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Pseudo-multicomponent reactions

Julio C. Flores-Reyes,[a] Vanesa del C. Cotlame-Salinas,[a] Ilich A. Ibarra,[b]* Eduardo González-Zamora[a]* and Alejandro Islas-Jácome[a]*

Classical multicomponent reactions (MCRs) are domino-type one-pot processes in which three or more different reactants are combined sequentially in the same reactor to synthesize compounds containing all or almost all atoms coming from the reactants. Besides, pseudo-MCRs are also domino-type one-pot processes involving combinations of at least three reactants but in which at least one of them takes part in two or more reaction steps. In consequence, the products synthesized through pseudo-MCRs contain also all or almost all atoms but coming from two or more identical reactants. Thus, pseudo-MCRs differ from classical MCRs because the first ones appear to involve an assembly of a higher number of different components than those that are being truly assembled. However, pseudo-MCRs are also useful synthetic tools to generate libraries of complex compounds in few experimental steps, and although the repeated reactants may make them appear less diverse than classical MCRs, this can be offset by the higher number of reactants that can participate in this type of reaction. Overall, there are two types of pseudo-MCRs. The first are those in which the duplicated reagents participate in different steps of the corresponding reaction mechanism. The second kind of pseudo-MCRs are those in which one or more components react simultaneously with a main reagent containing two or more identical functional groups. These latter are known as repetitive pseudo-MCRs. Thus, the aim of the present review is to cover for the first time selected works mainly published in the last two decades about pseudo-MCRs and their repetitive versions toward the synthesis of novel, complex, and highly symmetrical molecules, often including their interesting applications in various fields of science and technology. The manuscript has been categorized considering the number of reagents participating in the corresponding pseudo-MCRs, aiming to give readers novel insights for their future investigations.

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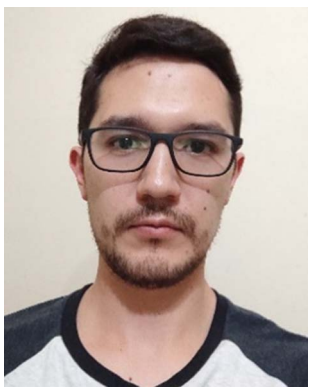
[a]*Departamento de Química, Universidad Autónoma Metropolitana-Iztapalapa, Av. Ferrocarril San Rafael Atlixco 186, Col. Leyes de Reforma 1A Sección, Iztapalapa, Ciudad de México C.P. 09310, Mexico. E-mail: egz@xanum.uam.mx; aij@xanum.uam.mx*

[b]*Laboratorio de Fisicoquímica y Reactividad de Superficies, (LaFReS), Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Circuito Exterior S/N, CU, Coyoacán, Ciudad de México, Mexico. E-mail: argel@unam.mx*



Julio César Flores-Reyes was born in Puebla, México, in 1989. He received his Bsc in biochemical engineering in 2013 from Universidad Autónoma Metropolitana – Iztapalapa (UAM-I). Then, he joined Professor Eduardo González-Zamora's research group in 2018 at UAM-I, where he got his MSc in chemistry in 2020 working on the synthesis of polytetrazole-based ligands toward new MOFs. He is currently enrolled as a PhD student working on multicomponent reactions, optical properties of complex polyheterocycles, and the ESIPT effect.

Vanesa del Carmen Cotlame-Salinas was born in Veracruz, Mexico in 1995. She received her BSc in Industrial Chemistry from the Universidad Veracruzana (UV) in 2019 and obtained her MSc degree in Chemistry from Universidad Autónoma Metropolitana – Iztapalapa (UAM-I) Mexico under the guidance of Professor Eduardo Gonzalez-Zamora in 2022 working on the synthesis of new MOFs to capture CO_2 and other gases with greenhouse effect, and in pseudo-multicomponent reactions. She is currently Professor of Chemistry at the Instituto Tecnológico Superior de Zongolica (ITSZ).

1. Introduction

Synthetic organic chemistry is a rapidly growing field due to the constant research behind new methodologies that minimize the negative environmental impact. All this can be achieved with the guidance of the 12 principles of green chemistry,[1] such as atom economy, less hazardous synthesis, energy efficiency, benign solvents, reduced derivatives, and by-products, among others. Multicomponent reactions (MCRs) are powerful tools leading modern synthetic organic chemistry, which exactly face the environmental challenges with many advantages like straightforward design, and processes requiring less time, resources, and efforts. In these kinds of reactions, all reagents are added sequentially in a single vessel (one-pot procedures) to assemble complex products with high structural diversity *via* a series of chemical transformations without needing solvent shifts, extra workups, or purifications in each reaction step.[2]

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 post-doctoral 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.

Eduardo González-Zamora was born in 1961 in Mexico City. He obtained his PhD in 1998 from Paris XI University in France under the supervision of Professor R. Beugelmans. After one year of a post-doctoral position 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 with Professor J. Zhu. In 2011, he moved to UCLA (USA) as a visiting Professor in the M.A. Garcia-Garibay group. His research interests include synthesis via multicomponent reactions, MOF chemistry, and total synthesis.

Since the first MCR reported by Strecker in the mid-19th century,[3] the impact of MCR-based strategies has been increasing in the last two decades compared to classical techniques, which is reflected in the large amount of publications describing the synthesis of new and complex organic molecules like heterocycles and polyheterocycles, multifunctional peptides, and natural products,[4] that lead to the creation of extensive chemical libraries with potential biological activity, especially desirable for pharmaceutical[5] and agrochemical[6] industries, as well as the design of novel materials.[7] For these reasons, there are many publications about MCRs in books,[8] book chapters,[9] recent reviews,[10] and also in other sources. However, to date, there is no review about pseudo-MCRs.

Pseudo-MCRs (pretended, indented to be, or false MCRs) involve the sequential combination of two or more identical reactants with at least one different reactant in the same reactor. Indeed, pseudo-MCRs are domino-type one-pot process, equal to the classical MCRs, but the stoichiometry for one or more reactants is duplicated, triplicated, or more. It is worth noting that pseudo-MCRs have some limitations in comparison to classical MCRs such as less structural diversification and a relatively low degree of functional flexibility, which are offset by the high molecular symmetry that can be achieved with them.[11] Pseudo-MCRs are divided into two major groups: (1) pseudo-MCRs (Fig. 1a), in which the duplicated, triplicated, or more, reactants participate in different steps of the reaction mechanism, and (2) repetitive pseudo-MCRs (Fig. 1b), in which a main reagent contains two or more identical functional groups to react simultaneously with also two or more reagents, just depending on the number of functional groups that are present in the main reactant. Fig. 1 shows a schematic example of a pseudo-4CR (in representation of any pseudo-MCR), and a repetitive pseudo-5CR, also on behalf of any repetitive pseudo-MCR.

Pseudo-MCRs have led to a variety of compounds with interesting biological properties, especially desirable in pharmaceutical industry. For example, compound **1** exhibited

Alejandro Islas-Jácome was born in Veracruz, México in 1981. He got his BSc in 2005 and PhD in 2011, both in chemistry and under the guidance of Professor Eduardo González-Zamora, in UAM-I, México. Then, he took up a post-doctoral position in the Rocío Gámez-Montaño research group from 2012 to 2016 at the Universidad de Guanajuato, México. He has been a full-time professor since 2017 at the Departamento de Química, UAM-I, México. His research interests include the synthesis of polyheterocycles via multicomponent reactions, click chemistry, reaction mechanisms, optical properties, as well as medicinal chemistry.

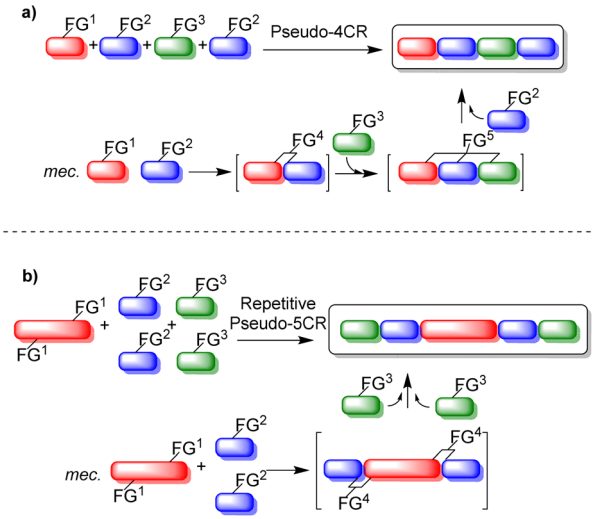


Fig. 1 Schematic representation of (a) pseudo-MCRs, and (b) repetitive pseudo-MCRs.

anticancer activity on a panel of human cell lines,[12a] while compound **2** showed antitubercular activity.[12b] Moreover, other compounds synthesized through pseudo-MCRs were tested due to their potential applications in materials science. For instance, the polyheterocycle **3** exhibited moderate anticorrosive activity,[12c] and the hexasubstituted anilines **4** showed a high fluorescence emission (Fig. 2).[12d]

There are many research programs worldwide in which pseudo-MCRs (or their repetitive versions) play a central role. Thus, the present review covers selected works on the topic, mainly published in the last decade, and focusing on the reaction mechanisms. These were selected based on the number of participating reactants and the complexity of the products. The paper is classified by the number of reagents involved in the corresponding discussed one-pot procedure. It is worthy to note that a colour-key is used to highlight the 'repeated' reagents.

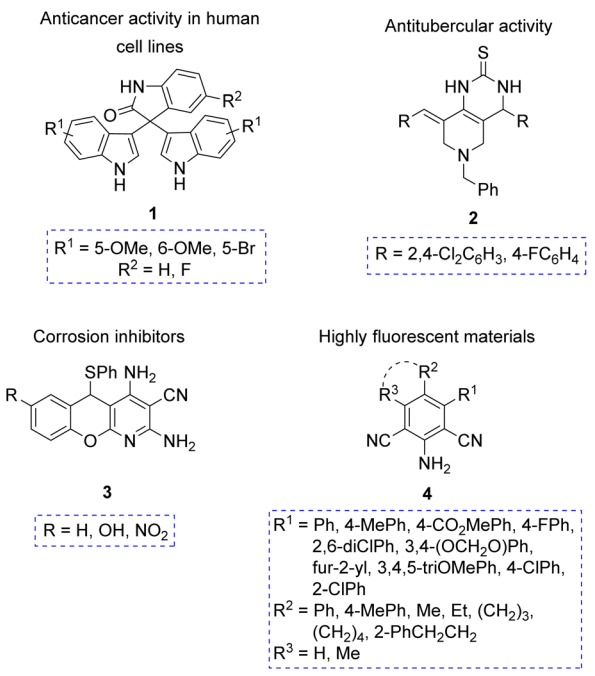
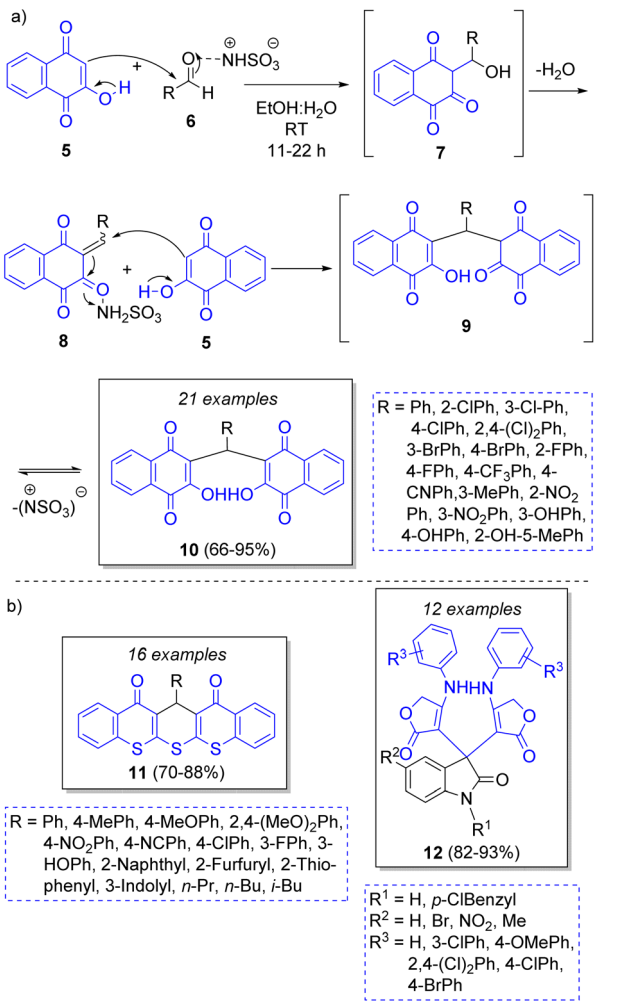


Fig. 2 Molecules synthesized *via* pseudo-MCRs or repetitive pseudo-MCRs, and their applications.

2. Pseudo-three component reactions

2.1 Knoevenagel condensation/Michael addition

A highly diverse strategy employed in pseudo-3CRs involves a Knoevenagel condensation coupled to a Michael addition. Brahmachari[13] reported the synthesis of many functionalized bis-lawsone derivatives using two equivalents of lawsone **5** (2-hydroxy-1,4-naphthoquinone), one equivalent of aromatic aldehydes **6** and sulfamic acid as organo-catalyst, under mild reaction conditions. A reaction mechanism is proposed (Scheme 1a): the aldehydes **6**, previously activated by sulfamic



Scheme 1 (a) Synthesis of bis-lowsone derivatives *via* Knoevenagel condensation/Michael addition. (b) Synthesized thiopyrano{2,3-*b*:6,5-*b*′}bis(thiocromene)-12,14(13*H*)-diones and 3,3′-bis-substituted-2-oxindoles.

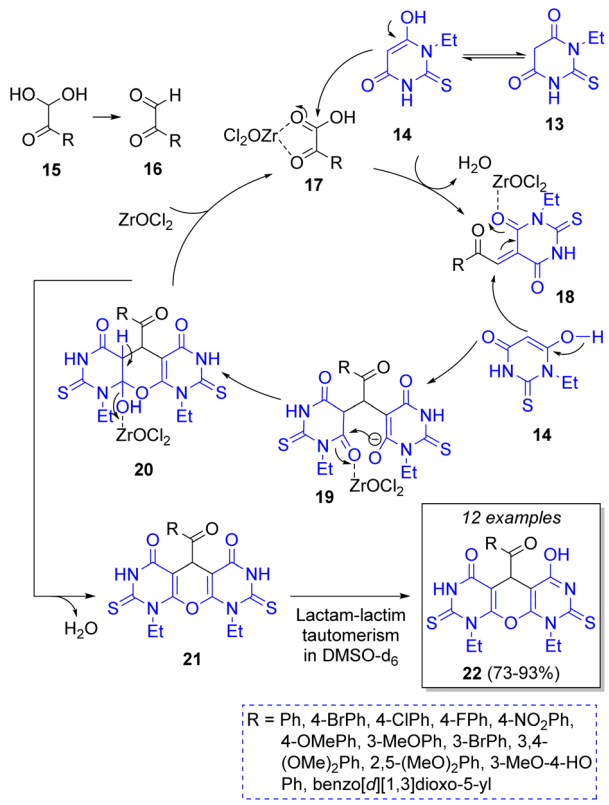
acid, react with a molecule of lawsone **5** *via* a Knoevenagel condensation forming the intermediates **7**, which produce the alkenes **8** after dehydration. Then, **8** react with a second molecule of lawsone **5** *via* a Michael addition, producing the intermediates **9**, which tautomerize towards the final bis-lawsones **10**. Over the years, it has been known that bis-lawsones have numerous biological activities as well as cosmetics applications. Khan and co-workers[14] reported a novel domino pseudo-MCR to synthesize thiopyrano{2,3-*b*:6,5-*b*′}bis(thiocromene)-12,14(13*H*)-diones **11** involving a Knoevenagel condensation/Michael-type addition, followed by intramolecular cyclization and loss of H_2S (Scheme 1b). Using the same method, Naimee-Jamal and Ghahremanzadeh[15] synthetized the 3,3′-bis-substituted-2-oxindoles **12** using cyclohexyl isocyanide (Scheme 1b). Similar techniques were employed to synthesize series of furo[3,2-*c*]coumarins (using $I_2/K_2S_2O_8/NA_2CO_3$ as catalyst),[16] 10-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-methyl-1*H*,10*H*-pyrano[4,3-*b*]chromen-1-ones (using $H_3PMo_{12}O_{40}$ as catalyst),[17] tricyclic spiro-dihydrofurans[18] and spirocyclopropanes.[19]

Following this approach, in 2019 Rimaz and co-workers[20] reported a moderate to high-yielding synthesis of a series of many pyrano[2,3-*d*:6,5-*d*′]dipyrimidines using two equivalents of 1-ethyl-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione (**13**), an equivalent of arylglyoxal monohydrates **15**, and 1,4-diazabicyclo [2.2.2]octane (DABCO) and $ZrOCl_2 \cdot 8H_2O$ as green catalysts. The Scheme 2 illustrates the reaction catalyzed by $ZrOCl_2 \cdot 8H_2O$. The mechanism begins with a regioselective Knoevenagel condensation between thioxidihydropyrimidine **14** and arylglyoxals **17** activated by $ZrOCl_2 \cdot 8H_2O$ to form the intermediates **18**. Then, a Michael addition of another molecule of **14** to **18** affords the intermediates **19**. Finally, an intramolecular cyclization followed by a lactam-lactim tautomerization leads to the final products **22**.[21]

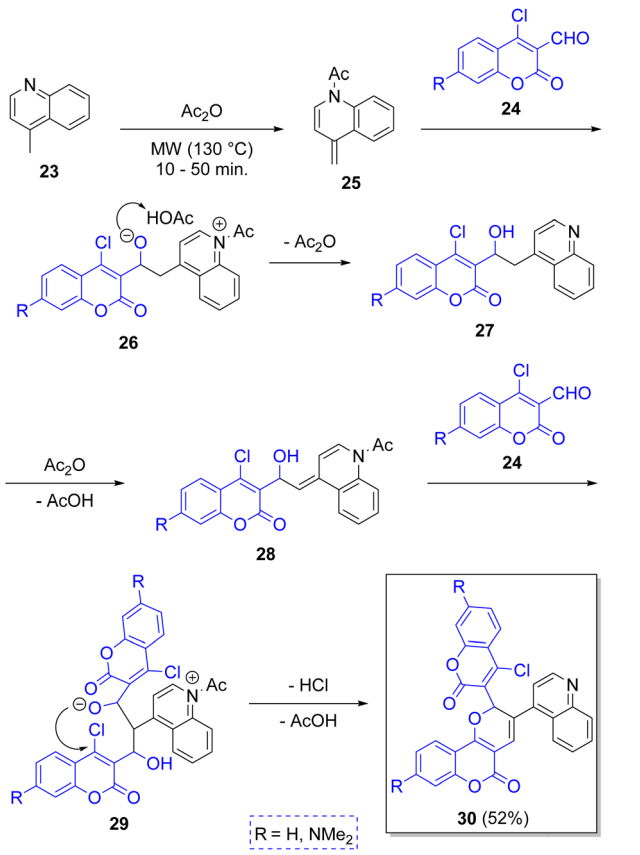
2.2 Others

In 2012 Yang and co-workers[22] described the synthesis of pyranocoumarins **30** *via* a microwave-assisted pseudo-3CR starting from the 4-methylquinoline (**23**) and two equivalents of coumarins **24** in acetic anhydride as solvent. The proposed reaction mechanism begins with an acetylation of **23** by acetic anhydride to generate the intermediates **25**, which add electrophilically to coumarins **24** to produce the alcoholates **27**, after leaving one Ac_2O molecule. This new intermediates react with another molecule of Ac_2O to generate **28**, which react with a second molecule of **24** to afford the zwitterions **29**, which after an intramolecular cyclization followed by dehydration, furnish the final products **30** (Scheme 3). These products were found to be sensible to UV light, and thus, the aim behind their syntheses was to use them as molecular switches.

In 2014, Rao and co-workers[23] described a practical high-yielding domino MCR for the synthesis of hexa-substituted 1,4-dihydropyridines **37** (1,4-DHPs) by a reaction between a variety of aromatic aldehydes **31**, nitroketene-*N*,*S*-acetals **32** (2



Scheme 2 Synthesis of pyrano[2,3-*d*:6,5-*d*′]dipyrimidines.

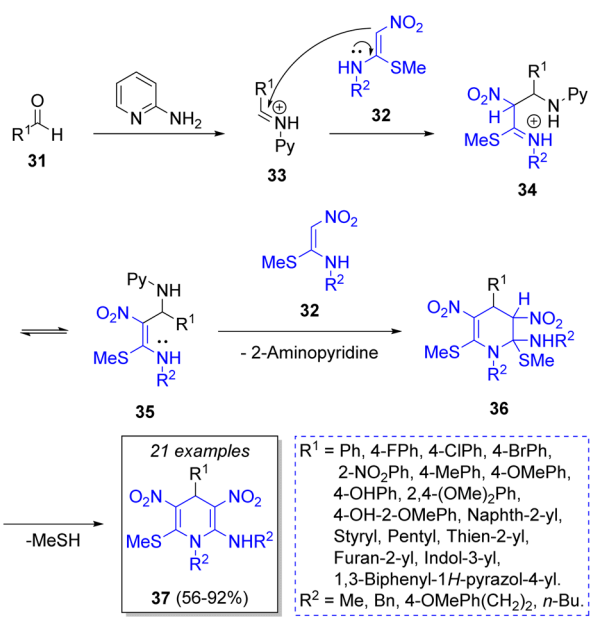


Scheme 3 Synthesis of pyranocoumarins *via* a pseudo-3CR.

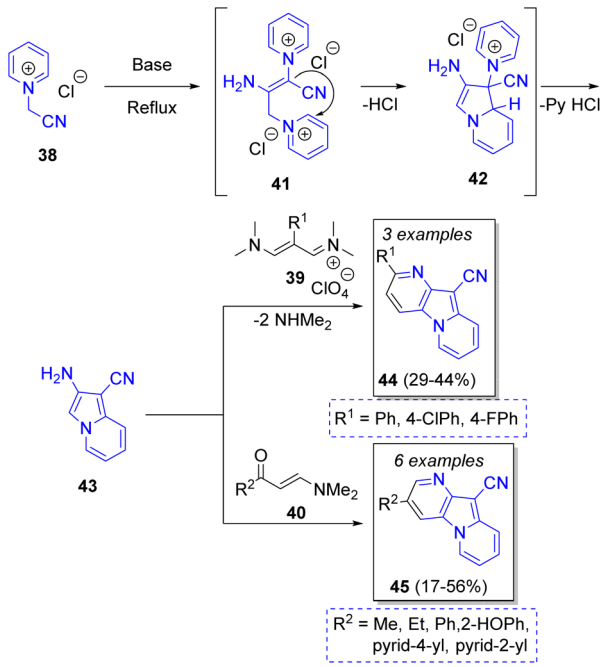
equiv.), and 2-aminopyridine as a catalyst. As Scheme 4 depicts, the reaction mechanism begins with the formation of iminium ion **33** from the condensation of aromatic aldehyde **31** with 2-aminopyridine (2-AP) **33**. Then, it reacts with a molecule of *N*-methyl-*S*-methyl nitroethylene (NMSM, **32**) forming the intermediate **34**, which adopts the tautomeric form of **35**. Then, intermediate **35** reacts with another molecule of **32** to give **36**. The final product **37** results from an intramolecular elimination of methanethiol (MeSH). Encouraged by these results, the authors designed and synthesized a small library of 1,4-DPHs, functionalizing the C-4 and C-2 positions of benzaldehyde with electron-withdrawing groups (EWGs) and electron-releasing groups ERGs. 1,4-DHPs have important biological activities because of their similarity with the coenzymes NADH (nicotinamide adenine dinucleotide) and NADPH (nicotinamide adenine dinucleotide phosphate).

Festa and Voskressensky[24] reported an efficient synthesis of many 3- and 2-substituted pyrido[2,3-*b*]indolizines by a reaction between two equivalents of *N*-(cyanomethyl)pyridinium (**38**) and vinamidinium salts **39** or enaminones **40**. The reaction mechanism showed in the Scheme 5 begins with the base-promoted dimerization of pyridinium salt **41**, which then undergoes an intramolecular cyclization to form the intermediate **42**. Then, elimination of pyridinium hydrochloride forms the aromatic compound aminoindolizine **43**, which condenses with 1,3-dielectrophiles to give the pyridoindolizines **44** or **45**. The optical properties of synthesized indolizines were investigated, showing a strong visible emission ranging from blue to green regions. The products have promising structures for preparing materials to fabricate OLED devices.

