbonyl derivatives. Synlett 1671–1674
164. Lieby-Muller F, Constantieux T, Rodriguez J (2007) Highly efficient access to original polycyclic pyrrolopiperazine scaffolds by a three-component reaction with 1,3-dicarbonyls. Synlett 1323–1325
165. Lieby-Muller F, Constantieux T, Rodriguez J (2005) Multicomponent domino reaction from beta-ketoamides: highly efficient access to original polyfunctionalized 2,6-diazabicyclo 2.2.2 octane cores. J Am Chem Soc 127:17176–17177
166. Habib-Zahmani H, Viala J, Hacini S, Rodriguez J (2007) Synthesis of functionalized spiroheterocycles by sequential multicomponent reaction/metal-catalyzed carbocylizations from simple beta-ketoesters and amides. Synlett 1037–1042
167. Radi M, Bernardo V, Bechi B, Castagnolo D, Pagano M, Botta M (2009) Microwave-assisted organocatalytic multicomponent Knoevenagel/hetero Diels-Alder reaction for the synthesis of 2,3-dihydropyran 2,3-c pyrazoles. Tetrahedron Lett 50:6572–6575
168. Giorgi G, Miranda S, Lopez-Alvarado P, Avendano C, Rodriguez J, Menendez JC (2005) Unique Michael addition-initiated domino reaction for the stereoselective synthesis of functionalized macrolactones from alpha-nitroketones in water. Org Lett 7:2197–2200
169. Tietze LF, Bohnke N, Dietz S (2009) Synthesis of the deoxyaminosugar (+)-D-forosamine via a novel domino-Knoevenagel-hetero-Diels-Alder reaction. Org Lett 11:2948–2950

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