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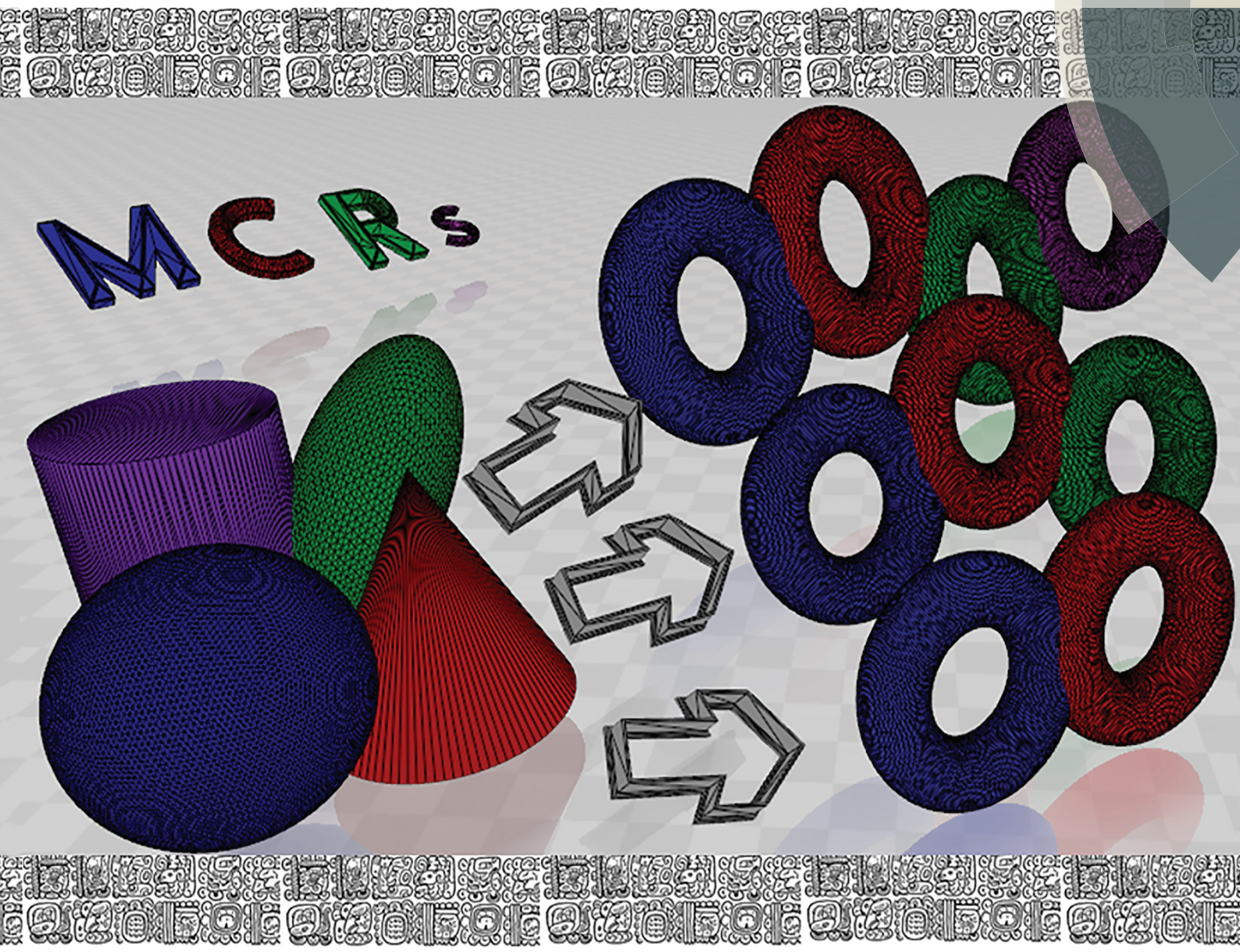

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REVIEW

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Synthesis of polyheterocycles *via* multicomponent reactions

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Polyheterocycles are one of the most desired synthetic targets due to their numerous and valuable applications in various fields. Multicomponent reactions (MCRs) are highly convergent *one-pot* processes, in which three or more reagents are combined sequentially to construct complex products, with almost all the atoms coming from the starting reagents. In this context, the syntheses of 'heterocycles' *via* MCR-based processes have been reviewed a number of times. However, there is not a single review (recent or otherwise) covering the synthesis of 'polyheterocycles' *via* a direct MCR or *via* a one-pot process involving MCRs coupled to further cyclizations (*via* ionic, metal-catalyzed, pericyclic, or free-radical-mediated cyclizations). This issue is consequently the main topic of the present review, which considers work from the last decade. The work is categorized according to the key processes involved in the syntheses of polyheterocycles, aiming to give readers an easy understanding of this MCR-based chemistry and to provide insights for further investigations. The reaction mechanisms providing novel elements to these MCR-based methods for the synthesis of polyheterocycles are also discussed.

1 Introduction

Polyheterocycles are complex organic molecules formed by two (bis-heterocycles) or more (tris-, tetra-, and so on) heterocyclic moieties joined in different forms or connectivities (merged, bound, fused, linked, or spaced). According to their origin, polyheterocycles can be classified into natural[1] or synthetic products.[2] Representative examples of the former include

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Ilich A. Ibarra

Ilich A. Ibarra was born in Mexico City in 1981. He completed his BSc at UAM-I, Mexico in 2005. Later, in 2010, he obtained his PhD in Chemistry under the supervision of Professor Martin Schröder at Nottingham University (UK). He then took a postdoctoral position, 2010–2012, at The University of Texas at Austin (USA) under the supervision of Professor Simon Humphrey. Then, in 2013 he was awarded a Wenner-Gren researcher position at Stockholm University (Sweden) under the supervision of Professor Xiaodong Zou. In 2014, he moved to UNAM (IIM, Mexico), working as an assistant professor. In 2017, he was promoted to associate professor.

Alejandro Islas-Jácome

Alejandro Islas-Jácome was born in Veracruz, México, in 1981. He got his BSc in 2005 and PhD in 2011 under the guidance of Professor Eduardo González-Zamora in UAM-I, México. Then, he was a post-doctoral fellow in Rocío Gámez-Montaño's research group in 2012–2016 at the Universidad de Guanajuato, México. Currently, he is a visiting professor in the Departamento de Química, UAM-I, México. His research interests include the sustainable synthesis of polyheterocycles via *multicomponent reactions, click chemistry, computational studies of reaction mechanisms, experimental determination of optical properties, as well as biomolecular chemistry.*

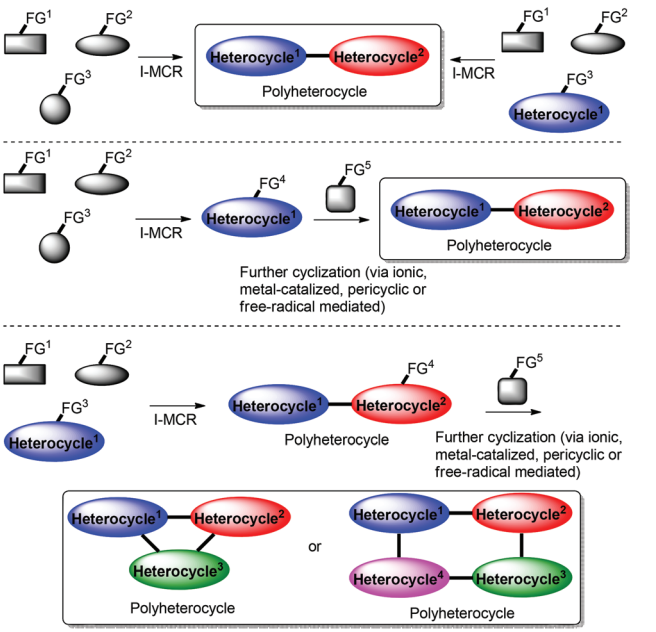
(±)-Aspidofractinine, (+)-Rebeccamycin, and Didemnimide A, which are indole-based tris-heterocycles.[3] Polyheterocycles have found many interesting applications in various fields; for example, in optics,[4] dyes and pigments science,[5] materials and polymer science,[6] coordination chemistry,[7] and agrochemistry.[8] However, their main importance lies in medicinal chemistry because a wide variety of bioactive compounds and commercially available drugs contain polyheterocyclic systems in their structures.[9] Of course, the size, structural complexity, and molecular weights increase directly with the number of heterocycles embedded in the same polyheterocyclic molecules. In this context, the rules and parameters related to the applicability of organic compounds in drugs (those favorable for small molecules with MW < 500 Da), such as the Lipinski rules,[10] Ghose rules,[11] and Veber criteria,[12] are not commonly obeyed by polyheterocycles. Even so, vancomycin (potent post-surgical antibiotic characterized by having macrocyclic and polypeptidic biaryl/biaryl-ether moieties) is a clear example that bigger polyheterocycles can be used in medicinal chemistry, despite their 'big/XL size'.[13]

Moreover, as was discussed by M. Yus, multicomponent reactions (MCRs) are privileged one-pot processes, which should be differentiated from other kinds of processes, like tandem, cascade, and zipper processes, because they involve sequential combinations of at least three reagents in the same pot (flask, tube, reactor, *etc.*).[14] MCRs have found their main usefulness in Diversity Oriented Synthesis (DOS),[15] where a series of novel polyheterocycles with different skeletons have been synthesized in a one-pot manner based on the four strategies proposed by R. V. A. Orru, namely: (i) Single Reactant Replacement (SRR); (ii) Modular Reaction Sequences (MRS); (iii) Conditions-Based Divergence (CBD); and (iv) A combination of two or more MCRs.[16] Another key area of organic synthesis for medicinal chemistry that has been strongly influenced by MCRs is Combinatorial Chemistry (CC). D. G. Hall reviewed the synthesis of novel compounds containing the same heterocyclic system (chemical libraries) under ultra-high output modes by changing the substituents (*i.e.*, *via* decoration) of the starting reagents.[17] In addition, from the Target Oriented Synthesis (TOS) approach, MCRs can be considered as key synthetic tools because a variety of complex specific targets (or at least their precursors) and some natural products containing polyheterocycles in their structures have been synthesized successfully by multistep strategies in which an MCR was involved in the beginning, middle, or end of the synthetic methodology. As a very sound example, the polyheterocyclic schistosomiasis-drug Praziquantel (PZQ) was synthesized first by A. Dömling using an MCR-based method in a truly excellent overall yield (77%), considering the molecular complexity of the PZQ and the robustness of his synthetic strategy.[18] As can be seen from this example, MCRs allow the synthesis of novel and complex polyheterocycles from the three key approaches for organic synthesis in medicinal chemistry (DOS, CC, and TOS).[19]

Moreover, R. Lavilla proposed four key roles of MCRs in heterocyclic chemistry: (i) synthesis of heterocycles *via* direct MCRs; (ii) synthesis of heterocycles *via* MCRs/further cyclizations; (iii) synthesis of heterocycles using starting reagents decorated with heterocyclic moieties; and (iv) functionalization of heterocycles *via* MCRs.[20] These four key roles of MCRs can be extrapolated to 'polyheterocyclic chemistry' in order to increase the molecular complexity and substrate scope of MCR-based synthetic strategies (Scheme 1). Besides, MCRs can be divided into two major groups: (i) Isocyanide-based MCRs (I-MCRs), and those not based on the use of isocyanides as starting reagents. It is noteworthy that the isocyanide (RNC) is

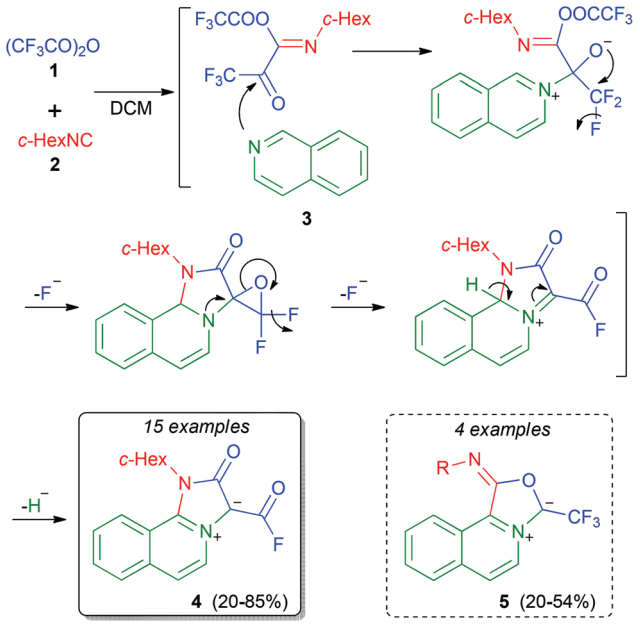
Eduardo González-Zamora

Eduardo González-Zamora, full professor at UAM-I, Mexico, was born in 1961 in Mexico City. He received his MSc degree from UAM-I in 1988. In 1994, he moved to France and obtained his PhD (1998) from Paris XI University (France) under the supervision of Professor R. Beugelmans. After one year of post-doctoral work with Professor R. Cruz at the Instituto de Química (UNAM, Mexico), he joined the "Institut de Chimie des Substances Naturelles", CNRS (France) in 2000 as a post-doctoral fellow for two years working with Professor J. Zhu. In 2011, he moved to UCLA (USA) as a visiting professor in M. A. Garcia-Garibay's group. His research interests include the synthesis of heterocycles by MCR, MOFs' chemistry, peptides, and total synthesis.