A collection of 1,6-dihydroazaazulenes was achieved by Cortes-García and co-workers[25] *via* a pseudo-3CR strategy using an acid-catalyzed cyclization of pyrrolyl-enones. The reaction comprises but-3-en-2-one (2 equiv., **46**), functionalized pyrroles

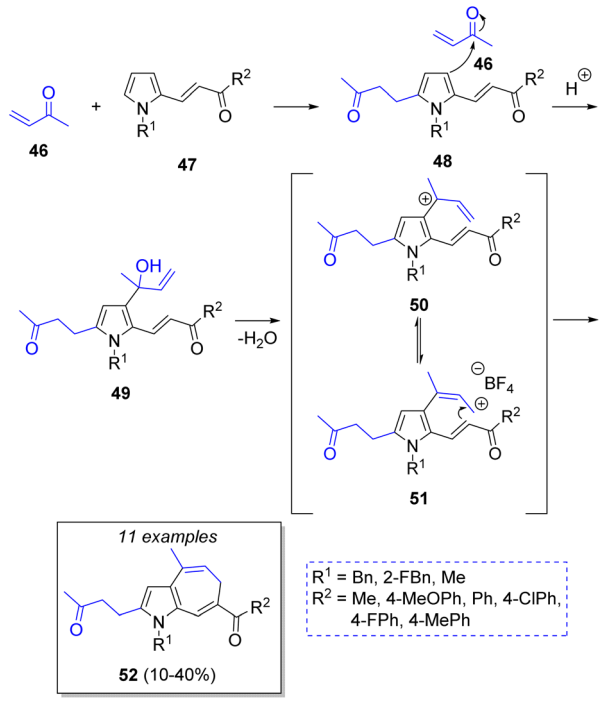


Scheme 4 Synthesis of hexasubstituted 1,4-DHPs.

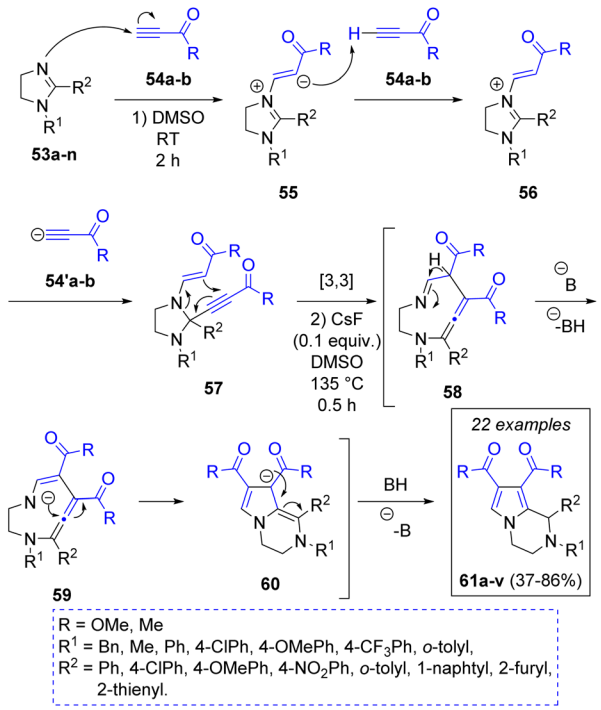


Scheme 5 Synthesis of pyridoindolizines.

47 and ionic liquid as catalyst (1-butyl-3-methylpyridinuim tetrafluoroborate, BMPy-BF_4). The suggested mechanism is depicted in Scheme 6. Initially, the butenone **46** reacts with pyrroles **47** *via* Michael addition to produce the intermediates **48**, which then undergo an 1,2 addition of a second molecule of **46** to produce the corresponding allylic alcohols **49**, followed by



Scheme 6 Synthesis of 1,6-dihydroazaazulenes *via* a pseudo-3CR.

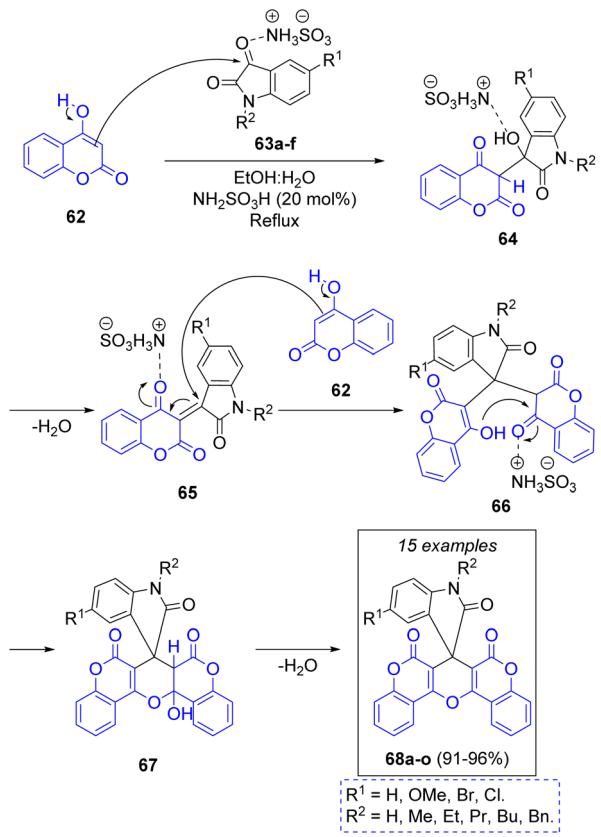


Scheme 7 Synthesis of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines.

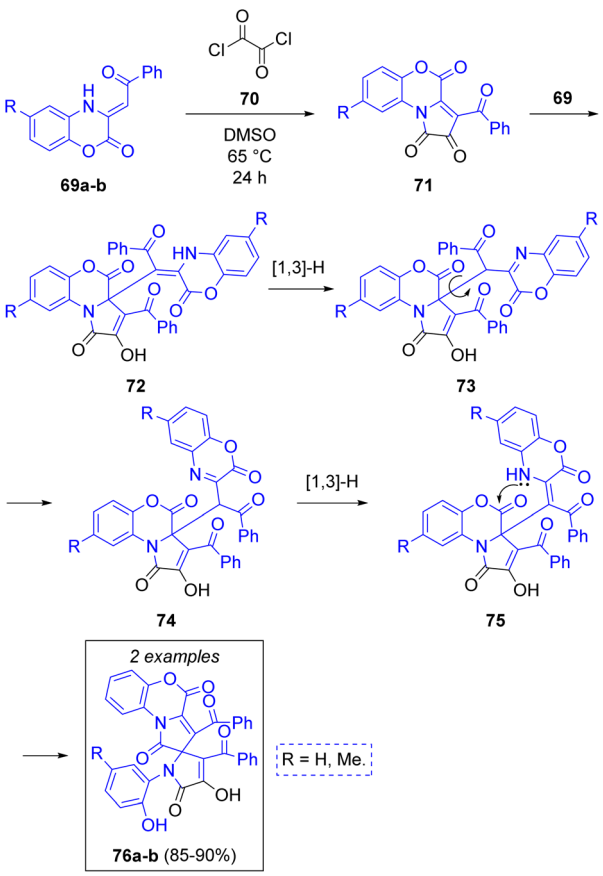
a dehydration to form allylic carbocation intermediates **50**. Upon electrophilic addition of **51** to the double bond of the enones and a subsequent deprotonation, the desired products **52** are formed.

In 2022 N. E. Golantsov and L. V. Voskressensky[26] reported a base catalyzed one-pot synthesis of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines *via* a pseudo three-component reaction between imidazolines **53a–n** and two equivalents of electron-deficient terminal alkynes (methyl propiolate **54a** or acetylacetylene **54b**), obtaining the products **61a–v** in moderate to excellent yields. To explain the transformation of imidazolines to pyrazines, the authors proposed a reaction mechanism (Scheme 7). The first step is a Michael addition of imidazolines to one molecule of terminal alkynes to form the zwitterions **55**, which in turn deprotonate the second molecule of alkyne, producing the anions **54′a–b**, which attack position 2 of the imidazolium ions **56** producing the key adducts **57**. Under heating conditions, this adduct undergoes a [3,3]-sigmatropic rearrangement leading to the formation of a 9-membered intermediates **58**, which are deprotonated by the base at their imino α-position, producing **59**, which prompt a transannular cyclization leading to the formation of the target 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **61a–v** after protonation of **60**.

In 2022 C. Mukhopadhyay and co-workers reported the synthesis of a library of substituted spirooxindolopyrans *via*



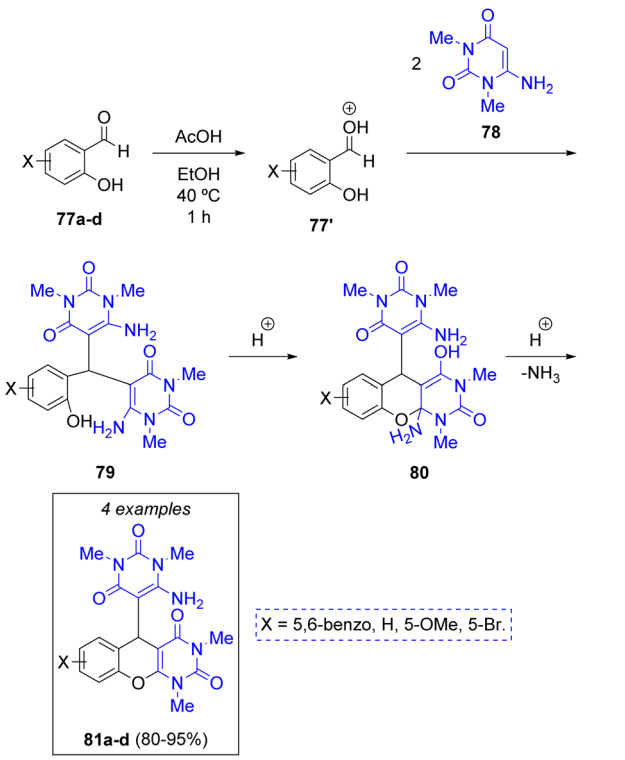
Scheme 8 Synthesis of spirooxindolopyrans.



Scheme 9 Synthesis of 3′-dibenzoyl-4-hydroxy-1-(2-hydroxyaryl)-1′*H*,4′*H*-spiro[pyrrole-2,2′-pyrrolo[2,1-*c*][1,4]benzoxazine]-1′,4′,5(1*H*)-triones.

a green one-pot pseudo-3CR between substituted isatins **63a–f** and two equivalents of 4-hydroxycoumarin (**62**) using a mixture of ethanol and water as solvent system, and sulfamic acid as catalyst. To explain the formation of the target products, the authors propose that the first step of the mechanism (Scheme 8) is the activation of the isatin's C-3 by sulfamic acid, prompting a nucleophilic addition of coumarin to form the intermediates **64**, which after loss of a water molecule produces the key intermediates **65**. These ones are attacked by other coumarin molecules to form **66**, which undergo an intramolecular ring closure to generate the cycloadducts **67**. Elimination of another water molecule generates the target compounds **68a–o**. This remarkable methodology produced a compound library in excellent yields, and to further demonstrate the robustness of their methodology, the authors performed the synthesis of a single product in a multigram scale, obtaining the target molecule in an excellent yield of 94%.[27]

A. N. Maslivets and co-workers[28] reported the synthesis of fused pyrrolobenzoxazines *via* a pseudo-3CR. The first step is a reaction between one equivalent of 3-benzoylmethylidene-3,4-dihydro-2*H*-1,4-benzoxazin-2-ones **69a–b** with oxalyl chloride (**70**) to produce 3-aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones (**71**), which are attacked by another molecule of **69** to produce the intermediates **72**. Next, tautomerization of **72** *via* [1,3]-H shift followed by rotation of the recently added benzoxazine fragment (**73**) to a less hindered position (**74**) and another [1,3]-H shift allows for an intramolecular ring closure *via* lactamization (**75**) with subsequent cleavage of the lactone rings to produce the spirocyclic target compounds **76a–b** in excellent yield (Scheme 9).



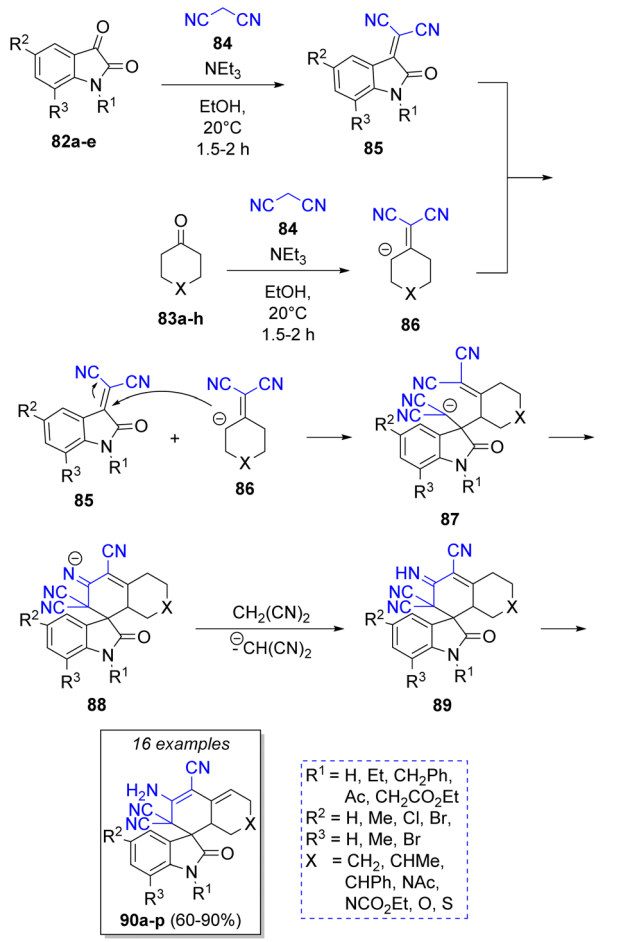
Scheme 10 Synthesis of fused pyranopyrimidinediones.

F. Farzaneh and co-workers[29] synthesized four new fused pyranopyrimidinediones with antibacterial activity *via* a green, acetic acid catalyzed pseudo-3CR between substituted salicylaldehydes **77a–d** and two equivalents of 6-amino-1,3-dimethyluracil (**78**), a derivative of the nucleobase uracil. The authors suggest that the first step towards the formation of the target molecule is a protonation of salicylaldehydes **77** by acetic acid, followed by a double condensation with the uracil derivatives to produce intermediates **79**. Next, an intramolecular cyclization *via* Michael addition of the hydroxy group from salicylaldehyde unto the enamine moiety generates intermediates **80**, which upon elimination of an ammonia molecule assisted by the acid catalyst, furnished the target products **81a–d** in excellent yields (Scheme 10).

3. Pseudo-four component reactions

3.1 Knoevenagel condensation/Michael addition

Knoevenagel condensation/Michael addition is also a common strategy used in pseudo-4CRs. For instance, Elinson and co-workers[30] achieved a feasible and stereoselective synthesis of a spiroindole-3,1′-naphthalene tetracyclic system using the isatins **82**, cyclic ketones **83a–h**, two equivalents of malononitrile

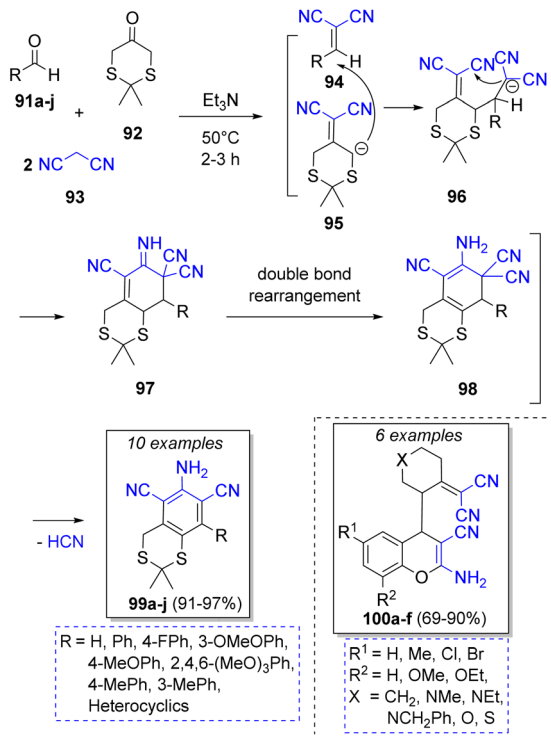


Scheme 11 Synthesis of spiroindole-3,1′-naphthalene tetracyclic systems.

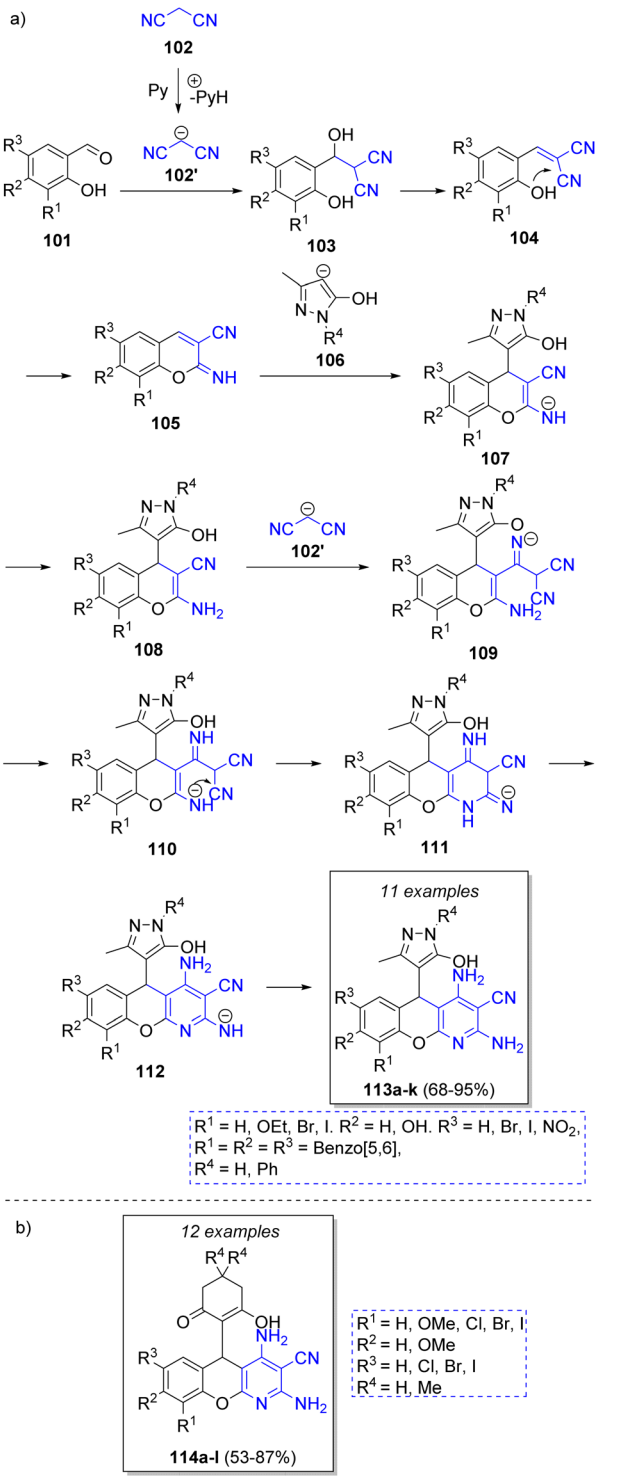
(**84**) and triethylamine as catalyst. The proposed reaction mechanism is illustrated in the Scheme 11. Initially, a Knoevenagel condensation takes place between isatins **82** and malononitrile (**84**) to generate the intermediates **85.** Simultaneously, another malononitrile molecule (**84**) reacts with the cyclic ketones **83** to afford **86**. Then, intermediates **86** are deprotonated by triethylamine, and then react with isatilidenemalononitriles **85** to afford **87**. An intramolecular cyclization produces the anions **88** and finally, a proton abstraction from another malononitrile molecule provides the final products **90a–p** in good to excellent yields.

Abaee and co-workers[31] reported the synthesis of a collection of dicyanoanilines fused to a dithiane ring *via* a facile and efficient reaction among aldehydes **91a–j**, 1,3-dithia-5-one (**92**), two equivalents of malononitrile (**93**) and triethylamine as catalyst. The proposed mechanism is depicted in Scheme 12. First, two parallel Knoevenagel condensations take place between aldehyde **91** and **92** with a molecule of malononitrile **93**, respectively, to form the corresponding intermediate olefins **94** and **95** under basic conditions. Both intermediates then react *via* a Michael addition to afford the tetracyano intermediates **96.** An intra-molecular cyclization forms intermediates **97**. The aromatic final products **99a–j** are obtained after a double bond rearrangement and the loss of one HCN molecule from **98**. Diverse compounds such as 4-[2-(dicyanomethylene)cyclic or heterocyclic]-2-amino-4*H*-chromenes **100a–f**[32] dicyanoanilines,[33] 2-amino-4-(aryl)-5,6,7,8,9,10-hexahydrobenzo[*a*]cyclo-octene-1,3-dicarbonitriles,[34] hexahydrobenzo[8]-annulene[35] have been prepared using similar methodologies.

Ryzhkov and co-workers[36] reported a pseudo-4CR approach for the synthesis of 5*H*-chromeno[2,3-*b*]pyridines *via* a Knoevenagel condensation/Pinner reaction/Michael addition/Pinner reaction strategy. The suggested mechanism is illustrated in the Scheme 13a. Initially, malononitrile anion (**102′**) (previously deprotonated by pyridine) reacts with salicylaldehydes **101** *via*



Scheme 12 Synthesis of dicyanoanilines fused to heterocyclic dithiane ring.



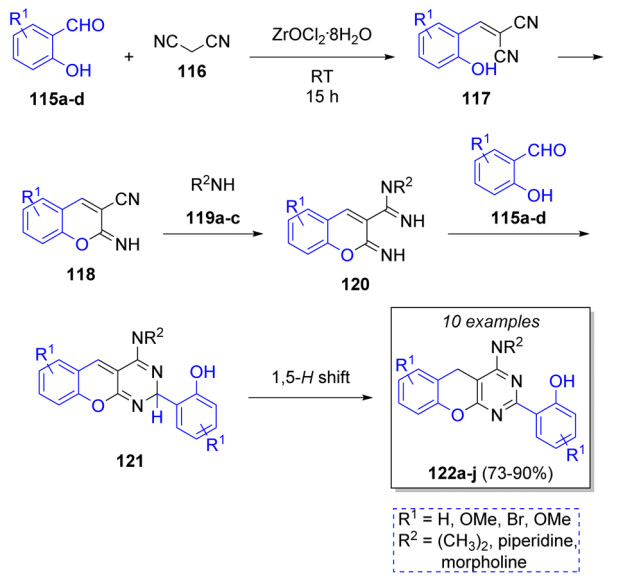
Scheme 13 (a) Synthesis of 5*H*-chromeno[2,3-*b*]pyridines *via* pseudo-4CR. (b) Chromeno-pyridines synthesized *via* a pseudo-4CR.

a Knoevenagel condensation to form **103**, followed by an intramolecular Pinner cyclization to form **105**. Then, intermediates **105** react with 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one anions **106** *via* Michael addition to produce **107**. The regeneration of malononitrile anion produces the compounds **108**. Then, the nitrile group of **108** is attacked by the malononitrile anion to form anions **109**, which are better stabilized in **110**. An intramolecular Pinner cyclization produces **111**, which after tautomerization and protonation produce the final products **113a–k**. A similar strategy was employed by Vereshchagin and co-workers.[37] The synthesis of 5-C-substituted 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **114a–l** was accomplished by the reaction of salicylaldehydes, two equivalents of malononitrile, 1,3-cyclohexanediones and triethylamine as catalyst (Scheme 13b).

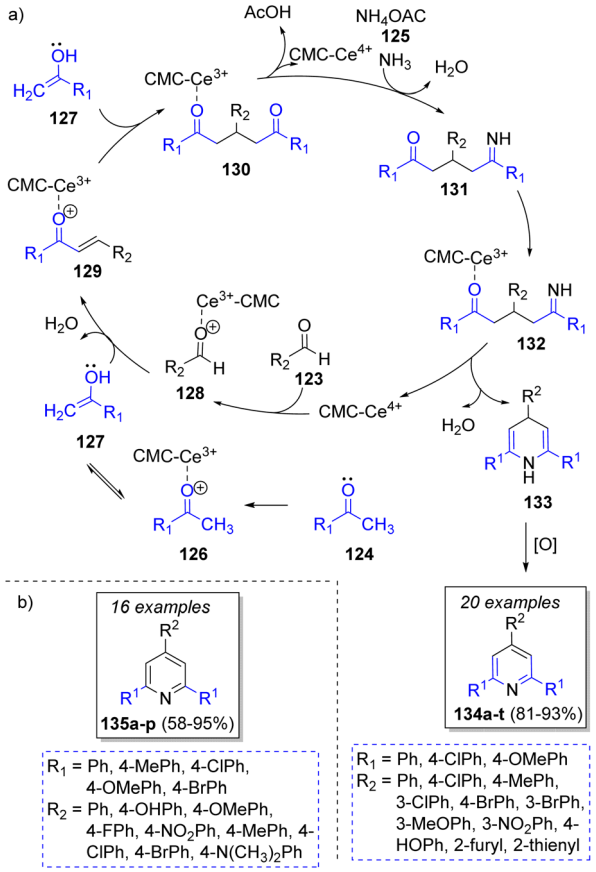
3.2 Others

An efficient method for the synthesis of benzopyranpyrimidines was developed by Bazgir and co-workers[38] in 2013 *via* a Knoevenagel condensation/Pinner reaction, using two equivalents of salicylaldehydes **115a–d**, malononitrile (**116**) and a variety of amines **119a–c** with zirconyl chloride ($ZrOCl_2 \cdot 8H_2O$) as catalyst. The proposed reaction mechanism is depicted in Scheme 14. A Knoevenagel condensation between aldehydes **115** and malononitrile (**116**) forms **117**, followed by a Pinner reaction to form intermediates **118**. Then, amines **119** react with intermediates **118** to form diimines **120**. These intermediates react with another molecule of **115** to form **121**, which form the final products **122a–j** after a 1,5-hydrogen shift. The authors have also explored the use of lithium perchlorate as catalyst, obtaining similar yields.[39]

In 2017, Li and co-workers[40] reported a highly efficient method to obtain 2,4,6-triphenylpyridines using aromatic aldehydes **123**, two equivalents of aromatic ketones **124**,



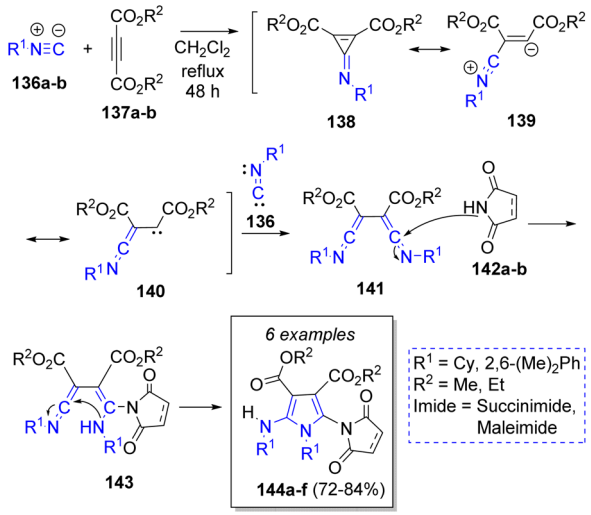
Scheme 14 $ZrOCl_2$-catalyzed synthesis of fused benzopyranopymidines.



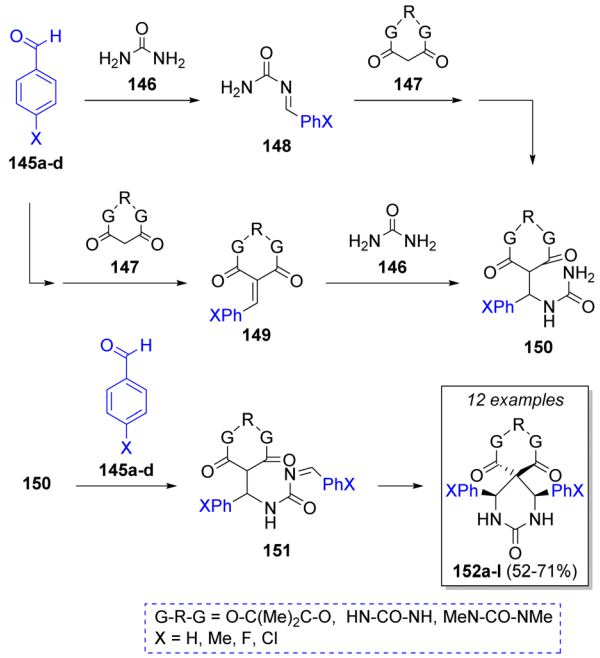
Scheme 15 (a) Reaction mechanism for the synthesis of 2,4,6-triphenylpyridines. (b) Synthesized compounds *via* a pseudo-4CR.

ammonium acetate **125** and cerium(IV)carboxymethylcellulose (CMC-Ce^{IV}) as catalyst. The proposed catalytic cycle for this transformation is illustrated in Scheme 15a. Initially, CMC-Ce^{IV} promotes the formation of the enol tautomers of the complex **126**, which react with **128** *via* a nucleophilic addition to form the α,β-unsaturated compounds **129**. These intermediates perform a Michael addition with a second molecule of enol **127** to form the 1,5-diketone intermediates **130**, which then react with ammonium acetate (**125**) to form intermediates **131**, followed by an intramolecular cyclization promoted by CMC-Ce^{IV}, and tautomerization to form the dihydropyridines **133**. Upon air oxidation of the last intermediates, the formation of the desired products **134a–t** is completed. Another collection of 2,4,6-triarylpyridines **135a–p** was prepared in the presence of salicylic acid as catalyst (Scheme 15b).[41]

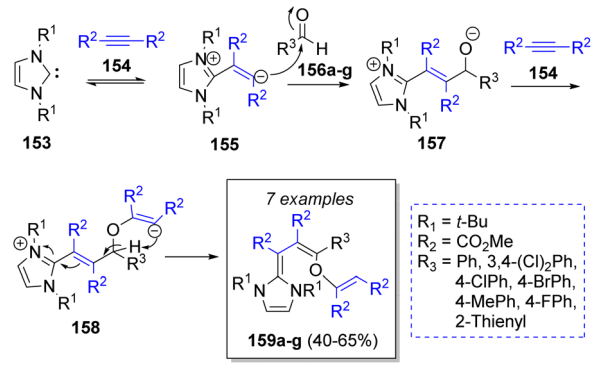
In 2004, Shaabani and co-workers[42] performed a pseudo-4CR-based method to obtain some highly functionalized pyrroles from commonly available precursors. The reaction involved two equivalents of unhindered isocyanides **136a–b**, one equivalent of dialkyl acetylenedicarboxylates **137a–b** and one equivalent of five-membered cyclic imides (*i.e.* succinimide or maleimide) **142a–b** to give 1′-alkyl, aryl-5′alkyl or arylamino-2,5-dioxo-2,3,4,5-tetrahydro- or 2,5-dihydro-1′*H*-[1,2′]bipyrrole-3′,4′-dicarboxylic acid dialkyl esters **144a–f**. The suggested reaction mechanism is illustrated in Scheme 16. First, the



Scheme 16 Synthesis of penta-substituted pyrroles.



Scheme 17 Synthesis of spiro-heterobicyclic rings.



Scheme 18 Synthesis of diene derivatives using *N*-heterocyclic carbenes.

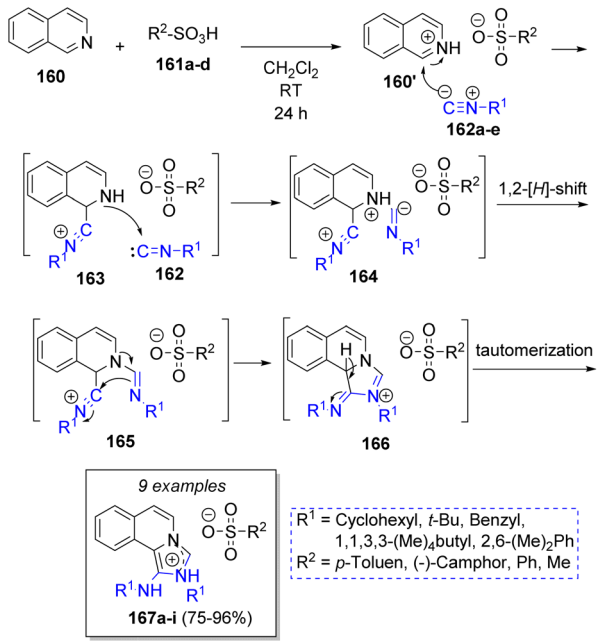
intermediates **138** are generated by the reaction between isocyanides **136** and alkynes **137**. Then, the addition of another molecule of isocyanides **136** produces the bis-ketenimine intermediates **141**, which react with **142** to afford **143.** Finally, an intramolecular cyclization forms the products **144a–f** in moderate yields.

In the same year, Shaabani and co-workers[43] also described a regioselective Biginelli-like pseudo-MCR of σ-symmetric spiro heterobicyclic rings extended to *para*-substituted aldehydes, including two equivalents of aldehydes **145a–d** (*para*-substituted benzaldehydes with EWGs), an equivalent of urea (**146**), and a cyclic β-diester or β-diamides (Meldrum's acid or barbituric acid) **147**. According to the authors, two probable reaction pathways were proposed, as illustrated in Scheme 17. The first starts with the nucleophilic addition of urea **146** to aldehydes **145** to afford the *N*-acylimines **148.** Then, Meldrum's acids **147** react with **148** *via* Michael addition to afford **150.** Then, addition of a second molecule of aldehydes **145** provided the intermediates **151**, which after a cyclization gives the final products **152a–l.** In the second pathway, aldehydes **145** react with cyclic β-diester or β-diamides **147** *via* Knoevenagel condensation to afford the intermediates **149**, a Michael addition of urea **146** gives the intermediates **150**, which react with another molecule of aldehydes **145** to afford **151.** A final cyclization also provides the spiro heterobicyclic products **152a–l.**

The synthesis of some dienes was described by Nair and co-workers[44] in 2005. The synthetic approach included the use of one equivalent of the *N*-heterocyclic carbene 1,3-di-*tert*-butylimidazole-2-ylidenes **153**, two equivalents of dimethyl acetylenedicarboxylates (DMAD, **154**) and one equivalent of aromatic aldehydes **156a–g.** The reaction mechanism was suggested as illustrated in Scheme 18. At first, the dipolar intermediates **155** are produced from the reaction between the carbenes **153** and DMAD **154**, which then react with the aldehydes **156** to form the alkoxide intermediates **157.** Then, the addition of another molecule of DMAD **154** lead to the zwitterionic intermediates **158.** A proton abstraction provides the final products **159a–g.**

In 2008, Shaabani and co-workers[45] described an efficient pseudo MCR condensation to afford 1-aminoimidazol[5,1-*a*] isoquinolinium salts, which involved the reaction of one equivalent of isoquinoline (**160**), two equivalents of isocyanides **162a–e** and sulfonic **161a–d** or bromic acids. The suggested mechanism is illustrated in Scheme 19. Initially, isoquinoline (**160**) is protonated by sulfonic acids **161**, which then reacts with isocyanides **162a–e** to form intermediates **163**, which are trapped by second isocyanide molecules **162a–e** to form **164.** A hydrogen shift followed by intramolecular cyclization affords the intermediates **166.** The reaction is completed after tautomerization of **166** to form the ionic products **167a–i.**

Shaabani and co-workers[46] also developed a novel good to high yielding technique for the synthesis of tetrahydrodiisoindoloquinoxalines and tetrahydrobenzodiisoindolo-quinoxalines *via*

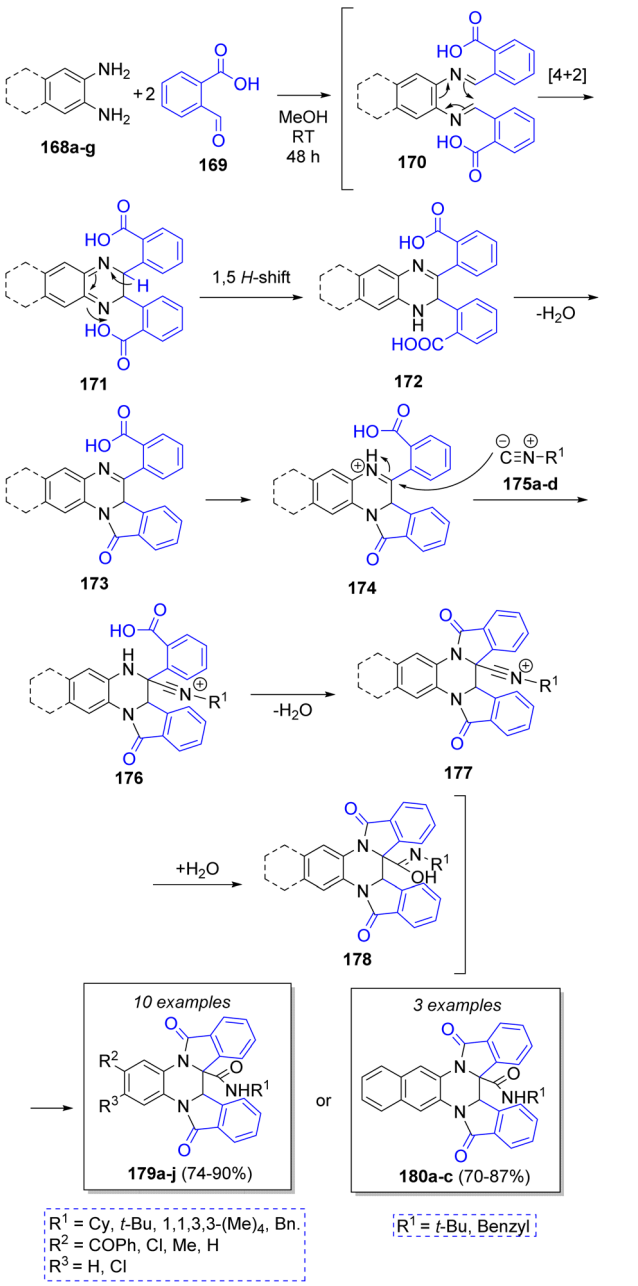


Scheme 19 Synthesis of 1-aminoimidazol[5,1-*a*]isoquinolinium salts.

the reaction between aromatic 1,2-diamines **168a–g**, 2-formylbenzoic acid **169**, and isocyanides **175a–d**. The proposed mechanism is showed in Scheme 20. First, diimine intermediates **170** are formed by the condensation between **168a–g** and two molecules of **169**. Then, **174** is formed by $4n + 2$ electrocyclic reaction followed by a [1,5] hydrogen shift and release of a water molecule *via* lactamization. Then, nucleophilic addition of isocyanides **175a–d** to the imine, followed by release of another water molecule gives rise to the second indole ring in **177**. The addition of one of the released water molecules unto the nitrilium ions **177** forms intermediates **178**. Finally, a tautomerization affords either **179a–j** or **180a–c**.

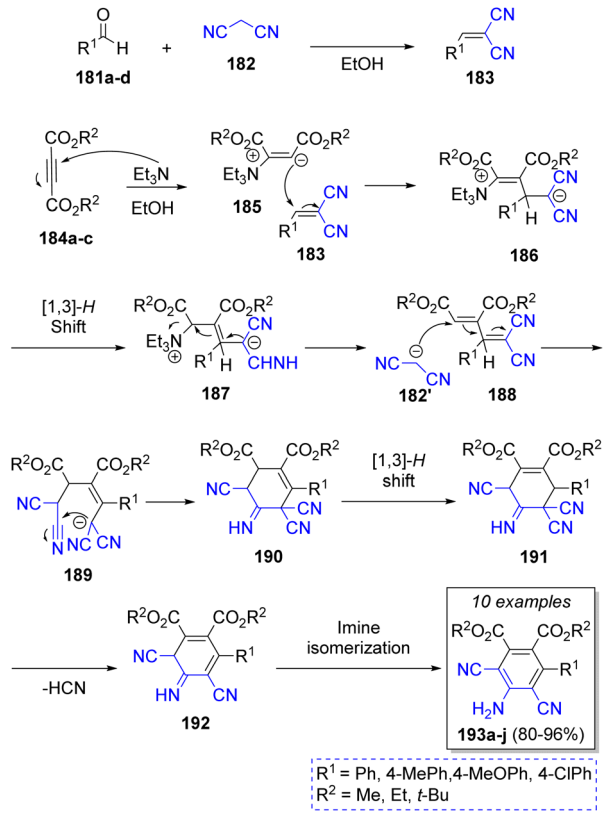
A series of 4-amino-3,5-dicyano-6-arylphthalates catalyzed by triethylamine were successfully synthetized by Mohammadi and co-workers[47] in 2013. The synthesis was achieved in satisfactory yields from the reaction of different benzaldehydes **181a–d**, two equivalents of malononitrile (**182**), and dialkyl acetylenedicarboxylates **184a–c**, in the presence of triethylamine as catalyst. A suggested mechanism is illustrated in Scheme 21. The reaction plausibly starts with a Michael addition of triethylamine to acetylenic esters **184a–c** to form zwitterions **185**, which react with the previously *in situ* formed arylidenemalononitriles **183** to afford the adducts **186**, which after a [1,3]-proton shift the new zwitterions **187** are formed. Elimination of Et_3N affords the electro-deficient 1,3-butadienes **188**, which are attacked by another molecule of malononitrile **182** to give the intermediates **189**, which after an intramolecular cyclization afford **190**. The desired products **193a–j** are formed after a [1,3]-proton shift (**191**), followed by HCN elimination (**192**), and finally by an imine isomerization.

Khan[48] reported a regioselective $Yb(OTf)_3$-catalyzed synthesis of tri-substituted 3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-ones *via* reaction between two equivalents of aldehydes

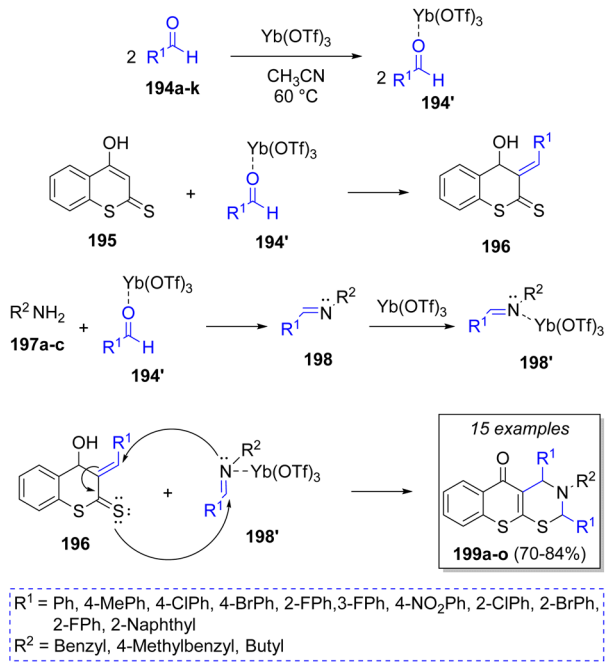


Scheme 20 Synthesis of tetrahydrodiisoindoloquinoxalines and tetrahydrobenzodiisoindoloquinoxalines.

194a–k, 4-hydroxydithiocoumarin (**195**), and aliphatic primary amines **197a–c**. A plausible mechanism for this reaction was suggested as illustrated in Scheme 22. Accordingly, adducts **194′** are formed by the reaction of aldehydes **194** and ytterbium triflate, which then react with hydroxydithiocoumarin **195** to produce the compounds **196** *via* a Knoevenagel condensation. Simultaneously, the other adducts **194′** react with the amines **197** to form imines **198**. Furthermore, imines **198** form dienophiles **198′** when activated by ytterbium triflate. Finally, hetero-Diels–Alder cyclization between dienes **196** and dienophiles **198′** gives the desired products **199a–o**.



Scheme 21 Synthesis of 4-amino-3,5-dicyano-6-arylphthalates.

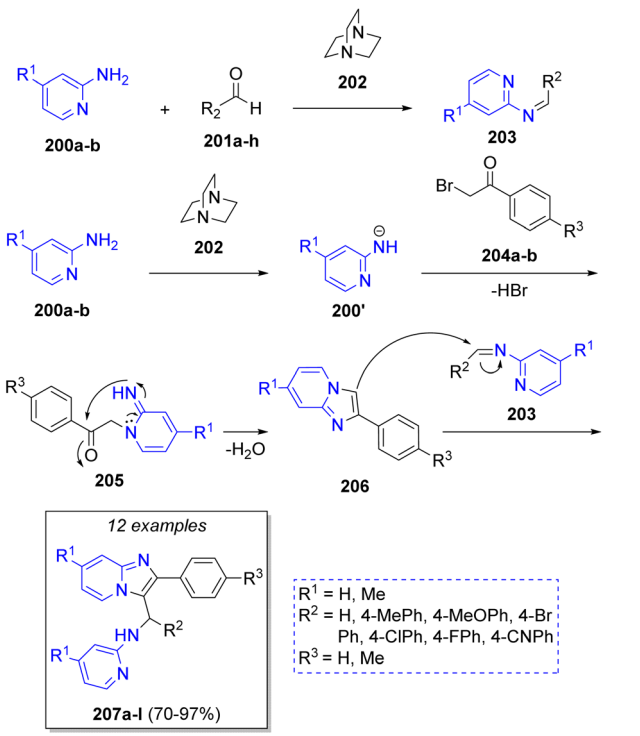


Scheme 22 Synthesis of di- and tri-substituted 3,4-dihydrothiochromeno[3,2-*e*][1,3]thiazin-5(2*H*)-ones.

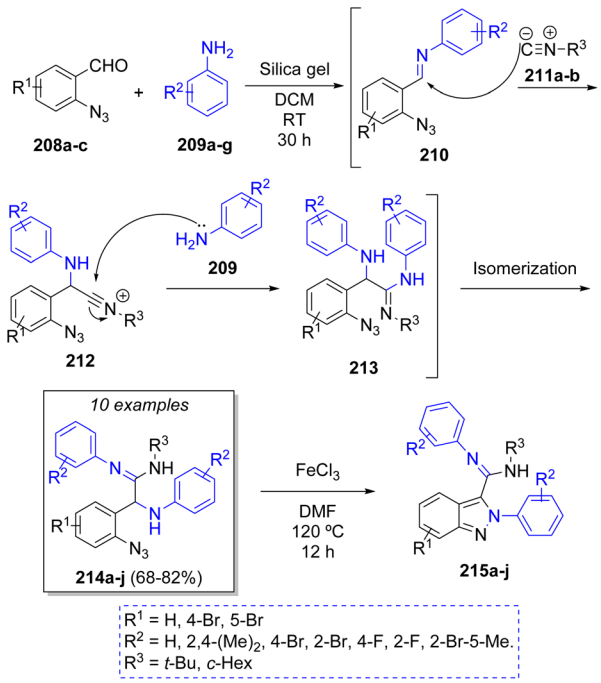
Sanaeishoar[49] in 2015 reported a sophisticated strategy to synthesize functionalized imidazo-[1,2-*a*]pyridines *via* the reaction of 2-aminopyridines **200a–b,** aromatic aldehydes **201a–h** and phenacyl bromides **204a–b**, using DABCO (**202**) as catalyst under solvent-free conditions. The proposed reaction mechanism is depicted in the Scheme 23. First, the reaction between 2-aminopyridines **200** and aldehydes **201** in the presence of DABCO (**202**), produces the imine-type intermediates **203.** A second molecule of 2-aminopyridines **200** react with phenacyl bromides **204** *via* S_N2 to afford the intermediates **205**, which undergo an intramolecular cycloaddition to form the 2-aryl-imidazo[1,2-*a*]pyridines **206.** Finally, the products **207a–l** are generated *via* a nucleophilic attack of intermediates **206** on the imine intermediates **203.**

D. S. Sharada[50] published an environmentally friendly silica gel-promoted pseudo-4CR *via* a cascade process to synthesize first the α-aminoamidines **214** and then, an *in situ* iron(III) chloride-catalyzed cyclization towards the substituted 2*H*-indazoles **215a–j.** The authors employed the 2-azidobenzaldehydes **208a–c,** two equivalents of anilines **209a–g** and alkyl isocyanides **211a–b** to produce the corresponding α-aminoamidines in 68 to 82% overall yields. A plausible reaction mechanism for this transformation is proposed in the Scheme 24. Accordingly, the reaction between **208** and **209** produces imine intermediates **210.** Then, the weakly Brønsted acidic nature of silica gel acted as activator of the imines **210** to promote the nucleophilic attack by the isocyanides **211** producing the intermediates **212,** which are attacked by a second molecule of anilines **209,** generating the intermediates **213.** These compounds undergo an isomerization process affording the corresponding α-aminoamidines **214.**

Sharma[51] reported the synthesis of bis-amides *via* an organocatalytic oxidative pseudo-4CR. The reaction was carried out

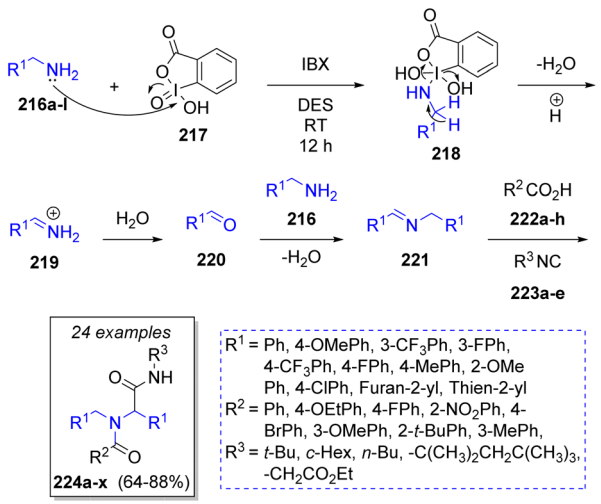


Scheme 23 Synthesis of functionalized imidazo-[1,2-*a*]pyridines.



Scheme 24 Synthesis of α-amino amidines and its cyclization towards 2*H*-indazoles.