Scheme 1 Synthesis of polyheterocycles *via* I-MCR-based processes.

a special kind of functional group that can act as a nucleophile or electrophile depending on its substituents and substrates because it has a very reactive carbenic carbon atom.[21] Classic I-MCRs, like the Van Leusen,[22] Passerini,[23] and Ugi reaction[24] in all of its variants (3-CR, 4-CR, Ugi-azide, Ugi-Smiles, Ugi-Nenajdenko, Ugi-Reissert, and Ugi-interrupted (Groebke–Blackburn–Bienaymé)), represent the great majority of the MCRs in current reports describing the synthesis of polyheterocycles *via* MCRs. The covering of this issue is the main objective of the present review (chapters 2 to 6). In addition, a few reports describing the use of non-isocyanide-based MCRs toward polyheterocycles are also covered as a miscellaneous topic (chapter 7.1). Thus, the synthesis of polyheterocycles (bis-, tris-, and tetra-) *via* direct MCRs and one-pot processes involving MCRs coupled to further cyclizations (*via* ionic, metal-catalyzed, pericyclic, or free-radical-mediated cyclizations) are reviewed (Scheme 1). On the contrary, the synthesis of 'monoheterocycles' *via* MCRs (whether or not based on the use of isocyanides) will not be considered.[20a,25] It is noteworthy that polyheterocycles containing up to four heterocycles have been synthesized successfully *via* MCR-involved processes, but in the same way, we considered it pertinent not to address them in the present review.



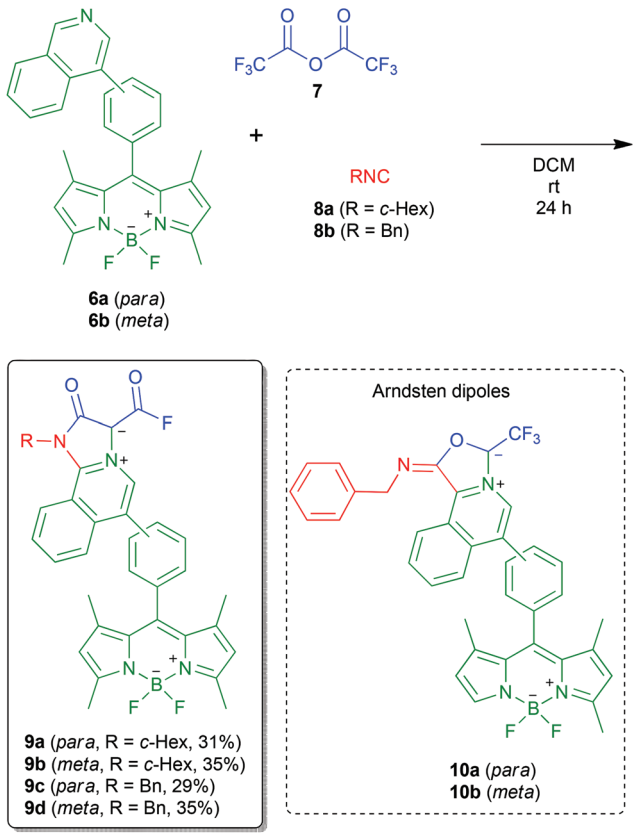
Scheme 2 Synthesis of the mesoionic polyheterocycles **4** and **5** *via* a novel direct 3-CR.

2 Synthesis of polyheterocycles *via* direct I-MCR

Despite it being most common to synthesize polyheterocycles *via* I-MCRs/further cyclizations (chapters 3 to 6), in the present chapter some representative direct I-MCR-based methods toward a variety of polyheterocyclic-based compounds are reviewed.

Thus, R. Lavilla reported in 2009 a novel synthetic method toward various mesoionic polyheterocycles *via* a direct functionalization of polysubstituted azines **3** (pyridines, pyridazines, quinolines, isoquinolines, and phthalazines) with a variety of isocyanides **2** (alkyl and aryl) and some halogen-containing acylating agents **1** using DCM as a solvent.[26] The proposed reaction mechanism involved an initial acylation step for the isocyanide (cyclohexyl isocyanide was chosen to show the mechanism) with a halogen-containing acylating agent (TFAA was chosen to show the mechanism), followed by *N*-sp^2 nucleophilic attack of the corresponding azine (isoquinoline was chosen to show the mechanism) to synthesize the acid-fluoride-functionalized polyheterocycles **4** after some sequential steps. It is noteworthy that the Arndtsen dipoles **5** (depending on the azine and isocyanide used) were obtained as byproducts (Scheme 2).

By using his previously developed methodology, in 2016, R. Lavilla synthesized four new BODIPY-containing mesoionic acid fluorides **9a–d** *via* a direct 3-CR using the isoquinoline-BODIPYs **6a–b**, trifluoroacetic anhydride (**7**), and the isocyanides **8a–b** under mild reaction conditions (DCM, rt, 24 h) in 29% to 35% yields (Scheme 3). The Arndsten dipoles **10a–b** were detected as byproducts when BnNC (**8b**) was used in the

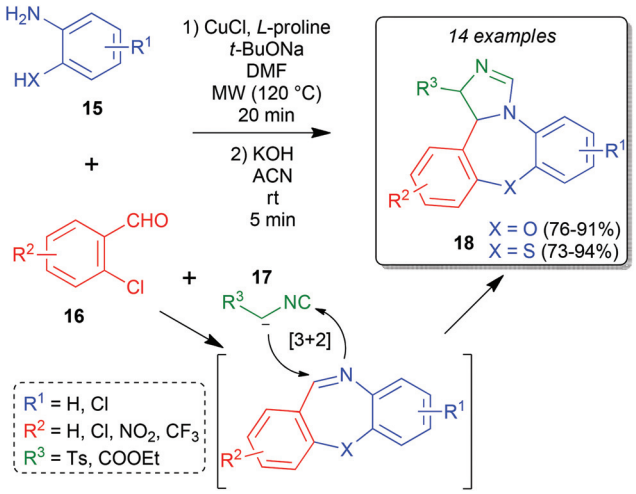


Scheme 3 Synthesis of the fluorescent polyheterocycles **9a–d** (quantum yield, Φ = 45–59% in EtOH) *via* a direct 3-CR.

MCRs. Compounds **9a–d** were synthesized to take advantage of the acid fluoride functional group for the fluorescent derivatization of amine-containing biomolecules under mild and catalysis-free conditions. In fact, the antifungal drug natamycin was peptidically coupled to the product **9b** for imaging into fungal cells, which in turn was done successfully.[27]

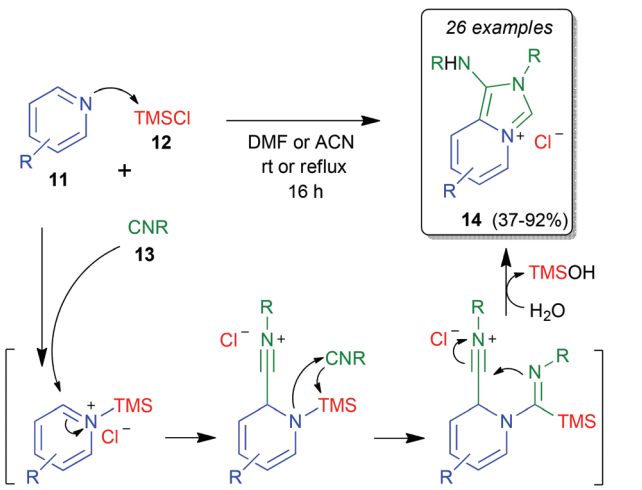
A closer work was reported by R. Lavilla and R. Gámez-Montaño in 2016, where a variety of polysubstituted azines **11** (isoquinolines, bis-isoquinolines, quinolines, quinoxalines, and phtalazines) were combined sequentially with the TMSCl (**12**) and a variety of isocyanides **13** (alkyl and aryl) to synthesize the fused-type imidazo-isoquinolin chlorides **14** in 37% to 92% yields *via* a 3-CR, which involved presumably the insertion of a first isocyanide molecule into the N–Si bond of the corresponding *N*-activated azine followed by the further nucleophilic attack of a second isocyanide molecule under a Reissert-type process (Scheme 4). The hypothesis behind this plausible reaction mechanism was supported by computational studies by calculating the Intrinsic Reaction Coordinates (IRCs). Finally, some of the products **14** were evaluated *in vitro* against the parasites causing two of the most disseminated tropical diseases: *Trypanosona brucei* (African sleeping sickness) and *Trypanosona cruzi* (Chagas disease), finding pharmacologically relevant values of EC_{50}, for example, of 0.50 μM against *T. brucei*, and 1.02 μM for *T. cruzi*.[28]

In 2017, A. Sharma synthesized a series of novel polyheterocyclic dihydrodibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]azepines **18** *via* a Van Leusen reaction from the *ortho*-functionalized anilines **15** (–OH or –SH), the *ortho*-chlorobenzaldehydes **16**, and the isocyanides **17** in 73% to 94% yields using microwave as a heat source to improve the initial condensation step between **15** and **16** (Scheme 5).[29] It is noteworthy that there are few reports describing the synthesis of this class of imidazo-fused polyheterocycles, but *via* stepwise methods, which involve the use of more resources, like solvents, materials for chromatography, time, and energy.

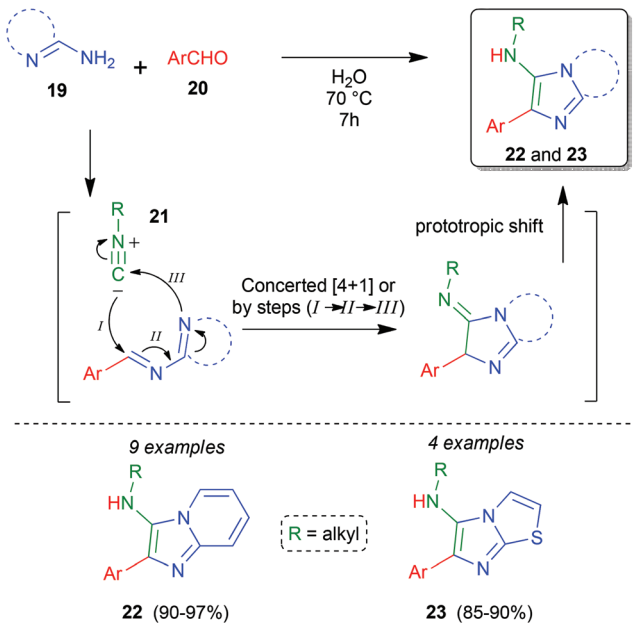


Scheme 5 Synthesis of the polyheterocycles **18** *via* a direct Van Leusen reaction.

In 2007, M. Adib reported a direct catalyst-free three-component reaction from the 2-aminoazines **19**, aldehydes **20**, and isocyanides **21** using water as a solvent to synthesize the bis-heterocycles **22** (analogs of the hypnotic drug Zolpidem) and **23** (analogs of the anthelmintic drug Levamisole) in excellent yields, 85–97% (Scheme 6).[30] It is noteworthy that this I-MCR is an interrupted variant of the classic Ugi-3CR, which was then known as the Groebke–Blackburn–Bienaymé Reaction (GBB) in honor of its developers in 1998.[31]



Scheme 4 Synthesis of the mesoionic polyheterocycles **14** *via* a direct 3-CR involving an unprecedent insertion of an isocyanide molecule into a *N–Si* bond.

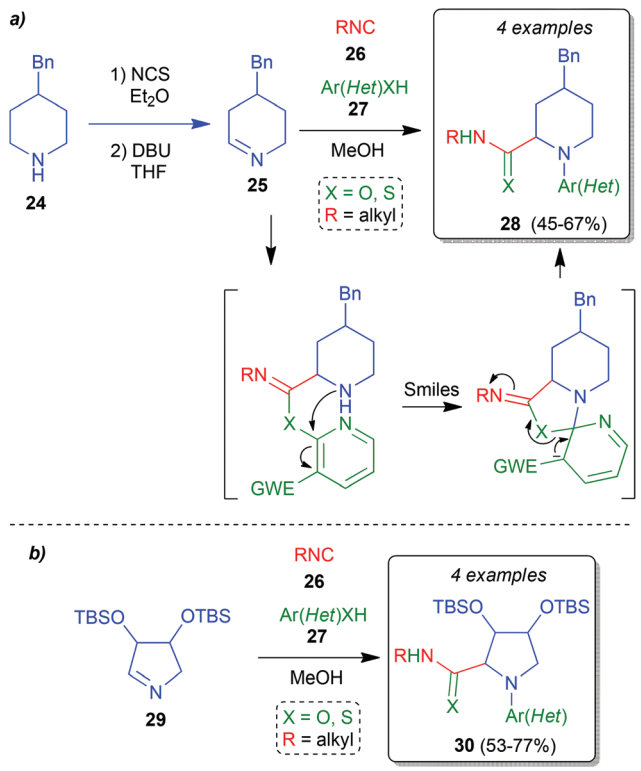


Scheme 6 Synthesis of the polyheterocycles **22** and **23** *via* a direct 3-CR Groebke–Blackburn–Bienaymé.

Actually, there is some controversy about the mechanism involved in the GBB reaction because the cyclization step to construct the polyheterocyclic system can occur in two manners: concerted or step-by-step.[32] This reaction has been used extensively toward a variety of fused-type polyheterocycles with interesting applications in medicinal chemistry and agrochemistry.[33]

In 2009, L. Grimaud and L. El Kaïm reported the first example of an Ugi-Smiles 4-CR to construct polyheterocyclic architectures. Ugi-Smiles is a variant of the Ugi reaction, in which carboxylic acids are replaced by deactivated phenols or hetero-aryl alcohols. It is noteworthy that L. Grimaud and L. El Kaïm have become known as the pioneers behind this MCR-based chemistry. Thus, *N*-(hetero-aryl)piperidines **28** were synthesized by combining sequentially the imine **25** (prepared *in situ* from the amine **24**) with the corresponding isocyanides **26** and the hetero-aryl alcohols **27** *via* a mechanism involving an ionic Smiles-rearrangement (Scheme 7a). The scope of this synthetic methodology was evaluated by preparing the five-membered polyheterocyclic analogs **30** using the imine **29** (prepared *in situ* from its corresponding amine using NCS) in the Ugi-Smiles reaction (Scheme 7b).[34]

As seen, an ionic cyclization step (Smiles-type rearrangement) occurred in the reaction mechanism previous to the formation of the polyheterocycles **28** and **30**. The next chapter covers some I-MCR/ionic cyclization strategies to construct complex polyheterocyclic architectures.



Scheme 7 (a) Ugi-Smiles-based synthesis of the *N*-(hetero-aryl)piperidines **28** and (b) *N*-(hetero-aryl)pyrrolidines **30**.

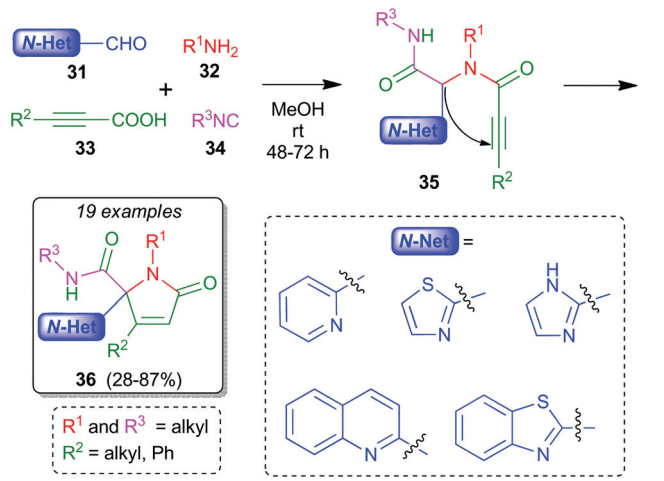
3 Synthesis of polyheterocyles *via* I-MCR/ionic cyclizations

I-MCR/ionic cyclization strategies have been used successfully toward the synthesis of various polyheterocyclic products. In this context, the following methodologies are reviewed as representative examples.

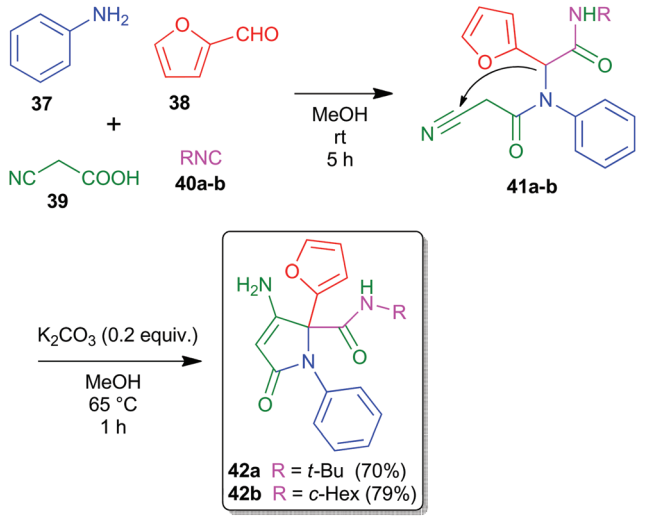
E. van der Eycken reported in 2016 the synthesis of various novel *N*-heterocycle-containing α,β-unsaturated-γ-lactams *via* an Ugi-4CR/intramolecular Michael addition in moderate to good yields. Thus, the N-heterocycle (pyridine, thiazole, imidazole, quinoline, and benzo[*d*]thiazole)-containing aldehydes **31** were combined sequentially with the amines **32**, the α,β-alkynyl carboxylic acids **33**, and the corresponding isocyanides **34** in MeOH at room temperature to afford the stable Ugi-adducts **35**, which in turn were cyclized *via* a 5-*endo-dig* Michael addition to access the desired bis-heterocycles **36** in 28% to 87% yields (Scheme 8).[35]

In 2015, L. El Kaïm and R. Gámez-Montaño reported the synthesis of various 4-amino-pyrrolydin-2-ones *via* a strategy of Ugi-4CR/base-assisted intramolecular cyclization using aromatic aldehydes and cyanoacetic acid as key reagents for the intramolecular cyclization process (Scheme 9).[36] Among the products prepared, the furyl-containing polyheterocycles **42a–b** were synthesized by combining sequentially in MeOH at room temperature for 5 h the aniline (**37**), 2-furylcarbaldehyde (**38**), cyanoacetic acid (**39**), and the isonitriles **40a–b** to give the stable Ugi-adducts **41a–b**, which by addition of substoichiometric amounts of potassium carbonate in MeOH at 65 °C afforded the products **42a–b** after 1 h. It is noteworthy that the usefulness of cyanoacetic acid as a key reagent in I-MCRs toward heterocycles was reviewed in 2008 by Shestopalov.[37]

In 2012, C. Hulme reported an Ugi-4CR/aldol sequence toward a variety of linked-type polyheterocycles. Thus, amines **43** were combined sequentially with oxalyl-type aldehydes **44**, oxalyl-type carboxylic acids **45**, and the *N*-Boc protected *ortho*-



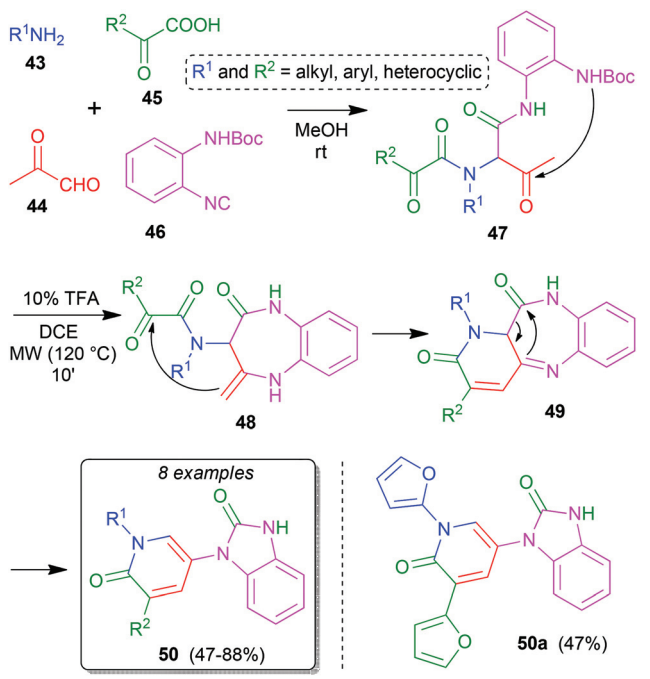
Scheme 8 Synthesis of the *N*-heterocyclic α,β-unsaturated-γ-lactams **36** *via* an Ugi-4CR/intramolecular Michael addition.



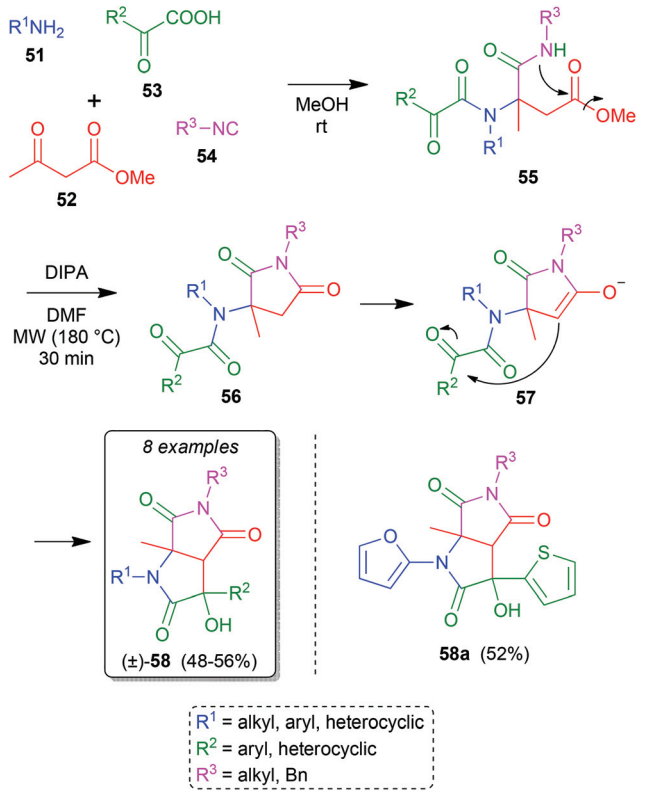
Scheme 9 Synthesis of the furyl-pyrrolidinones **42a–b** *via* a cyanoacetic acid-based Ugi-4CR/base-assisted intramolecular cyclization.

amino phenyl isocyanide (**46**) in MeOH at room temperature to give the Ugi-adducts **47**, which after a domino aldol sequence afforded the products **50** in 47–88% yields (Scheme 10).[38] As a selected example, the *tetra*-heterocycle **50a** is shown. As can be seen, the furyl moieties can be used for further transformations, such as Diels–Alder cycloadditions, to increase the molecular complexity.