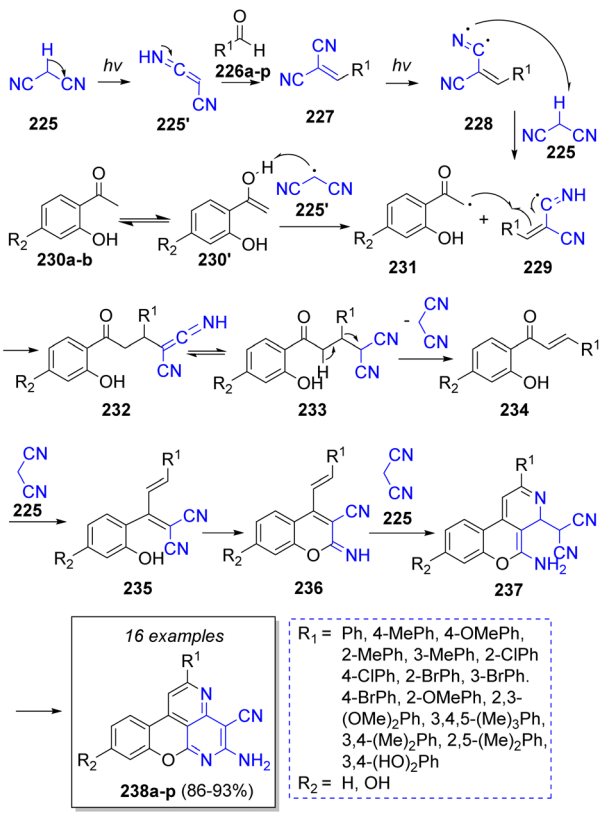
in a deep eutectic solvent (DES, choline chloride/urea mixture), which are considered as a greener alternative to organic solvents, and the oxidant (*o*-iodoxybenzoic acid) was soluble in such solvent system, which allowed the reaction to occur in homogeneous conditions. Thus, the authors utilized a variety of aryl and heterocyclic primary amines **216a–l**, carboxylic acids **222a–h** and alkyl isocyanides **223a–e** (Scheme 25). The proposed reaction mechanism for the oxidative coupling of amines and the Ugi reaction begins when *o*-iodoxybenzoic acid **217** oxidizes the primary amines **216a–l** generating the iminium ions **219** through the intermediates **218**, after loss of water molecule.



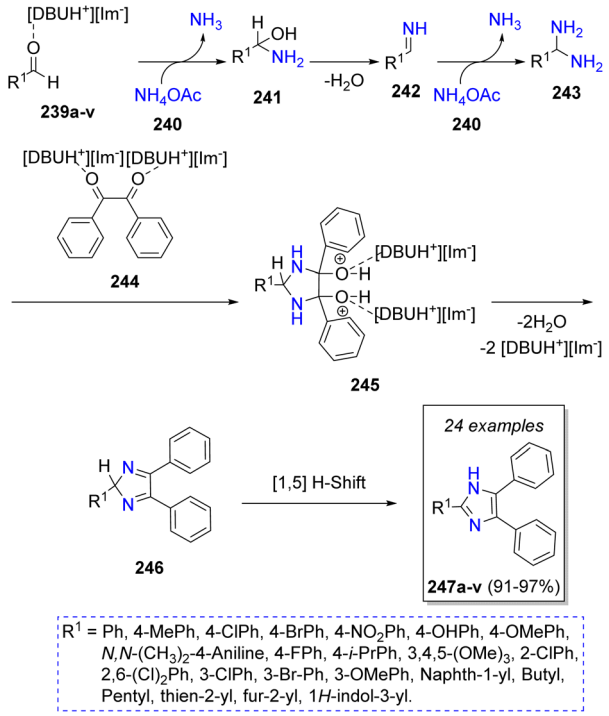
Scheme 25 Synthesis of bis-amides *via* a hybrid oxidative pseudo-Ugi-4CR strategy.

Then, **219** are hydrolyzed leading to the formation of aldehydes **220**. The presence of benzoic acid catalyses the condensation between aldehydes **220** and other amine molecules **216a–l**, producing the corresponding Schiff bases **221**. These imines react with carboxylic acids **222a–h** and isocyanides **223a–e** affording the pseudo-Ugi-4CR products **224a–x.**

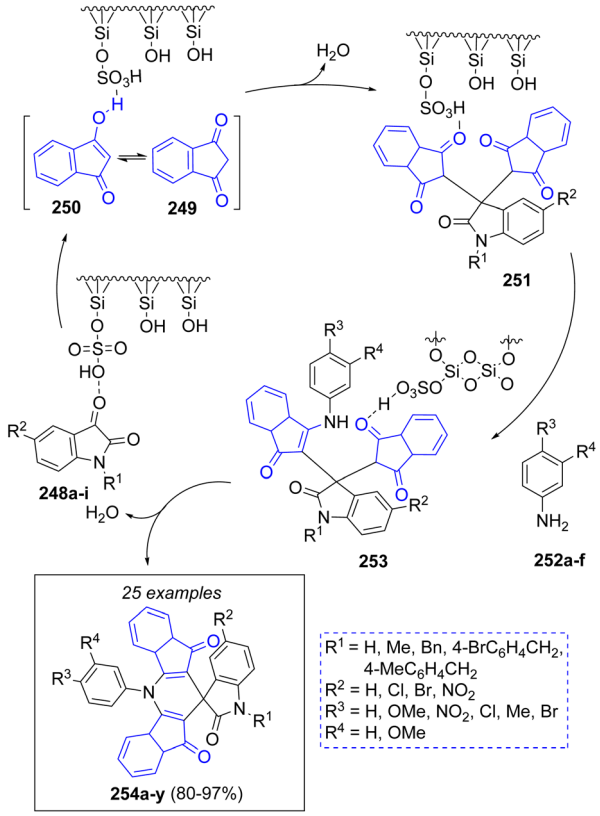
In 2018, Shaterian and Mohammadi[52] reported a highly efficient visible light-induced pseudo-4CR synthesis of many new chromeno[4,3,2-*de*][1,6]naphthyridines by using two equivalents of malononitrile (**225**), aromatic aldehydes **226a–p** and 2′-hydroxyacetephenones **230a–b.** Scheme 26 illustrates the plausible reaction mechanism proposed by the authors. Initially, light irradiation induced malononitrile (**225**) to react with aldehydes **226** to form benzylidene malononitriles **227** followed by formation of radical intermediates **228.** Then, these intermediates **228** induced the formation of malononitrile radical by abstracting a methylenic hydrogen to form the intermediates **229.** The malononitrile radical **225′** reacts with enol intermediates **230′** to form **231.** Later, intermediates **231** react with **229** to form **232,** which upon tautomerization generates **233.** Then, the elimination of malononitrile group produces chalcones **234.** Intermediates **235** are formed *via* the reaction of chalcones **234** and a molecule of malononitrile (**225**), and after an intramolecular Pinner reaction **236** is formed. Subsequently, another molecule of malononitrile (**225**) reacts with **236** to form **237,** further intramolecular cyclization and aromatization generates the desired products **238a–p.**



Scheme 26 Synthesis of chromeno[4,3,2-*de*][1,6]naphthyridines.



Scheme 27 Synthesis of trisubstituted imidazoles.



Scheme 28 Synthesis of spiro[diindenopyridine-indoline]triones.

Gill and co-workers[53] reported a highly efficient (up to 91%) pseudo-4CR for the synthesis of trisubstituted imidazoles using a cheap and recoverable ionic liquid as catalyst. Following the Scheme 27, the reaction initially proceeds *via* nucleophilic attack of ammonia (from NH_4OAc, **240**) to aromatic aldehydes **239a–v** (previously activated by [$DBUH^+$][Im^-]) to form the hydroxylamines **241**, which after loss of water produces the imine-type intermediates **242**. Then, a second attack of ammonia forms the diamine intermediates **243**, which react with a previously activated reagent **244** to give the intermediates **245**. Upon loss of water, [$DBUH^+$][Im^-] and a 1,5-*H* shift, the trisubstituted imidazoless **247a–v** are formed. One of the synthetized products demonstrated a potential cytotoxic activity against the human breast cancer cell line PC-3.

A novel technique for the synthesis of spiro[diindenopyridine-indoline]triones was reported by Naimi-Jamal and co-workers,[54] using a reusable heterogeneous nano-ordered mesoporous SO_3H functionalized-silica (MCM-41-SO_3H) catalyst. Following the proposed mechanism depicted in Scheme 28, isatins **248a–i** are activated by the SO_3H groups, which attack the enolic form **250** of 1,3-indanedione **249** to give intermediates **251**. The final products **254a–y** are afforded after the addition of anilines **252a–f**, followed by a cyclization reaction.

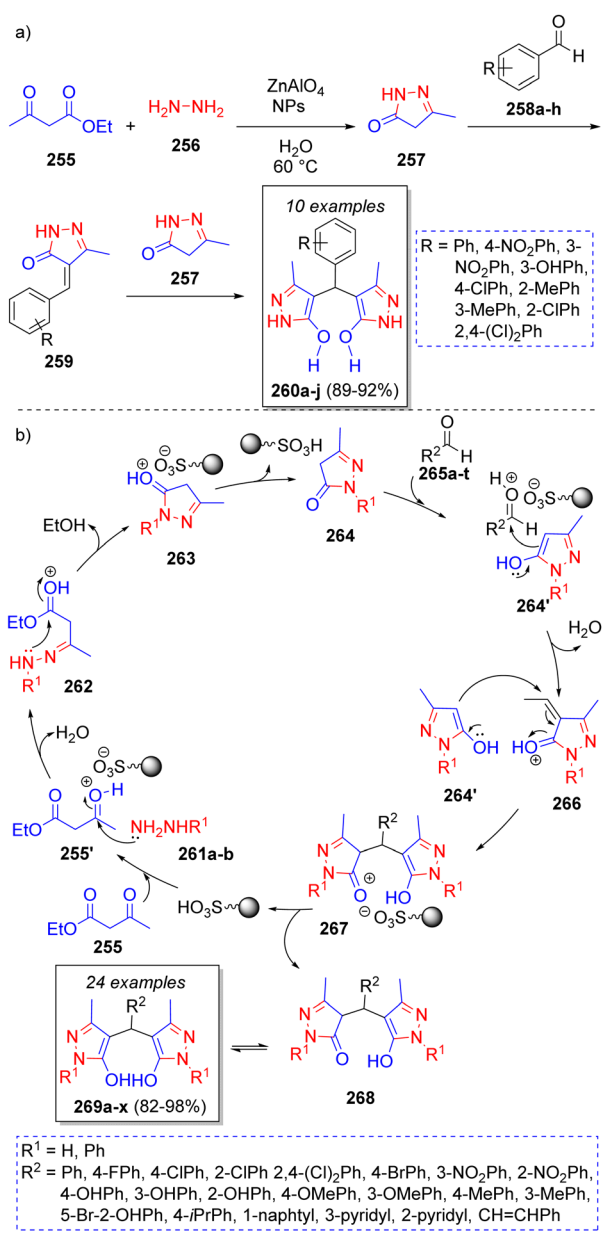
4. Pseudo-five component reactions

4.1 Knoevenagel condensation/Michael addition

Safaei-Ghomi and co-workers[55] reported an efficient strategy for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) derivatives catalyzed by $ZnAl_2O_4$. This pseudo-5CR involves the reaction between two equivalents of ethyl acetoacetate (**255**), two equivalents of hydrazine hydrate (**256**) and aromatic aldehydes **258a–h**. The process is shown in the Scheme 29a. Initially, hydrazine **256** reacts with ethyl acetoacetate **255** to form a pyrazole intermediate **257**, which then undergoes a Knoevenagel condensation with the aldehydes **258a–h** to form intermediates **259**. Finally, another previously formed pyrazole **257** reacts with **259** to form the final products **260a–j**.

Later in 2017, Jahanshashi and Akhlaghinia[56] reported a similar synthesis of a large collection of new 4,4′-(arylmethylene)bis(3-methyl-1*H* pyrazol-5-ol)s *via* a one-pot pseudo-5CR in the presence of sulfonated honeycomb coral (HC–SO_3H) as green catalyst. Scheme 29b depicts the proposed reaction mechanism. Accordingly, pyrazolone intermediates **264** (and their tautomeric form **264′**) are formed by the reaction between the protonated form of ethyl acetoacetate **255′** and phenylhydrazine/hydrazine **261a–b**, followed by an intramolecular cyclization. Consequently, enol intermediates **264′** condense with aromatic aldehydes **265a–t**, which are also activated by the acid catalyst, followed by a loss of water to afford **266**. Finally, the desired products **269a–x** are formed after a Michael addition of another **264′** molecules unto the intermediates **266** to form **268**, which undergo a tautomeric proton shift.

A similar work to the previous two was recently reported by A. Kohzadian and co-workers[57a] for the pseudo-5CR synthesis of bis(pyrazolyl)methanes from the substituted benzaldehydes

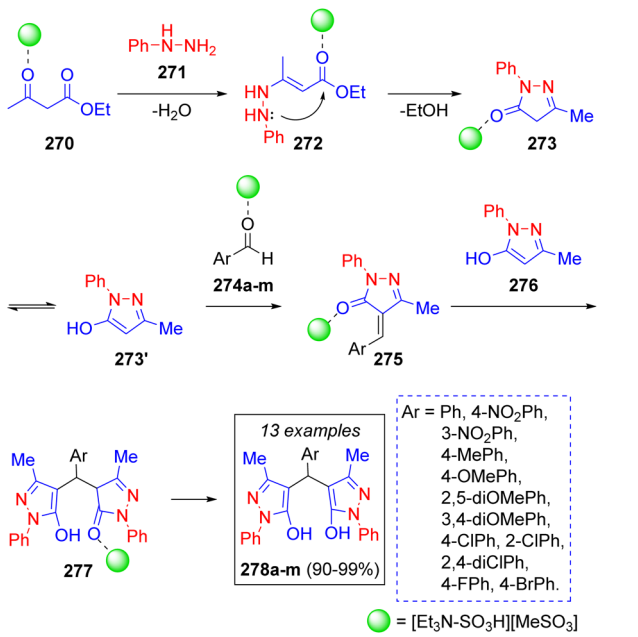


Scheme 29 (a) Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol)s. (b) Synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol)s.

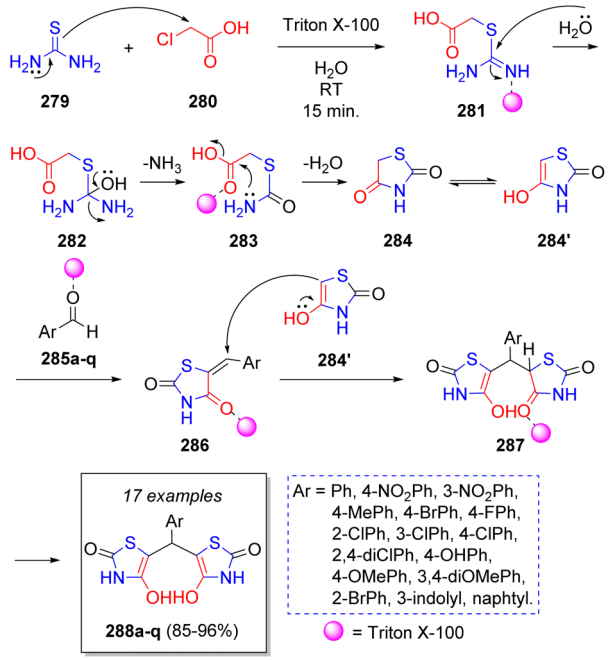
274a–m and two equivalents of phenylhydrazine (**271**) and ethyl acetoacetate (**270**), respectively. This multicomponent reaction was catalyzed by the acidic ionic liquid (*N*,*N*-diethyl-*N*-sulfoethanaminium methane sulfonate [Et_3N-SO_3H][$MeSO_3$]), which allowed the authors to obtain their target compounds in truly remarkable yields. Thus, a plausible reaction mechanism was proposed (Scheme 30): ethyl acetoacetate (**270**) is activated by the acidic catalyst facilitating a nucleophilic attack by a molecule of phenylhydrazine (**271**) producing the enamine **272**, which cyclizes to produce the intermediate **273** after loss of an ethanol molecule followed by tautomerization. Pyrazole **273′** undergoes Knoevenagel condensation with the catalyst-activated benzaldehydes **274a–m**, affording intermediates **275**. Michael addition of another molecule of **276** affords intermediates **277** which tautomerize to the target compounds **278a–m**. A similar strategy was recently utilized by N. Sarmasti and co-workers,[57b] with the use of a different catalyst (Fe_3O_4@SiO_2/Si(OEt)$(CH_2)_3$NH/CC/EDA/Cu$(OAc)_2$). A very interesting review about the syntheses of compounds based on the 4,4′-arylmethylene-bis-1*H*-pyrazol-5-ol scaffold was recently published by S. U. Deshmukh.[57c]

Following a similar reaction sequence as in the previous entries, M. Heravi and co-workers[58] reported in 2022 a green synthesis of 5,5′-(arylmethylene)bis(4-hydroxythiazol-2(3*H*)-ones) **288a–q** *via* a reaction between chloroacetic acid (**280**), thiourea (**279**) and aromatic aldehydes **285a–q**, using Triton X-100, which is a non-ionic surfactant, as catalyst in water as reaction medium. The antibacterial activity of these molecules was evaluated against antibiotic-resistant bacterial strains, as well as their antifungal activity. To explain the formation of the products, a reaction mechanism was proposed (Scheme 31): the first 4-hydroxythiazol intermediate **284′** is synthesized *via* a series of reactions starting with a nucleophilic substitution between thiourea (**279**) and chloroacetic acid (**280**). This intermediate condenses with the aldehyde molecules **285a–q** to produce **286**, which are attacked by another molecule of **284′** to form **287**, which tautomerize to the target compounds **288**.

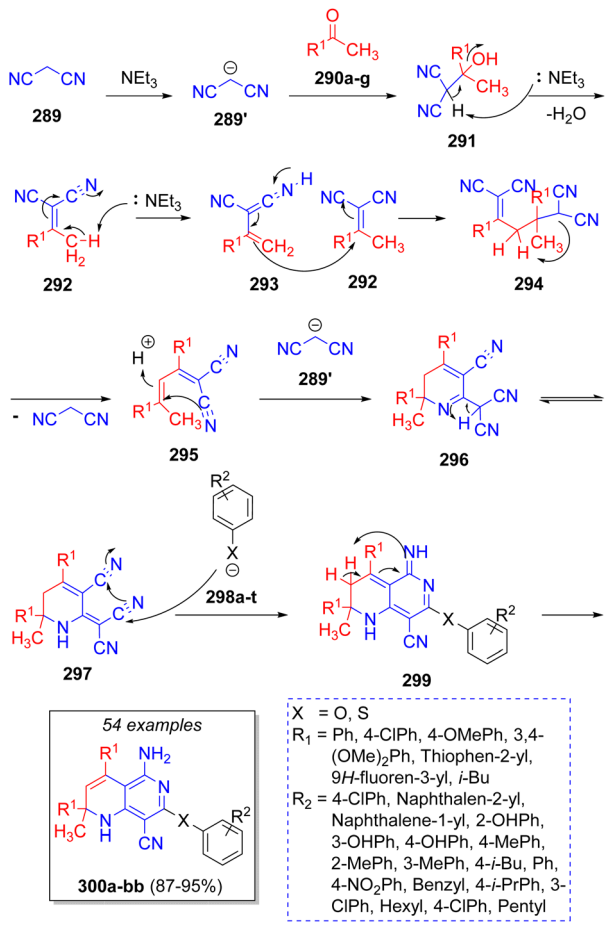
Das and co-workers,[59] in 2014, synthesized a collection of [1,6]naphtyridines *via* a domino pseudo-5CR, involving the reaction between two equivalents of malononitrile (**289**), two equivalents of methyl ketones **290a–g**, and phenols or thiols **298a–t** on water as solvent. A reaction mechanism was proposed as illustrated in Scheme 32. Intermediates **292** are formed *via*



Scheme 30 Synthesis of bis(pyrazolyl)methanes *via* an ionic liquid-catalyzed pseudo 5-CR.



Scheme 31 Synthesis of 5,5′-(arylmethylene)bis(4-hydroxythiazol-2(3*H*)-ones) *via* a pseudo-5CR.

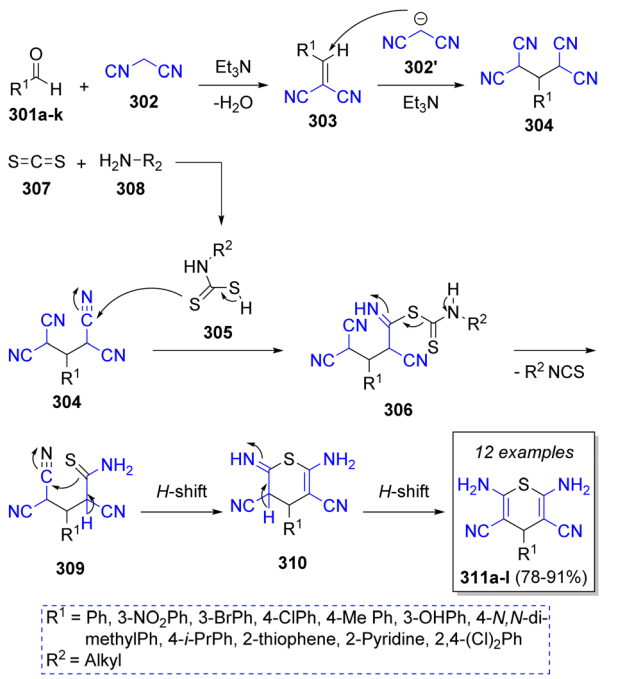


Scheme 32 Synthesis of [1,6]naphtyridines.

a Knoevenagel condensation of malononitrile anion **289′** with ketones **290a–g** promoted by triethylamine, followed by Michael addition of another previously formed intermediates **292** to afford **295** upon loss of a malononitrile fragment. Next, the attack of another malononitrile anion forms the cyclic intermediates **296**, which then tautomerize to **297**. After nucleophilic attack of phenols or thiols **298a–t** on the electrophilic nitrile group and further aromatization, the final products **300a–b** are formed.

A collection of 4*H*-thiopyrans was successfully synthesized by Bodaghifard and co-workers[60] in 2016. This pseudo-5CR involves a variety of aromatic aldehydes **301a–k**, two equivalents of malononitrile (**302**), carbon disulfide (**307**), primary amines **308**, and triethylamine as catalyst. A mechanistic pathway for the synthesis of 4*H*-thiopyran derivatives was suggested as illustrated in Scheme 33. Initially, Knoevenagel condensation of aldehydes **301** and malononitrile **302** generates arylidene malononitrile intermediates **303**, which then react with anion **302′** *via* Michael addition to form intermediates **304**. Simultaneously, intermediates **305** are formed from the addition of **308** to carbon disulfide (**307**), which then react with intermediates **304** to form **306**. A hydrogen shift and loss of an isothiocyanate fragment leads to the formation of intermediates **309**. Next, another *H*-shift induces an intramolecular cyclization by the attack of sulfur unto the cyano group. After a final *H*-shift the desired products **311a–l** are formed.

A method to synthesize *tris*-amides *via* a microwave-assisted pseudo-5CR was achieved in excellent yields by Hosseini-Tabatabaei and co-workers[61] in 2017. This MCR included the use of Meldrum's acid (**312**), aryl aldehydes **313a–f**, alkyl isocyanides **315a–b** and two equivalents of aniline (**317**). The proposed mechanism for this reaction comprises an initial

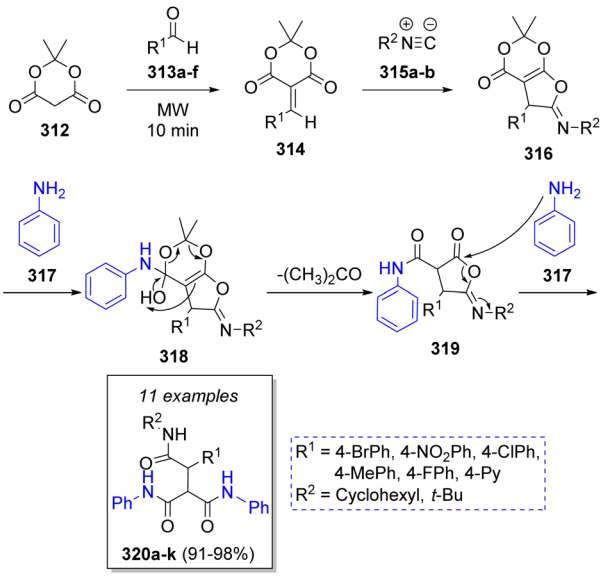


Scheme 33 Synthesis of 4*H*-thiopyran derivatives.