In the same report, a series of novel fused-type bis-pyrrolidinones were synthesized as a racemic mixture *via* a smart modification of the methodology reviewed above. Thus, amines **51** were combined sequentially with the acetoacetic methyl ester (**52**), oxalyl-type carboxylic acids **53**, and the isocyanides (**54**) in MeOH at room temperature to give the Ugi-adducts **55**, which after a domino aldol sequence allowed the synthesis of the products (±)-**58** in 48–56% yields (Scheme 11).[38] As selected example, the *tetra*-heterocycle **58a** is shown. As can be seen, the furyl and thienyl moieties can be used also for further transformations.



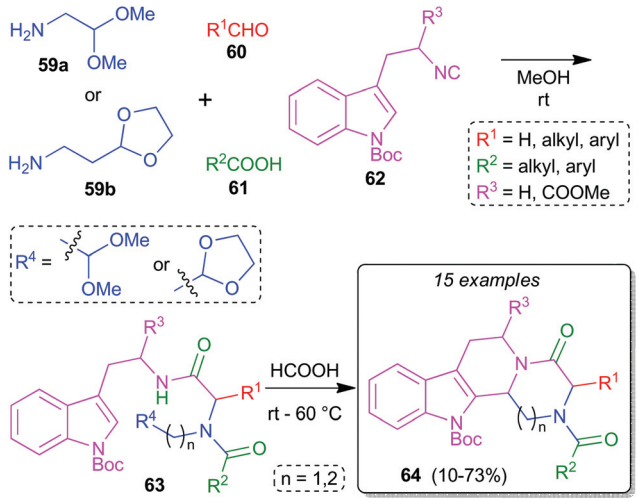
Scheme 10 Synthesis of the polyheterocycles **50** *via* a domino Ugi-4CR/aldol strategy.



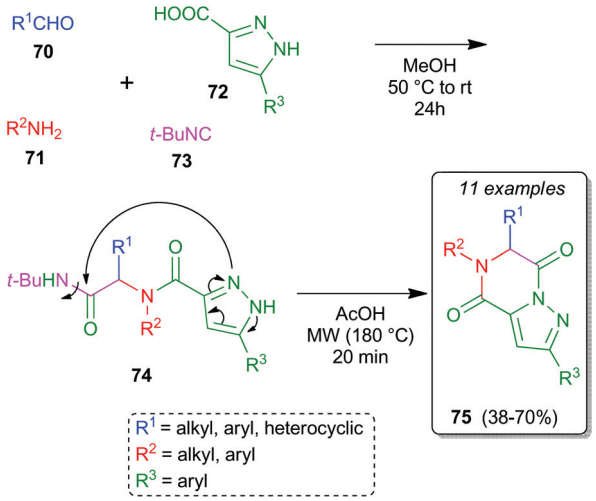
Scheme 11 Synthesis of the polyheterocycles **58** *via* a domino Ugi-4CR/aldol strategy.

In 2009, A. Dömling developed an Ugi-4CR/Pictet–Spengler strategy toward a variety of indole-based polyheterocycles. Thus, the masked amines **59** were combined sequentially with the aldehydes **60**, carboxylic acids **61**, and the tryptamine-like isocyanide **62** in MeOH at room temperature to give the Ugi-adducts **63**. Then, formic acid was added to unprotect the aldehyde from the amine moiety and to trigger the Pictet–Spengler cyclization to give the desired polyheterocycles **64** in 10% to 73% yields (Scheme 12).[39] It is noteworthy that when R^3 was a methyl ester and R^1 was hydrogen, mixtures of diasteroisomers were obtained that were favorable to the *trans* form in ratios from 1.6 : 1 to 2.4 : 1.

A very interesting variant of the above-reviewed methodology was developed in 2010 by A. Dömling also; whereby a replacement of the aldehyde and carboxylic acid reagents by a bifunctional reagent allowed the construction of complex linear polyheterocycles. Thus, the masked amine **65** reacted together with 2-formyl benzoic acid (**66**) and the tryptamine-

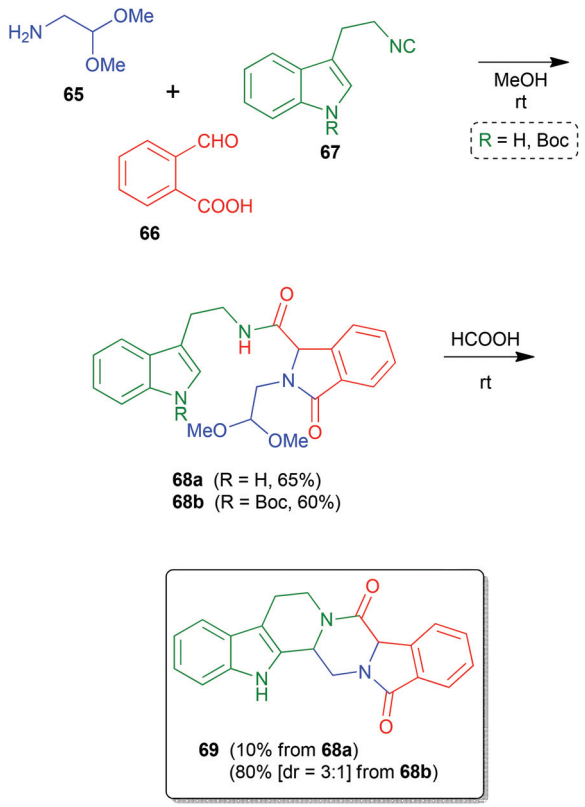


Scheme 12 Synthesis of the indole-based polyheterocycles **64** *via* an Ugi-4CR/PS cyclization.



Scheme 14 Synthesis of the polyheterocycles **75** *via* an Ugi-4CR/intramolecular *N*-acylation using convertible isocyanides.

like isocyanides **67** in MeOH at room temperature to construct the Ugi-adducts **68**. Then, formic acid was added to unprotect the aldehyde from the amine moiety and to trigger the Pictet–Spengler sequence to give the polyheterocycles **69** in 10% to 80% yields (Scheme 13).[40] Motivated by these results, more analogs of **69** were synthesized by using a variety of bifunctional (carbonyl-carboxylic acid) reagents. This is a clear example that MCR/ionic-cascade-based strategies can be used successfully toward structural diversity (DOS approach).

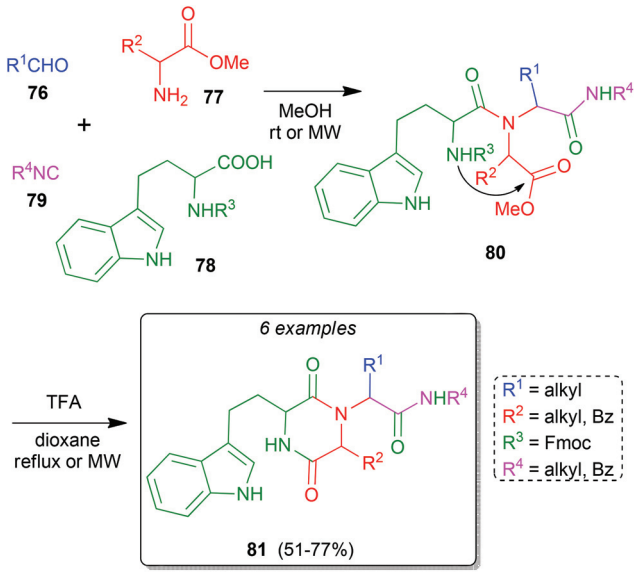


Scheme 13 Synthesis of the bis-indole-based polyheterocycles **69** *via* an Ugi-3CR/PS reaction.

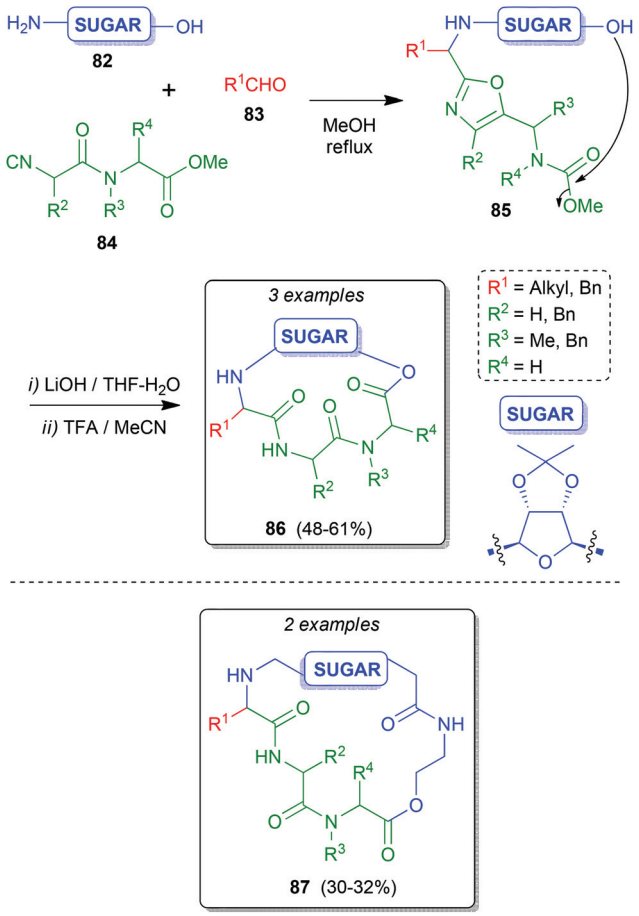
In 2009, M. Krasavin reported a new strategy to construct the pharmacologically important 5,6-dihydropyrazolo[1,5-*a*] pyrazine-4,6-dione system *via* an Ugi-4CR/intramolecular *N*-acylation. Thus, the aldehydes **70** were combined sequentially with the amines **71**, pyrazolo-containing carboxylic acids **72**, and the *tert*-butyl isocyanide (**73**) in methanol to give the Ugi-adducts **74**, which after treatment using acetic acid gave the polyheterocycles **75** in good to excellent yields (38–70%) using MW as a heat source (Scheme 14).[41] As seen, the key idea behind this valuable strategy was the use of a convertible isocyanide (*t*-BuNC) to form a leaving group to trigger the final cyclization step *via* intramolecular *N*-acylation.

In 2008, L. A. Wessjohann reported a pioneering work for the synthesis of indole and piperazin-dienone-based spaced-type polyheterocycles *via* an Ugi-4CR/ionic intramolecular cyclization. Thus, the aldehydes **76** were combined with the α-amino-esters **77**, *N*-Fmoc-protected tryptophan (**78**), and the isocyanides **79** using MeOH as a solvent and conventional or MW heating conditions to give the Ugi-adducts **80**. Then, strong acidic conditions (TFA) were used to trigger the 6-*exo-trig* cyclization to construct the polyheterocycles **81** in 51% to 77% yields (Scheme 15).[42] It is noteworthy that compounds **81** have potential application in medicinal chemistry because they are structural analogs of Tryprostatin B and Fumitremorgin B, which are potent inhibitors of mammalian cell cycle progression at the G2/M transition.

In 2007, J. Zhu developed an exquisite 3-CR/acid-triggered macrocyclization toward a variety of macrocyclic sugar-amino-acid- or amino-alcohol-containing polyheterocycles. Thus, the stepwise-prepared bifunctional (amino-alcohol) sugars **82** were combined sequentially with the aldehydes **83** and the ring-chain tautomerizable isocyanides **84** (prepared from amino acids) in methanol at reflux to give the corresponding 5-amino



Scheme 15 Synthesis of the indole and piperazin-dienone-based polyheterocycles **81** *via* an Ugi-4CR/ionic intramolecular cyclization.



Scheme 16 Synthesis of the sugar-based macro-polyheterocycles **86** and **87** *via* an Ugi-3CR/acid-assisted macrocyclization.

oxazoles **85**, which after treatment with LiOH and TFA triggered a domino macrocyclization toward the sugar-containing macrocyclic polyheterocycles **86** and **87** in 30% to 61% yields (Scheme 16).[43] The utility of ring-chain tautomerizable isocyanides toward diverse macrocyclic polyheterocycles is noteworthy. Indeed, J. Zhu and H. Bienaymé are the pioneers behind the use of ring-chain taumerizable isocyanides in MCRs from the early 2000s.[44] Besides, L. A. Wessjohann reviewed MCR/macrocyclization-based strategies toward macrocycle diversity up to 2009.[45]

As the last example of an I-MCR/ionic-based strategy herein reviewed, in 2007, L. El Kaïm reported a pioneering work about the use of α-ketoacids toward polyheterocyclic 2,5-diketopiperazines, which are very important frameworks in medicinal chemistry.[46]

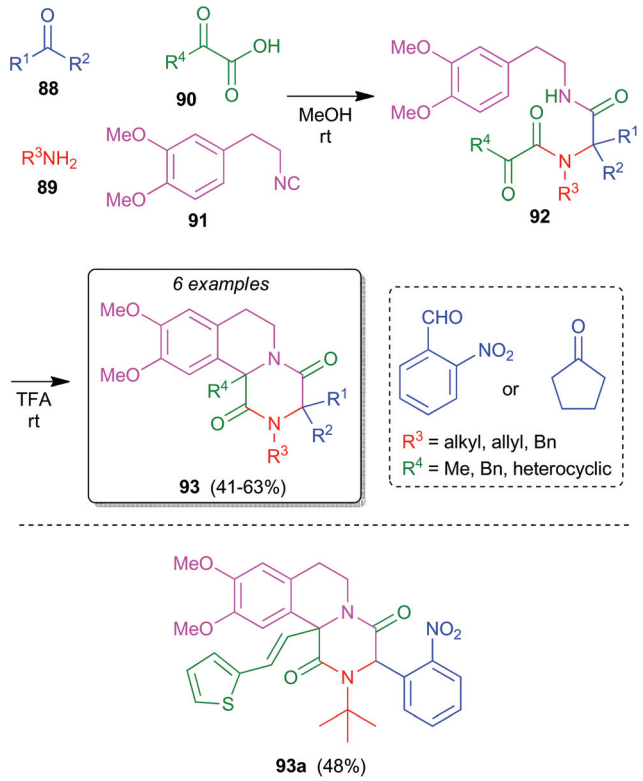
Thus, the aldehydes or ketones **88** were combined sequentially with the amines **89**, the α-ketoacids **90**, and 3,4-dimethoxyphenethyl isocyanide (**91**) in MeOH at room temperature to give the Ugi-adducts **92**. Then, TFA was added to trigger the Pictet–Spengler cyclization to construct the polyheterocycles **93** in 41% to 73% yields (Scheme 17).[47]

4 Synthesis of polyheterocyles *via* I-MCR/metal-catalyzed cyclizations

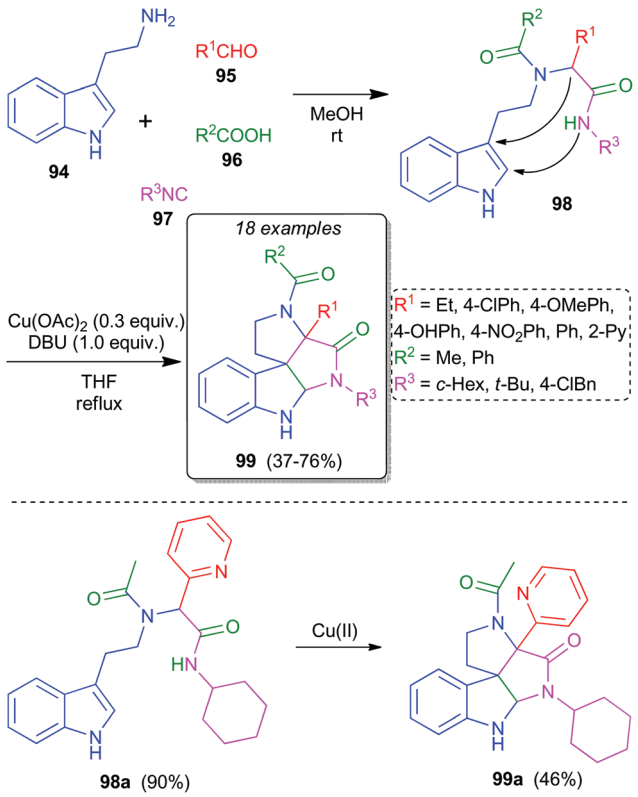
Metal-catalyzed post-I-MCR methods toward a variety of heterocycle-containing products were summarized masterfully by T. J. J. Müller (up to 2005)[48] and E. Van der Eycken (up to 2015).[49] Thus, in this chapter, three representative examples of the synthesis of 'polyheterocyles' *via* I-MCRs/metal-catalyzed cyclizations are described. In 2011, L. Grimaud, L. D. Miranda and L. El Kaïm synthesized a variety of indole-based complex polyheterocycles containing two sp^3-quaternary carbon atoms *via* an Ugi-4CR/Cu(II)-catalyzed oxidative cyclization at the peptidyl position. Thus, tryptamine (**94**), aldehydes **95**, carboxylic acids **96**, and isocyanides **97** were combined sequentially in MeOH at room temperature to give the Ugi-adducts **98** in 83% to 94% yields, which were cyclized to afford the polyheterocycles **99** in 37% to 76% yields (Scheme 18).[50]

The product **99a** (prepared from **98a**) was selected to be shown in Scheme 18 because is a tetra-heterocycle. As seen, the scope and robustness of this methodology was evaluated by synthesizing some bigger polyheterocycles, like **99a**. It is noteworthy that five of the products **99** were synthesized in a one-pot manner coupling both sequential processes (Ugi-3CR and Cu(II) catalyzed cyclization) in the same flask. Copper(II) is one of the greenest metals for catalysis in organic chemistry, and which can be useful to construct polyheterocyclic architectures with potential applications in medicinal chemistry.[51] Another interesting fact is that when an aliphatic aldehyde was used (EtCHO), the cyclization process did not occur.

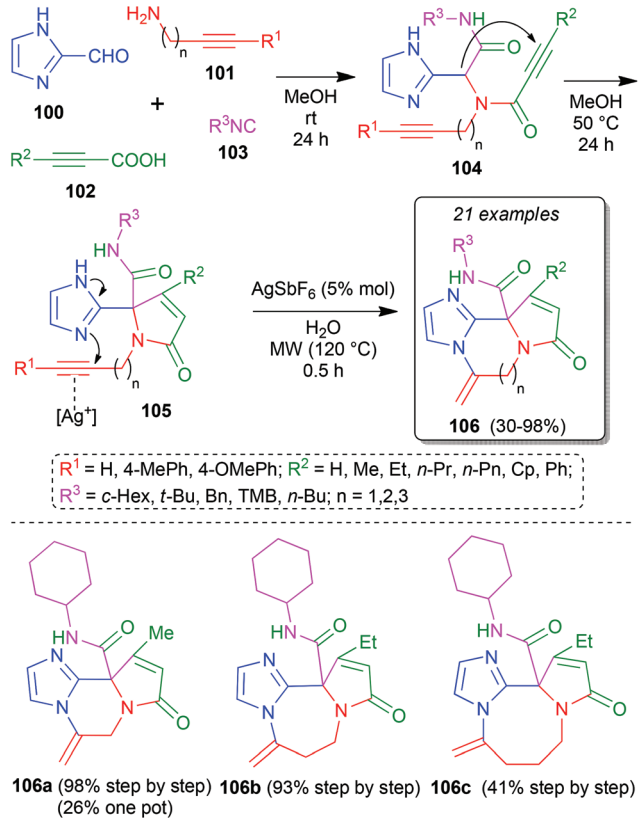
In 2016, E. Van der Eycken reported a diversity oriented synthesis of novel tris-heterocyclic imidazo-pyrrolo-(pyrazines/diazepines/diazocines) *via* a domino Ugi-4CR/Michael/Ag(I)-catalyzed heteroannulation process. Thus, the imidazole-2-carbal-



Scheme 17 Synthesis of the polyheterocycles **93** *via* Ugi-4CR/PS cyclization.



Scheme 18 Synthesis of the indole-based polyheterocycles **99** *via* Ugi-3CR/Cu(II) catalyzed oxidative cyclization.

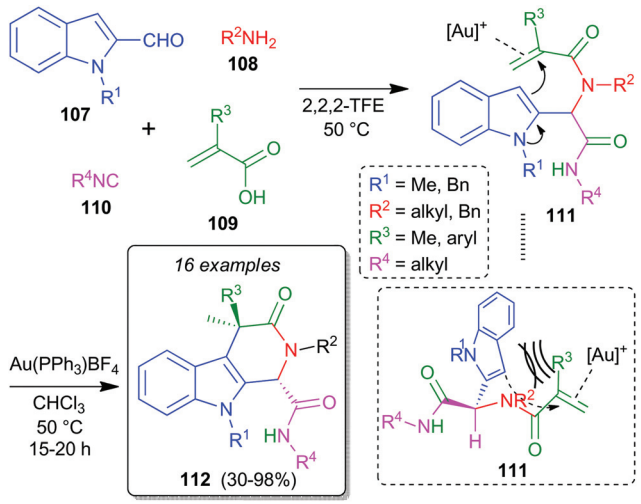


Scheme 19 Synthesis of the fused-type polyheterocycles **106** *via* a Ugi-4CR/Ag(I)-catalyzed domino-heteroannulation.

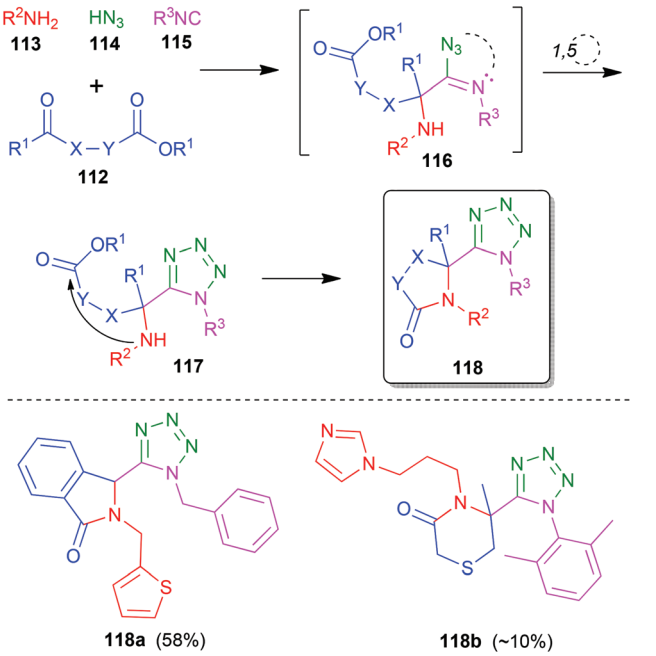
dehyde (**100**) was combined sequentially with the alkynyl amines **101**, α,β-alkynyl carboxylic acids **102**, and the corresponding isocyanides **103** in MeOH at room temperature for 24 h to afford the Ugi-adducts **104**, which were cyclized *via* a 5-*endo-dig* Michael addition to access the imidazo-pyrrolidinone type bis-heterocycles **105**,[35] which was cyclized *via* a 6-*exo-dig* Ag(I)-catalyzed heteroannulation to construct the complex polyheterocycles **106** (Scheme 19).[52]

It is important to highlight that the polyheterocycle **106a** was synthesized in a one-pot manner by coupling sequentially the three processes in the same flask. However, the overall yield was decreased to 26%. As seen, one of the goals of the I-MCR-based methodologies toward polyheterocycles is to carry out all the synthetic strategy in a one-pot manner to decrease the use of solvents and workup procedures and to gain a time-saving.