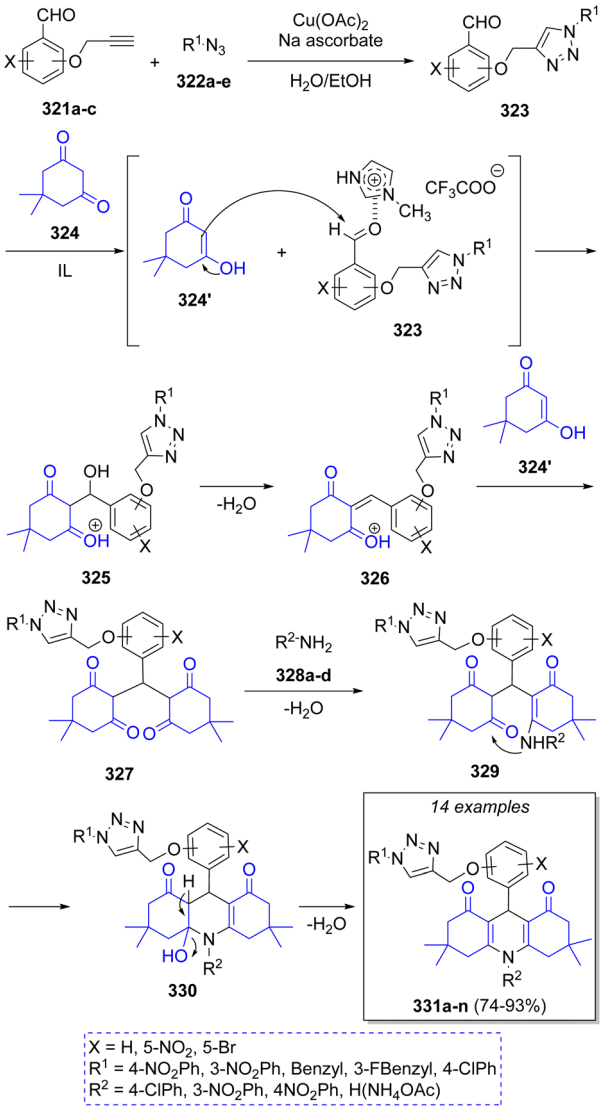
Knoevenagel condensation between Meldrum's acid **312** and aldehydes **313a–f** to form the conjugated electron-deficient heterodienes **314**, which react with isocyanides **315a–b** *via* Michael addition to give aminolactone intermediates **316**. Next, the reaction of aminolactones **316** with aniline **317** affords the vinylogous carbonates **318**. Upon loss of acetone and a final ring-opening reaction with another molecule of aniline **317**, the desired products **320a–k** are formed (Scheme 34).

Dabiri and Salehi[62] reported a series of triazolyl methoxyphenyl 1,8-decahydroacridine derivatives using aromatic propargylated aldehydes **321a–c**, a variety of azides **322a–e**, two equivalents of dimedone (**324**) and amines **328a–d** in the presence of $Cu(OAc)_2$/sodium ascorbate and 1-methylimidazolium trifluoroacetate ([*Hmim*]TFA) as catalyst. The proposed reaction mechanism for this transformation is illustrated in Scheme 35. Initially, aromatic propargylated aldehydes **321** react with azides **322** to form, *via* a click reaction, the intermediate 1,2,3-triazolyl methoxy benzaldehydes **323**. Then, dimedone **324** reacts with intermediates **323** *via* a Knoevenagel condensation, with acidic ionic liquid (IL) acting as catalyst, to afford intermediates **326** after loss of water. Subsequently, a second molecule of dimedone **324′** reacts, *via* Michael addition, with **326** to afford **327**. Lastly, a nucleophilic attack of amines **328a–d** followed by intramolecular cyclization and loss of a water molecule affords the final products **331a–n**.

An efficient and high-yielding method to obtain highly functionalized [1,6]naphthyridines *via* pseudo-5CR was achieved by Khan and co-workers[63] using two equivalents of arylmethyl ketones or alkyl methyl ketones **332a–j**, two equivalents of malononitrile (**333**) and alkyl alcohols or thiols **337a–d**, with sodium hydroxide as catalyst. The reaction was proposed to proceed as is depicted in the Scheme 36. An initial Knoevenagel condensation between methyl ketones **332a–j** and malononitrile (**333**) forms the intermediates **334**, followed by an auto-Michael addition of ylidenes **334**, which after loss of one



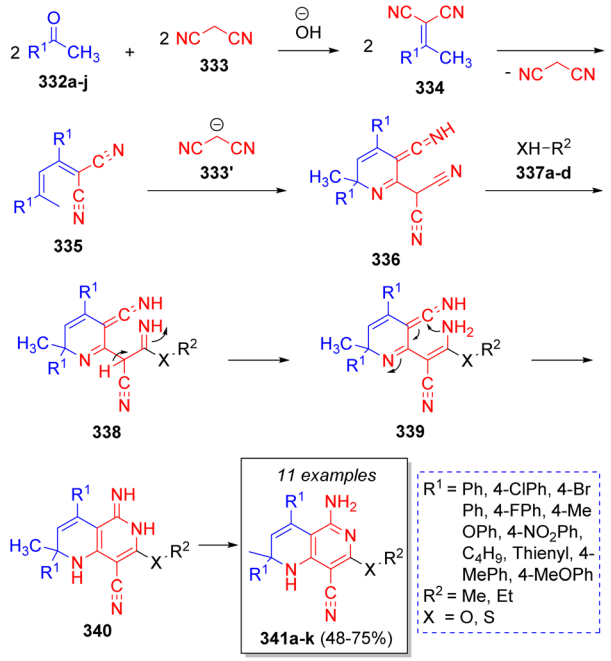
Scheme 34 Synthesis of *tris*-amides *via* pseudo-MCRs.



Scheme 35 Synthesis of triazolyl methoxyphenyl 1,8-decahydroacridine derivatives.

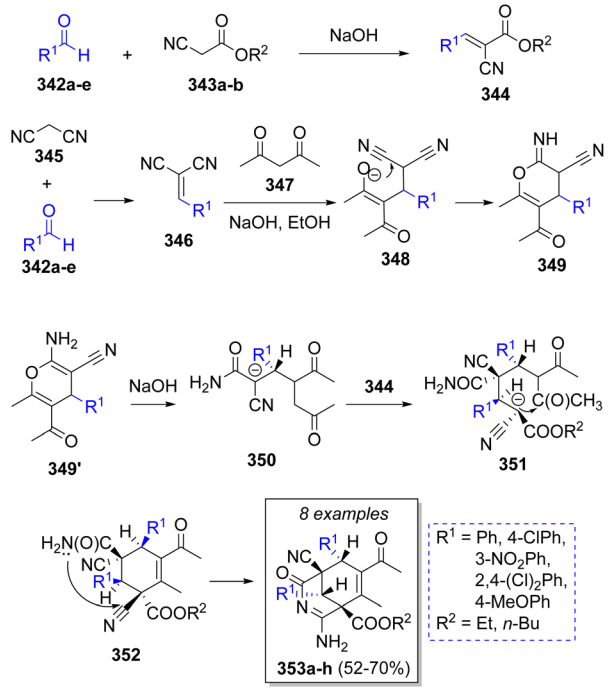
molecule of malononitrile give the intermediates **335**. Upon a reaction with another malononitrile molecule, intermediates **336** are formed. Subsequently, alcohols or thiols **337a–d** attack to form intermediates **338**. A proton shift affords intermediates **339**, which undergo an intramolecular cyclization to form **340**. A final aromatization step affords the desired products **341a–k**.

A small library of highly functionalized 3-azabicyclo[3.3.1]nona-2.7-dienes was reported by Ismiyeva and co-workers[64] *via* a stereoselective cascade pseudo-5CR, comprising the aromatic aldehydes **342a–e** (2 equivalents), cyanoacetic esters **343a–b**, malononitrile (**345**) and acetylacetone (**347**). The probable reaction mechanism is illustrated in Scheme 37. Initially, cyanoacetic esters **343a–b** undergo a Knoevenagel condensation with **342a–e** to produce intermediates **344**. Simultaneously, the same happens with malononitrile **345** and another molecule of **342a–e** to form arylidenemalononitrile-type intermediates **346**. Next, **346** reacts with acetylacetone **347** to form **348**, which upon



Scheme 36 Synthesis of highly functionalized [1,6]-naphthyridines.

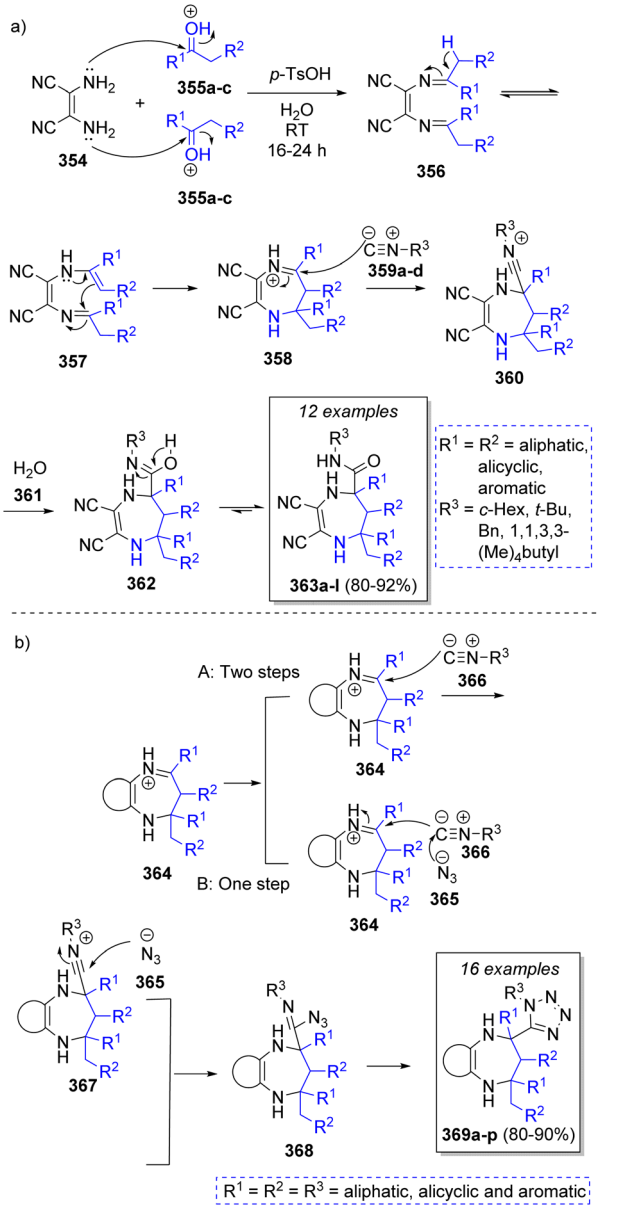
further heterocyclization form 4*H*-pyrans **349**. Then, an acyclic intermediates **350** result from OH-assisted nucleophilic cleavage of **349**, followed by a Michael addition of anions **350** to the previously formed arylidenemalononitriles **344** and a carbocyclization to give **352**. Upon an intramolecular cyclization, the final products **353a–h** are obtained.



Scheme 37 Synthesis of 3-azabicyclo[3.3.1]nona-2.7-dienes.

4.2 Condensation/cyclization

In 2008, Shaabani and co-workers[65] reported a high-yielding pseudo-5CR synthesis of 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamides using 2,3-diaminomaleonitrile (DAMN, **354**), two equivalents cyclic or acyclic ketones **355a–c**, isocyanides **359a–d**, and water **361** with *p*-toluenesulfonic acid as catalyst. As depicted in Scheme 38, the proposed reaction mechanism begins with two simultaneous condensations between DAMN **354** and acid activated ketones **355a–c** to form the diimine intermediates **356**, which upon an imine-enamine tautomerization followed by intramolecular cyclization affords iminium ion intermediates **358**. Then, α-attack by the isocyanides **359a–d** affords nitrilium ion intermediates **360**. Finally, the desired products **363a–l** are formed by water addition to nitrilium ions



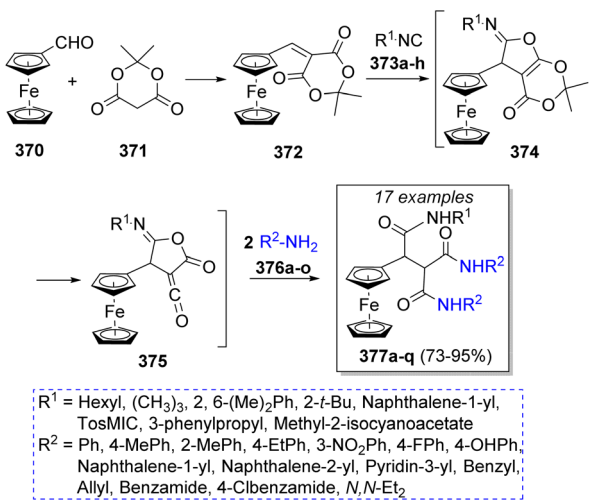
Scheme 38 Synthesis of (a) 4,5,6,7-tetrahydro-1*H*-1,4-diazepine-5-carboxamides, and (b) 1*H*-tetrazolyl-benzo[*b*][1,4]diazepines.

360 and a final tautomerization process. Similarly, a series of bifunctional diazepine-tetrazoles **369a–p** were synthesized by Shaabani and co-workers[66] using 2,3-diaminomaleonitrile or aromatic diamines, ketones, trimethylsilylazide, isocyanides and *p*-toluenesulfonic acid as catalyst in methanol. A similar mechanism was proposed by the authors, upon formation of iminium ions **364**, there are two possible pathways to form intermediates **368**, pathway A involves two steps, first a nucleophilic attack of isocyanides **366** to iminium ions **364** to form **367**, followed by a nucleophilic attack by the azide ion **365**. The second pathway involved a one-step concerted reaction with the nucleophilic attack of azide ion **365** to isocyanides **366**, followed by isocyanides **366** attack to iminiums **364**. The last step consists of an intramolecular [3 + 2] cycloaddition to afford the final products **369a–p** (Scheme 38).

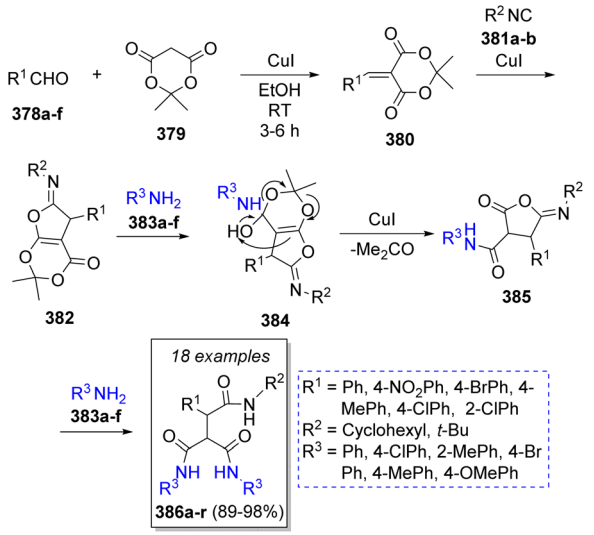
4.3 Knoevenagel condensation/[1,4] cycloaddition

In 2011, Teimouri and Akbari-Moghaddam[67] reported an efficient method to obtain ferrocene-triamides from the reaction of ferrocenecarboxaldehyde (**370**), Meldrum's acid (**371**) with alkyl or aryl isocyanide **373a–h** and two equivalents of different amines **376a–o** in anhydrous dichloromethane as solvent. Scheme 39 illustrates the synthetic methodology. The first step is a Knoevenagel condensation of ferrocenecarboxaldehyde (**370**) with Meldrum's acid **371** to form the electro-deficient heterodiene **372**. A [1 + 4] cycloaddition reaction with isocyanides **373a–h** leads to iminolactone intermediates **374**; after loss of acetone, **375** reacts with two molecules of anilines **376** to form the final products **377a–q**.

Likewise, Safaei-Ghomi and co-workers[68] published a high-yielding method to obtain functionalized tricarboxamides using two equivalents of benzaldehydes **378a–f**, Meldrum's acid (**379**), isocyanides **381a–b**, and anilines **383a–f** in the presence of catalytic amounts of copper(I) iodide nanoparticles. It is noteworthy that the catalyst proved to be recyclable as it was recovered and reused several times. The suggested reaction



Scheme 39 Synthesis of ferrocene-triamides.

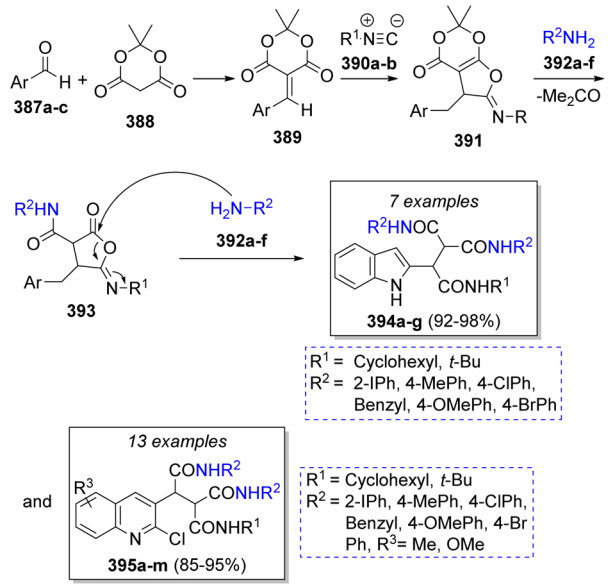


Scheme 40 Synthesis of tricarboxamides.

mechanism is depicted in Scheme 40. Initially, a Knoevenagel condensation between benzaldehydes **378a–f** and Meldrum's acid **379** is catalyzed by CuI nanoparticles to afford intermediates **380**, which then react with isocyanides **381a–b** in a [1 + 4] cycloaddition to form iminolactones **382**. Subsequently, iminolactones **382** react with an aniline molecule **383a–f** to produce vinylogous carbonates **384**. Ultimately, **384** is converted into the desired products **386a–r** through the reaction with another molecule of amine **383a–f**.

The synthesis of a library of indole and quinoline tricarboxamides was achieved by Shiri and Heravi[69] using aromatic aldehydes (2-formylindole or 2-Cl-3-formyl quinolines) **387a–c**, Meldrum's acid (**388**), isocyanides **390a–b** and aromatic amines **392a–f** (two equivalents) in dichloromethane as solvent. According to the suggested mechanism (Scheme 41), aldehydes **387a–c** and Meldrum's acid (**388**) react *via* Knoevenagel condensation to afford imine intermediates **389** which then undergo a [1 + 4] cycloaddition with isocyanides **390a–b** to give aminolactone intermediates **391**. Then, nucleophilic addition of arylamines **392a–f** to **391** with subsequent releasing of an acetone molecule forms the intermediates **393**, followed by the addition of a second molecule of amines **392a–f** at lactone carbonyl group to form the desired products **394a–g** and **395a–m** in excellent yields.

In 2022 M. Mojtahedi and co-workers[70] reported a novel pseudo-5CR synthesis of dicyanoanilines **409a–k** by reacting different substituted aromatic aldehydes **396a–k** with four equivalents of malononitrile (**397**) in the presence of triethylamine. To explain this transformation the authors proposed the following reaction mechanism: the first step is a Knoevenagel condensation of the aldehydes **396** with a molecule of malononitrile to produce the intermediates **398**. Simultaneously, two molecules of malononitrile react to form dimer **399**. Then, **398** and **399** undergo a cycloaddition to produce the intermediates **400**, which after loss of an HCN molecule, followed by annulation and ring rearrangement generates **403**, which reacts with



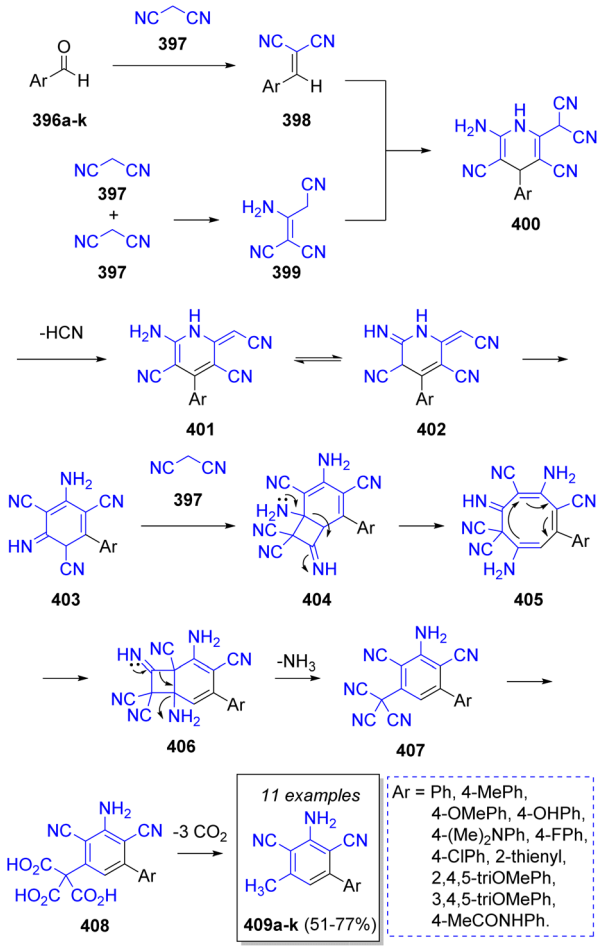
Scheme 41 Synthesis of indole and quinoline tricarboxamides.

another molecule of malononitrile followed by a ring expansion and contraction sequence and a decarboxylation to afford the target compounds **409a–k** in good to excellent yields (Scheme 42).

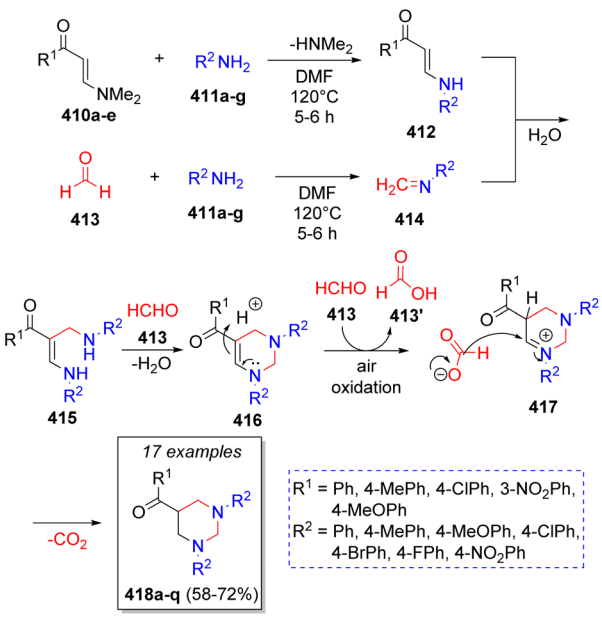
4.4 Others

In 2012, Perumal and co-workers[71] reported a domino pseudo-5CR for the synthesis of 11 examples of 5-aroyl-1,3-diarylhexahydropyrimidines involving the use of the (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-ones **410a–e**, formaldehyde (four equivalents, **413**), and aromatic amines (2 equivalents) **411a–g**. A reasonable reaction mechanism was suggested as depicted on Scheme 43. The reaction initially proceeds *via* Michael addition of amines **411a–g** to **410a–e**, the subsequent loss of the dimethylamine moiety affords intermediates **412**. Simultaneously, formaldehyde **413** condenses with another molecule of amines **411a–g** to form the corresponding imines **414**. Then, a Mannich-type reaction occurs between **412** and **414** to produce the intermediates **415**, which condense with a second molecule of formaldehyde to afford intermediates **416**. Upon protonation and reduction, induced by the formic acid arising from the air oxidation of excess of formaldehyde, the final products **418a–q** are formed.

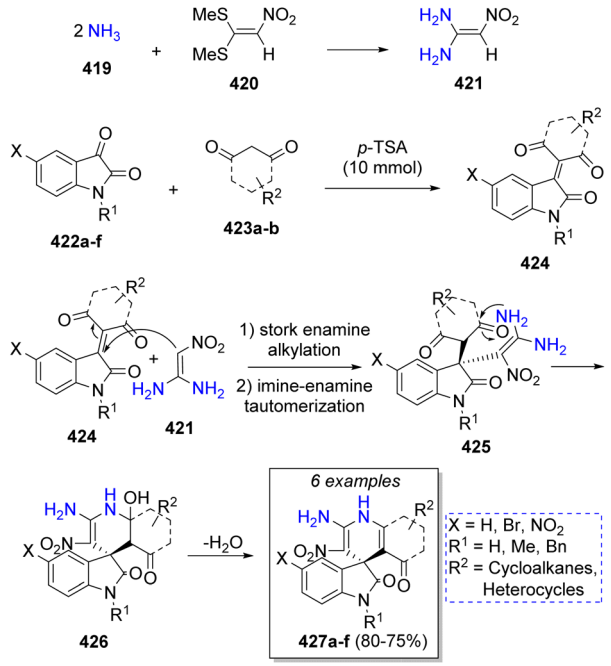
In the same year, a series of spirooxindoles were prepared from a pseudo-5CR by Alizadeh and co-workers,[72] comprising the reaction of two equivalents of ammonia **419**, 1,1-bis(methylthio)-2-nitroethylene (**420**), isatin (or derivatives) **422a–f** and 1,3-dicarbonyl compounds **423a–b** in water as solvent. A plausible reaction mechanism was proposed for this reaction as illustrated in Scheme 44. This pseudo MCR starts with two nucleophilic attacks of ammonia **419** on 1,1-bis(methylthio)-2-nitroethylene (**420**) which resulted in the formation of ketene diaminal **421**. Later, a Knoevenagel condensation between isatins **422a–f**, 1,3-dicarbonyl



Scheme 42 Synthesis of dicyanoanilines *via* a pseudo-5CR.



Scheme 43 Synthesis of 5-aroyl-1,3-diarylhexahydropyrimidines.