In 2015, D. D. Vachhani and E. Van der Eycken reported an elegant remote amide moiety-controlled Au(I)-catalyzed stereoselective hydro-heteroarylation strategy as a post-Ugi cyclization toward a variety of biologically important tetrahydro-β-carboline-type polyheterocycles. Thus, indole-2-carbaldehydes **107**, amines **108**, atropic acids analogs **109**, and the corresponding isocyanides **110** were combined sequentially in 2,2,2-trifluoroethanol at 50 °C to give the indole-containing Ugi-adducts **111**, which were then treated with 5% mol of freshly prepared $Au(PPh_3)BF_4$ in $CHCl_3$ at 50 °C for 15 to 20 h



Scheme 20 Stereoselective synthesis of the 1,2,3,4-tetrahydro-β-carboline-type polyheterocycles **112** *via* an Ugi-4CR/Au(I)-catalyzed hydro-heteroarylation.



Scheme 21 Synthesis of the tetrazole-containing polyheterocycles **118** *via* Ugi-azide/further cyclization.

to afford the products **112** in 30% to 98% yields (Scheme 20).[53] It is noteworthy that all the attempts to use *N*-unprotected indole, pyrrole, benzofurane, and benzothiophene instead of a protected indole as pivotal heterocycles for the heteroarylation process proved unsuccessful. As seen, the role of the acrylamide substituent (R^3) was crucial to direct the indole 6-*exo-trig* attack (cyclization) to the more hindered α-position of the alkene-Au(I) coordinated site. As seen, the three examples of metal-catalyzed post I-MCR strategies toward polyheterocycles described above used Cu(I), Ag(I), and Au(I). However, there are reports describing the use of other transition metals.[49]

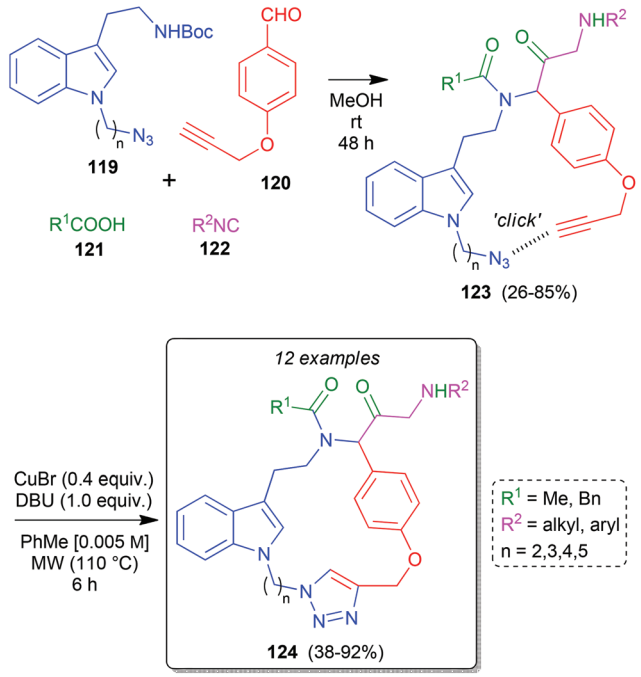
5 Synthesis of polyheterocycles *via* I-MCR/pericyclic cyclizations

Pericyclic reactions (electrocyclizations, cycloadditions and σ-rearrangements) have been used also as post I-MCR transformations toward heterocycles, and a little less frequently, toward polyheterocycles. Of course, this approach (I-MCR/pericyclic cyclization) is an opportunity area for further investigations toward novel polyheterocycle-based products with potential application in medicinal chemistry due to the wide substrate scope that can be reached easily and quickly.

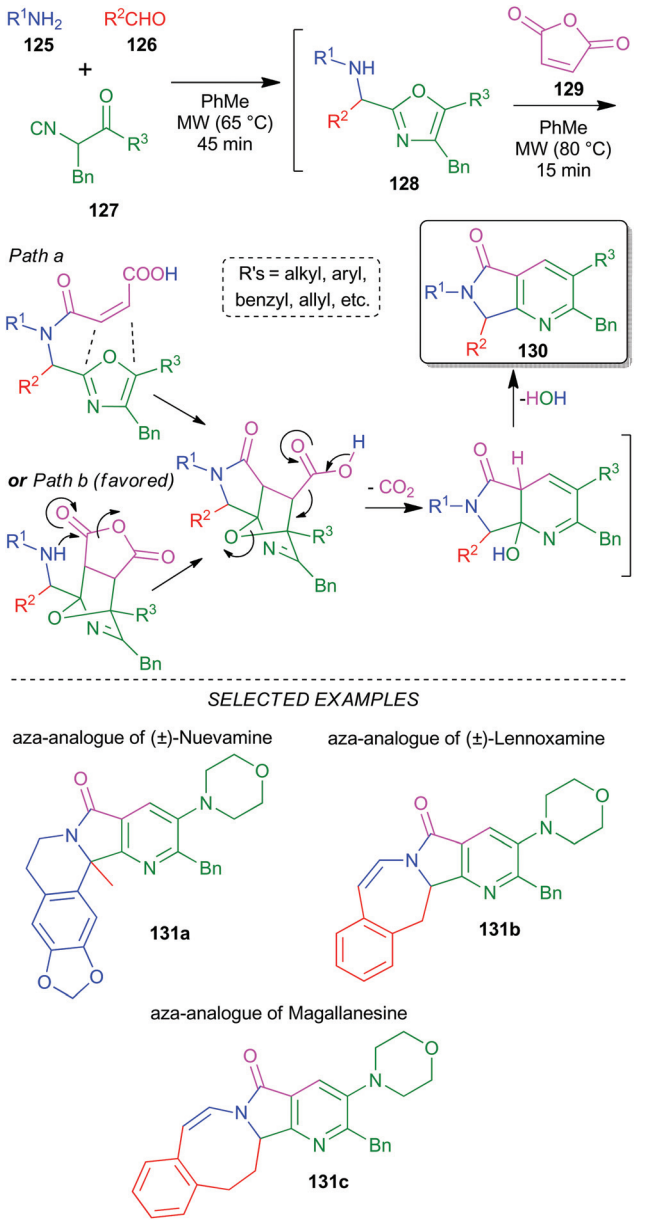
As an example, in 2013, C. Hulme reported the synthesis of various 1,5-disubstituted-tetrazole-based polyheterocycles coupled to substituted lactams in a bound manner using as a key process an Ugi-azide reaction, which is a variant of the classic Ugi reaction that involves the use of hydrazoic acid (commonly generated *in situ* by proton exchange between the protic solvents or water and $TMSN_3$ or NaN_3) instead of carboxylic acids.[54] It is noteworthy that in 2017, R. Gámez-Montaño investigated experimentally the Ugi-azide reaction mechanism.[55] Thus, the carbonyl-containing compounds **112**, amines **113**, hydrazoic acid (**114**), and isocyanides **115** were reacted together to give the intermediates **116**, which by a thermal 1,5-electrocyclization process afforded the lactam-containing 1,5-disubstituted-tetrazoles **117**. These latter compounds were the direct precursors of the tetrazole-lactam-containing polyheterocycles **118** (Scheme 21). As selected examples, the products **118a** (58%) and **118b** (10% overall) are shown, which contain three heterocycles (interesting for medicinal chemistry) embedded in the same molecule.

It is noteworthy that C. Hulme, L. El Kaïm, S. Marcaccini, A. Dömling, R. Gámez-Montaño, and A. Maleki[56] are considered the pioneers behind Ugi-azide-based methods toward heterocycles and polyheterocycles. In the same context, some Passerini-azide based methods toward some polyheterocycles have been reported very recently.[57] Finally, the Groebke–Blackburn–Bienaymé reaction (which involves a [4 + 1] dipolar cycloaddition) was used by C. Hulme to construct a variety of novel nitrogen-enriched polyheterocycles.[58]

In addition to electrocyclizations, cycloadditions have been used successfully as post I-MCR transformations to construct a wide variety of interesting polyheterocyclic systems. For example, in 2015, L. D. Miranda reported an exquisite Ugi-4CR/microwave-assisted azide–alkyne 1,3-dipolar cycloaddition (CuAAC)[59] method toward a series of new macrocycles containing indole and 1,2,3-triazole heterocyclic systems embedded in the same complex molecules linked by a peptoid moiety. Thus, the orthogonal-bifunctional tryptamine-azides **119** (synthesized from *N*-Boc-tryptamine) were combined sequentially with the alkyne-containing benzaldehyde **120**, carboxylic acids **121**, and the corresponding isocyanides **122** in MeOH as a solvent at room temperature for 48 h to afford the Ugi-adducts



Scheme 22 Synthesis of the macrocyclic polyheterocycles **124** *via* Ugi-4CR/click process.



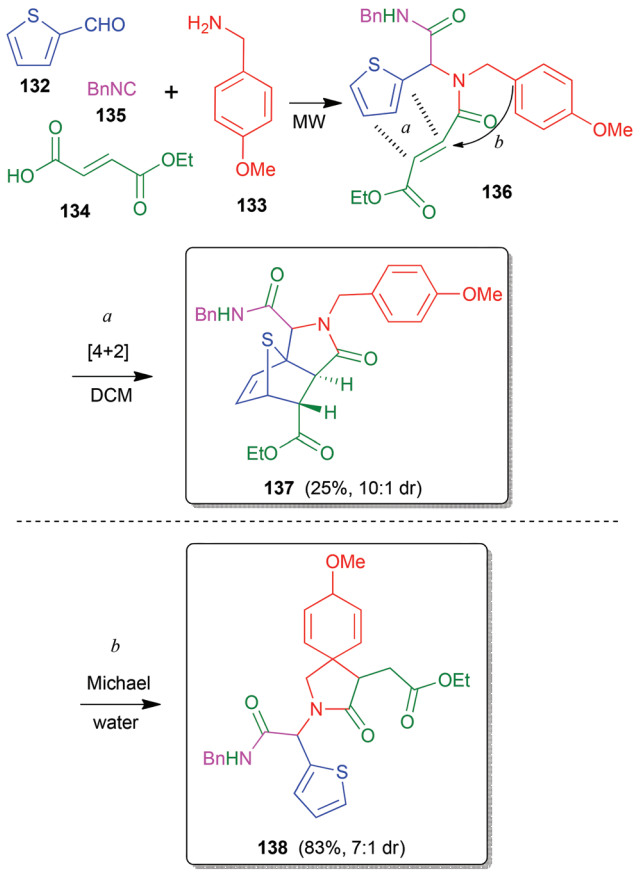
Scheme 23 Diversity oriented synthesis of the pyrrolo[3,4-*b*]pyridin-5-one based polyheterocycles **131** *via* Ugi-3CR/aza Diels–Alder cycloaddition/further cyclizations.

123 in 26% to 85% yields. Then, these latter compounds reacted with 0.4 equiv. CuBr and 1.0 equiv. DBU in toluene [0.005 M] at 110 °C (MW) for 4 h to give the desired macropolyheterocycles **124** in 38% to 92% yields (Scheme 22).[60]

As part of our ongoing research program to develop short, efficient and versatile I-MCR/pericyclic cyclization-based methodologies toward linear polyheterocyclic systems, we synthesized a series of novel aza-analogs of natural alkaloids, like (±)-Nuevamine, (±)-Lenoxamine, and Magallanesine. Our most recent results are herein summarized.

Thus, the amines **125** were combined sequentially with aldehydes **126** and the chain-ring tautomerizable isocyanides **127** to afford the 5-aminooxazoles **128** *via* a MW-assisted Ugi-3CR. Then, maleic anhydride (**129**) was *in situ* added to construct the pyrrolo[3,4-*b*]pyridin-5-ones **130** *via* a triple process involving an aza Diels–Alder cycloaddition, a *N*-acylation, and a further aromatization. It is noteworthy that the conversion of **128** to **130** can follow two reaction routes: (a) intermolecular *N*-acylation/intramolecular DA cycloaddition/aromatization, or (b) intermolecular DA cycloaddition/intramolecular *N*-acylation/aromatization (Scheme 23). DFT-based computational calculations suggested that (b) is the most kinetic and thermodynamically *via*ble reaction pathway due to the stereoelectronic effects coming from the 5-aminooxazole moiety and a sufficient GAP to carry out the aza Diels–Alder cycloaddition before the *N*-acylation step.[61] Finally, as previously mentioned, the one-pot Ugi-3CR/(intermolecular aza DA cycloaddition/intramolecular *N*-acylation/aromatization) process was combined successfully with further cyclization methods, like free-radical mediated,[62] Pummerer,[63] Pictet–Spengler,[64] and Pomeranz-Fritsch[65] cyclizations, toward the synthesis of a variety of fused-type linear polyheterocycles **131** (Scheme 23). In the same context, we developed an oxidative[66] and a repetitive version[67] of the methodology used in Ugi-3CR/aza Diels–Alder/*N*-acylation/aromatization toward aza-analogs of the natural alkaloid (±)-Nuevamine and the hexamethylene-bis-(3-pyridine)amide (HMBPA), respectively.

P. R. Andreana synthesized tricyclic- and spiro-polyheterocycles *via* a combination of an Ugi-4CR with either, Diels–Alder cycloaddition or intramolecular Michael addition, depending on the solvent used. Thus, 2-thiophenyl carbaldehyde (**132**) was combined sequentially with the 4-methoxy-



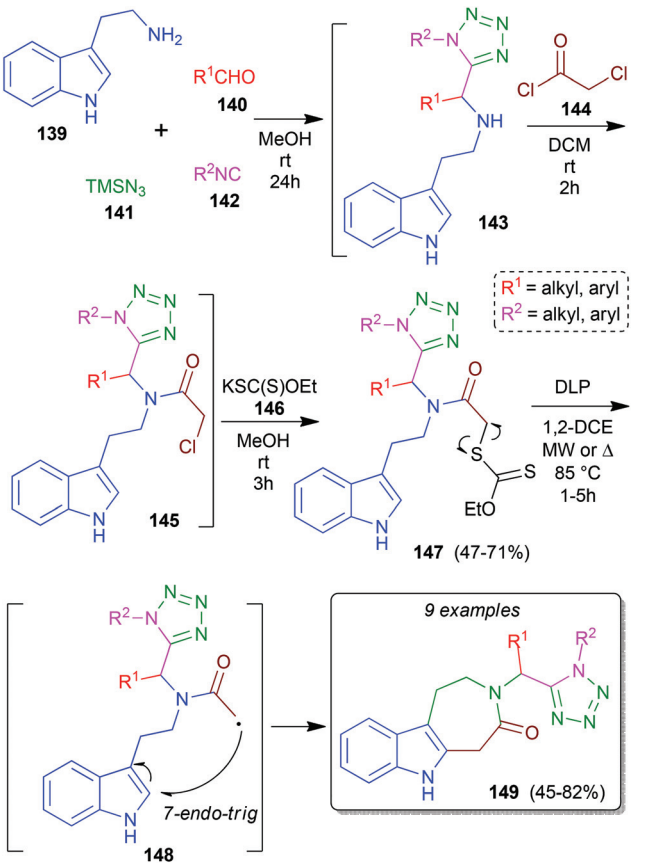
Scheme 24 Synthesis of the fused-type tricyclic polyheterocycle **137** *via* Ugi-4CR/intramolecular Diels–Alder cycloaddition and the spirocyclic polyheterocycle **138** *via* Ugi-4CR/intramolecular Michael addition.

benzyl amine (**133**), mono-ethyl ester fumaric acid (**134**), and the benzyl isocyanide (**135**) to give the Ugi-adduct **136** in a quantitative yield. Then, the intermediate **136** underwent an intramolecular Diels–Alder cycloaddition to give the polyheterocycle **137** in a 25% yield as a mixture of diasteroisomers in a 10 : 1 ratio using the non-polar DCM as a solvent. Moreover, when water was used as the solvent, the product was the spiro[cyclohexendienone-3,3′-pyrrolidinone] **138** in an 83% yield as a mixture of diasteroisomers in a 7 : 1 ratio *via* an intramolecular Michael addition (Scheme 24).[68]

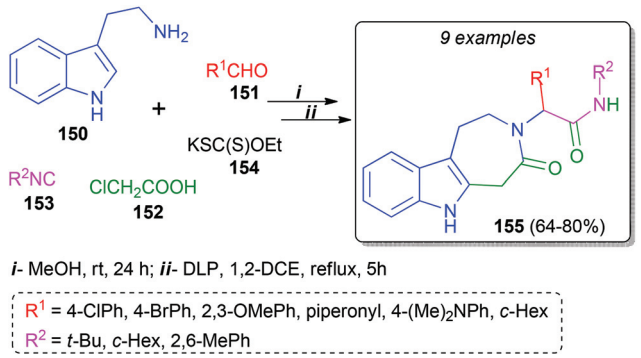
6 Synthesis of polyheterocycles *via* I-MCR/free-radical-mediated cyclizations

I-MCR/free-radical-mediated cyclization-based strategies are powerful tools toward molecular complexity and, hence, they have been used to successfully synthesize polyheterocyclic compounds. However, most reports describing the use of these strategies involve the preparation of *mono*-heterocyclic compounds. On this basis, it is noteworthy that the combination of I-MCRs with free-radical-based cyclizations is also an opportunity area to populate the chemical space. In this context, we review some representative examples to show the potential of this synthetic strategy for the synthesis of polyheterocycles of high interest in medicinal chemistry.

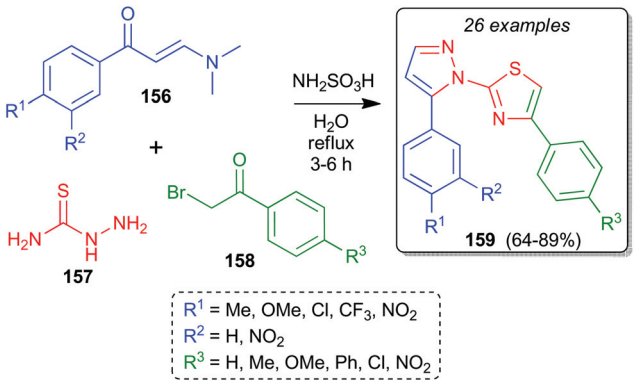
In 2013, R. Gámez-Montaño reported the synthesis of nine novel tris-heterocyclic-type 3-tetrazolyl-azepino[4,5-*b*]indol-4-ones *via* a sequential combination of a one-pot process (Ugi-azide/*N*-acylation/S_N2)/xanthate free-radical-mediated cyclization. Thus, tryptamine (**139**) was combined sequentially with the aldehydes **140**, azidotrimethylsilane (**141**), and the isocyanides **142** using methanol as the solvent at room temperature for 24 h to give the corresponding indole-tetrazoles **143**, which underwent a *N*-acylation with chloroacetyl chloride **144** to give the chlorides **145**. These latter compounds afforded the bis-heterocyclic xanthates **147** in 47% to 71% yields after a S_N2 reaction with potassium ethyl xanthogenate salt **146**. Then, DLP was added portion-wise in 1,2-dichloroethane at 85 °C (using conventional or MW heating modes) to generate the carbamoylmethyl free-radicals **148**, which performed a highly favored 7-*endo-trig* cyclization to construct the azepino[4,5-*b*]indol-4-one heterocyclic system present in the final tris-heterocycles **149** with yields of 45% to 82% (Scheme 25).[69]



Scheme 25 Synthesis of the 3-tetrazolyl-azepino[4,5-*b*]indol-4-ones **148** *via* a one-pot (Ugi-azide/*N*-acylation/S_N2)/xanthate free-radical-mediated cyclization.



Scheme 26 Synthesis of the 3-acetamide-azepino[4,5-*b*]indol-4-ones **155** *via* a one-pot (Ugi-4CR/S_N2)/xanthate free-radical-mediated cyclization.



Scheme 27 Synthesis of the pyrazolyl-thiazole bound-type bis-heterocycles **159** *via* an '*in water*' direct non-isocyanide-based 3-CR.

More recently R. Gámez-Montaño and J. Robles synthesized a series of nine new bis-heterocyclic analogs of the compounds **149** based on the non-classic bioisosterism relationship between 1,5-disubstituted tetrazoles and the *cis*-amide bond of peptides. Thus, they modified the methodology described above to result in a combination of a one-pot (Ugi-4CR/S_N2)/free-radical-mediated cyclization from the tryptamine (**150**), aldehydes **151**, chloroacetic acid (**152**), isocyanides **153**, and the potassium ethyl xanthogenate salt **154** to afford the 3-acetamide azepino[4,5-*b*]indol-4-one type bis-heterocycles **155** in 64% to 80% overall yields (Scheme 26).[70] It is noteworthy that both series (**149** and **155**) were *in vitro* tested as 5-Ht_6 receptor ligands.

Both the synthetic strategies reviewed above involved pericyclic reactions (1,5-electrocyclization to construct the tetrazole ring) and ionic reactions (*N*-acylation and S_N2) as post I-MCR transformations. However, the final and key step to construct the polyheterocycles was a free-radical mediated cyclization, which used a xanthate functional group and DLP as both a free-radical initiator and oxidant.[71] Other reagents having the same functionality as the AIBN/tributyltin hydride system, such as Et_3B or SmI_2, have also been used to synthesize polyheterocyclic compounds.[72]

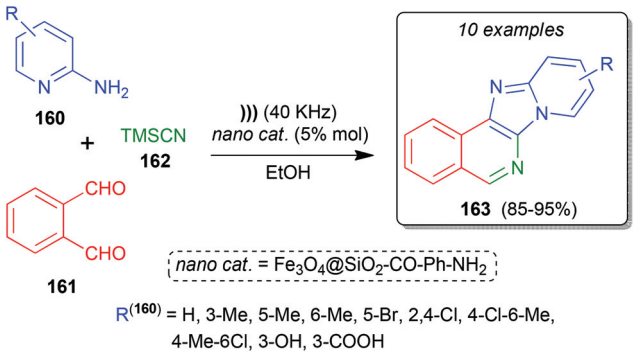
7 Miscellaneous

7.1 Synthesis of polyheterocyles *via* non-isocyanide-based MCRs

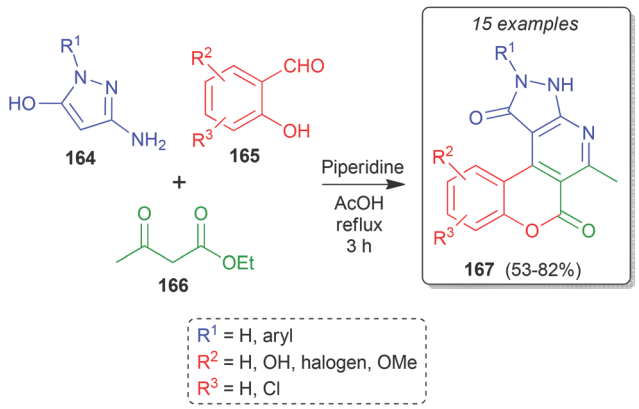
A considerably smaller number of reports describing the synthesis of polyheterocycles *via* non-isocyanide-based MCRs (with respect to I-MCR-based ones) have been developed over many years. However, they mostly adopted the approach of 'heterocyclic chemistry'. Thus, we herein show a few representative methodologies toward polyheterocycles of interest in medicinal chemistry.

H. M. Meshram and A. Kamal reported in 2017 an '*in water*' synthesis of 26 new pyrazolyl-thiazoles *via* a sulfamic acid-catalyzed non-isocyanide-based three-component reaction and *in vitro* assays against three human cancer cell lines: A549 (lung cancer), MCF-7 (breast cancer), and HeLa (cervical cancer). Thus, the β-aminocarbonylic compounds **156** were combined sequentially with the thiosemicarbazide (**157**), *para*-substituted bromo-acetophenones **158** and sulfamic acid in water under reflux for 3 to 6 h, obtaining the polyheterocyclic products **159** in 64% to 89% yields (Scheme 27).[73] It is noteworthy to highlight the good substrate scope and the compatibility of MCR-based processes with green conditions, such as the use of water as the solvent.