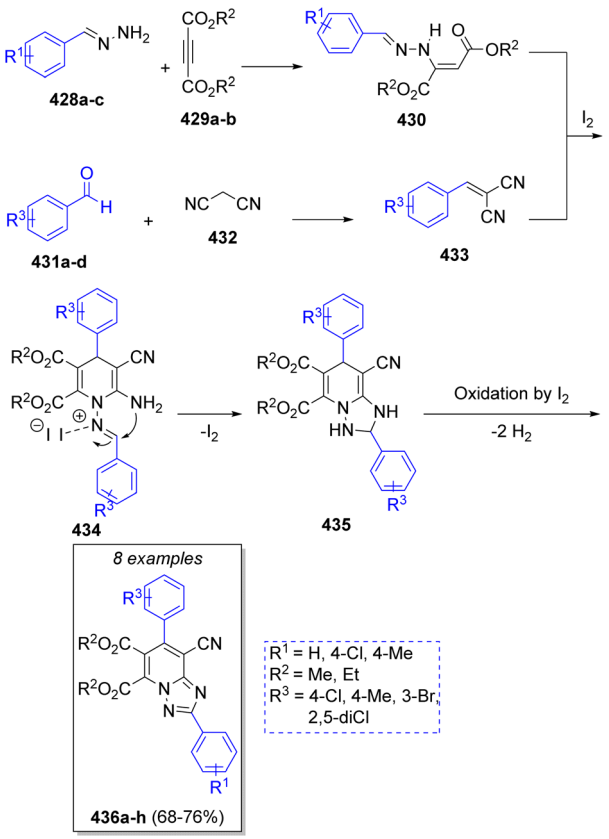


Scheme 44 Synthesis of spirooxindoles.

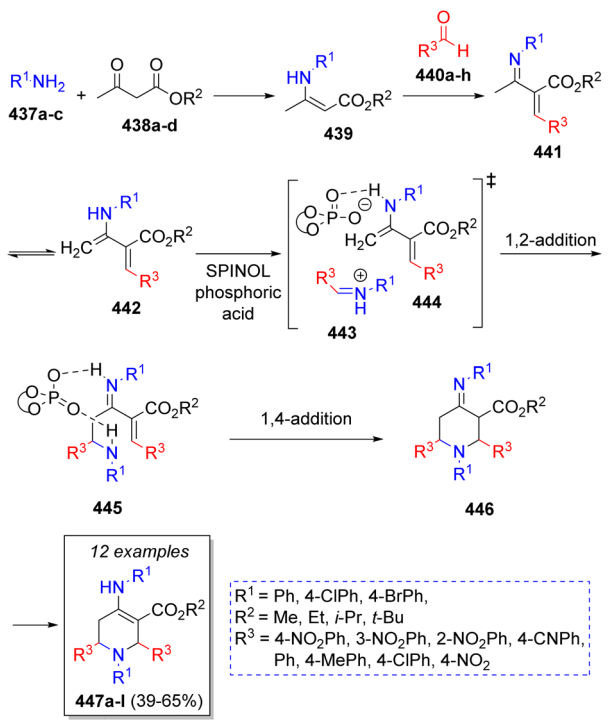
compounds **423a–b** with *p*-toluenesulfonic acid (*p*-TSA) as catalyst forms intermediates **424**. Intermediates **425** are formed after a Stork enamine alkylation between **421** and **424**. Further intramolecular cyclization and loss of a water molecule leads to the formation of the final products **427a–f**.

A series of 1,2,4-triazolo[1,5-*a*]pyridines were synthesized by Alizadeh and co-workers[73] in 2013. Their syntheses involved the reaction between the benzylidene-hydrazines **428a–c**, acetylene-dicarboxylates **429a–b**, two equivalents of aromatic aldehydes **431a–d** and malononitrile (**432**) in ethanol, with molecular iodine as catalyst. Scheme 45 shows the proposed mechanism for the reaction. It is likely that, initially, enaminone compounds **430** are formed *via* the reaction of benzylidenehydrazines **428a–c** with dialkyl acetylenedicarboxylates **429a–b**. Simultaneously, aldehydes **431a–d** condense with malononitrile *via* a Knoevenagel reaction to form intermediates **433**, which then react with the previously formed enaminones **430** to yield the intermediates **434**. Upon iodine coordination to the imine group and intramolecular nucleophilic attack of amine group, intermediates **435** are formed, which after oxidation leads to the desired products **436a–h**.

A library of chiral tetrahydropyridines were obtained by Lin and co-workers[74] *via* an organocatalytic asymmetric pseudo-5CR using two equivalents of aromatic amines **437a–c**, β-ketoesters **438a–d**, two equivalents of aromatic aldehydes **440a–h** and SPINOL-derived phosphoric acid as catalyst. The reaction sequence is illustrated in the Scheme 46. Initially, the reaction is proposed to proceed *via* condensation of amines **437a–c** with β-ketoesters **438a–d** to give enamines **439**, which further react with aldehydes **440a–h** to form intermediates **441**. These compounds undergo an imine-enamine tautomerization to afford the diene intermediates **442**. Simultaneously, another



Scheme 45 Synthesis of 1,2,4-triazolo[1,5-*a*]pyridines.

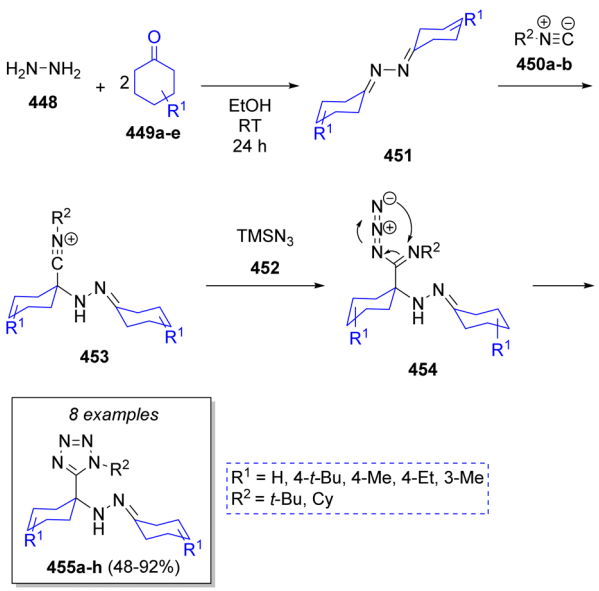


Scheme 46 Synthesis of pentasubstituted-tetrahydropyridines.

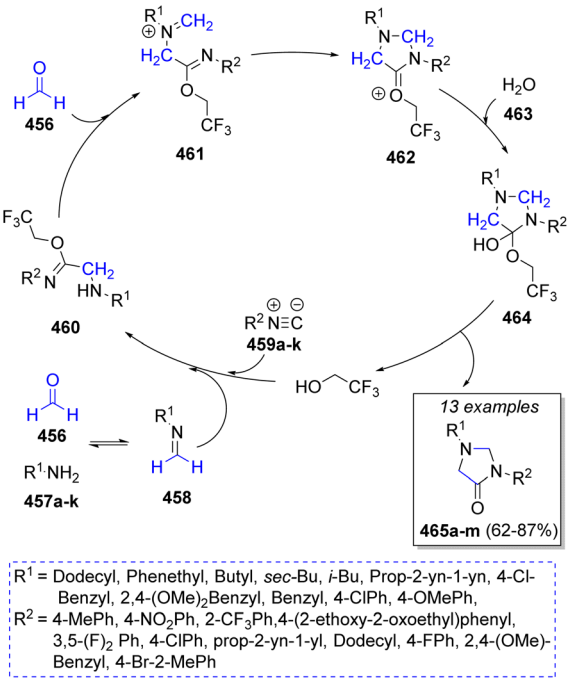
molecule of aldehydes and amines react to form imines **443**, which are activated *via* protonation of the amine and hydrogen bonding between enamines **442** and SPINOL-phosphoric acid to afford **444**. Then, a pseudo-intramolecular 1,2-addition gives the iminium ions **445**, which undergo an intramolecular-1,4-addition to afford intermediates **446**. Finally, a tautomerization of these later ones leads to the final products **447a–l**.

A high-yielding and diastereoselective synthesis of α-hydrazino tetrazole scaffolds were reported by Balalaie and co-workers[75] *via* an Ugi-azide pseudo-5CR. The strategy involved the sequential combination of hydrazine hydrate (**448**), cyclic ketones **449a–e**, trimethylsilyl azide (**452**) and isocyanides **450a–b**. A plausible mechanism was proposed as depicted in Scheme 47. Apparently, diimines **451** are generated *via* the condensation of hydrazine **448** with cyclic ketones **449a–e**. Next, nucleophilic attack of isocyanides **450a–b** affords nitrilium ion intermediates **453**, which are then attacked by the azide anion **452** from $TMSN_3$ to produce the intermediates **454**, which undergo a final intramolecular cyclization to afford the products **455a–h**.

A synthesis of a series of *N*,*N*′-substituted-4-imidazolidinones was successfully accomplished by Ramirez and co-workers[76] in 2018 *via* a pseudo-5CR using two equivalents of formaldehyde (**456**), primary amines **457a–k**, isocyanides **459a–k**, water **463** and trifluoroethanol as solvent. The proposed mechanism for this MCR is depicted in Scheme 48. This reaction is assumed to begin with the formation of the imines **458** from the condensation of formaldehyde (**456**) with amines **457a–k**, followed by their protonation. Next, a reaction with isocyanides **459a–k** leads to the formation of nitrilium ions, which are trapped by trifluoroethanol to give the imidates **460**. Then, a second molecule of formaldehyde condenses with **460** to form intermediates **461**, followed by an intramolecular cyclization to give **462**. Finally, addition of a water molecule affords hemi-orthoamides **464**, which after release of a solvent molecule generates the desired products **465a–m**.



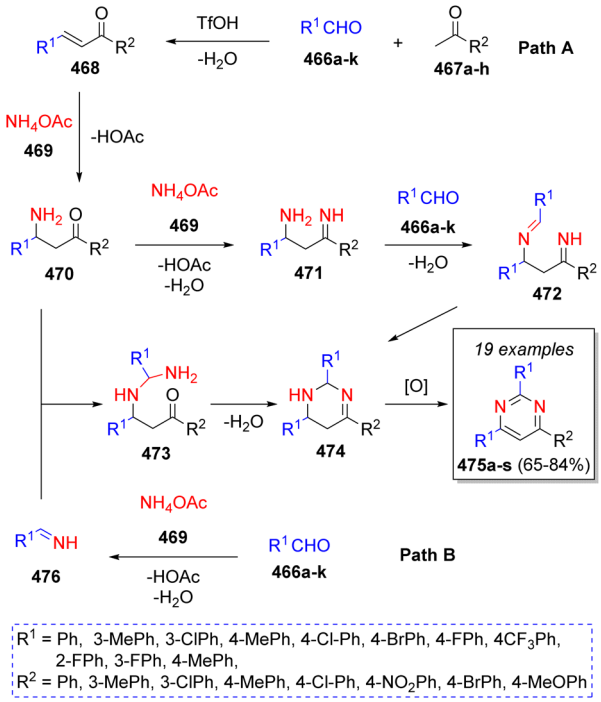
Scheme 47 Synthesis of α-hydrazino tetrazoles *via* a pseudo-5CR.



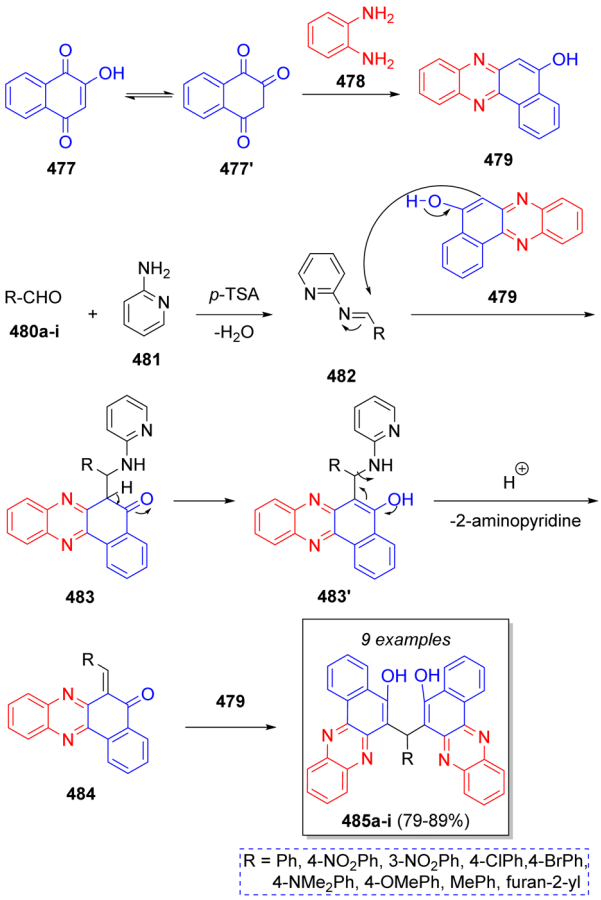
Scheme 48 Synthesis of *N*,*N*′-substituted 4-imidazolidinones.

In 2020, Ma and co-workers[77] reported an acid-catalyzed synthesis of 2,4,6-triarylpyrimidines using a variety of methyl ketones **467a–h**, two equivalents of aromatic aldehydes **466a–k**, two equivalents of ammonium acetate (**469**) and trifluoromethanesulfonic acid (TfOH) as catalyst. Two plausible mechanisms were proposed as Scheme 49 depicts. In path A, α,β-unsaturated ketones **468** are formed *via* aldol condensation of aldehydes **466a–k** and methyl ketones **467a–h** in the presence of TfOH, which react with ammonium acetate (**469**) *via* 1,4-Michael addition, followed by the loss of AcOH to afford intermediates **470**, which then condense with another molecule of ammonium acetate (**469**) to form the imine-type intermediates **471**, which further condense with a second molecule of aldehydes **466** to afford **472** and upon a final intramolecular cyclization and oxidation, the products **475a–s** are formed. On the other hand, *via* path B, intermediates **470** react with previously formed imines **476** (from the reaction between aldehydes **466a–k** and NH_4OAc (**469**)) to form the intermediates **473**, which then undergo an intramolecular cyclization producing the intermediates **474**, which upon air oxidation, generates the final products **475a–s**.

Recently, in 2020 a series of 6,6′(arylmethylene)bis(benzo[*a*]phenazine-5-ol)s were synthesized by Olyaei and co-workers,[78] using 2-hydroxynaphthalene-1,4-dione (**477**), *o*-phenylenediamine (**478**), aromatic aldehydes **480a–i**, with *p*-toluensulfonic acid (*p*-TsOH) as catalyst and 2-aminopyridine (**481**) as co-catalyst, *via* a tandem pseudo-5CR. According to the proposed reaction mechanism illustrated in Scheme 50, **477** tautomerizes to **477′**, which then reacts with *o*-phenylenediamine (**478**) to



Scheme 49 Synthesis of triarylpyrimidines *via* pseudo-5CR.



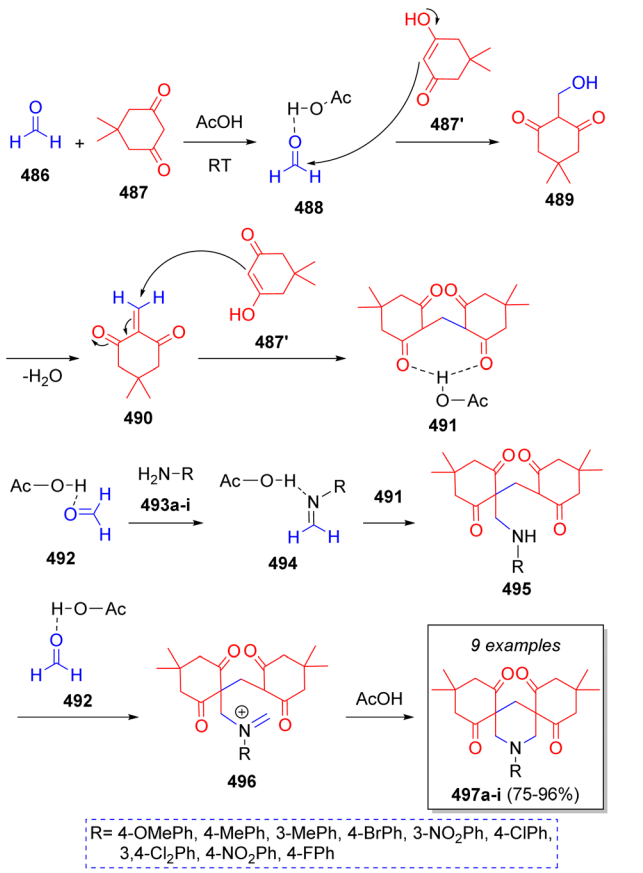
Scheme 50 Synthesis of 6,6′(arylmethylene)-bis(benzo[*a*]phenazine-5-ol).

afford benzo[*a*]phenanzin-5-ol **479**. Additionally, aromatic aldehydes **480a–i** condense with 2-aminopyridine (**481**), in the presence of *p*-TsOH producing Schiff bases **482** as intermediates. Next, intermediate **479** reacts with intermediates **482** affording **483**, which then tautomerize to compounds **483′**. Upon loss of a 2-aminopyridine fragment, *o*-quinonemethide **484** is produced. The desired products **485a–i** are formed after Michael addition of benzo[*a*]phenazine-5-ol **479** unto the **484** intermediates.

5. Pseudo-six component reactions

5.1 Knoevenagel/Michael addition

In 2016, Mousavi and co-workers[79] reported a simple and eco-friendly method to obtain bis-spiro piperidines using formaldehyde (**486**), dimedone (**487**), aromatic amines **493a–i** and acetic acid as solvent and catalyst. The proposed mechanism for this pseudo-6CR is illustrated in the Scheme 51. Initially, formaldehyde (**486**) is protonated and dimedone (**487**) tautomerized by acetic acid. Subsequently, intermediate **488** and enol form of **487′** react *via* Knoevenagel condensation to afford intermediate **489**, which after the loss of water, the α,β-unsaturated carbonyl compound **490** is produced. Next, intermediate **491** is formed from the Michael addition of another enol

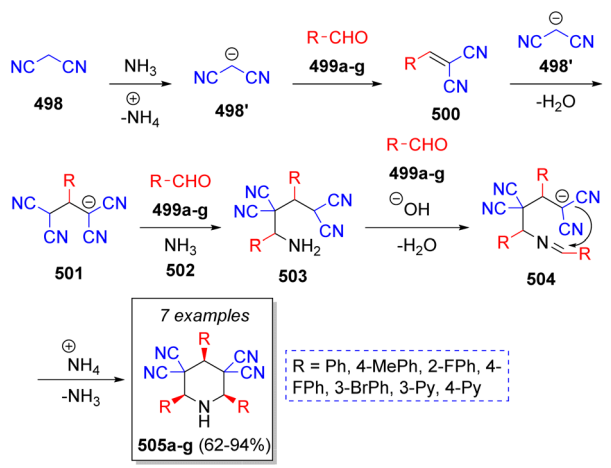


Scheme 51 Synthesis of bis-spiro piperidines *via* a Mannich type pseudo-6CR.

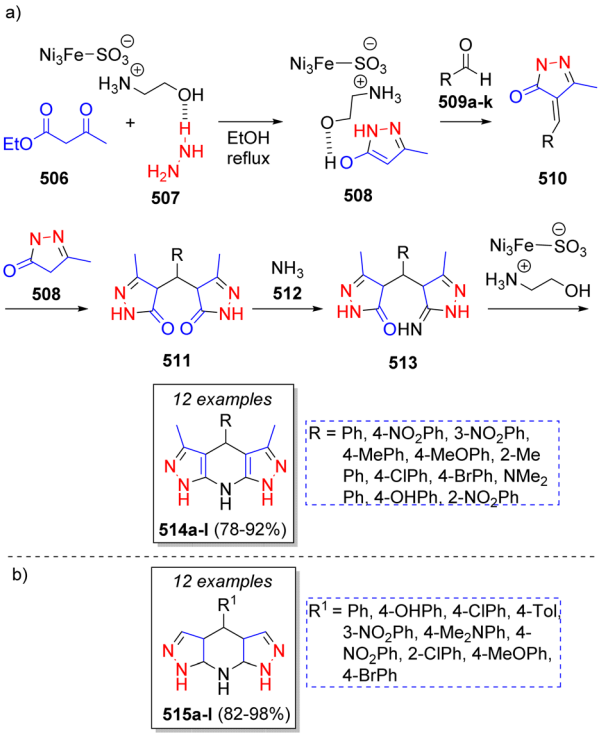
molecule **487′** to intermediate **490**. On the other hand, the reaction between an activated aldehyde **492** and amines **493a–i** produces imine intermediates **494** which then react with intermediate **491** *via* Mannich reaction to give intermediates **495**. Further reaction with another activated formaldehyde **492** generates iminium ions **496**. The final products **497a–i** are formed after an intramolecular cyclization *via* Mannich reaction.

A stereoselective synthesis of *cis*,*cis*-2,4,6-triaryl-3,3,5,5-tetracyanopiperidines was achieved by Vereshchagin and co-workers.[80] The cascade pseudo-6CR involved the use of two equivalents of malononitrile (**498**), three equivalents of aromatic aldehydes **499a–g**, and ammonium acetate or aqueous ammonia **502**, in methanol as solvent. The reaction sequence is depicted in the Scheme 52. Initially, ylidene-malononitriles **500** are formed from the reaction between malononitrile anion **498′** and aromatic aldehydes **499a–g** *via* Knoevenagel condensation prompted by ammonium acetate. Michael addition of another molecule of malononitrile anion **498′** to **500** affords the 1,1,3,3-tetracyanopropene anions **501**. Next, tetracyanoamides **503** are produced from the Mannich reaction of **501**, aldehydes **499a–g** and ammonia (from ammonium acetate). These intermediates then react with another molecule of aldehydes **499a–g** which leads to Schiff bases **504**, which upon further intramolecular cyclization afford the final cyclic amines **505a–g**.

A collection of fused tetrahydrodipyrazolopyridines was synthesized by Safaei-Ghomi and co-workers[81] *via* a highly efficient pseudo-6CR using ionic liquid supported on $FeNi_3$ as nanocatalyst. This procedure involved the reaction between ethyl acetoacetate (**506**), hydrazine (**507**), aromatic aldehydes **509a–k**, and ammonium acetate **512** as source of ammonia. A plausible reaction mechanism was suggested for the synthesis of the products as illustrated in Scheme 53a. The first step consists of a nucleophilic attack of hydrazine **507** on ethyl acetoacetate **506** to form the pyrazolone intermediate **508**. This intermediate then reacts with activated aldehydes **509a–k** *via*



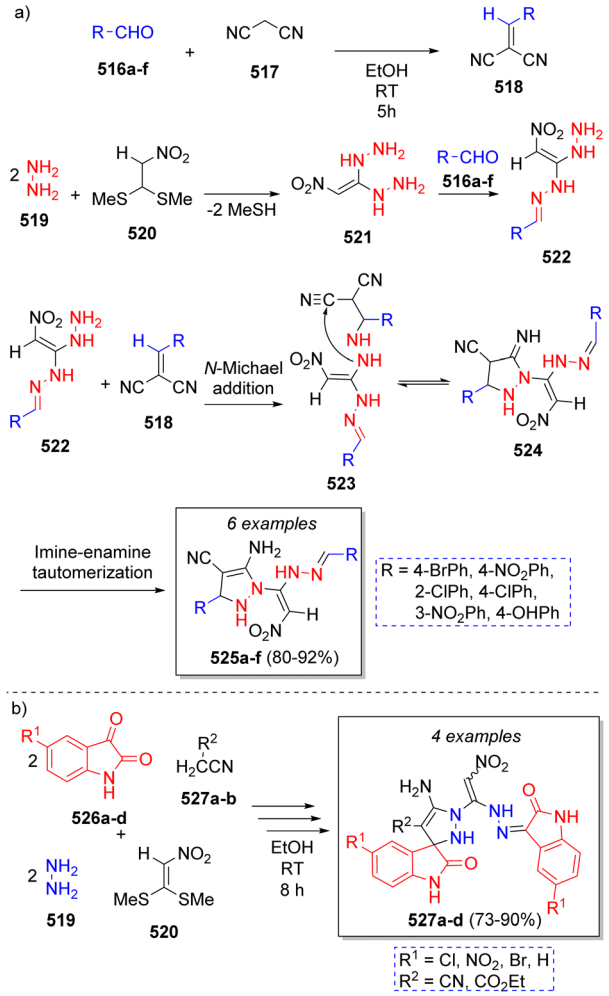
Scheme 52 Synthesis of *cis*,*cis*-2,4,6-triaryl-3,3,5,5-tetracyanopiperidines.



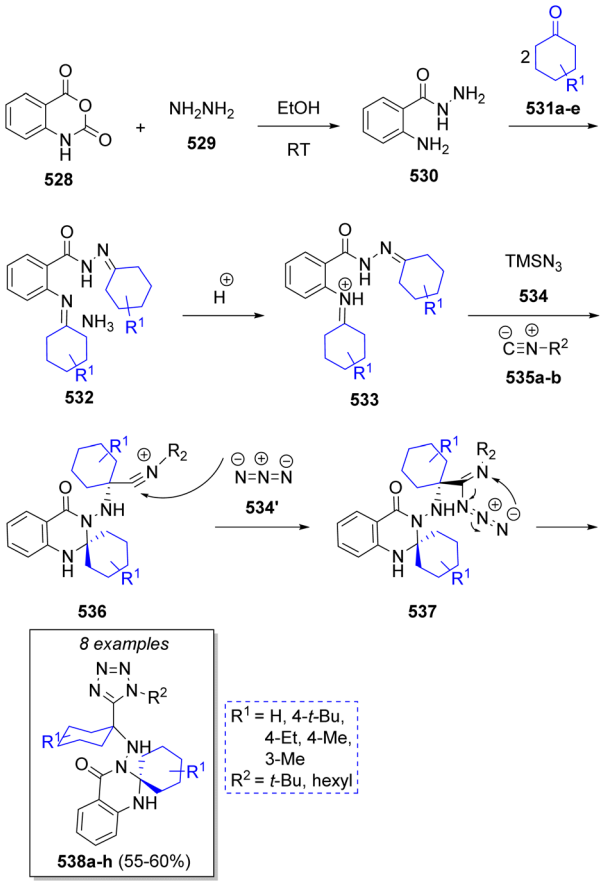
Scheme 53 (a) Synthesis of tetrahydrodipyrazolo pyridines. (b) Library of tetrahydrodipyrazolopyridines reported by Tamaddon and Khorram.

Knoevenagel condensation to form intermediates **510**. Then, another molecule of pyrazolone **508** attacks intermediates **510** to afford **511**. Afterwards, intermediates **511** are attacked by ammonia producing **513**, which upon a subsequent intramolecular condensation, the desired products **514a–l** are formed. Other collection of tetrahydrodipyrazolopyridines **515a–l** (Scheme 53b) were synthetized by Tamaddon and Khorram[82] using a similar strategy in water. This environmentally friendly procedure involved alkyl acetoacetates (two equivalents), hydrazine hydrate (two equivalents), ammonium carbonate and a variety of aromatic aldehydes.

The synthesis of many novel substituted pyrazoles were reported in 2018 by Rezvanian and co-workers[83] using aromatic aldehydes **516a–f**, malononitrile (**517**), hydrazine (**519**), and nitro ketene dithioacetal (**520**). The mechanism for the pseudo-6CR is depicted on Scheme 54a. Initially, aldehydes **516a–f** react with malononitrile **517** *via* Knoevenagel condensation to form intermediates **518**. Next, the S_N2 reaction of a 2.5 : 1 ratio of hydrazine (**519**) with nitro ketene dithioacetal (**520**) leads to the formation of 1,1-dihydrazino-2-nitroethylene (**521**) with the subsequent loss of two molecules of MeSH. The reaction of **521** with another molecule of aromatic aldehydes **516a–f** affords intermediates **522**. Subsequently, amine group of intermediates **522** attack the previously formed intermediates **518** producing **523**. Finally, **523** undergo an intramolecular cyclization *via* nucleophilic attack of amino group onto the CN group to form **524**, which then carry out a rapid imine-enamine tautomerization to afford the final products **525a–f**.



Scheme 54 (a) Synthesis of substituted 1*H*-pyrazoles-4-carbonitriles. (b) Synthesis of highly functionalized spiropyrazolines.



Scheme 55 Synthesis of tetrazolospiroquinazolinones.

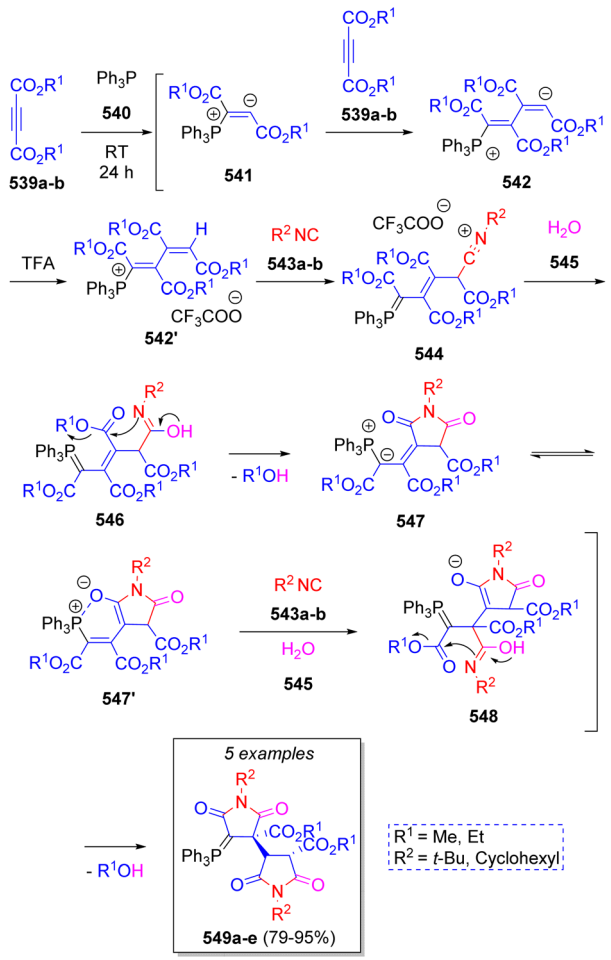
Using a similar reaction sequence, Rezvanian and Babashah[84] reported the synthesis of highly functionalized spiropyrazolines *via* a pseudo six-component reaction comprising isatins **526a–d** as the carbonylic component, active methylene compounds **527a–b**, hydrazine hydrate (**519**) and nitro ketene dithioacetal (**520**), which afforded the products **527a–d** as a mixture of two diastereomers in good to excellent yields (Scheme 54b).

5.2 Others

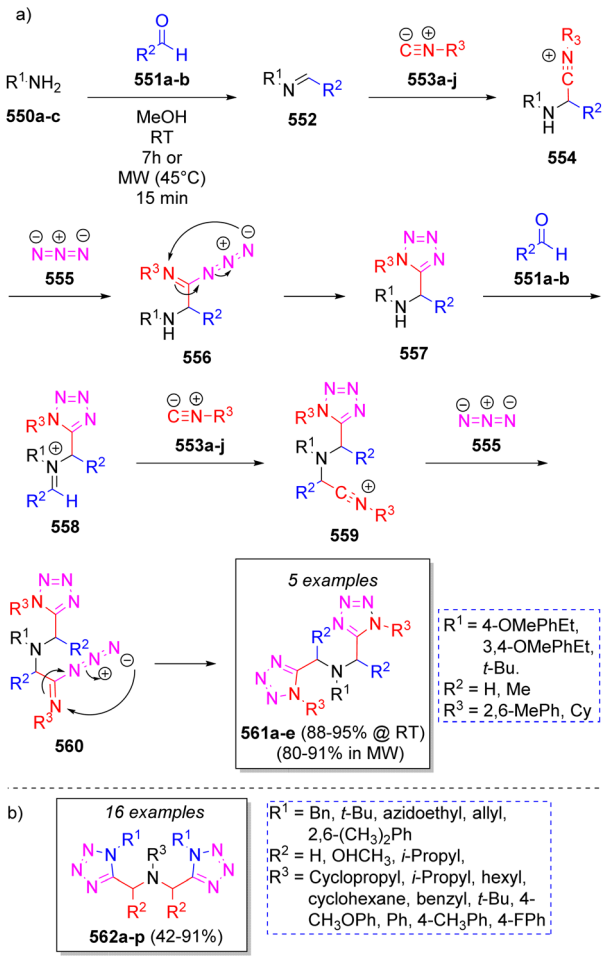
A series of tetrazolo-spiroquinazolinones were synthesized by Balalaie and co-workers[85] *via* a one-pot stereoselective pseudo-6CR comprising isatoic anhydride (**528**), hydrazine (**529**), cyclic ketones **531a–e** (2 equivalents), isocyanides **535a–b** and trimethylsilyl azide (**534**). The proposed reaction mechanism is outlined in Scheme 55. It is proposed that initially, hydrazine (**529**) reacts into the carbonyl group of isatoic anhydride (**528**), followed by ring opening and CO_2 elimination to afford the intermediate **530**. Upon a double condensation with cyclic ketones **531a–e**, hydrazones **532** are formed and upon protonation, the corresponding intermediates **533** are produced. Aminal intermediates **536** are generated by intramolecular nucleophilic attack of the amide nitrogen onto the imine moiety and axial nucleophilic attack of isocyanides **535a–b** on the imine. These intermediates undergo a nucleophilic addition of the azide ion producing **537**, followed by a final cyclization to generate the 1,5-disubstituted tetrazoles **538a–h**.

6. Pseudo-seven component reactions and more

In 2010, a small collection of new phosphanylidene bis(2,5-dioxotetrahydro-1*H*-pyrrole-3-carboxylates) were prepared by Alizadeh and co-workers[86] *via* a diastereoselective pseudo-7CR. The reaction involved two equivalents of dialkyl acetylenedicarboxylates (DAAD) **539a–b**, triphenylphosphine (TPP, **540**), two equivalents of isocyanides **543a–b** and two molecules of water (**545**). As Scheme 56 depicts, the mechanism proceeds initially *via* the formation of zwitterions **541** by the addition of TPP to **539a–b**, which then react with another molecule of DAAD **539a–b** to produce intermediates **542**. Then, **542** are protonated by TFA to generate the ion-paired intermediates **542′**. Nucleophilic addition of isocyanides **543a–b** produces nitrilium ion intermediates **544** to which a water molecule is added to



Scheme 56 Synthesis of phosphanylidene bis(2,5-dioxotetrahydro-1*H*-pyrrole-3-carboxylates).

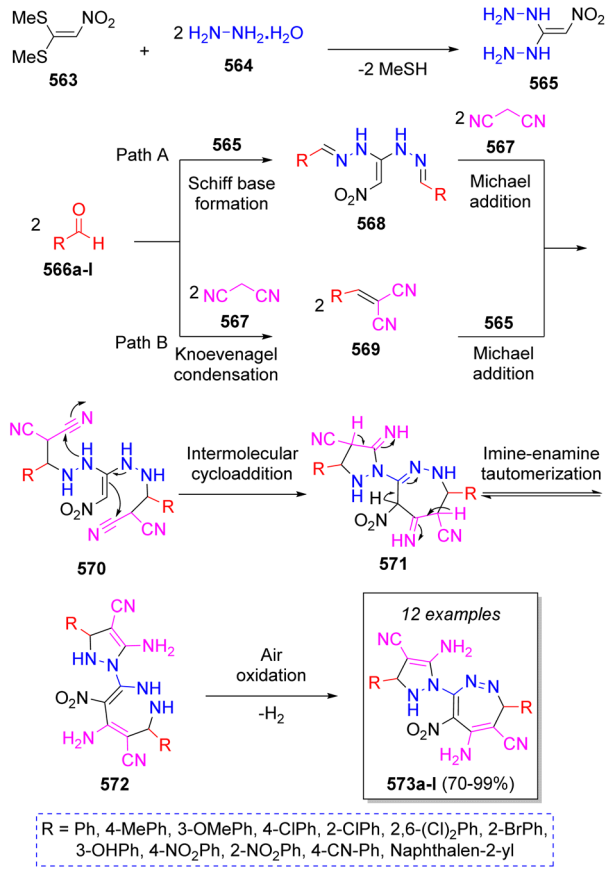


Scheme 57 (a) Synthesis of bis-1,5-disubstituted-1*H*-tetrazoles. (b) Compound library synthesized by Nenajdenko and co-workers.

produce **546**. These intermediates undergo an intramolecular cyclization to afford ylides **547**, followed by addition of isocyanides **543a–b** and a water molecule to afford intermediates **548**. Finally, a proton shift prompts another intramolecular cyclization, expelling an alcohol molecule, to provide the desired products **549a–e**.

In 2015, a series of bis-1,5-disubstituted-1*H*-tetrazoles were reported by Gámez-Montaño and co-workers *via* pseudo seven double Ugi-azide MCR, obtaining excellent yields (88–95%) at room temperature and slightly lower yields (80–91%) using MW conditions but in a reduced time.[87] The reaction involved different amines **550a–c**, two equivalents of a variety of aldehydes **551a–b**, two equivalents of isocyanides **553a–j**, and two equivalents of azide anion (**555** from trimethylsilyl azide) in methanol. Scheme 57a illustrates a reasonable mechanism for the reaction. Initially, intermediates **552** are formed from condensation of amines **550a–c** and aldehydes **551a–b** to which isocyanides **553a–j** are added to afford nitrilium ions **554**. Next, azide anion **555** adds to **554** to give intermediates **556** which undergo an intramolecular cyclization to afford the monotetrazoles **557**. These intermediates react again with aldehydes **551a–b** to afford iminium ions **558**, which react with isocyanides **553a–j** to afford **559**, and then a second molecule of azide **555** provides intermediate **560**, which after an intramolecular cyclization leads to the final products **561a–e**. Other collection of bis-1,5-disubstituted-1*H*-tetrazoles **562a–p** *via* pseudo seven-component Ugi-azide reactions were reported in 2019 by Nenajdenko and co-workers[88] using various amines, carbonyl compounds, isocyanides and TMS (as source of N_3) in methanol at room temperature. Scheme 57b illustrates the compounds reported in this work.

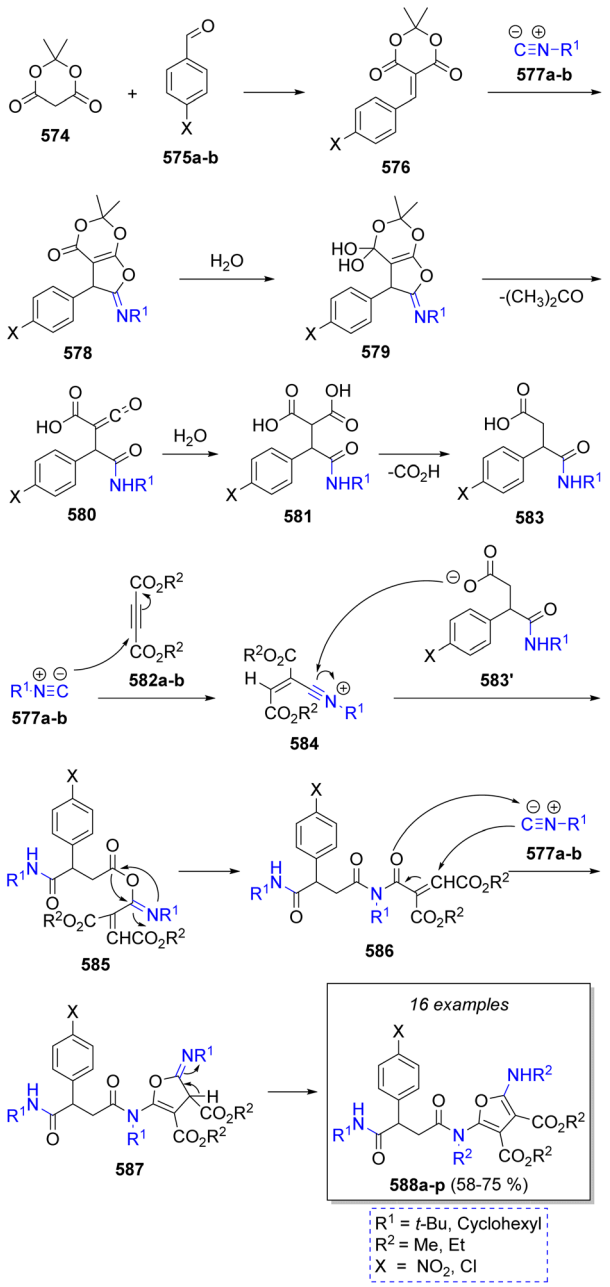
In 2018, Hasaninejad and Mojikjalifen[89] reported the synthesis of novel poly substituted pyrazolyl-1,2-diazepine scaffolds *via* a one-pot pseudo-7CR from condensation of 1,1-bis(methylthio)-2-nitroethylene (BMTNE) (**563**), two equivalents of hydrazine (**564**), two equivalents of aryl aldehydes **566a–l**, and two equivalents of malononitrile (**567**) in EtOH as solvent. The synthetic strategy is depicted in the Scheme 58. Initially, a nucleophilic substitution of hydrazine **564** on methylsulfanyl groups of BMTNE (**563**) leads to the formation of intermediate **565**. Now, two pathways (A and B) are possible. In pathway A, intermediates **570** are formed from the Schiff base formation between **565** and aryl aldehydes to form diimines **568**, which then react with two molecules of malononitrile **567**. In pathway



Scheme 58 Synthesis of poly substituted pyrazolyl-1,2-diazepines.

B, intermediates **570** are formed from the Knoevenagel condensation of malononitrile with aryl aldehydes **566a–l** to form intermediates **569** which then undergo Michael addition of **565**. Next, intermediates **570** undergo an intermolecular cycloaddition to afford **571**, followed by three imine-enamine tautomerizations to produce **572** and after a final air oxidation the desired products **573a–l** are formed.

A collection of fully substituted furans containing pseudo-peptide base were successfully prepared *via* an efficient pseudo-7CR by Shaabani and co-workers[90] in 2020. The reaction comprises Meldrum's acid (**574**), benzaldehydes **575a–b**, two different isocyanides **577a–b**, and acetylenedicarboxylates **582a–b** in a mixture of water and acetonitrile at 70 °C. According to Scheme 59, the proposed reaction proceeds *via* Knoevenagel condensation between aromatic aldehydes **575a–b** and Meldrum's acid (**574**) to give intermediates **576**, followed by a [1 + 4] cycloaddition of isocyanides **577a–b** to produce iminolactones **578**, which then react with water to produce **579**. These intermediates lose an acetone molecule to produce ketenes **580**, to which a water molecule is added producing **581**. These compounds undergo decarboxylation to afford mono carboxylic acids **583**. Simultaneously, the reaction between acetylenedicarboxylates **582a–b** and isocyanides **577a–b** produce a zwitterionic species which are protonated by **583** affording nitrilium ions **584** and carboxylate **583′**. Both intermediates then react to



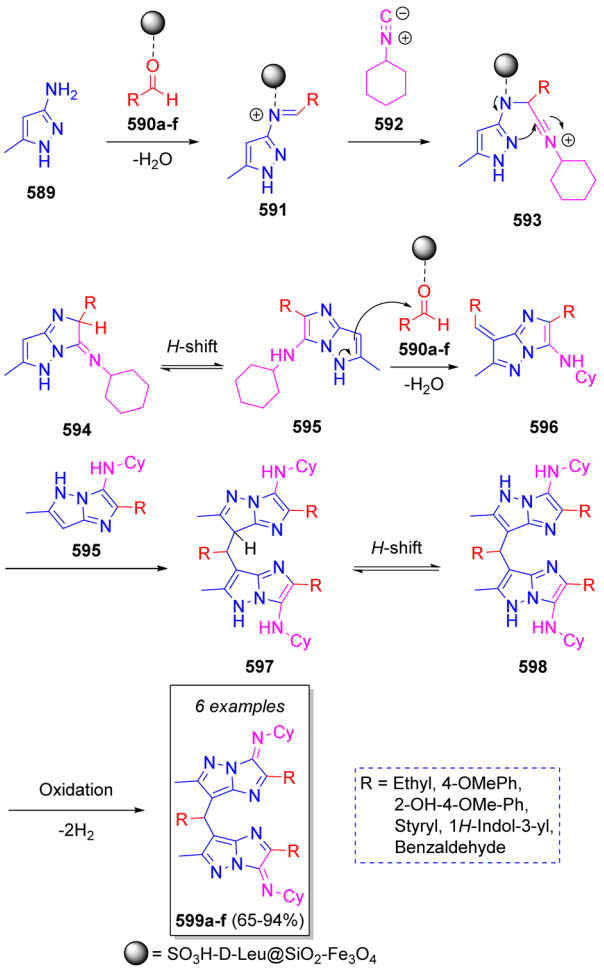
Scheme 59 Synthesis of fully substituted furans containing pseudo-peptide base.

produce **585**, which undergo a Mumm rearrangement to generate **586**. A [1 + 4] cycloaddition of isocyanides **577a–b** with the newly formed **586** affords iminolactones **587** which tautomerize to provide the final products **588a–p**.

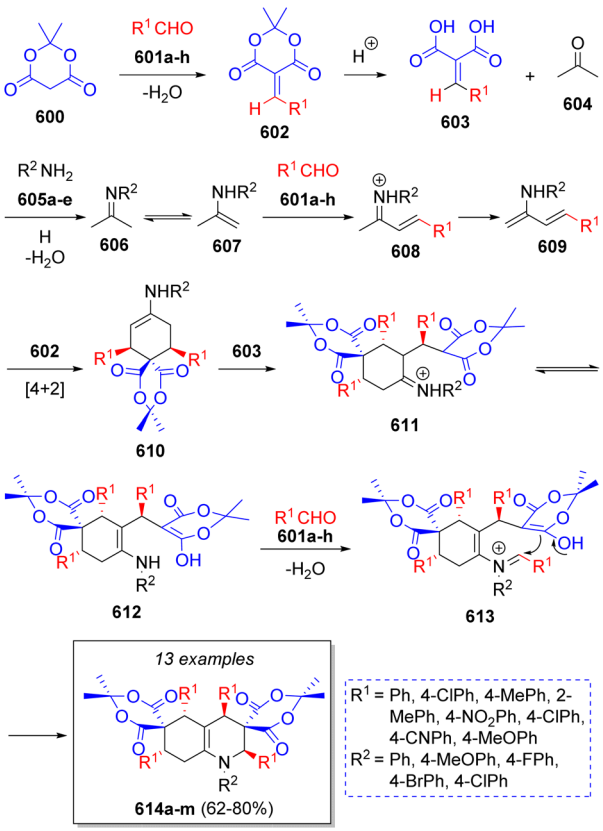
Yielzoleh and Nikoofar[91] reported the synthesis of a collection of 7,7′-((aryl/alkyl)methylene)bis(*N*-cyclohexyl-2-(aryl/alkyl)-6-methyl-3*H*-imidazo[1,2-*b*]pyrazol-3-imines) *via* a one-pot pseudo-7CR using 3-amino-5-methylpyrazole (**589**, 2 equiv.), aldehydes **590a–f** (3 equiv.) and cyclohexyl isocyanide (**592**, 2 equiv.) in ethanol as solvent. The suggested reaction mechanism is depicted in Scheme 60. Initially, 3-amino-4-

methylpyrazole **589** reacts with aldehydes **590a–f** (previously activated by SO_3H-*D*-Leu@SiO_2–Fe_3O_4) to produce imines **591** activated as the iminium salts by catalyst complexation. Next, iminium ions **591** are attacked by cyclohexyl isocyanide (**592**) to produce the intermediate nitrilium ions **593**, which then undergo an intramolecular cyclization to form imines **594**. Upon [1,3]-H shift, imidazopyrazoles **595** are formed, which then react with another molecule of aldehydes to produce **596** after releasing a water molecule. This is followed by a condensation of intermediates **595** and **596** to obtain the dimerized imidazopyrazoles **597**. Upon [1,3]-H shift and oxidation, the final products **599a–f** are obtained.

In 2014, Hazeri and co-workers[92] reported a diastereoselective synthesis of poly-substituted hydroquinolines *via* a one-pot domino pseudo-8CR, using three equivalents of Meldrum's acid (**600**), four equivalents of aromatic aldehydes **601a–h**, aromatic amines **605a–e**, in acetonitrile in the presence of trichloroacetic acid. A reaction mechanism was proposed as Scheme 61 depicts. Initially, the reaction between Meldrum's acid **600** and benzaldehydes **601a–h** *via* Knoevenagel condensation affords benzylidenes of Meldrum's acid **602**, which in acidic conditions are decomposed to **603** and acetone.



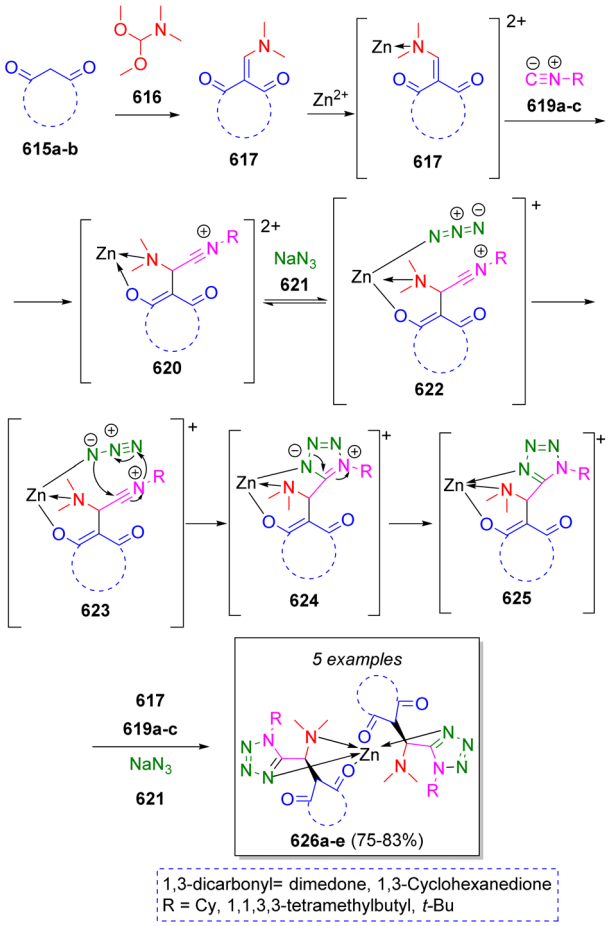
Scheme 60 Synthesis of 7,7′-((aryl/alkyl)methylene)bis(*N*-cyclohexyl-2-(aryl/alkyl)-6-methyl-3*H*-imidazo[1,2-*b*]pyrazol-3-imines).