Continuing with the green approach of non-isocyanide-based MCRs, in 2017, A. Maleki reported an ultrasound-assisted 3CR method toward ten fused-type polyheterocycles using the nanomagnetic catalyst Fe_3O_4@SiO_2-CO-Ph-NH_2. Thus, the series of polysubstituted 2-aminopyridines **160** were combined sequentially with the *ortho*-phtalaldehyde (**161**) and the TMSCN (**162**) in ethanol as the solvent to access the novel pyridoimidazo-isoquinolines **163** in 85% to 95% yields (Scheme 28).[74] This methodology can be considered as a non-isocyanide-based version of the Groebke–Blackburn–Bienaymé reaction, which is a very useful I-MCR-based strategy toward the synthesis of fused-type polyheterocyclic compounds.



Scheme 28 Synthesis of the fused polyheterocycles **163** *via* a nano-catalyzed and sonicated 3-CR.



Scheme 29 Synthesis of the polyheterocycles **167** *via* a non-isocyanide-based 3-CR.

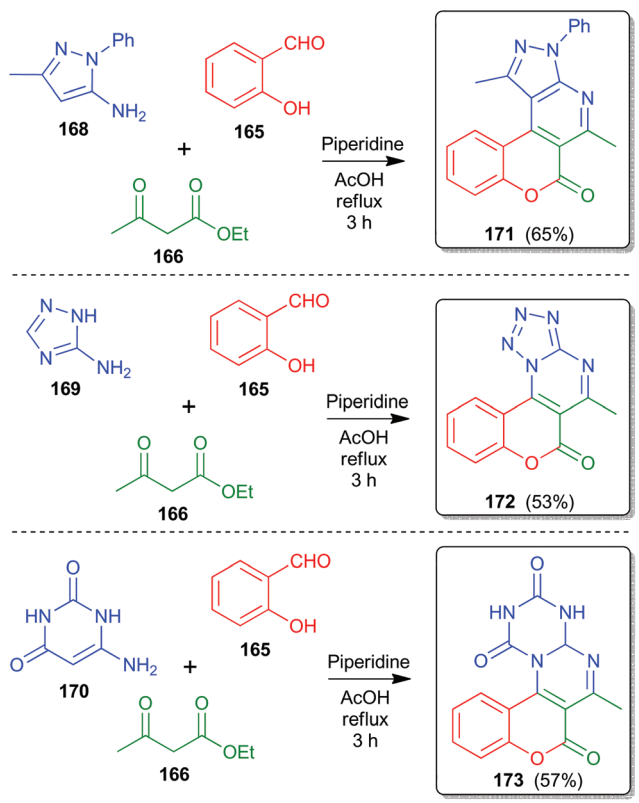
In 2011, I. V. Magedov synthesized a series of polyheterocycles *via* a non-isocyanide-based 3CR and performed *in vitro* studies against *Staphylococcus epidermis* and *Staphylococcus aureus*, obtaining promising values of MIC. Thus, the 3-aminopyrazol-5-ones **164** were reacted with substituted salicylic aldehydes **165** and the ethyl acetoacetate (**166**) in acetic acid as a solvent at reflux for 3 h to afford the novel 2,3-dihydrochromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-1,6-diones **167** in 53% to 82% yields (Scheme 29).[75]

By using the same methodology, but replacing the 3-aminopyrazol-5-ones **164** by the 5-amino-1-phenyl-3-methylpyrazole (**168**), 3-amino-1,2,4-triazole (**169**), or 6-aminouracyl (**170**), the polyheterocycles **171–173** were synthesized successfully in 65%, 53%, and 57% yields, respectively (Scheme 30).[75]

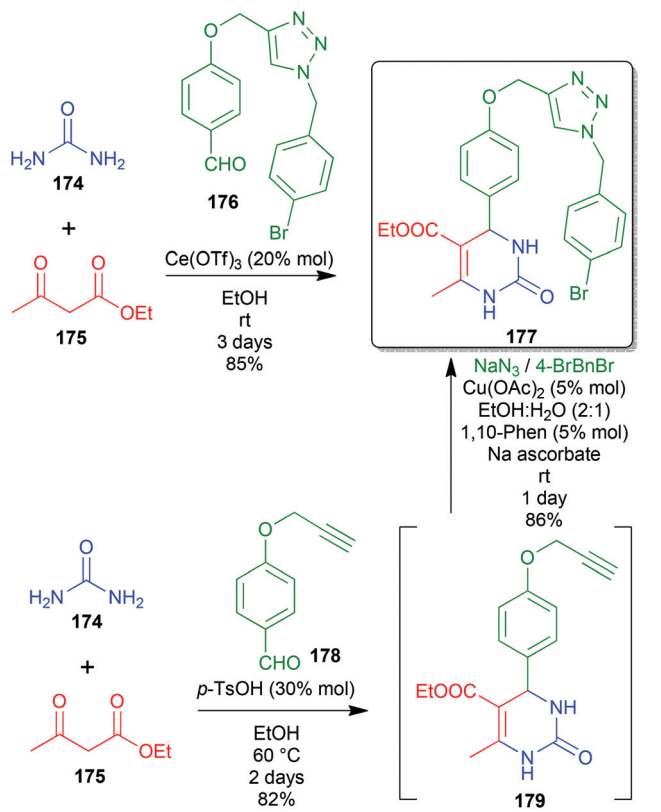
In 2016, G. E. Negrón-Silva reported the use of a Biginelli reaction toward a series of five novel dihydropyrimidinones.[76] One of them was the spaced-type 1,2,3-triazolyl-containing bisheterocycle **177**, which was synthesized by combining urea (**174**) with ethyl acetoacetate (**175**) and the triazolyl-containing benzaldehyde **176** in ethanol at room temperature for 3 days using cerium(III) triflate in substoichiometric amounts (20% mol) to improve the yield (85%) (Scheme 31). As an alternative route toward **177**, the alkynyl-containing benzaldehyde **178** was used instead of **176** to afford the Biginelli-adduct **179** in an 82% yield, which reacted immediately with the 4-bromobenzyl bromide *via* a click[77] Cu(II)-catalyzed azide–alkyne dipolar cycloaddition (CuAAC) to give the polyheterocycle **177** in an 86% yield (Scheme 31).

7.2 Synthesis of polyheterocylic-based natural products *via* MCRs

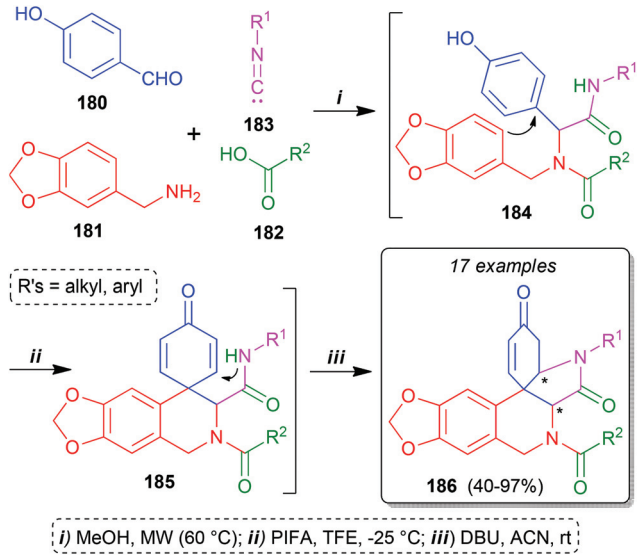
Natural products were the first contact of research with bioactive products and drugs (in the current context).[9] Many of them contain polyheterocycles in their structures.[78] Consequently, MCR-involved synthetic strategies have been



Scheme 30 Synthesis of the polyheterocycles **171–173** *via* a non-isocyanide-based 3-CR.



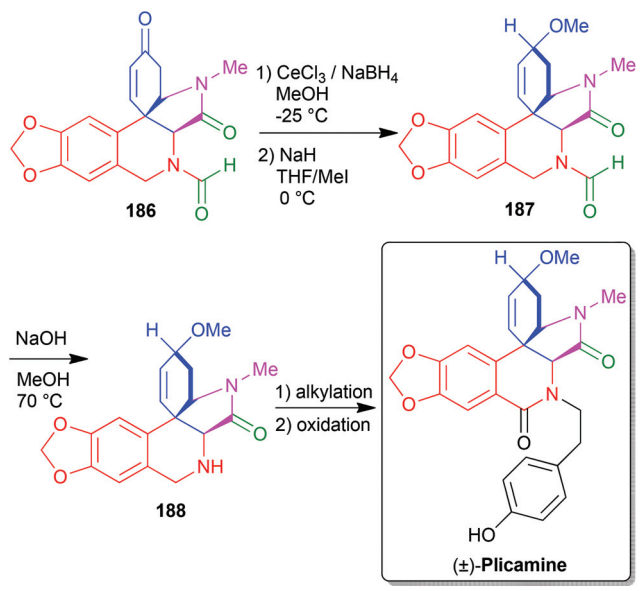
Scheme 31 Synthesis of the spaced-type polyheterocycles **177** *via* an MCR/[2 + 3] dipolar cycloaddition.



Scheme 32 Synthesis of the polyheterocycles **186** *via* an MCR/cascade process.

developed to synthesize both natural products, like polyheterocycles, and their structural analogs due to 'Diversity Oriented Synthesis', 'Combinatorial Chemistry' and 'Target Oriented Synthesis' approaches that can be achieved by using MCRs or their combination with further cyclization processes (*i.e.*, ionic, metal-catalyzed, pericyclic and/or free-radical-mediated cyclizations). Thus, a selected representative example is reviewed to show the potential application of MCRs toward the synthesis of natural products.

In 2016, L. D. Miranda reported the synthesis of 17 new indolo[3,3*a*–*c*]-isoquinolin-3,6-dione-type polyheterocycles *via* a sequential process Ugi-4CR/one-pot (phenolic oxidation/intramolecular coupling). Then, one of these compounds



Scheme 33 Synthesis of the (±)-Plicamine.

allowed the synthesis of the natural product (±)-Plicamine. Thus, the *para*-hydroxyphenol (**180**) was combined sequentially with piperonylamine (**181**), carboxylic acids **182**, and the isocyanides **183** to access the α-substituted bis-amides **184** as Ugi-adducts. Then, these compounds underwent a cascade (dearomative phenolic coupling (**185**)/intramolecular Michael addition) to give the polyheterocycles **186** (Scheme 32).[79]

Then, starting from a polyheterocycle **186** (R^1 = Me; R^2 = H), the (±)-Plicamine was synthesized successfully. Thus, a stepwise sequence reduction-methoxylation (**187**)/*N*-formyl reduction (**188**)/alkylation-oxidation allowed the construction of the targeted polyheterocyclic natural product (Scheme 33).[79]

As seen, an I-MCR (Ugi-4CR) was used to assemble the structural skeleton of the natural product (±)-Plicamine. However, several further steps were required for its formal synthesis. It is important to bear in mind the usefulness of MCR-involved processes for the Target Oriented Synthesis.

8 Conclusions and outlook

Direct MCRs or their combination with further cyclization processes (*via* ionic, metal-catalyzed, pericyclic, and free-radical mediated cyclizations) are powerful synthetic tools toward the rapid access to a wide variety of heterocyclic and polyheterocyclic products with potential application in several fields, mainly in medicinal chemistry. From this latter approach, the interest behind the synthesis of polyheterocycles lies in their ability to contain two or more pharmacophores, which can result in hybrid compounds. The synthesis of polyheterocycles *via* MCRs is an opportunity field to explore and populate the chemical space. In fact, DOS, CC, and TOS approaches toward the synthesis of new/novel polyheterocycles can be achieved by using MCR-involved synthetic procedures. Thus, further efforts to synthesize natural products, bioactive molecules, and pharmaceuticals containing polyheterocycles in their structures need to be investigated. We hope this review covering the progress over the last decade on the synthesis of bis-, tris-, and tetra-heterocycles *via* MCRs can provide new insights for further investigations behind new reactions and/or novel one-pot-based strategies.

Conflicts of interest

There are no conflicts to declare.

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