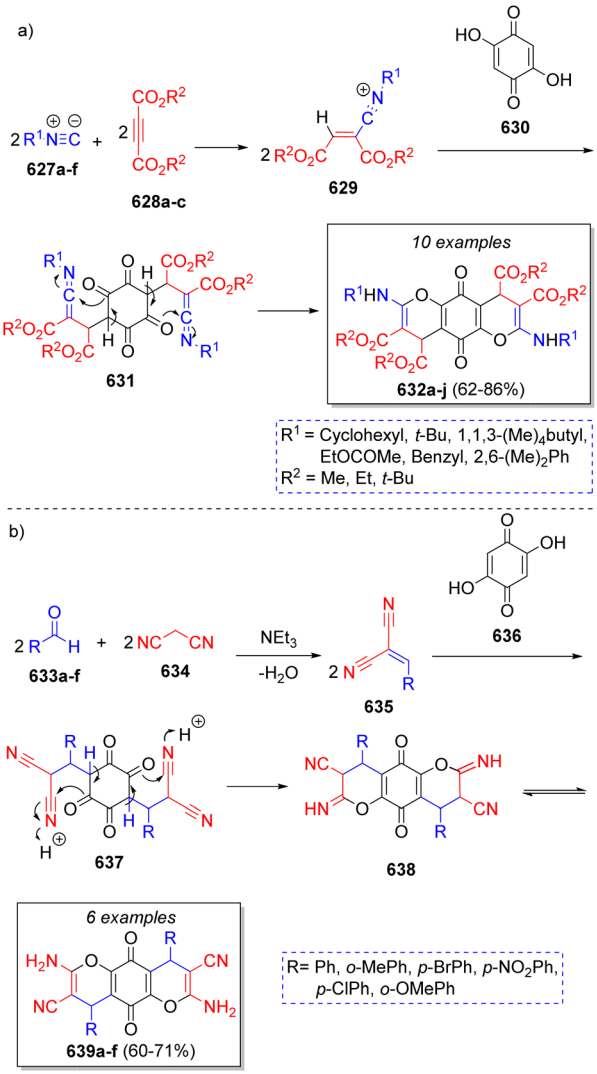
Scheme 61 Synthesis of poly-substituted tetrahydroquinolines.

Subsequently, acetone reacts with anilines **605a–e** to produce imines **606** which further tautomerize to enamines **607**, which react with the aldehydes to afford dienamines **609**. These compounds act as a diene and undergo Diels–Alder cycloaddition with **602** to form intermediates **610**. Finally, the Michael addition of the previously formed **603** produces **611**, which tautomerize to their enamine-enol forms **612**. Then, the reaction with aldehydes **601a–h** affords intermediates **613**, which after an intramolecular cyclization afford the desired products **614a–m**. Notably, the product contains four stereocenters and 10 new bonds were generated in a single vessel operation. Other collections of poly-substituted hydroquinolines were reported using benzoic acid,[93] Brønsted acid ionic liquid[94] and phthalic acid[95] as catalyst.

In 2011, a small collection of zinc 1,5-disubstituted-1*H*-tetrazol-5-yl coordination complexes were prepared by Shaabani and co-workers[96] *via* one-pot pseudo-9CR. The reaction plausibly proceeds *via* condensation of 1,3-dicarbonyls **615a–b** and DMF-DMA (**616**) to produce intermediates **617**, which then coordinate to Zn(II), followed by a Michael addition of isocyanides **619a–c** to give the nitrilium ions **620**. These intermediates coordinate with the azide anion **621** producing **622**, which allow an intramolecular 1,5-cycloaddition to generate the intermediates **624**, which further tautomerize to **625**. Upon reaction with another molecule of **617**, **619** and NaN_3 (**621**), the complete complexes **626a–e** are produced (Scheme 62).



Scheme 62 Synthesis of 1,5-disubstituted 1*H*-tetrazol-5-yl coordination complexes.

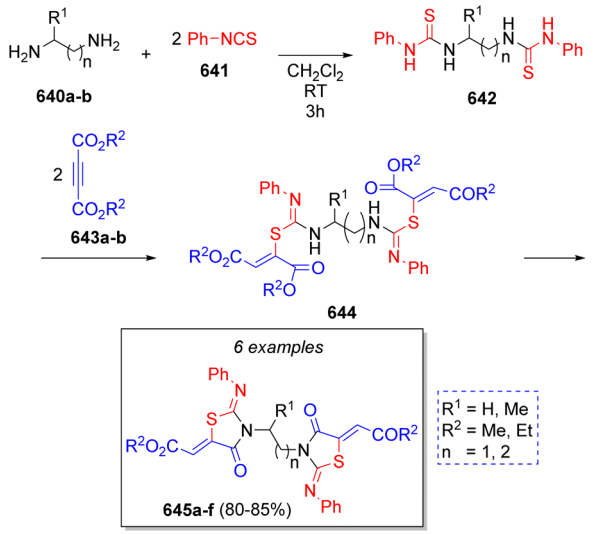


Scheme 63 (a) Synthesis of bis(4*H*-chromene)-3,4-dicarboxylates. (b) Synthesis of highly functionalized benzo[*g*]- and dihydropyrano[2,3-*g*] chromenes.

7. Repetitive pseudo-MCRs

Repetitive pseudo-MCRs are a subgroup of pseudo-MCRs in which there is a bifunctional reactant participating in the reaction sequence. Most of the examples depicted in this section could be classified as pseudo five-component reactions as well, but the difference in the reaction mechanism leading to the products is enough to warrant its own separate classification. In this case, an MCR occurs simultaneously on both functional groups of the bifunctional reactant. As it will become apparent throughout this section, the products of repetitive pseudo-MCRs are highly symmetrical, which is of high interest for ligand design and can also lead to compounds with interesting optical properties due to the high π-conjugation that can be achieved.

Shaabani and co-workers[97] reported a method to obtain bis(4*H*-chromene)-3,4-dicarboxylates *via* the reaction of two equivalents of isocyanides **627a–f**, two equivalents of acetylenedicarboxylates **628a–c** and 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (**630**) in acetonitrile. The proposed reaction mechanism is illustrated in Scheme 63a. The vinylisonitrilium cations **629** are generated by the reaction between isocyanides **627a–f** and alkynes **628a–c** *via* Michael addition. Then, a double aldol condensation takes place between the nucleophilic 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (**630**) and two cations **629** producing the keteneimides **631**, which *via* an intramolecular cyclization produce the final products **632a–j** *via* a repetitive pseudo-5CR. During the same year, the same authors[98] also reported a similar method to obtain highly functionalized benzo[*g*]- and dihydropyrano[2,3-*g*]chromenes *via* the reaction of two equivalents of aldehydes **633a–f**, two equivalents of malononitrile (**634**) and 2,5-dihydroxycyclohexa-2,5-diene-1,4-dione (**636**), with triethylamine as catalyst. The suggested mechanism is depicted in Scheme 63b. Initially, a Knoevenagel condensation between aldehydes **633a–f** and malononitriles (**634**) forms intermediates **635**, which undergo a double aldol-type condensation with the 2,5-dihydroxycyclohexa-2,5-diene-1,4,-dione (**636**) producing the intermediates **637**, followed by a cyclization to form **638**, and

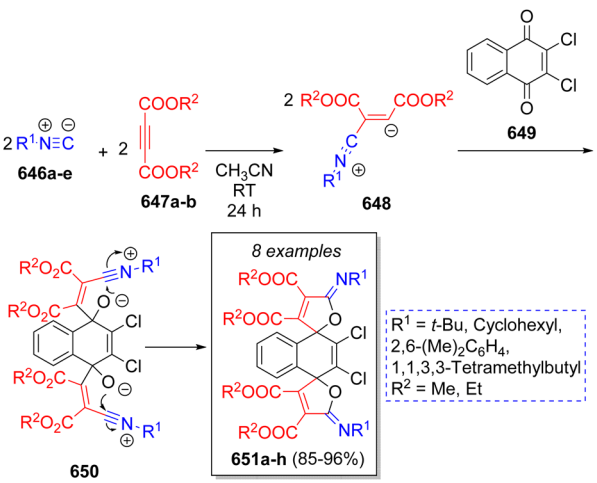


Scheme 64 Synthesis of bis[2-(arylimino)-1,3-thiazolidin-4-ones].

a further imine/enamine tautomerization that result in the final products **639a–f.**

In 2010, Alizadeh and co-workers[99] described the synthesis of some bis[2-(arylimino)-1,3-thiazolidin-4-ones] *via* the reaction of aliphatic diamines **640a–b**, two equivalents of isothiocyanatobenzene (**641**) and two equivalents of dialkyl but-2-ynedioate **643a–b**. Scheme 64 illustrates the synthetic methodology. Initially, aliphatic diamines react with two molecules of isothiocyanatobenzene (**641**) leading to the bis-thiourea intermediates **642**, which in turn react with the dialkyl but-2-ynedioates **643a–b** to produce the intermediates **644**. The desired products **645a–f** are obtained after intramolecular lactamization of intermediates **644**.

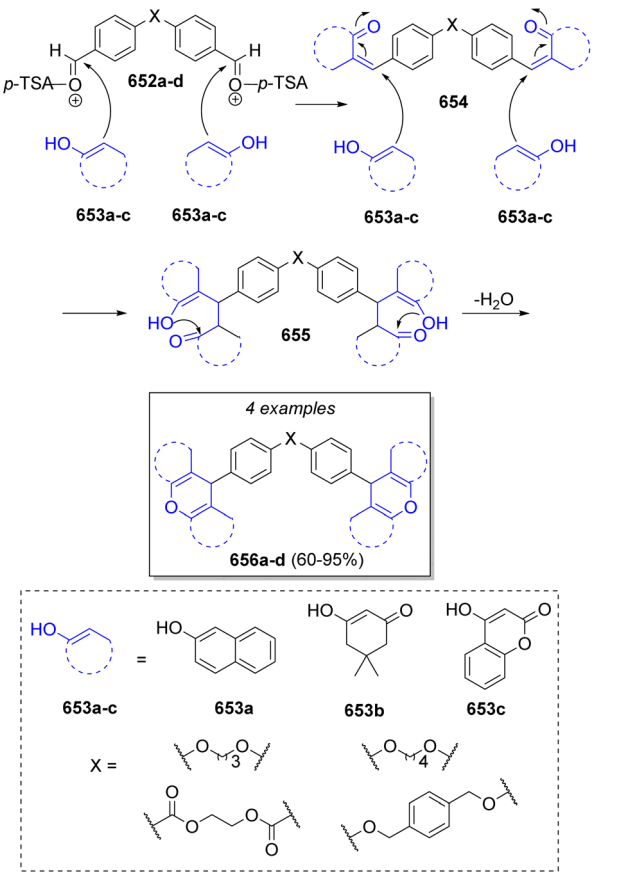
In 2014, Ghahremanzadeh and co-workers[100] reported a high yielding repetitive pseudo-5CR to obtain a collection of dispiro[furan-2,1′-naphthalene-4′,2″-furan] compounds, using two equivalents of isocyanides **646a–e**, two equivalents of acetylenedicarboxylates **647a–b** and 2,3-dichloronaphthalene-1,4-dione (**649**). A suggested reaction mechanism for this transformation is shown in Scheme 65. Initially, isocyanides **646a–e** and dialkyl acetylenedicarboxylates **647a–b** react to form zwitterionic intermediates **648**, which then react simultaneously with the 2,3-dichloronaphthalene-1,4-dione (**649**) to afford the dipolar intermediates **650**. Next, these latter ones undergo a double intramolecular cyclization to form the final di-spiro compounds **651a–h.**



Scheme 65 Synthesis of dispiro[furan-2,1′-naphthalene-4′,2″-furan] compounds.

In 2021, Abdelhamid and Elwahy[101] achieved the synthesis of novel bis(14*H*-dibenzo[*a*,*j*]xanthenes), bis(pyrano[3,2-*c*:5,6-*c*′] dichromenedione) and bis(dihydrobenzo[*a*]-xanthenones) using *p*-toluenesulfonic acid as catalyst. The repetitive pseudo-5CR involved bis-aldehydes **652a–d** and two equivalents of β-alcohols **653a–c**. Scheme 66 illustrates the suggested reaction mechanism. Initially, bis-aldehydes **652a–d** are activated by AcOH or *p*-TsOH, then undergoing a Knoevenagel condensation with β-alcohols **653a–c** to produce **654**, followed by a Michael addition of another molecule of **653a–c**, producing the intermediates **655**. Finally, an intramolecular dehydrative cyclization affords the final products **656a–d.**

A small collection of indole-3-aminopropenylidene merocyanine dimers was synthesized by Müller and co-workers[102]

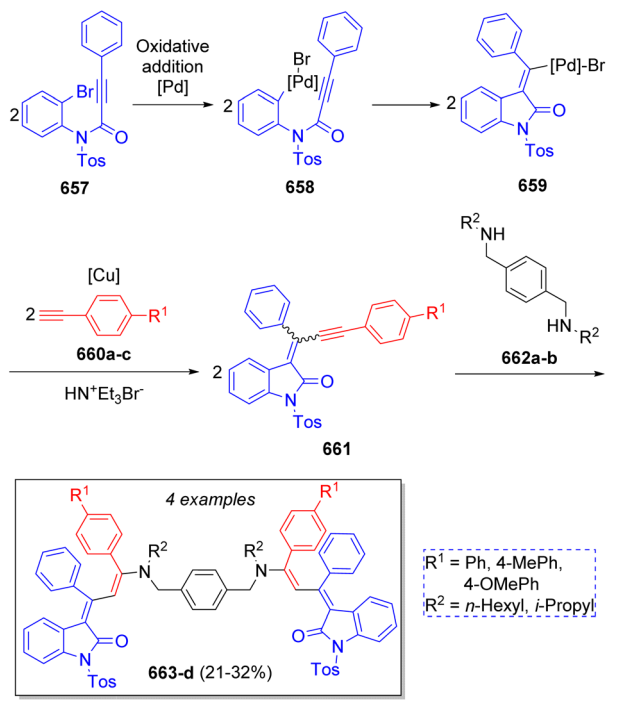


Scheme 66 Synthesis of bis(14*H*-dibenzo[*a*,*j*]xanthenes), bis(pyrano[3,2-*c*:5,6-*c*′]dichromenedione) and bis(dihydrobenzo[*a*]-xanthenones).

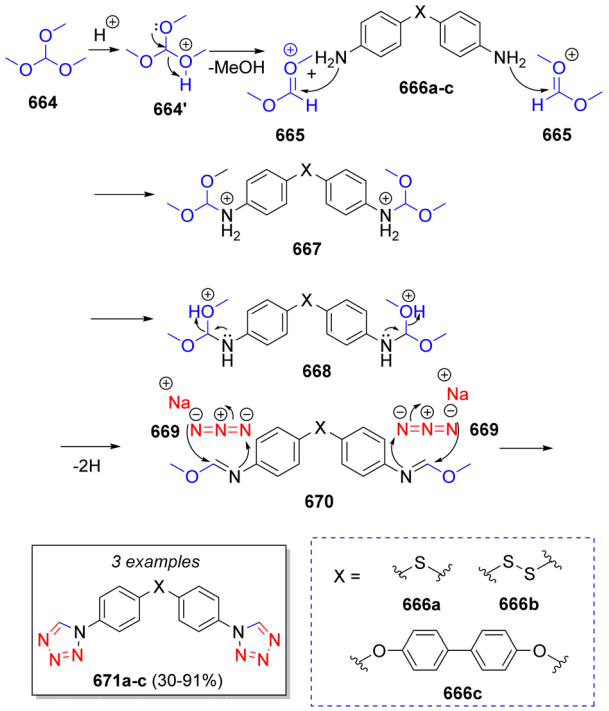
via a repetitive pseudo five-component reaction using 2 equivalents of *N*-tosyl 3-phenyl propynoyl *ortho*-bromo anilide (**657**), two equivalents of aryl alkynes **660a–c**, and *N*,*N*′-(1,4-phenylenebis(methylene))dialkanamines **662a–b**. According to the literature,[103] the mechanism occurs *via* an intramolecular Pd-catalyzed coupling of propynoyl *ortho*-bromo anilides **657** to produce the key intermediates **658** and **659**, which further couple with the aryl alkynes **660a–c** to form alkynylidene indolones **661**. These intermediates then react simultaneously with the bifunctional reactant *N*,*N*′-(1,4-phenylenebis(methylene))-dialkanamines **662a–b** to produce **663a–d** *via* a double nucleophilic addition (Scheme 67).

The synthesis of three novel bis-1-substituted-1*H*-tetrazoles were reported by Islas-Jácome and co-workers[104] *via* repetitive-type pseudo-MCR heterocyclizations from symmetric dianilines **666a–c** with two equivalents of trimethyl orthoformate (**664**), and sodium azide (**669**), respectively, in acetic acid as solvent. The proposed mechanism is illustrated in Scheme 68. Initially, protonation of the trimethylorthoester (**664**) by the acidic medium results in loss of a methanol molecule and formation of electrophile **665**. Iminoester **670** is formed from the reaction between intermediate **665** and dianilines **666a–c** after loss of another methanol molecule, followed by 1,3-dipolar cycloaddition with the azide ion **669** to form the corresponding bis-1-substituted 1*H*-tetrazoles **671a–c** with subsequent loss of final methanol molecules.

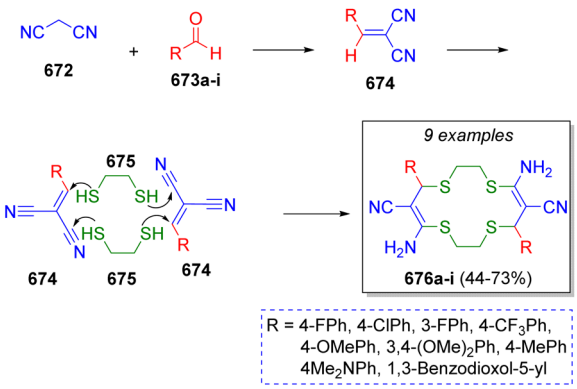
A collection of substituted 1,4,8,11-tetrathiacyclotetradeca-5,12-dienes was obtained by Akhmetova and co-workers[105] *via* a repetitive pseudo-6CR macroheterocyclization using malononitrile (**672**), aromatic aldehydes **673a–i**, and 1,2-ethanedithiol



Scheme 67 Synthesis of indole-3-aminopropenylidene merocyanine dimers.



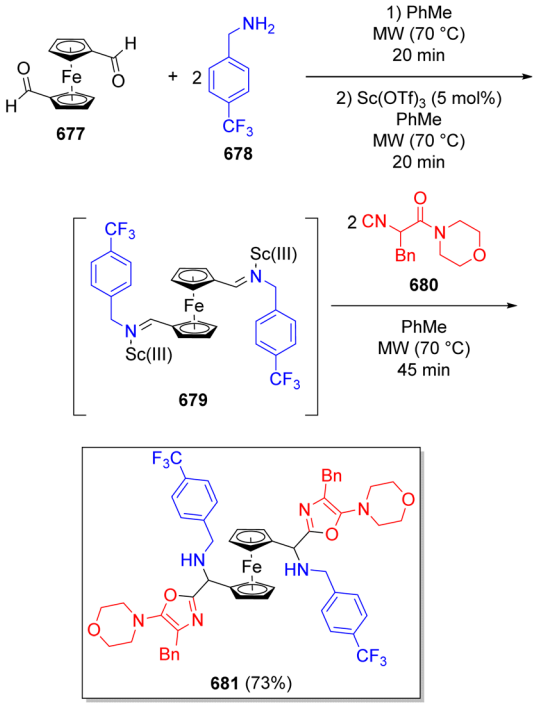
Scheme 68 Synthesis of bis 1-substituted-1*H*-tetrazoles.



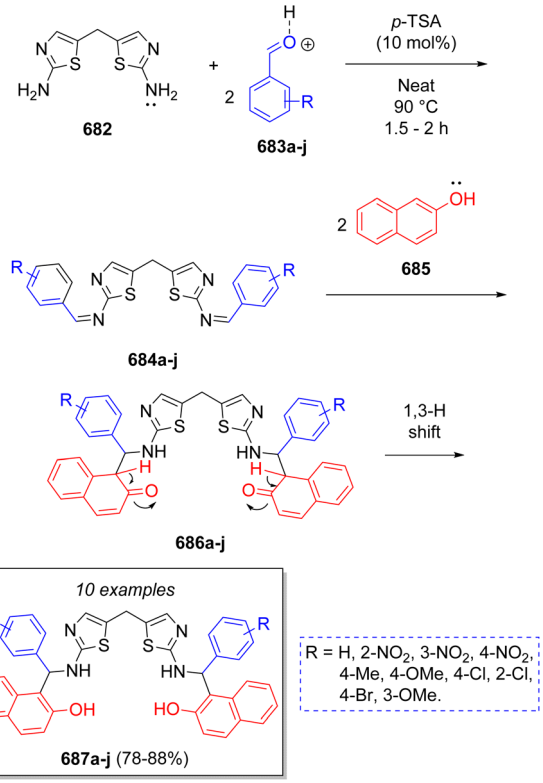
Scheme 69 Synthesis of 1,4,8,11-tetrathiacyclotetradeca-5,12-dienes.

(**675**) (in a 2 : 2 : 1 ratio), using triethylamine in ethanol as catalyst. The proposed mechanism is illustrated in Scheme 69. It its suggested that the reaction proceeds *via* Knoevenagel condensation between malononitrile (**672**) and aromatic aldehydes **673a–i** to form intermediates **674**. Subsequently, a reaction with two molecules of dithiol **675** to two molecules of intermediates **674** yield the symmetrical products **676a–i** in moderate yields.

Islas-Jácome and co-workers recently published the synthesis of bis-5-aminooxazoles linked through a ferrocene unit *via* a Sc(III)-catalyzed repetitive pseudo-5C Ugi–Zhu reaction. The central oxazole-ferrocene-oxazole motif makes this complex molecule a potential candidate to be an antimalarial



Scheme 70 Synthesis of ferrocene-linked bis-5-aminooxazole *via* a repetitive pseudo-5C Ugi–Zhu reaction.



Scheme 71 Synthesis of bis-aminomethylnaphtols *via* a repetitive-type pseudo-5C Betti condensation.

agent, while the presence of the trifluoromethyl groups could further enhance its pharmacokinetics. To synthesize the target compound, 1,1′-ferrocenedicarboxaldehyde (**677**) was condensed with two equivalents of 4-(trifluoromethyl)benzylamine (**678**) to afford the bis-imine **679**. This intermediate was activated towards nucleophilic addition with scandium(III) triflate, after which two equivalents of isocyanoacetamide **680** were added to afford the target ferrocene-linked bis-5-aminooxazole **681** (Scheme 70). The product was obtained in a one-pot fashion in under 2 hours of reaction time and in 73% yield, which is remarkable for such a complex molecule.[106]

M. Sadeghpour and co-workers[107] recently reported the synthesis of a small compound library of bis-aminomethylnaphtols *via* a repetitive pseudo-5C Betti reaction, which is a modified Mannich-type reaction involving a diamine **682**, two equivalents of different benzaldehydes **683** and two equivalents of 2-naphthol (**685**). Once the optimal reaction conditions were found by the authors, they synthesized a compound library using *p*-toluenesulfonic acid as organocatalyst, affording the target compounds in good to excellent yields. The authors also proposed a reaction mechanism: first, the bis-heterocyclic diamine component **682** undergoes a condensation with two equivalents of different benzaldehydes **683a–j** in the presence of the acid catalyst to afford the bis-Schiff bases **684a–j**. These intermediates react with two equivalents of 2-naphthol (**685**) to produce the intermediates **686a–j**, and after a [1,3]-H shift the target products **687a–j** are obtained (Scheme 71). It is worth noting that the products have potential use as ligands in coordination chemistry and were obtained in good yields in a one-pot procedure without solvent, making these conditions environmentally benign.

8. Conclusions and outlook

Multicomponent reactions are very useful tools for rapidly generating molecular complexity and diversity in few experimental steps, especially when they are coupled with further processes such as post synthetic transformations, allowing access to a large variety of chemical libraries of heterocyclic and polyheterocyclic compounds with various potential applications, particularly in medicinal chemistry, agrochemical industry, optics, and innovative materials design. In this sense, it is important to generate bibliographic material that documents the development of new methodologies based on MCRs. With this review, it was intended to provide attention to a subclass of MCRs, namely, pseudo-MCRs, as well as proposing a simple classification for the most commonly encountered synthetic strategies when pseudo-MCRs are employed: pseudo-MCRs, which have one or more reactants in a stoichiometric ratio equal or higher than 2 : 1, and repetitive pseudo-MCRs, in which one of the reactants have two or more identical functional groups with react simultaneously with the reactants stoichiometrically in excess (also equal or higher than 2 : 1), often generating highly symmetrical products. In addition, we consider this review will provide new insights for further investigations behind new reactions and/or novel domino-type one-pot based strategies.

Author contributions

J. C. F.-R and V. C. C.-S. (writing – original draft), I. A. I. (writing – review & editing), E. G.-Z. (supervision), A. I.-J. (conceptualization & funding acquisition).

Conflicts of interest

There are no conflicts to declare.

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